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C4-aldehyde of guaiazulene: synthesis and derivatisation†

Georgia E. Williams,^a Gabriele Kociok-Köhn,^b Tony D. James^{a,c} and Simon E. Lewis^{a*}

Guaiazulene is an alkyl-substituted azulene available from natural sources and is a much lower cost starting material for the synthesis of azulene derivatives than azulene itself. Here we report an approach for the selective functionalisation of guaiazulene which takes advantage of the acidity of the protons on the guaiazulene C4 methyl group. The aldehyde produced by this approach constitutes a building block for the construction of azulenes substituted on the seven-membered ring. Derivatives of this aldehyde synthesised by alkenylation, reduction and condensation are reported, and the halochromic properties of a subset of these derivatives have been studied.

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Introduction

Azulene (**1**) is a non-alternant bicyclic aromatic hydrocarbon, that has significantly different properties to those of its isomer naphthalene (**2**).¹ Whereas the HOMO–LUMO gap in naphthalene leads to absorption in the UV region, the corresponding molecular orbitals are closer in energy in azulene, hence leading to an absorption in the visible region. Thus, naphthalene is colourless but azulene is blue. Azulene also displays anomalous fluorescence characteristics, being an exception to Kasha's rule, with the $S_2 \rightarrow S_0$ transition being the dominant mode of emission.² Additional interesting optical properties such as halochromism,³ solvatochromism⁴ and barochromism⁵ have also been reported for certain azulenes. Azulene also has a dipole moment of 1.08 D, unusually high for a simple hydrocarbon.⁶ This arises from the contribution of resonance structure **1'**, in which both individual rings are 6π aromatic systems (Fig. 1). These notable properties have led to azulenes being used extensively as both colorimetric⁷ and fluorescent⁸ probes for various analytes. Azulenes have also been employed in solar cells⁹ and organic electronics,¹⁰ as well as in medicinal chemistry.¹¹

These various applications have been enabled by the development of synthetic routes to substituted azulenes.¹² One

approach is to synthesise the azulene ring from a precursor which already incorporates the desired substituents, for example by aromatisation of 1,1-dicyanodihydroazulenes¹³ or by a carbene insertion/ring expansion approach.¹⁴ Another strategy is to employ synthetic methodology that introduces the desired substituents onto a pre-existing azulene ring. Approaches for functionalisation of the 5-membered ring of azulene include S_EAr reactions,¹⁵ cross-coupling¹⁶ and C–H activation.¹⁷ Approaches for functionalisation of the 7-membered ring of azulene are less numerous, but include vicarious nucleophilic substitution¹⁸ and nucleophilic addition/rearomatisation.^{16g,19} However, regardless of the diversity of approaches for azulene derivatisation, work in this area is hindered by the high cost of azulene itself – preparation of the parent hydrocarbon requires multistep procedures and/or reagents that are themselves costly.^{15a,20} There is therefore a motivation to use an alternative azulene starting material which is abundantly available from natural sources and hence has a much lower cost, namely guaiazulene (**3**).

Guaiazulene and its derivatives are sesquiterpene natural products produced by various organisms, in particular gorgonian octocorals and the fungal genus *Lactarius*.²¹ Moreover, guaiazulene may be produced from the essential oils isolated from genera such as *Eucalyptus*,²² *Matricaria* (chamomile)²³ and others.²⁴ These processes proceed *via* the dehydration/

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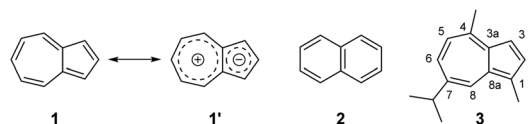


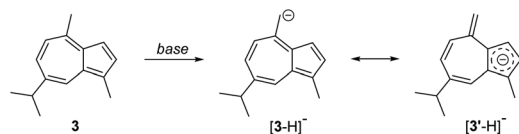
Fig. 1 Structures of azulene, naphthalene and guaiazulene.



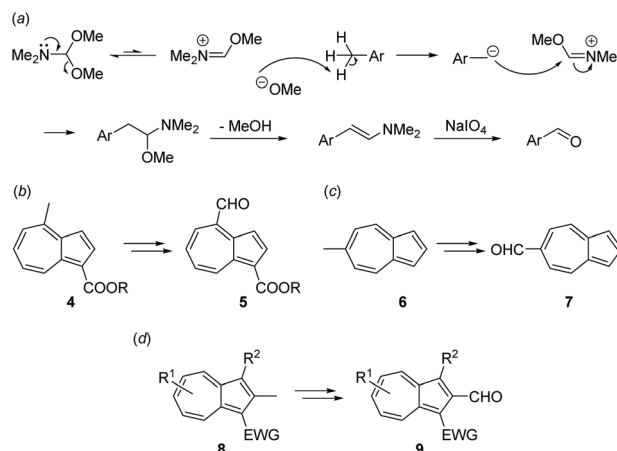
dehydrogenation of other sesquiterpenes such as guaialol and occur in high yields, permitting the large scale production of guaiazulene at low cost. The main uses of guaiazulene and its derivative sodium guaiazulene-3-sulfonate are as anti-inflammatory agents and in cosmetics.²⁵

The alkyl groups on guaiazulene do not influence the azulene chromophore significantly, but they impart a much lower melting point (30–33 °C)²⁶ and guaiazulene can undergo very slow decomposition on exposure to air.²⁷ However, derivatives bearing electron withdrawing groups are generally stable. Methods for derivatisation of guaiazulene are not as extensively developed as for azulene itself and in some instances may be hindered by the alkyl substituents. On the other hand, the alkyl substituents of guaiazulene can be seen as handles for further derivatisation themselves.²⁸ One strategy to achieve this exploits the known acidity of the protons on the guaiazulene C4 methyl group.^{3h,17n,29} The low pK_a of these protons arises from the resonance stabilisation of the corresponding conjugate base, [3-H]⁻ that may be attributed to resonance structure [3'-H]⁻ (Scheme 1) that comprises an aromatic cyclopentadienide substructure.

Amide acetals such as dimethylformamide dimethyl acetal (DMFDMA) are versatile reagents able to effect a variety of synthetic transformations.³⁰ Reaction of an amide acetal with aryl methyl groups to give the corresponding enamines was first reported by Meerwein³¹ and was further developed by Brederick.³² Oxidative cleavage of such enamines is possible using sodium periodate (with no requirement for osmium tetroxide).³³ Taken together, these two procedures allow formation of an aryl aldehyde in two steps from the corresponding aryl methyl group. The reaction mechanism requires that the arene is able to stabilise a benzylic anion, hence electron-poor arene substrates are generally required (Scheme 2a). We reasoned that this synthetic sequence could be applicable to guaiazulene, resulting in a regioselective transformation of the C4 methyl group to an aldehyde, although whether the C4 methyl protons were sufficiently acidic was unclear at the outset. To our knowledge there are three prior reports of azulene methyl groups in this way. In 2006, Kim, Osuka and co-workers reported the reaction of a 4-methylazulene **4**, bearing an electron-withdrawing ester at the 1-position, which would lower the pK_a of the C4 methyl protons (Scheme 2b).³⁴ In 2015, Leino and co-workers reported the reaction of 6-methylazulene **6**, which lacks any other substituents (Scheme 2c).³⁵ Most recently, in 2018 Shoji and co-workers reported the reaction of various 2-methylazulenes of type **8**, finding that the reaction



Scheme 1 Guaiazulene deprotonates preferentially at the C4 methyl group.



Scheme 2 (a) Mechanism for transformation of aryl methyl group to aryl aldehyde. (b) Work of Kim, Osuka and co-workers. (c) Work of Leino and co-workers. (d) Work of Shoji and co-workers.

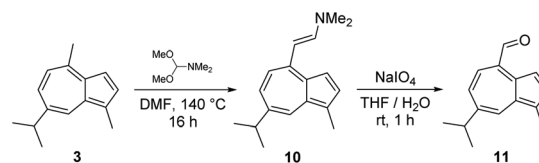
did not proceed without an electron-withdrawing group at the 1-position (Scheme 2d).³⁶

In this paper we describe the first synthesis of guaiazulene-4-carbaldehyde, as well as some further transformations of this compound.

Results and discussion

Treatment of guaiazulene **3** with DMFDMA in DMF gave crude enamine **10** as a green solid after aqueous workup.† This proved to be somewhat unstable and could not be purified by chromatography on silica. Thus, **10** was used crude, and was directly subjected to oxidative cleavage with NaIO₄ to give novel aldehyde **11** in 77% yield over two steps (Scheme 3). In contrast to **10**, aldehyde **11** could be purified by chromatography on silica, and is stable in pure form. Crystals of **11** were subjected to X-ray diffraction analysis and the resultant structure is shown in Fig. 2.

We anticipate that aldehyde **11** may find various uses in synthesis, since it is accessible in a concise fashion from a cheap azulenic starting material. Reduction of **11** with NaBH₄ furnished alcohol **12** in sufficient purity that chromatography



Scheme 3 Synthesis of guaiazulene-4-carbaldehyde **11**.

† Although **10** has not been reported previously, various substituted analogues have been described, having been formed under Vilsmeier conditions – see ref. 41.



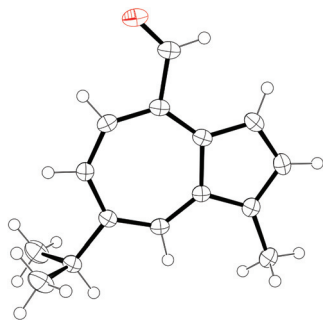
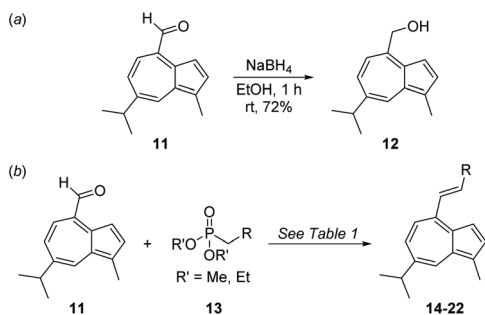


Fig. 2 ORTEP representation of the X-ray structure of **11**. Ellipsoids are shown at 50% probability. Hydrogens are shown as spheres of arbitrary radius. CCDC 2047319.†

was not required (Scheme 4a). Alkenylation of **11** by Horner–Wadsworth–Emmons reaction was carried out using a variety of phosphonates (Scheme 4b, Table 1).³⁷ Alkenes **20** and **21** were synthesised from phosphonate reagents containing additional Lewis basic groups, and as such the modified Masamune–Rousch reaction conditions were employed in these instances.³⁸

C4-alkenylated guaiazulene derivatives such as **14–22** have been reported previously,^{3h,11j,29c,j,29l–n,29r} although in these cases the C4 methyl carbon reacted as a nucleophile, as opposed to as an electrophile as is the case here. A notable property of certain C4-alkenylated guaiazulenes described previously is their halochromism.^{3h,29c} Accordingly, selected alkenylated derivatives of **11** and their response to Brønsted acid were studied. 4-Fluorostyrylazulene **19** was titrated against increasing quantities of trifluoroacetic acid in CH₂Cl₂ and UV/vis absorption spectra were acquired (Fig. 3).

The absorption maxima at $\lambda = 289$ nm and $\lambda = 319$ nm decreased in intensity with increasing acid concentration, whereas a new absorption maximum at $\lambda = 447$ nm (in the blue region) was seen to increase in intensity; an isosbestic point was observed at $\lambda \approx 388$ nm. ¹H-NMR spectra of **19** in CDCl₃ and in CDCl₃/TFA were acquired (Fig. 4), and show the site of protonation to be the guaiazulene C3 position. Specifically, for the spectrum in CDCl₃, the H-3 resonance is observed as a 1H doublet at 7.46 ppm, whereas in TFA/CDCl₃



Scheme 4 (a) Reduction of **11**. (b) Horner–Wadsworth–Emmons reaction of **11**.

Table 1 Horner–Wadsworth–Emmons reactions of **11**

Entry	R	Product	R'	Method ^{a,b}	Yield (%)
1		14	Et	A	38
2		15	Et	A	46
3		16	Et	A	18
4		17	Et	A	56
5		18	Et	A	42
6		19	Et	A	44
7		20	Me	B	41
8		21	Et	B	33
9		22	Et	A	50

^a Method A: 60% NaH (2 eq.), THF, rt, 2 h. ^b Method B: LiCl (3 eq.), DBU (3 eq.), THF, 0 °C, 3 h.

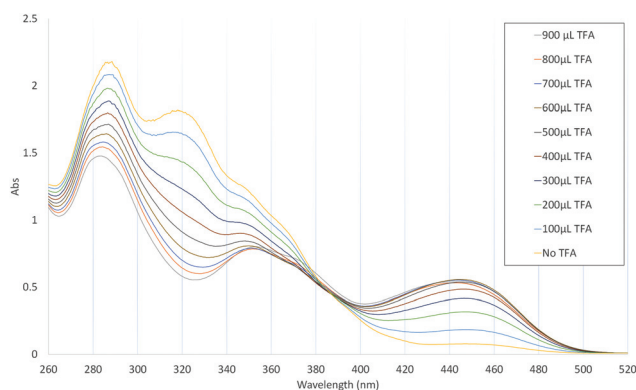


Fig. 3 Titration of **19** (0.08 mM) with TFA (1 M in CH₂Cl₂) in CH₂Cl₂.

it is observed as a 2H broad singlet at 4.08 ppm, this chemical shift being indicative of an sp³-hybridised carbon. Further support for the guaiazulene C3 position being the site of protonation comes from comparison with spectra of similar azulenium cations generated by hydride abstraction from dihydroazulenes.^{13d,39}

Cyano-substituted **15**, chloro-substituted **18** and α,β -unsaturated ester **20** were investigated in a similar fashion, and all were observed by NMR to undergo protonation at the same position (Fig. S1–S3†). Whereas **15** and **18** exhibited similar maxima and isosbestic points to **19** (Fig. S4 and S5†), the isosbestic point for **20** was blue shifted (Fig. S6†). As a further demonstration of the scope for functionalisation of **11**, formation of a nitron was attempted. Azulenyl nitrones are of



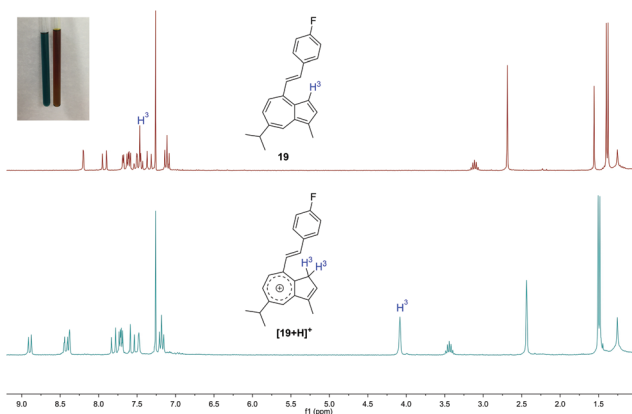
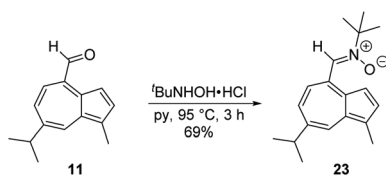


Fig. 4 Top: ^1H -NMR spectrum of **19** in CDCl_3 . Bottom: ^1H -NMR spectrum of **19** in TFA/ CDCl_3 1 : 9. Inset: NMR tubes containing **19** in CDCl_3 (left) and **19** in TFA/ CDCl_3 (right).



Scheme 5 Synthesis of nitrone **23**.

interest as free radical spin traps with neuroprotective activity and potential clinical utility.⁴⁰ In the present case, condensation of **11** with *N*-*tert*-butylhydroxylamine gave nitrone **23** (Scheme 5).

Conclusions

We have described the concise synthesis of an azulene bearing an aldehyde at the 4-position (**11**). The use of a low-cost, commercially available azulene starting material and the requirement for only one purification step render **11** an attractive building block for the synthesis of more complex azulenes bearing substituents at the 4-position. We have demonstrated the utility of **11** through its use in reduction, alkenylation and condensation reactions.

Experimental

General details

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of argon. Reaction solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. In most cases, solvents were purchased as “anhydrous” grade from Fisher Scientific. “Petrol” refers to petroleum spirit b.pt. 40–60 °C. TLC was performed using aluminium backed plates pre-coated

with Alugram®SIL G/UV 254 nm. Where needed, visualisation was accomplished by UV light and/or KMnO_4 or using phosphomolybdic acid (PMA) dip followed by gentle warming. Following work up, the organic layers were routinely dried using anhydrous MgSO_4 and evaporated using a Büchi rotary evaporator. When necessary, further drying was facilitated by high vacuum. During purification, flash column chromatography was carried out using 60 angstroms (Å) silica gel (40–75 micron) purchased from Sigma Aldrich. ^1H and ^{13}C NMR spectra were acquired on Agilent ProPulse 500 MHz or Bruker Advance 250, 300, 400 or 500 megahertz (MHz) instruments at 298 K. All spectra were referenced to residual solvent peaks; chemical shifts are reported in parts per million (ppm) relative to residual chloroform ($\delta = 7.26$ ppm, ^1H ; 77.16 ppm, ^{13}C). All $^{13}\text{C}\{^1\text{H}\}$ resonances are singlets, unless stated otherwise. Coupling constants, J , reported in Hz, were calculated using MestreNova 9.0 to the nearest 0.1 Hz. The following abbreviations are used to label the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sex, sextet; sep, septet; dd, doublet of doublets; dq, doublet of quartets; td, triplet of doublets; m, multiplet and br, broad. ^1H and $^{13}\text{C}\{^1\text{H}\}$ assignments for novel compounds are corroborated through 2D (COSY, HSQC, HMBC). Infrared (IR) spectra were recorded on a PerkinElmer Spectrum 100 ATR-FTIR spectrometer with only selected absorbances quoted as ν in cm^{-1} . For mass spectrometry a microTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used. Data are reported in the form of m/z . The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula. Melting points (mp) were determined on a Stanford Research Systems OptiMelt automated capillary melting point apparatus in open capillary tubes and are uncorrected. X-Ray intensity data for **11** were collected at 150(2) K on a Rigaku SuperNova Dual EosS2 single crystal diffractometer using monochromated Cu-K α radiation ($\lambda = 1.54184$ Å). Unit cell determination, data collection data reduction and absorption correction were performed using the CrysAlisPro software (version 1.171.40.43a, Rigaku Oxford Diffraction, 2019). The structure was solved with SHELXT and refined by a full-matrix least-squares procedure based on F2 (SHELXL-2018/3). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed onto calculated positions and refined using a riding model.

7-Isopropyl-1-methylazulene-4-carbaldehyde (11). Under an atmosphere of nitrogen, guaiazulene (0.32 g, 1.6 mmol, 1.0 eq.) was dissolved in degassed anhydrous DMF (5.0 mL), to which *N,N*-dimethylformamide dimethyl acetal (0.43 mL, 3.2 mmol, 2.0 eq.) was added. The reaction was heated to 140 °C and stirred for 9 h, during which the solution turned from blue to green. The solution was cooled to room temperature and diluted with ethyl acetate (30 mL). The organic mixture was washed with water (30 mL) and 5% $\text{LiCl}_{(\text{aq})}$ solution (2×30 mL). The organic phase was dried over MgSO_4 and filtered, and the filtrate was concentrated under reduced pressure to give crude **10**, used immediately. Under aerobic



conditions, the crude material was re-dissolved in THF/H₂O (30 mL, 1 : 1, v/v), to which NaIO₄ (1.0 g, 4.8 mmol, 3.0 eq.) was added. The solution was stirred room temperature for 2.5 hours, turning from green to blue, then diluted with ethyl acetate (30 mL). The organic phase was washed with water (30 mL) and sat. NaHCO_{3(aq)} solution (2 × 30 mL), for which the initial aqueous extract was orange and the latter extract was colourless. The organic phase was dried over MgSO₄ and filtered, and the filtrate was concentrated under reduced pressure. The crude material was purified by silica column chromatography, eluting with EtOAc/petrol (5 : 95, R_f = 0.50) to give 7-isopropyl-1-methylazulene-4-carbaldehyde **11** (0.21 g, 62%) as a blue-brown solid. ¹H NMR (500 MHz, CDCl₃) δ 1.40 (d, *J* = 6.9 Hz, 6H, -CH(CH₃)₂), 2.71 (s, 3H, C1-CH₃), 3.15 (hept, *J* = 6.9 Hz, 1H, -CH(CH₃)₂), 7.56 (d, *J* = 10.4 Hz, 1H, C5-H), 7.63 (dd, *J* = 10.5, 1.9 Hz, 1H, C6-H), 7.92 (d, *J* = 3.6 Hz, 1H, C3-H), 8.08 (d, *J* = 3.7 Hz, 1H, C2-H), 8.25 (d, *J* = 1.3 Hz, 1H, C8-H), 10.77 (s, 1H, -CHO) ppm. ¹³C NMR (500 MHz, CDCl₃) δ 13.0, 24.6, 39.0, 112.4, 123.8, 126.2, 133.9, 134.1, 134.7, 136.2, 141.4, 141.6, 145.1, 195.1 ppm. IR ν_{max} 701, 761, 1682, 2861, 2924, 2955 cm⁻¹. Melting point 81–84 °C. HRMS (ESI⁺): calculated for C₁₅H₁₆O [M + H]⁺ 213.1274, found 213.1278.

(7-Isopropyl-1-methylazulene-4-yl)methanol (12). To a solution of **11** (75 mg, 0.3 mmol, 1.0 eq.) in EtOH was added NaBH₄ (27 mg, 0.7 mmol, 2.0 eq.). The solution was stirred for 1 h at rt and was then quenched with water (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL), dried over MgSO₄ and filtered, then the filtrate was evaporated under reduced pressure to give (7-isopropyl-1-methylazulene-4-yl)methanol as a turquoise gum (54 mg, 72%). ¹H NMR (500 MHz, (CD₃)₂CO) δ 1.37 (d, *J* = 6.9 Hz, 6H, -CH(CH₃)₂), 2.65 (s, 3H, C1-CH₃), 3.14 (hept, *J* = 6.9 Hz, 1H, -CH(CH₃)₂), 4.57 (t, *J* = 5.8 Hz, 1H, -OH), 5.18 (d, *J* = 5.3 Hz, 2H, -CH₂OH), 7.25 (d, *J* = 3.7 Hz, 1H, C3-H), 7.52 (d, *J* = 10.7 Hz, 1H, C5-H), 7.62–7.59 (m, 2H, C2-H, C6-H), 8.27 (d, *J* = 2.0 Hz, 1H, C8-H) ppm. ¹³C NMR (500 MHz, (CD₃)₂CO) δ 12.9, 25.0, 39.0, 64.5, 111.3, 121.3, 125.4, 133.9, 135.7, 135.7, 137.2, 138.6, 141.4, 147.4 ppm. IR ν_{max} 1008, 1386, 2924, 2956, 3316 cm⁻¹. HRMS (ESI⁺): calculated for C₁₅H₁₈O [M + H]⁺ 215.1430, found 215.1438.

General procedure A for Horner–Wadsworth–Emmons reactions

To a stirred solution of 60% NaH (11 mg, 0.3 mmol, 2.0 eq.) in anhyd. THF (3 mL) was added dropwise a solution of the required phosphonate (0.3 mmol, 2.0 eq.) in anhyd. THF (4 mL) under nitrogen. The mixture was stirred for 10 min after which a solution of **11** (30 mg, 0.1 mmol, 1.0 eq.) in anhyd. THF (3 mL) was added dropwise. The mixture was stirred at rt until the starting material was consumed as shown by TLC (approx. 2 h). The reaction mixture was diluted with water (10 mL) and extracted with CH₂Cl₂ (3 × 30 mL). The combined organic fractions were dried over MgSO₄ and filtered, then the filtrate was evaporated under reduced pressure. Purification was achieved by column chromatography to give the desired alkenylazulene.

(E)-4-(4-Iodostyryl)-7-isopropyl-1-methylazulene (14). General procedure A was used with diethyl (4-iodobenzyl)phosphonate (100 mg) to give the product as a green waxy gum (22 mg, 38%) following purification *via* column chromatography using Petrol (100%, R_f 0.50). ¹H NMR (500 MHz, (CD₃)₂CO) δ 1.38 (d, *J* = 6.9 Hz, 6H, -CH(CH₃)₂), 2.66 (s, 3H, C1-CH₃), 3.15 (hept, *J* = 6.9 Hz, 1H, -CH(CH₃)₂), 7.48 (d, *J* = 16.2 Hz, 1H, C₆H₄-CH=CH-), 7.58–7.61 (m, 5H, C3-H, C5-H, C6-H, *m*-I-Ar-H), 7.67 (d, *J* = 3.9 Hz, 1H, C2-H), 7.80 (d, *J* = 8.4 Hz, 2H, *o*-I-Ar-H), 8.20 (d, *J* = 16.2 Hz, 1H, C₆H₄-CH=CH-), 8.25 (s, 1H, C8-H) ppm. ¹³C NMR (500 MHz, (CD₃)₂CO) δ 13.1, 24.9, 38.9, 94.2, 113.1, 120.8, 126.7, 130.0, 130.9, 133.7, 133.7, 135.6, 137.5, 137.7, 137.8, 138.0, 138.8, 141.0, 142.1 ppm. IR ν_{max} 763, 950, 2958 cm⁻¹. HRMS (ESI⁺): calc. for C₂₂H₂₁I [M + H]⁺ 413.0761, found 413.0771.

(E)-4-(2-(7-Isopropyl-1-methylazulene-4-yl)vinyl)benzotrile (15). General procedure A was used with diethyl (4-cyanobenzyl)phosphonate (72 mg) to give the product as a green gum (20 mg, 46%) following purification *via* column chromatography using Petrol (100%, R_f 0.40). ¹H NMR (500 MHz, (CD₃)₂CO) δ 1.38 (d, *J* = 6.9 Hz, 6H, -CH(CH₃)₂), 2.66 (s, 3H, C1-CH₃), 3.16 (hept, *J* = 6.9 Hz, 1H, -CH(CH₃)₂), 7.59 (d, *J* = 15.9 Hz, 1H, C₆H₄-CH=CH-), 7.59–7.60 (m, 2H, C5-H, C6-H), 7.63 (d, *J* = 3.9 Hz, 1H, C3-H), 7.70 (d, *J* = 3.9 Hz, 1H, C2-H), 7.81 (d, *J* = 8.4 Hz, 2H, *m*-CN-Ar-H), 7.98 (d, *J* = 8.3 Hz, 2H, *o*-CN-Ar-H), 8.28 (s, 1H, C8-H), 8.33 (d, *J* = 16.3 Hz, 1H, C₆H₄-CH=CH-) ppm. ¹³C NMR (500 MHz, (CD₃)₂CO) δ 13.0, 24.9, 38.9, 112.1, 113.2, 119.4, 120.8, 126.8, 128.7, 133.0, 133.4, 133.7, 133.9, 135.7, 137.7, 138.1, 138.2, 141.4, 141.6, 142.7 ppm. IR ν_{max} 738, 787, 1262, 2222, 2849, 2917, 2959 cm⁻¹. HRMS (ESI⁺): calc. for C₂₃H₂₁N [M + H]⁺ 312.1747, found 312.1753.

(E)-7-Isopropyl-1-methyl-4-(4-nitrostyryl)azulene (16). General procedure A was used with diethyl (4-nitrobenzyl)phosphonate (77 mg) to give the product as a dark green waxy gum (8.6 mg, 18%) following purification *via* column chromatography using Petrol (100%, R_f 0.40). ¹H NMR (500 MHz, CDCl₃) δ 1.40 (d, *J* = 6.9 Hz, 6H, -CH(CH₃)₂), 2.70 (s, 3H, C1-CH₃), 3.13 (hept, *J* = 6.9 Hz, 1H, -CH(CH₃)₂), 7.40 (d, *J* = 16.2 Hz, 1H, C₆H₄-CH=CH-), 7.43 (d, *J* = 10.9 Hz, 1H, C5-H), 7.45 (br s, 1H, C3-H), 7.54 (dd, *J* = 10.9, 1.9 Hz, C6-H), 7.72 (s, 1H, C2-H), 7.74–7.77 (m, 2H, *m*-NO₂-Ar-H), 8.15 (d, *J* = 16.2 Hz, 1H, C₆H₄-CH=CH-), 8.23 (d, *J* = 1.9 Hz, 1H, C8-H), 8.26–8.30 (m, 2H, *o*-NO₂-Ar-H). ¹³C NMR (500 MHz, (CD₃)₂CO) δ 13.0, 24.9, 39.0, 113.2, 120.9, 124.8, 126.9, 128.9, 132.6, 133.9, 134.6, 135.7, 137.7, 138.2, 138.3, 141.4, 141.6, 144.8, 148.2 ppm. IR ν_{max} 744, 1335, 1511, 1592, 2924, 2957 cm⁻¹. HRMS (ESI⁺): calc. for C₂₂H₂₁NO₂ [M + H]⁺ 332.1645, found 332.1653.

(E)-7-Isopropyl-1-methyl-4-(4-(trifluoromethyl)styryl)azulene (17). General procedure A was used with (4-(trifluoromethyl)benzyl)phosphonate (74 mg) to give the product as a green waxy gum (25 mg, 56%) following purification *via* column chromatography using Petrol (100%, R_f 0.60). ¹H NMR (500 MHz, (CD₃)₂CO) δ 1.38 (d, *J* = 6.9 Hz, 6H, -CH(CH₃)₂), 2.66 (s, 3H, C1-CH₃), 3.15 (hept, *J* = 7.0 Hz, 1H, -CH(CH₃)₂), 7.59 (d, *J* = 16.2 Hz, 1H, C₆H₄-CH=CH-), 7.61–7.60 (m, 2H,



C5-H, C6-H), 7.62 (d, $J = 3.9$ Hz, C3-H), 7.69 (d, $J = 3.8$ Hz, 1H, C2-H), 7.76 (d, $J = 8.1$ Hz, 2H, *m*-CF₃-Ar-H), 7.99 (d, $J = 7.8$ Hz, 2H, *o*-CF₃-Ar-H), 8.27 (s, 1H, C8-H), 8.30 (d, $J = 16.2$ Hz, 1H, C₆H₄-CH=CH-). ¹³C NMR (500 MHz, (CD₃)₂CO) δ 142.2 (q, ⁴ $J_{CF} = 1.5$ Hz), 141.8, 141.3, 138.1, 138.1, 137.6, 135.7, 133.8, 133.2, 132.9, 130.1 (q, ² $J_{CF} = 32.0$ Hz), 128.5, 126.8, 126.5 (q, ³ $J_{CF} = 3.9$ Hz), 125.4 (q, ¹ $J_{CF} = 270.9$ Hz), 120.9, 113.2, 38.9, 24.9, 13.0 ppm. IR ν_{max} 825, 1065, 1106, 1320, 1413, 2960 cm⁻¹. HRMS (ESI⁺): calc. for C₂₃H₂₁F₃ [M + H]⁺ 355.1668, found 355.1655.

(E)-4-(4-Chlorostyryl)-7-isopropyl-1-methylazulene (18). General procedure A was used with diethyl (4-chlorobenzyl)phosphonate (74 mg) to yield a green waxy gum (19 mg, 42%) following purification *via* column chromatography using Petrol (100%, R_f 0.40). ¹H NMR (500 MHz, (CD₃)₂CO) δ 1.38 (d, $J = 7.0$ Hz, 6H, -CH(CH₃)₂), 2.66 (s, 3H, C1-CH₃), 3.15 (hept, $J = 6.8$ Hz, 1H, -CH(CH₃)₂), 7.44–7.48 (m, 2H, *m*-Cl-Ar-H), 7.54 (d, $J = 16.2$ Hz, 1H, C₆H₄-CH=CH-), 7.59–7.60 (m, 2H, C5-H, C6-H), 7.60–7.62 (m, 1H, C3-H), 7.67–7.68 (m, 1H, C2-H), 7.79–7.84 (m, 2H, *o*-Cl-Ar-H), 8.19 (d, $J = 16.2$ Hz, 1H, C₆H₄-CH=CH-), 8.26 (s, 1H, C8-H) ppm. ¹³C NMR (500 MHz, (CD₃)₂CO) δ 13.1, 24.9, 38.9, 113.1, 120.7, 126.6, 129.6, 129.7, 130.8, 133.5, 133.7, 134.3, 135.6, 137.1, 137.4, 137.7, 137.8, 141.0, 142.1 ppm. IR ν_{max} 772, 817, 1011, 1091, 1490, 2923 cm⁻¹. HRMS (ESI⁺): calc. for C₂₂H₂₁Cl [M + H]⁺ 321.1405, found 321.1412.

(E)-4-(4-Fluorostyryl)-7-isopropyl-1-methylazulene (19). General procedure A was used with diethyl (3-fluorobenzyl)phosphonate (70 mg) to give the product as a green waxy gum (19 mg, 44%) following purification *via* column chromatography using Petrol (100%, R_f 0.30). ¹H NMR (500 MHz, (CD₃)₂CO) δ 1.38 (d, $J = 6.9$ Hz, 6H, -CH(CH₃)₂), 2.66 (s, 3H, C1-CH₃), 3.15 (hept, $J = 6.9$ Hz, 1H, -CH(CH₃)₂), 7.21 (dd, ³ $J_{HH} = 8.8$ Hz, ³ $J_{HF} = 8.8$ Hz, 2H, *o*-F-Ar-H), 7.54 (d, $J = 16.2$ Hz, 1H, C₆H₄-CH=CH-), 7.59 (br s, 2H, C5-H, C6-H), 7.60 (d, $J = 4.0$ Hz, 1H, C3-H), 7.66 (d, $J = 4.0$ Hz, 1H, C2-H), 7.85 (dd, ³ $J_{HH} = 8.6$ Hz, ⁴ $J_{HF} = 5.5$ Hz, 2H, *m*-F-Ar-H), 8.12 (d, $J = 16.2$ Hz, 1H, C₆H₄-CH=CH-), 8.26 (s, 1H, C8-H) ppm. ¹³C NMR (500 MHz, (CD₃)₂CO) δ 13.1, 25.0, 38.9, 113.1, 116.5 (d, ² $J_{CF} = 21.8$ Hz), 120.8, 126.6, 129.9 (d, ⁵ $J_{CF} = 2.4$ Hz), 130.0 (d, ³ $J_{CF} = 8.1$ Hz), 133.6, 133.7, 134.8 (d, ⁴ $J_{CF} = 3.3$ Hz), 135.7, 137.4, 137.7, 138.0, 140.9, 142.4, 163.7 (d, ¹ $J_{CF} = 246.5$ Hz) ppm. IR ν_{max} 771, 1215, 1505, 2955 cm⁻¹. HRMS (ESI⁺): calc. for C₂₂H₂₁F [M + H]⁺ 305.1700, found 305.1706.

General procedure B for Horner–Wadsworth–Emmons reactions

To the required phosphonate (0.1 mmol, 1.0 eq.) in anhyd. THF (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (60 μ L, 0.4 mmol, 3.0 eq.) and lithium chloride (18 mg, 0.4 mmol, 3.0 eq.) under nitrogen. The mixture was stirred for 5 min after which a solution of **11** (30 mg, 0.1 mmol, 1.0 eq.) in anhyd. THF (5 mL) was added dropwise. The mixture was stirred at rt until the starting material was consumed as shown by TLC (approx. 3 h). The mixture was then quenched with water (2 mL) and sat. NH₄Cl. The mixture was then extracted with EtOAc (3 \times 20 mL) and the combined organic fractions

were washed with water (30 mL) and brine (30 mL), dried over MgSO₄ and filtered, then the filtrate was evaporated under reduced pressure. Purification was achieved by column chromatography to give the desired alkenylazulene.

Methyl (E)-3-(7-isopropyl-1-methylazulene-4-yl)acrylate (20). General procedure B was used with methyl 2-(diethoxyphosphoryl)acetate (26 mg) to give the product as a green waxy gum (15 mg, 41%) following purification *via* column chromatography using Petrol/EtOAc (95 : 5; R_f 0.5). ¹H NMR (400 MHz, CDCl₃) δ 1.39 (d, $J = 6.9$ Hz, 6H, -CH(CH₃)₂), 2.69 (s, 3H, C1-CH₃), 3.11 (hept, $J = 6.8$ Hz, 1H, -CH(CH₃)₂), 3.87 (s, 3H, -OCH₃), 6.65 (d, $J = 15.9$ Hz, 1H, -CH=CH-COOCH₃), 7.29 (d, $J = 10.8$ Hz, 1H, C5-H), 7.46 (d, $J = 3.9$ Hz, 1H, C3-H), 7.50 (dd, $J = 10.8, 2.0$ Hz, 1H, C6-H), 7.75 (d, $J = 3.3$ Hz, 1H, C2-H), 8.21 (d, $J = 1.9$ Hz, 1H, C8-H), 8.53 (d, $J = 15.9$ Hz, 1H, -CH=CH-COOCH₃) ppm. ¹³C NMR (500 MHz, CDCl₃) δ 13.1, 24.8, 38.6, 52.1, 112.6, 120.4, 122.8, 126.6, 133.6, 134.9, 137.3, 137.4, 138.4, 138.5, 141.8, 145.9, 167.3 ppm. IR ν_{max} 1018, 1169, 1273, 1718, 2958 cm⁻¹. HRMS (ESI⁺): calc. for C₁₈H₂₀O₂ [M + H]⁺ 269.1536, found 269.1535.

(E)-3-(7-Isopropyl-1-methylazulene-4-yl)acrylonitrile (21). General procedure B was used with diethyl (cyanomethyl)phosphonate (25 mg) to give the product as a dark green waxy gum (10 mg, 33%) following purification *via* column chromatography using Petrol/EtOAc (80 : 20; R_f 0.6). ¹H NMR (500 MHz, CDCl₃) δ 1.38 (d, $J = 6.9$ Hz, 6H, -CH(CH₃)₂), 2.69 (s, 3H, C1-CH₃), 3.12 (hept, $J = 6.8$ Hz, 1H, -CH(CH₃)₂), 6.13 (d, $J = 16.6$ Hz, 1H, -CH=CH-CN), 7.15 (d, $J = 10.7$ Hz, 1H, C5-H), 7.34 (d, $J = 3.8$ Hz, 1H, C3-H), 7.50 (dd, $J = 10.7, 2.0$ Hz, 1H, C6-H), 7.78 (d, $J = 3.7$ Hz, 1H, C2-H), 8.22 (d, $J = 1.9$ Hz, 1H, C8-H), 8.28 (d, $J = 16.7$ Hz, 1H, -CH=CH-CN) ppm. ¹³C NMR (500 MHz, CDCl₃) δ 13.1, 24.7, 38.6, 101.3, 112.4, 118.0, 119.4, 127.2, 134.0, 134.8, 136.4, 136.9, 137.9, 139.1, 142.5, 151.9 ppm. IR ν_{max} 721, 787, 918, 976, 1422, 2215, 2959 cm⁻¹. HRMS (ESI⁻): calc. for C₁₇H₁₇N [M - H]⁻ 234.1288, found 234.1290.

(E)-3-(7-Isopropyl-1-methylazulene-4-yl)-N-methoxy-N-methylacrylamide (22). General procedure A was used with diethyl (2-(methoxy(methyl)amino)-2-oxoethyl)phosphonate (68 mg) to give the product as a light blue waxy gum (28 mg, 50%) following purification *via* column chromatography using Petrol (100%, R_f 0.3). ¹H NMR (500 MHz, (CD₃)₂CO) δ 1.38 (d, $J = 6.9$ Hz, 6H, -CH(CH₃)₂), 2.67 (s, 3H, C1-CH₃), 3.16 (hept, $J = 6.9$ Hz, 1H, -CH(CH₃)₂), 3.30 (s, 3H, CH₃), 3.84 (s, 3H, CH₃), 7.36 (d, $J = 15.7$ Hz, 1H, -CH=CH-COO-), 7.46 (d, $J = 3.9$ Hz, 1H, C3-H), 7.50 (d, $J = 10.9$ Hz, 1H, C5-H), 7.61 (dd, $J = 10.9, 1.9$ Hz, 1H, C6-H), 7.74 (d, $J = 3.9$ Hz, 1H, C2-H), 8.30 (d, $J = 1.9$ Hz, 1H, C8-H), 8.51 (d, $J = 15.7$ Hz, 1H, -CH=CH-COO-) ppm. ¹³C NMR (500 MHz, (CD₃)₂CO) δ 13.0, 24.9, 32.6 (br), 39.0, 62.4, 113.0, 121.2, 122.5, 127.1, 134.2, 135.7, 138.0, 138.4, 138.8, 140.1, 142.2, 143.7, 166.7 (br) ppm. IR ν_{max} 977, 1001, 1378, 1414, 1652, 2958 cm⁻¹. HRMS (ESI⁺): calc. for C₁₉H₂₃NO₂ [M + H]⁺ 298.1810, found 298.1812.

(Z)-N-tert-Butyl-1-(7-isopropyl-1-methylazulene-4-yl)methanimine oxide (23). To aldehyde **11** (70 mg, 0.3 mmol, 1.0 eq.) was added *N*-tert-butylhydroxylamine hydrochloride (62 mg,



0.5 mmol, 1.5 eq.) and pyridine (5 mL) under nitrogen. The mixture was stirred at 95 °C until all the starting material was consumed by TLC (3 h). After cooling to rt, the pyridine was evaporated under reduced pressure. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 30 mL) and the combined organic fractions were washed with brine and dried over MgSO₄ and filtered. The filtrate was evaporated under reduced pressure to yield a turquoise/green waxy gum (64 mg, 69%). ¹H NMR (500 MHz, (CDCl₃) δ 1.38 (d, *J* = 6.9 Hz, 6H, -CH(CH₃)₂), 1.71 (s, 9H, C(CH₃)₃), 2.68 (s, 3H, C1-CH₃), 3.12 (hept, *J* = 6.9 Hz, 1H, -CH(CH₃)₂), 7.18 (d, *J* = 3.7 Hz, 1H, C3-H), 7.57 (dd, *J* = 11.0, 2.0 Hz, 1H, C6-H), 7.67 (d, *J* = 3.7 Hz, 1H, C2-H), 8.21 (d, *J* = 1.8 Hz, 1H, C8-H), 8.37 (s, 1H, -CH=N), 8.85 (d, *J* = 11.0 Hz, C5-H) ppm. ¹³C NMR (500 MHz, (CDCl₃) δ 13.1, 24.7, 28.6, 38.7, 72.6, 109.7, 121.5, 125.4, 129.5, 133.5, 134.0, 135.3, 137.1, 137.4, 138.4, 143.3 ppm. IR ν_{max} 766, 1131, 1361, 1537, 2958 cm⁻¹. HRMS (ESI⁺): calc. for C₁₉H₂₅NO [M + H]⁺ 284.2009, found 284.2019.

Conflicts of interest

There are no conflicts to declare.

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