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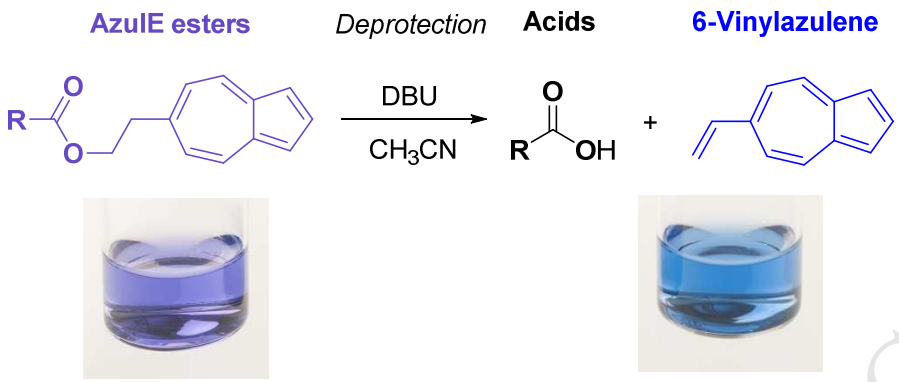
Graphical abstract:



A Colourful Azulene-Based Protecting Group for Carboxylic Acids

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Abstract

An intensely blue-coloured protecting group for carboxylic acids has been developed. The protecting group is introduced through a Steglich esterification that couples 6-(2-hydroxyethyl)azulene (AzulE) and the carboxylic acid substrate. Deprotection is effected under basic conditions by the addition of the amidine base DBU, whereupon cleavage occurs, accompanied by a colour change. A two-step deprotection methodology comprising activation with oxalyl chloride and deprotection with a very mild base was developed for use with base-sensitive substrates. The AzulE esters were found to be compatible with other commonly employed protecting groups – silyl ethers, MOM acetals – by studying their orthogonal and concomitant deprotections. The stability of the new protecting group towards various synthetic processes – oxidation, reduction, cross-coupling, olefination and treatment with base – provided the basis of a versatility profile. This indicated that AzulE esters are sensitive to strongly oxidising and basic agents while being compatible with reducing conditions and selected other reactions. The convenience of a highly coloured protecting group for tracking material (and avoiding loss of compound) through laboratory processes warrants further investigation of this and/or related species.

Keywords

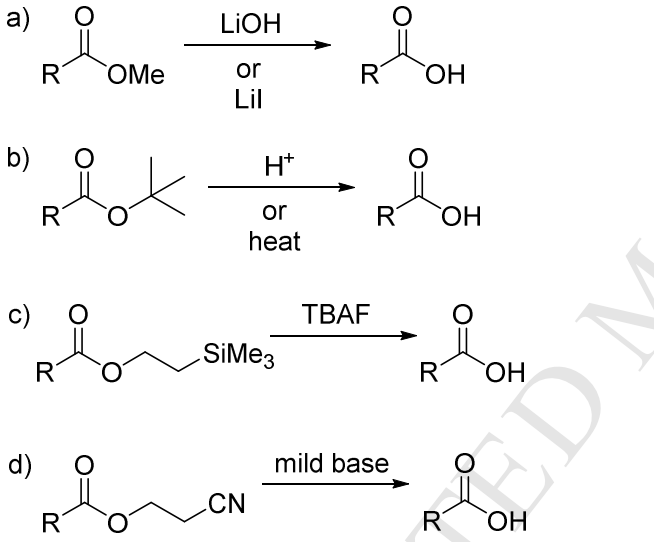
Azulene derivative; 6-(2-hydroxyethyl)azulene; protecting group; carboxylic acid; basic deprotection.

Introduction

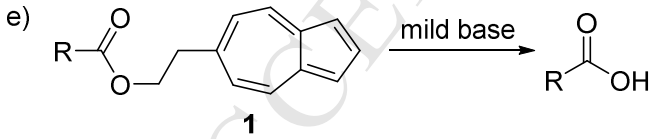
Target-oriented synthetic chemistry still relies overwhelmingly on the use of protecting groups to temporarily disable unwanted reactivity of functional groups in complex organic molecules, despite the ideals of protecting group-free synthesis.[1,2] Protecting groups may also improve handling properties compared to the unprotected substrate, such as decreased polarity and increased solubility in organic solvents.[3] Much attention is paid to the orthogonality of different protecting groups to each other and compatibility with key synthetic transformations in order to avoid undesired reactivity.[4,5]

The protecting groups typically used for carboxylic acids are ester-based (Scheme 1),[3] with the methyl ester being most common (Scheme 1a). Regeneration of the carboxylic acid is usually achieved by saponification or other hydrolytic methods, although non-basic reagents, such as lithium halides, are employed if the need arises.[3] Alternatively, more specialist esters may be used in cases where the methyl ester or its deprotection protocol is unsuitable.[3] These include, but are certainly not limited to, *tert*-butyl esters, deprotected by acid/heat (Scheme 1b), trimethylsilylethyl esters, deprotected with tetra-n-butylammonium fluoride (TBAF) (Scheme 1c), or 3-propionitrile (2-cyanoethyl) esters, deprotected by mild base (Scheme 1d).[3] The last type presents a useful orthogonality profile, in that mild base leads to few other reactions, including deprotective events. Deprotection of the propionitrile ester is achieved by elimination through an $E1_{cB}$ mechanism beginning with deprotonation of the acidic centre adjacent to the nitrile.

Established protecting groups for carboxylic acids:



New, coloured AzulE protecting group for carboxylic acids:



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Scheme 1. Ester-based protecting groups for carboxylic acids and their typical deprotection methods

Coloured protecting groups increase reaction efficiency by allowing the user to more effectively track the protected compound through all processes, including chromatography and workup.[6] Further advantage could be achieved by developing a protecting group that is colour-indicating for deprotection, orthogonal to other protecting groups, yet easy to deprotect.

With these principles in mind, we sought to develop a coloured ester protecting group for carboxylic acids. The bicyclic aromatic species azulene[7] is a non-alternant hydrocarbon,

whose deep-blue colour arises from a visible-wavelength electronic transition; this is caused primarily by the geometric dissimilarity between the HOMO and LUMO of azulene, which decreases electronic repulsion in the singlet excited state.[8] Further beneficial features are the small molecular weight and low polarity of azulene relative to other dye molecules. Despite these virtues, azulene-based protecting groups have only been sparingly employed previously: azulen-1-yl-oxoacetates for carbohydrate-based alcohols[9] and guaiazulene-based esters and carbamates for carbohydrate alcohols and glycoconjugate amines, respectively.[10,11]

Design of the new protecting group revolved around the stabilisation of anionic charges on centres adjacent to the seven-membered ring of azulene, due to the cyclopentadienyl anion resonance structure (Figure 1). The consequent acidity of these positions[12,13] should enable deprotection under basic conditions by an $E1_{cB}$ mechanism, analogous to the propionitrile esters described above. This, coupled with the obvious symmetry and consequent ease of spectroscopic analysis in the case of the 6-substituted azulene species, led to identification of 6-(2-hydroxyethyl)azulene as an ideal candidate to generate the so-named AzulE esters (Schemes 1e and 2).

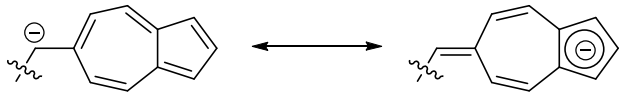
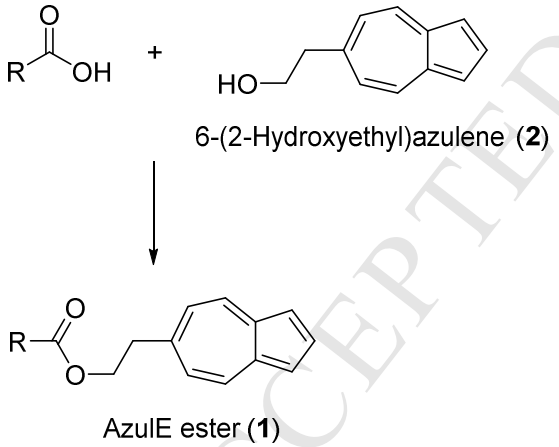


Figure 1. Resonance stabilisation of anionic charge at the 6-methyl(ene) position of 6-substituted azulenes

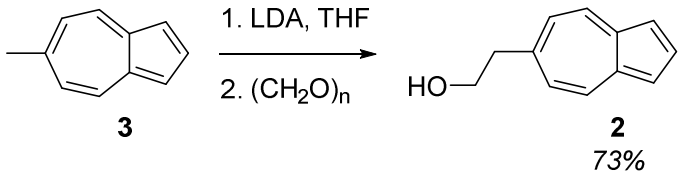


Scheme 2. Generation of AzulE esters (**1**) from carboxylic acids and 6-(2-hydroxyethyl)azulene (**2**)

Results and Discussion

6-(2-Hydroxyethyl)azulene (**2**)[14] was prepared from 6-methylazulene (**3**), itself readily available through a recent advance involving microwave heating,[15] by deprotonation with lithium diisopropylamide (LDA) followed by addition of paraformaldehyde (Scheme 3). It was found that cannulation of formaldehyde vapour, generated by cracking of

paraformaldehyde, into a solution of the 6-methylazulene anion provided the best yields of 6-(2-hydroxyethyl)azulene.

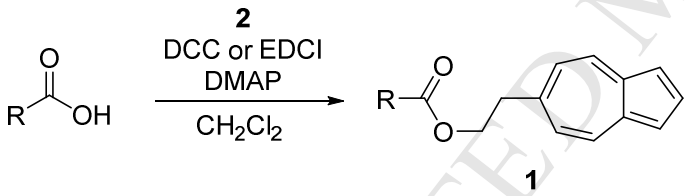


3 **2** *73%*

Scheme 3. Preparation of 6-(2-hydroxyethyl)azulene (**2**)

Protection of carboxylic acids as the corresponding 6-(2-hydroxyethyl)azulene (AzulE) esters was undertaken through Steglich-type esterification, which has benefits of providing reliably high yields and being relatively insensitive to air and moisture. A range of carboxylic acids was thus protected to form the corresponding AzulE esters (Table 1). High yields were typically obtained from reaction of aromatic (entries 1,2 and 12), heteroaromatic (entry 3), conjugated olefinic (entries 4–5) and aliphatic (entries 6–10) acids with 6-(2-hydroxyethyl)azulene in the presence of either *N*,*N*′-dicyclohexylcarbodiimide (DCC) or *N*-ethyl-*N*′-3-(dimethylamino)propylcarbodiimide (EDCI) and 4-(dimethylamino)pyridine (DMAP) catalyst at ambient temperature. The trichloroacetate (entry 11) was instead prepared by reaction of 6-(2-hydroxyethyl)azulene with the acid chloride.

Table 1. Protection of carboxylic acids as their AzulE esters[a]



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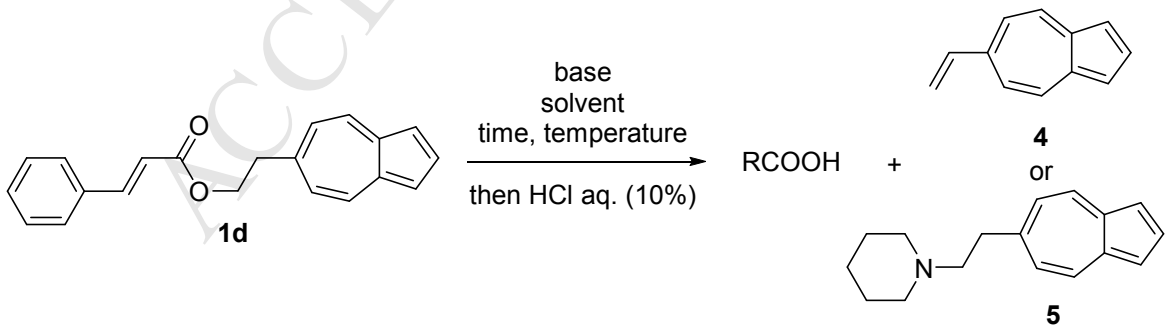
Entry	Carboxylic acid, RCO_2H	Product	Yield
1[b]	Benzoic acid	**1a**	84%
2[c]	1-Naphthoic acid	**1b**	83%
3[c]	2-Furoic acid	**1c**	83%
4	Cinnamic acid	**1d**	93%
5	Sorbic acid	**1e**	72%
6	Acetic acid	**1f**	59%
7	5-Bromovaleric acid	**1g**	80%
8	(Benzyloxy)acetic acid	**1h**	73%
9	Fmoc-Gly-OH	**1i**	93%
10[b]	Cyclohexanecarboxylic acid	**1j**	77%
11[d]	Trichloroacetic acid	**1k**	53%
12[e]	Azulene-1-carboxylic acid	**1l**	77%

[a] Unless stated otherwise, protections of carboxylic acids were performed with 6-(2-hydroxyethyl)azulene (1.0-1.25 equiv.), DCC (1.1–1.5 equiv.), DMAP (0.16–0.39 equiv.) in CH_2Cl_2 at r.t. for 3–5 hours.
[b] The reaction took 16 hours to reach completion.
[c] EDCI (1.6–2.2 equiv.) was used in place of DCC.
[d] Protection was achieved by reaction of trichloroacetyl chloride (5 equiv.) with 6-(2-hydroxyethyl)azulene and pyridine in CH_2Cl_2 at r.t. for 3 hours.
[e] More forcing conditions were required in this case: DMAP (1 equiv.) and heating at reflux overnight in CH_2Cl_2.

The deprotection of AzulE cinnamate (**1d**) with base was studied under a range of conditions (Table 2). Efficient deprotection was achieved through the use of either TBAF (entry 1) or the amidine bases 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entries 2–4) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (entry 5) at ambient temperature. The amine base piperidine did not fully deprotect the AzulE ester under the conditions usually employed for 9-fluorenylmethyloxycarbonyl (Fmoc)[16] deprotection (piperidine in DMF at ambient temperature, entry 8) but, with heating at reflux in acetonitrile, the deprotection proceeded with high conversion (entry 14). These results indicate a potential for orthogonality between Fmoc-protected amines and AzulE-protected carboxylic acids (see also Table 5 results). Weaker bases did not deprotect the AzulE ester efficiently (entries 15–23) and a control experiment in the absence of base (entry 24) led solely to recovery of the starting material **1d**, indicating that no thermally induced background reaction occurs. 6-Vinylazulene (**4**)[14] was the main by-product of most of these deprotection reaction, except with the nucleophilic base piperidine (entries 8–14) from which the base adduct **5** was obtained. This demonstrates that the 6-vinylazulene by-product may be intercepted with sufficiently nucleophilic bases,[17] which fits with the expected electron demand pattern of the azulene system.

Table 2. Deprotection studies on AzulE cinnamate



Entry	Base[a]	Solvent	Reaction time	Temperature	Conversion[b]
1	TBAF	THF	20 min	r.t.	100%
2	DBU	MeCN	3 hours	r.t.	100%
3	DBU	EtOH	3 hours	r.t.	Partial[c]

4	DBU	THF	3 hours	r.t.	100%
5	DBN	MeCN	3 hours	r.t.	100%
6	(-)-Sparteine	DMF	Overnight	r.t.	2%
7	(-)-Sparteine	MeCN	Overnight	r.t.	0%
8	Piperidine	DMF	Overnight	r.t.	70%[d]
9	Piperidine	MeCN	Overnight	r.t.	0%
10	Piperidine	EtOH	Overnight	r.t.	0%
11	Piperidine	THF	Overnight	r.t.	0%
12	Piperidine	EtOH	Overnight	Reflux	23%[d]
13	Piperidine	THF	Overnight	Reflux	18%[d]
14	Piperidine	MeCN	Overnight	Reflux	100%[d]
15	NaOH	1:1 H_2O/THF	Overnight	r.t.	37%
16	DIPEA	MeCN	Overnight	r.t.	0%
17	NEt_3	DMF	Overnight	r.t.	0%
18	NEt_3	MeCN	Overnight	r.t.	0%
19	NEt_3	MeCN	Overnight	Reflux	11%
20	DABCO	MeCN	Overnight	r.t.	3%
21	DABCO	MeCN	Overnight	Reflux	94%
22	DMAP	MeCN	Overnight	r.t.	0%
23	Morpholine	MeCN	Overnight	r.t.	0%
24	–	MeCN	Overnight	Reflux	0%

[a] Base loading was 3% v/v. Bases are listed in (approximately) decreasing order of base strength.

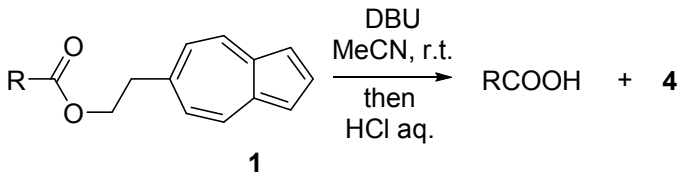
[b] Conversion was determined by integration of relevant signals in the ^{1}H NMR spectrum of the reaction mixture. The azulene species produced in the deprotection was 6-vinylazulene (**4**), unless otherwise noted.

[c] Relevant ^{1}H NMR peaks partially obscured. Conversion estimated at 90% deprotection according to baseline subtraction of the overlapping peaks.

[d] The azulene species formed in the deprotection was the corresponding base adduct **5**.

Using the effective deprotection conditions of DBU in acetonitrile, a selection of AzulE esters were converted to the corresponding carboxylic acids in excellent isolated yields (Table 3). Thus, aromatic (entries 1 and 2), heteroaromatic (entry 3), conjugated unsaturated (entries 4 and 5) and aliphatic carboxylic acids (entries 7–8) were liberated from their AzulE esters. The product obtained by deprotection of AzulE 5-bromovalerate (**1g**) was δ-valerolactone (entry 6), which presumably arises by substitutive lactonisation of the ω-bromocarboxylate that forms upon elimination.

Table 3. Deprotection of AzulE esters



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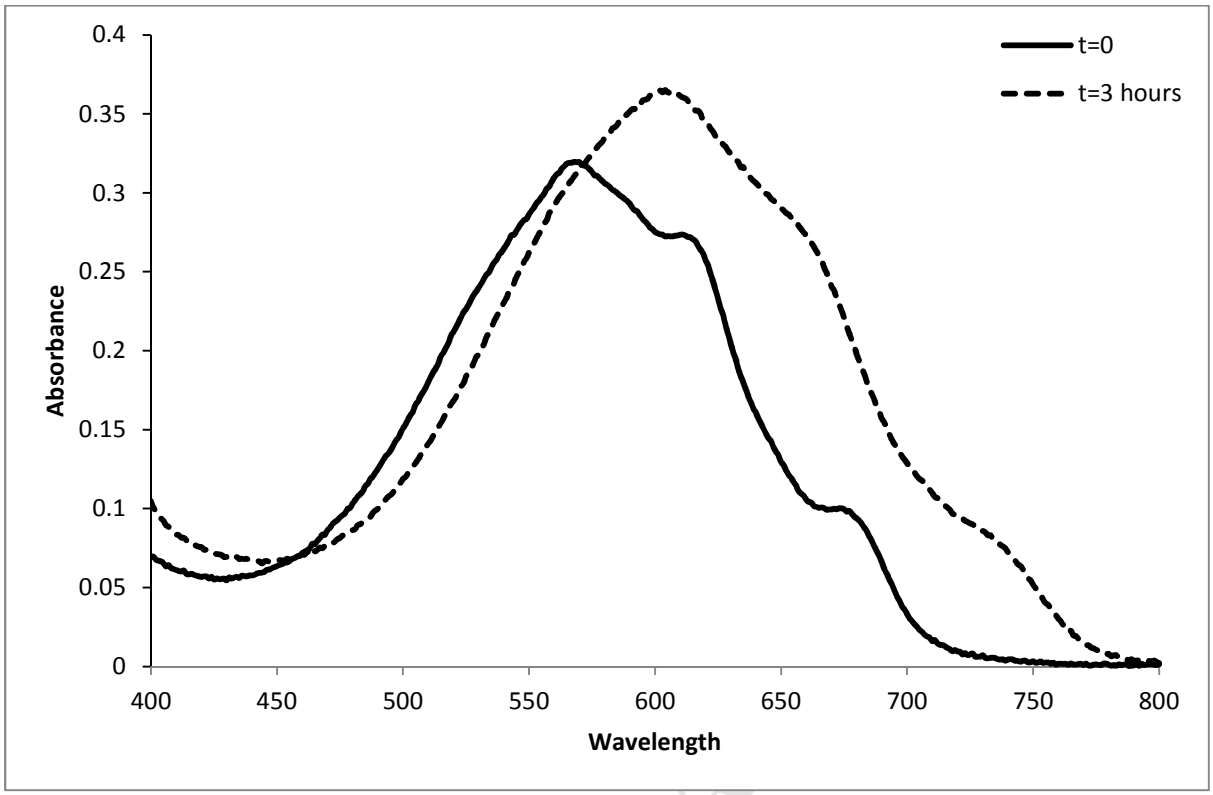
Entry	AzulE ester	Deprotected acid	Reaction time	Yield[a]
1	**1a**	Benzoic acid	3 hours	99%
2	**1b**	1-Naphthoic acid	3 hours	97%
3	**1c**	2-Furoic acid	4 hours	97%
4	**1d**	Cinnamic acid	8 hours	94%
5	**1e**	Sorbic acid	overnight	77%
6	**1g**	5-Bromovaleric acid	overnight	0%[b]
7	**1h**	(Benzyloxy)acetic acid	overnight	85%
8	**1j**	Cyclohexanecarboxylic acid	overnight	65%

[a] Isolated yield.

[b] The isolated product was δ-valerolactone, presumably formed by intramolecular nucleophilic attack on the bromoalkane by the carboxylate revealed in the deprotection.

With careful observation, the colour change that occurs during the deprotection can be used as a visual indicator of reaction progress. During cleavage of the protecting group, a subtle but nonetheless noticeable colour change from indigo/purple to blue can be observed. Visible light spectroscopy reveals a shift from λ_{max} = 571 nm for AzulE cyclohexanecarboxylate (**1j**) to λ_{max} = 608 nm for 6-vinylazulene (**4**) (Figure 2a). Visually, the change is distinct, with the starting esters appearing purple while the vinylazulene product is blue (Figure 2b and c). This enables facile TLC analysis of the reaction progress with no need for UV light or a stain to visualise the components (Figure 2d). It is also possible to tell from the colour of a reaction mixture whether the eliminative deprotection is complete or on-going (Figure 2e).

a)



b) c) d) e)

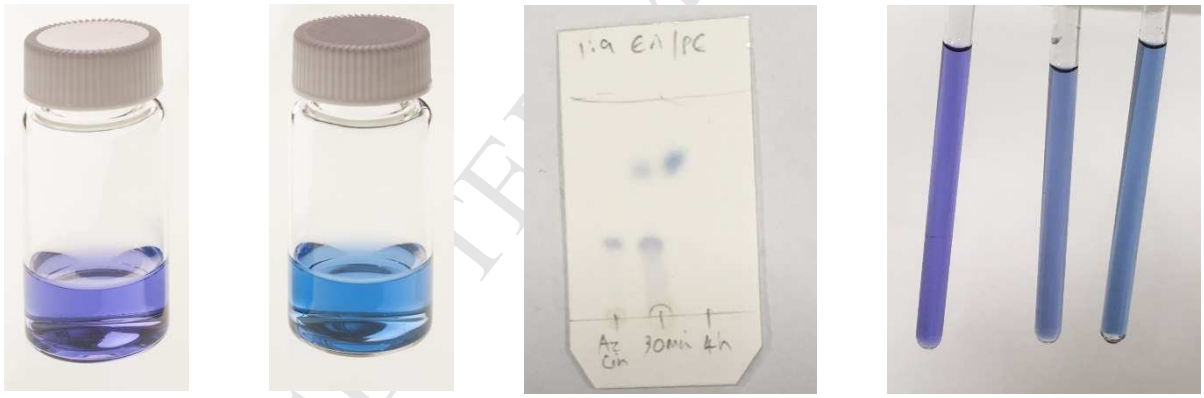


Figure 2. Colour change on deprotection. a) Visible light absorption spectrum of a deprotection reaction: AzulE cyclohexanecarboxylate (**1j**) in acetonitrile (solid line) and after 3 hours of reaction with DBU (dashed line); b) 6-(2-hydroxyethyl)azulene cinnamate (**1d**) in acetonitrile before addition of DBU; c) reaction of 6-(2-hydroxyethyl)azulene cinnamate (**1d**) in acetonitrile with DBU after 3 hours; d) TLC plate (silica gel, no stain required) showing AzulE cinnamate (left band), reaction with DBU in acetonitrile after 30 minutes showing starting material remaining and some 6-vinylazulene developing (middle band) and after 4 hours showing nearly full conversion (right band); e) AzulE cinnamate in 1:1 acetonitrile:dichloromethane (left, purple), during reaction with DBU: after 40 minutes (middle, purple-blue) and after 8 hours resulting in full conversion to 6-vinylazulene (right, blue).

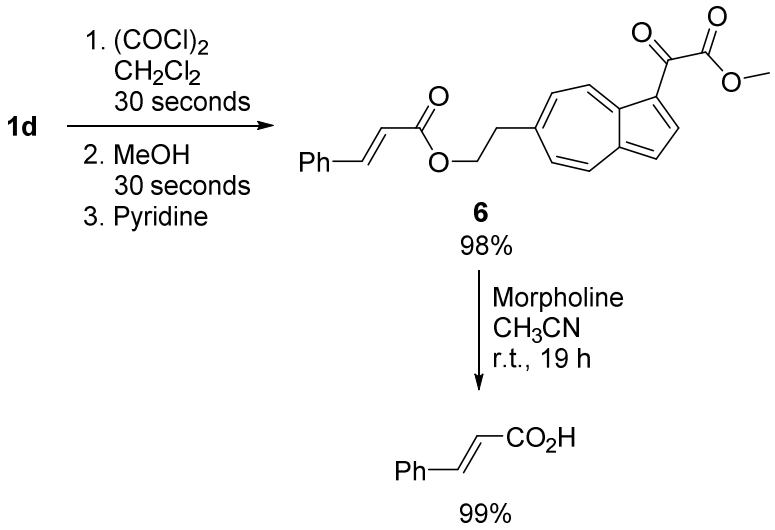
Based on the similarity of AzulE esters to 3-propionitrile and related esters,[3] an $E1_{cB}$ mechanism was initially proposed for these eliminative deprotections. This is questionable given the relative acidities of 6-methylazulene (pKa ~ 25.4 in organic solvent,[12,13] assumed to be somewhat higher for 6-(2-hydroxyethyl)azulene) and the conjugate acid of DBU (pKa = 24.3).[18] Kinetic experiments measuring the rate of deprotection of various AzulE esters were then conducted (Table 4, see Supporting Information for details of the experiments). There was a distinct correlation between pKa of the liberated carboxylic acid, as a surrogate for leaving group ability, and the rate of deprotection. This indicates that loss of the carboxylate is the rate-determining step, which is consistent with either an $E1_{cB}$ or an E2 mechanism. Further deconvolution of the mechanisms has not been accomplished to date.

Table 4. Rates of deprotection of AzulE esters and pKa of the corresponding carboxylic acids[a]

AzulE Ester	**Deprotection rate *1000/L·mol^{-1} s^{-1}**	**pKa of carboxylic acid**
1c	2.20 ± 0.64	3.12
1b	1.48 ± 0.34	3.69
1d	1.12 ± 0.43	4.44
1j	1.15 ± 0.26	4.9
1l	0.54 ± 0.15	6.99

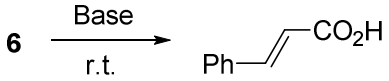
[a] Reactions were conducted with DBU (230 equiv.) in acetonitrile and monitored by visible spectroscopy.

Following these favourable results, a two-step, or "two-stage", deprotection strategy[4] was investigated for cases where the substrate would be sensitive to the standard basic conditions. Substitution of the azulene ring with an electron-withdrawing group would activate the protecting group towards deprotection, which could therefore be conducted with milder conditions. Treatment of AzulE cinnamate (**1d**) with oxalyl chloride, followed sequentially by methanol and pyridine gave the orange-red ketoester **6** in a near-quantitative yield (Scheme 4). Subjecting this activated AzulE ester to base treatment led to deprotection and isolation of the carboxylic acid (Table 5, entries 1–5). It is noteworthy that efficient deprotection of the activated AzulE ester occurred even with the weak bases trimethylamine and morpholine, which did not deprotect unactivated AzulE esters (*viz.* Table 2). Comparison of the results for the unactivated and activated AzulE esters indicate a rate acceleration between seven and eight orders of magnitude (see Supporting Information for details). It was possible to perform the activation and deprotection in a single pot, without isolation of the intermediate **6**.



Scheme 4. Two-step activation-deprotection sequence

Table 5. Deprotection of activated AzulE ester **6**[a]



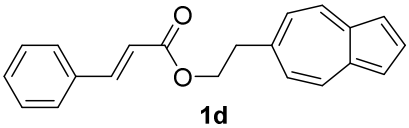
Entry	Base[b]	Time	Conversion[c]
1	DBU	<10 seconds	100%
2	Piperidine	<25 minutes	100%
3	NEt_3	5 hours	100%
4	DABCO	<1 minute	100%
5	Morpholine	Overnight	97%
6	2,4,6-Collidine	Overnight	0%
7	Pyridine	Overnight	0%

[a] Reactions were conducted in acetonitrile at room temperature.
[b] Bases are listed in decreasing strength (*i.e.* decreasing pKa of the conjugate acid).
[c] Conversion was determined by integration of the relevant signals in the ^{1}H NMR spectrum of the crude reaction mixture.

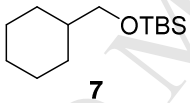
Preliminary assessment of the compatibility of the AzulE esters with other protecting groups and various reactions was then undertaken. Firstly, the orthogonality of AzulE esters with common alcohol and amine protecting groups was evaluated. Selective removal of the AzulE ester in the presence of the other protecting group, and *vice versa*, was sought. Conditions for global deprotection were not considered a requirement for orthogonality, but nevertheless would provide versatility benefits. In this study, the AzulE ester and other protecting group were usually contained within separate molecular entities for simplicity of analysis. The extent of deprotection of both species was assessed through integration of the relevant peaks in the ^{1}H NMR spectrum of the crude reaction mixture. For TBS ether **7**,[19] mildly acidic

conditions (pyridinium *para*-toluenesulfonate) removed the silyl group only (Table 6, entry 1), while mildly basic conditions (DBU) caused cleavage of only the AzulE ester **1d** (entry 2). In contrast, the basic fluoride reagent TBAF caused global deprotection of both the silyl ether and AzulE ester (entry 3). Similarly, methoxymethyl ether **8**[20] was selectively deprotected under acidic conditions in the presence of AzulE cinnamate (**1d**) (entry 4), while the reverse was achieved with DBU, as expected (entry 5). The AzulE ester of Fmoc-protected glycine (**1i**) provided a more challenging scenario, wherein both protecting groups are typically cleaved by base.[16] When treating with DBU, global deprotection was achieved (entry 6). In contrast, use of the milder base piperidine allowed selective Fmoc deprotection (entry 7). In order to selectively cleave the AzulE group, the two-step activation-deprotection methodology was invoked. To this end, protected glycine **1i** was treated with oxalyl chloride, followed by methanol and pyridine to afford the ketoester **9**. This activated the azulene ring sufficiently for deprotection with morpholine. In this way, the AzulE group was removed although the Fmoc group was also partially cleaved (entry 8). Further study with this latter case might allow determination of more orthogonal conditions for the selective deprotection of AzulE in the presence of Fmoc.

Table 6. Orthogonality of AzulE esters with other protecting groups



1d



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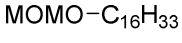

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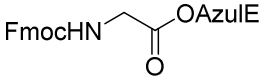
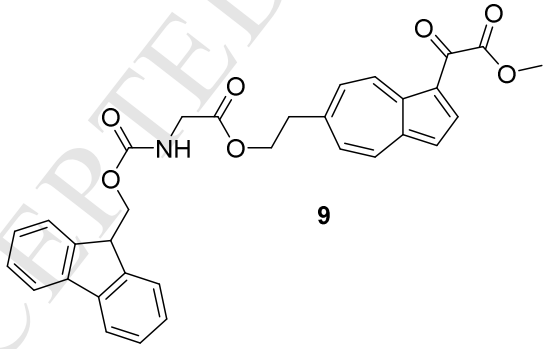


1i



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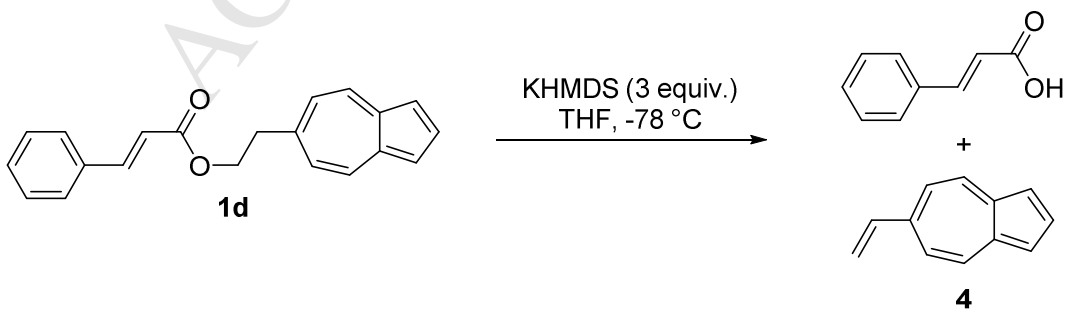
Entry	Other PG	Mixture	Reaction conditions	Effect on AzulE[a]	Effect on other PG[a]
1	TBS	**1d** + **7**	PPTS, MeCN, reflux, overnight	None	Deprotection
2	TBS	**1d** + **7**	DBU, THF, r.t., 7 hs	Deprotection	None
3	TBS	**1d** + **7**	TBAF, THF, r.t., 3.5 h	Deprotection	Deprotection
4	MOM	**1d** + **8**	PPTS, 3:1 EtOH/MeCN, reflux, overnight	None	Deprotection
5	MOM	**1d** + **8**	DBU, MeCN, r.t., overnight	Deprotection	None
6	Fmoc	**1i**	DBU, MeCN, r.t., 8 h	Deprotection	Deprotection

7	Fmoc	**1i**	Piperidine, MeCN, r.t., 30 min	None	Deprotection
8	Fmoc	**1i**	$(COCl)_2$, CH_2Cl_2, MeOH, pyridine, 0^0C, 50 s; then **9**, NEt_3, MeCN, 0^0C, 3 h	Deprotection	Partial[b] deprotection

[a]Determined by integration of the relevant peaks in the ^{1}H NMR spectrum of the crude reaction mixture.
[b]25% deprotection of Fmoc group.

Assessment of the compatibility of a protecting group with a selection of salient and representative reactions allows its utility in the wider context of synthetic chemistry to be determined. The reactivity of the azulene ring presents risks for the AzulE esters that should be evaluated. For instance, the 1-position of azulene is unusually nucleophilic for an aromatic hydrocarbon and may react with strong electrophiles. The base sensitivity of the protecting group may also need to be factored into synthetic planning.

The susceptibility of the AzulE ester to basic conditions was explored first. Given the basic deprotection conditions, it was a concern that the general application of AzulE esters in synthesis might be limited by their lability. This might be particularly pronounced with the strong bases used for reactions such as alkylations, olefinations, alkynylations, aldol reactions and ether formation (such as for base-promoted hydroxyl group protection with MOM, PMB, benzyl ethers, etc). A compatibility study to determine whether an AzulE-protected ester is susceptible to cleavage by the moderately strong organic base potassium bis(trimethylsilyl)amide (KHMDS) was therefore undertaken. This was performed by adding an excess of KHMDS to AzulE cinnamate (**1d**) in dry THF at -78 °C and monitoring the reaction by NMR analysis of aliquots over 90 minutes (see Supporting Information). It was found that, within 6 minutes, Azule cinnamate was fully converted to cinnamic acid and 6-vinylazulene (Scheme 5). This experiment confirms the incompatibility of this protecting group with strong base and hence the need to appropriately adapt synthetic sequences to avoid reaction of AzulE esters with strong bases.

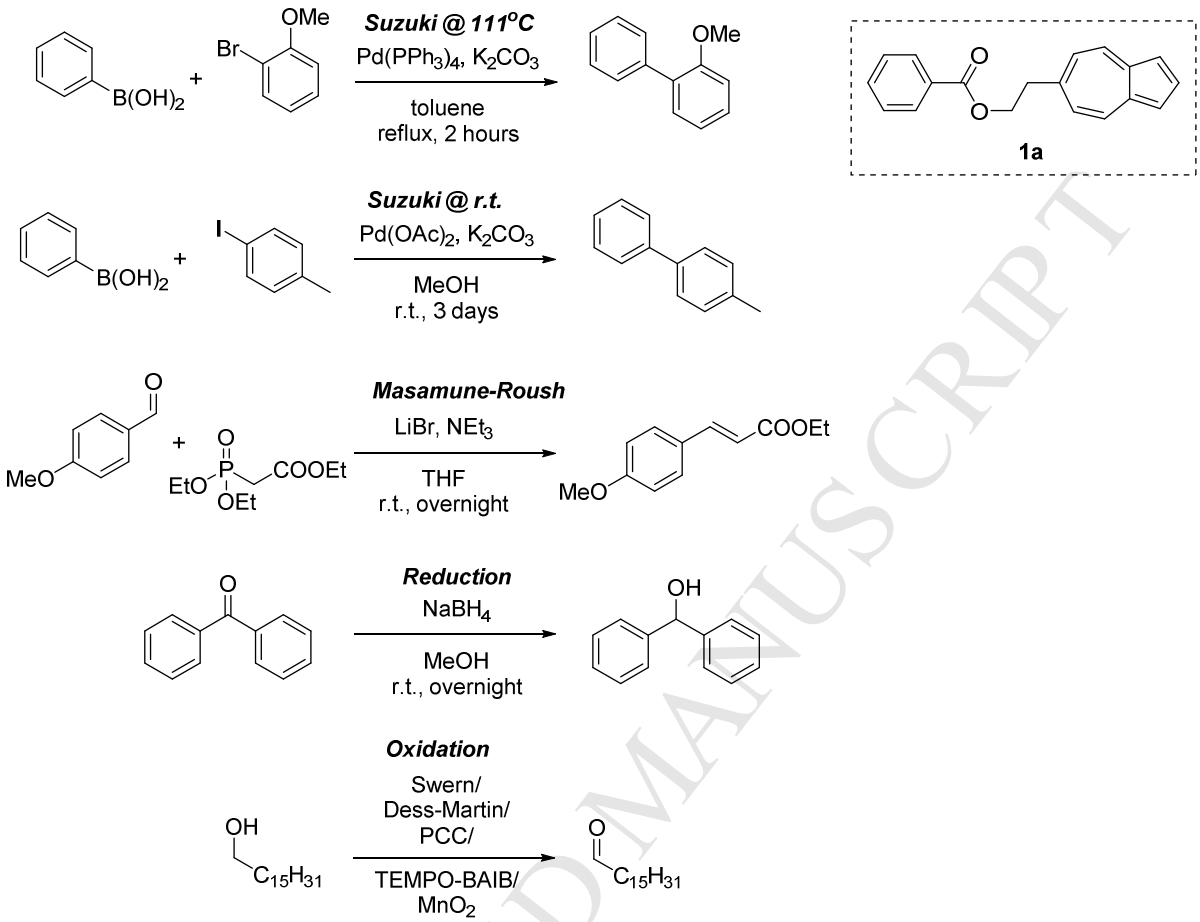


1d **4**

Scheme 5. Reaction of AzulE cinnamate with KHMDS

Several representative reactions were selected for explorations with the AzulE protecting group, including metal-catalysed cross coupling, aldehyde olefination, carbonyl reduction and alcohol oxidation. For each reaction, two experiments were performed in tandem on a model substrate: one control reaction and one reaction spiked with AzulE benzoate (**1a**). The relative abundance of each species was assessed through ^{1}H NMR integration, and the effect on the AzulE protecting group (as well as any impact of the protecting group on the reaction) was determined (Table 7). The Suzuki reaction was selected as a non-toxic and relatively benign cross coupling.[21] Investigation of Suzuki cross-coupling reactions demonstrated that, while the use of elevated temperatures caused significant amounts of deprotection (entry 1), the reaction at room temperature with a mild base was sufficiently compatible with the AzulE protecting group (entry 2). Wittig-type olefinations are very broadly employed for homologation of carbon chains;[22] the Horner-Wadsworth-Emmons variant[23] introduces two-carbon units in a manner that evokes polyketide synthesis, and is widely used in target synthesis. The basic conditions of the standard Horner-Wadsworth-Emmons reaction were expected to cause deprotection of the AzulE ester (vide supra), so Masamune-Roush conditions[24] were employed and found to be compatible (entry 3). Oxidation and reduction processes are widely used synthetic operations and so a knowledge of the compatibility of the new AzulE ester protecting group under typical reaction conditions is paramount. Sodium borohydride reduction of benzophenone in the presence of AzulE-benzoate (**1a**) led to no loss of AzulE ester (entry 4) and hence ketone/aldehyde reduction represents a compatible reaction. As anticipated, Swern oxidation[25] conditions elicited reaction at the azulene ring of the AzulE ester as well as performing the desired alcohol oxidation (entry 5). Similarly, Dess-Martin,[26] pyridinium chlorochromate (PCC)[27] and TEMPO-BAIB[28] oxidation conditions caused degradation of the azulene moiety and low yields of the oxidised product (entries 5–8). Thus, oxidations with strongly electrophilic reagents or catalysts represent a limitation of this protecting group. Encouragingly, manganese dioxide[29] was compatible with the AzulE esters and therefore oxidation of allylic (and, presumably, propargylic) alcohols to the corresponding aldehydes is possible in the presence of an AzulE protecting group. Further investigations into the scope of the manganese dioxide oxidations will be conducted.

Table 7. Compatibility of AzulE esters with Suzuki, Masamune-Roush, oxidation and reduction reactions.



Entry	Reaction	Conversion of control rxn[a]	Conversion of 1a-spiked reaction[a]	Effect on AzulE benzoate (1a)[a]
1	Suzuki @ 111°C	70%	45%	17% deprotection
2	Suzuki @ r.t.	Quant.	Quant.	8% hydrolysis
3	Masamune-Roush	Quant.	Quant.	none
4	$NaBH_4$ reduction	Quant.	Quant.	none
5	Swern oxidation	87%	75%	degradation
6	Dess-Martin	93%	72%	degradation
7	PCC oxidation	100%	31%	degradation
8	TEMPO-BAIB	90%	68%	degradation
9	MnO_2 oxidation	98%	98%	none

[a] Determined through integration of the relevant peaks in the ^{1}H NMR spectrum of the crude reaction mixture.

Conclusion

A new carboxylic acid protecting group, the AzulE ester, has been developed that is deprotected under basic conditions accompanied by a visible colour change. The AzulE esters display orthogonality with commonly used alcohol protecting groups (TBS ether,

MOM ether) and partial orthogonality with the amine protecting group Fmoc. They are stable under reduction, olefination and mild cross-coupling reaction conditions and in oxidations with manganese dioxide. However, the electron-rich azulene is susceptible to strongly electrophilic oxidation reagents. The reactivity of this protecting group with base also means it should be considered only for syntheses without such oxidation or strong bases. Nonetheless, the convenience of the colour in tracking protected material through various laboratory manipulations should encourage consideration of its use for target-based syntheses requiring protection of carboxylic acids. Further studies into the scope of this protecting group through its inclusion in synthetic endeavours are on-going in our laboratory.

Experimental Section

6-(2-Hydroxyethyl)azulene, 2.[14] An LDA solution was prepared by mixing THF (6 mL) and diisopropylamine (0.18 mL, 1.27 mmol, 1.15 eq.) at -30 ^{0}C (dry ice/ethylene glycol bath), followed by addition of *n*-BuLi (0.71 mL of a 1.77 M in cyclohexane solution, 1.25 mmol, 1.13 eq.). To this reaction mixture, a chilled (-30 ^{0}C) solution of 6-methylazulene[13] (157 mg, 1.10 mmol, 1 eq.) in THF (3 mL) was added via cannula. The reaction mixture rapidly changed colour from indigo to golden brown. A vial containing paraformaldehyde (129.5 mg, 4.3 mmol, 3.9 eq.) was heated to the point of sublimation and formaldehyde gas was transferred from this vessel into the reaction mixture via cannula, upon which the reaction mixture returned to a blue colour. Water (3 mL) was added and the reaction was stirred for one minute before workup. A separation was performed using CH_2Cl_2/H_2O and the organic layer was washed with saturated aqueous brine and concentrated by rotary evaporation. Column chromatography was performed on the residue using silica gel prepared with 2% NEt_3 in pet. ether, delivering recovered starting material (22.2 mg, 14%) by elution in 1:1 pet. ether/CH_2Cl_2, and the title compound **2** (138.6 mg, 73% yield) as an indigo solid eluting in 1:2 pet. ether/EtOAc. mp 82.3-83.8 ^{0}C [lit.[14] mp 78-80 ^{0}C]. IR (ATR): ν_{max} 3218, 2944, 2895, 1577, 1392, 1039, 822, 751, 744 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J*=9.5 Hz, 2H, H-4,8), 7.87 (t, *J*=3.5 Hz, 1H, H-2), 7.39 (d, *J*=3.5 Hz, 2H, H-1,3), 7.11 (d, *J*=9.5 Hz, 2H, H-5,7), 3.96 (t, *J*=7.0 Hz, 2H, H-10), 3.05 (t, *J*=6.5 Hz, 2H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9 (C, C-6), 139.0 (C, C-3a,8a), 136.3 (CH, C-2), 135.9 (CH, C-4,8), 124.2 (CH, C-5,7), 118.3 (CH, C-1,3), 64.3 (CH_2, C-10), 45.3 (CH_2, C-9). HRMS: *m/z* $C_{12}H_{13}O^+$ $[M+H]^+$ Calculated 173.0961, found 173.0964. The ^{1}H NMR data correspond with those reported previously.[14]

2-(Azulen-6-yl)ethyl benzoate (AzulE benzoate), 1a. Benzoic acid (40 mg, 0.32 mmol, 1.01 eq.), **2** (55 mg, 0.32 mmol, 1 eq.), DCC (77 mg, 0.37 mmol, 1.16 eq.) and DMAP (10 mg, 0.082 mmol, 0.26 eq.) were added together and dissolved in CH_2Cl_2 (6 mL). After 16 hours, a separation was performed with CH_2Cl_2/H_2O and the organic fraction was concentrated by rotary evaporation. Column chromatography was performed on the crude material using CH_2Cl_2 to obtain **1a** (67 mg, 75% yield) as an indigo semi-crystalline solid. mp 119.6-120.0 ^{0}C. λ_{max}: 566 nm. IR (ATR): ν_{max} 3067, 2952, 1711, 1580, 1261, 1105, 835, 743, 701 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J*=10.0 Hz, 2H, H-4,8), 8.01 (d, *J*=7.0 Hz, 2H, H-13),

7.87 (t, *J*=3.5 Hz, 1H, H-2), 7.56 (t, *J*=7.0 Hz, 1H, H-15), 7.43 (t, *J*=7.5 Hz, 2H, H-14), 7.38 (d, *J*=4.0 Hz, 2H, H-1,3), 7.18 (d, *J*=10.0 Hz, 2H, H-5,7), 4.65 (t, *J*=7.0 Hz, 2H, H-10), 3.27 (t, *J*=7.0 Hz, 2H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4 (C, C-11), 148.0 (C, C-6), 139.1 (C, C-3a,8a), 136.5 (CH, C-2), 135.9 (CH, C-4,8), 133.0 (CH, C-15), 130.1 (C, C-12), 129.6 (CH, C-13), 128.4 (CH, C-14), 124.2 (CH, C-5,7), 118.3 (CH, C-1,3), 65.7 (CH_2, C-10), 41.3 (CH_2, C-9). HRMS: *m/z* $C_{19}H_{17}O_2^+$ $[M+H]^+$ Calculated 277.1223, found 277.1224.

2-(Azulen-6-yl)ethyl 1-naphthoate (AzulE 1-naphthoate), 1b. 1-Naphthoic acid (96 mg, 0.55 mmol, 1 eq.), **2** (120 mg, 0.70 mmol, 1.25 eq.), EDCI (188 mg, 1.2 mmol, 2.2 eq.) and DMAP (12 mg, 0.094 mmol, 0.17 eq.) were added together in a RBF and dissolved in CH_2Cl_2 (4 mL). After 4 hours, a separation was performed using CH_2Cl_2/H_2O and the organic fraction was concentrated by rotary evaporation and purified by column chromatography in CH_2Cl_2 to afford AzulE naphthoate **1b** (167 mg, 82% yield) as an indigo solid. mp 87.4-88.3 ^{0}C. λ_{max}: 568 nm. IR (ATR): ν_{max} 3052, 2949, 2890, 1701, 1575, 1393, 1234, 1194, 1130, 1013, 778, 760 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J*=8.5 Hz, 1H, H-19), 8.31 (d, *J*=10.5 Hz, 2H, H-4,8), 8.12 (dd, *J*=7.5, 1.5 Hz, 1H, H-13), 8.01 (d, *J*=8.0 Hz, 1H, H-15), 7.88 (t, *J*=3.5 Hz, 1H, H-2), 7.87 (d, *J*=6.5 Hz, 1H, H-16), 7.51 (m, 2H, H-17, H-18), 7.47 (m, 1H, H-14), 7.40 (d, *J*=3.5 Hz, 2H, H-1,3), 7.22 (d, *J*=10.5 Hz, 2H, H-5,7). 4.75 (t, *J*=7.0 Hz, 2H, H-10), 3.33 (t, *J*=7.0 Hz, 2H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4 (C, C-11), 148.0 (C, C-6), 139.1 (C, C-3a,8a), 136.4 (CH, C-2), 135.9 (CH, C-4,8), 133.7 (C, C-15a), 133.4 (CH, C-15), 131.2 (C, C-19a), 130.2 (CH, C-13), 128.5 (CH, C-16), 127.7 (CH, C-18), 127.0 (C, C-12), 126.2 (CH, C-17), 125.7 (CH, C-19), 124.4 (CH, C-14), 124.2 (CH, C-5,7), 118.3 (CH, C-1,3), 65.9 (CH_2, C-10), 41.2 (CH_2, C-9). HRMS: *m/z* $C_{23}H_{19}O_2^+$ $[M+H]^+$ Calculated 327.1380, found 327.1388.

2-(Azulen-6-yl)ethyl 2-furoate (AzulE 2-furoate), 1c. 2-Furoic acid (67 mg, 0.59 mmol, 1 eq.), **2** (106 mg, 0.61 mmol, 1.03 eq.), EDCI (148 mg, 0.95 mmol, 1.6 eq.) and DMAP (25 mg, 0.2 mmol, 0.35 eq.) were added to a RBF and dissolved in CH_2Cl_2 (4 mL). After 4 hours, a separation was performed in CH_2Cl_2/H_2O and the organic fraction was concentrated by rotary evaporation. The crude mixture was subjected to column chromatography using CH_2Cl_2 to obtain AzulE furoate **1c** (133 mg, 83% yield) as an indigo solid. mp 92.8-93.7 ^{0}C. λ_{max}: 569 nm. IR (ATR): ν_{max} 3131, 3117, 2984, 2946, 1703, 1571, 1472, 1398, 1302, 1279, 1111, 792, 750 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J*=10.0 Hz, 2H, H-4,8), 7.87 (t, *J*=4.5 Hz, 1H, H-2), 7.58 (app. s, 1H, H-15), 7.38 (d, *J*=4.0 Hz, 2H, H-1,3), 7.15 (m, 3H, H-5,7, H-13), 6.50 (dd, *J*=1.5, 0.5 Hz, 1H, H-14), 4.62 (t, *J*=7.0 Hz, 2H, H-10), 3.24 (t, *J*=7.0 Hz, 2H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5 (C, C-11), 147.6 (C, C-6), 146.4 (CH, C-15), 144.5 (C, C-12), 139.1 (C, C-3a,8a), 136.5 (CH, C-2), 135.9 (CH, C-4,8), 124.2 (CH, C-5,7), 118.3 (CH, C-1,3), 118.1 (CH, C-13), 111.9 (CH, C-14), 65.6 (CH_2, C-10), 41.2 (CH_2, C-9). HRMS: *m/z* $C_{17}H_{15}O_3^+$ $[M+H]^+$ Calculated 267.1016, found 267.1016.

2-(Azulen-6-yl)ethyl (*E*)-cinnamate (AzulE cinnamate), 1d. Cinnamic acid (161 mg, 1.08 mmol, 1 eq.), DMAP (23 mg, 0.18 mmol, 0.16 eq.), DCC (255 mg, 1.23 mmol, 1.14 eq.) and 6-(2-hydroxyethyl)azulene (**2**) (207 mg, 1.20 mmol, 1.1 eq.) were added to a RBF and dissolved in CH_2Cl_2 (10 mL). After 3 hours, a phase separation was performed with H_2O/CH_2Cl_2 and the organic fraction was concentrated by rotary evaporation. Column

chromatography using CH_2Cl_2 was performed on the resulting product, eluting AzulE cinnamate **1d** (305 mg, 93% yield) as an indigo powder. mp 144.6-146.0 ^{0}C. λ_{max}: 567 nm. IR (ATR): ν_{max} 3079, 2944, 1710, 1633, 1562, 1307, 1168, 979, 837, 761, 740 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J*=10.5 Hz, 2H, H-4,8), 7.87 (t, *J*=4.0 Hz, 1H, H-2), 7.68 (d, *J*=16.0 Hz, 1H, H-13), 7.52 (m, 2H, H-15), 7.40-7.38 (complex m, 5H, H-1, H-3, H-16, H-17), 7.15 (d, *J*=10.5 Hz, 2H, H-5,7), 6.42 (d, *J*=16.0 Hz, 1H, H-12), 4.54 (t, *J*=7.0 Hz, 2H, H-10), 3.21 (t, *J*=7.0 Hz, 2H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8 (C, C-11), 148.0 (C, C-6), 145.1 (CH, C-13), 139.1 (C, C-3a,8a), 136.4 (CH, C-2), 135.9 (CH, C-4,8), 134.3 (C, C-14), 130.4 (CH, C-17), 128.9 (CH, C-16), 128.1 (CH, C-15), 124.2 (CH, C-5,7), 118.3 (CH, C-1,3), 117.8 (CH, C-12), 65.3 (CH_2, C-10), 41.3 (CH_2, C-9). HRMS: *m/z* $C_{21}H_{19}O_2^+$ $[M+H]^+$ Calculated 303.1380, found 303.1388.

2-(Azulen-6-yl)ethyl (2*E*, 4*E*)-hexa-2,4-dienoate (AzulE sorbate), 1e. Sorbic acid (44 mg, 0.39 mmol, 1.0 eq.), 6-(2-hydroxyethyl)azulene (70 mg, 0.41 mmol, 1.1 eq.), DCC (134 mg, 0.65 mmol, 1.7 eq.) and DMAP (13 mg, 0.11 mmol, 0.27 eq.) were added to dry DCM (5 mL) under nitrogen and stirred overnight under an atmosphere of nitrogen. An indigo solution was obtained which was washed with distilled water. The aqueous layer extracted with DCM (three times) and concentrated to dryness under reduced pressure to yield an indigo solid. Column chromatographic purification, using silica as the solid phase and DCM as the mobile phase afforded AzulE sorbate **1e** as an indigo oil (69 mg, 0.26 mmol, 66%). λ_{max}: 568 nm. IR (ATR): ν_{max} 1706, 1644, 1324, 1241, 1185, 1134, 1088, 993, 841, 746 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 10.5 Hz, 2H, H-4,8), 7.85 (t, *J* = 3.5 Hz, 1H, H-2), 7.36 (d, *J* = 3.5 Hz, 2H, H-1,3), 7.23 (dd, *J* = 15.5, 10.0 Hz, 1H, H-13), 7.12 (d, *J* = 10.5 Hz, 2H, H-5,7), 6.23 – 6.07 (complex m, 2H, H-14,15), 5.75 (d, *J* = 15.0 Hz, 1H, H-12), 4.45 (t, *J* = 7.0 Hz, 2H, H-10), 3.15 (t, *J* = 7.0 Hz, 2H, H-9), 1.85 (d, *J* = 5.5 Hz, 3H, H-16). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.1, 148.1, 145.4, 139.7, 139.1, 136.4, 135.9, 129.7, 124.2, 118.6, 118.2, 65.0, 41.3, 18.7. HRMS: *m/z* $C_{18}H_{19}O_2^+$ $[M+H]^+$ Calculated 267.1380, found 267.1377.

2-(Azulen-6-yl)ethyl acetate (AzulE acetate), 1f.[14] Acetic acid (0.034 mL, 0.60 mmol, 1.0 eq.), 6-(2-hydroxyethyl)azulene (114 mg, 0.66 mmol, 1.1 eq.), DCC (148 mg, 0.72 mmol, 1.2 eq.) and DMAP (15 mg, 0.12 mmol, 0.2 eq.) were dissolved in dry DCM under N_2. The reaction mixture was allowed to stir at room temperature for 3 hours until complete according to thin layer chromatographic analysis. The reaction mixture was diluted with DCM and washed with brine followed by water. The solvent was removed under reduced pressure. Chromatographic purification (petroleum ether/ethyl acetate, 1:1) yielded the protected carboxylic acid, AzulE acetate **1f** as an indigo oil (76 mg, 0.35 mmol, 59%). ^{1}H NMR (500 MHz, $CDCl_3$): 8.31 (d, *J* = 10.5 Hz, 2 H), 7.94 (t, *J* = 4.0 Hz, 1 H), 7.44 (d, *J* = 4.0 Hz, 2 H), 7.12 (d, *J* = 10.5 Hz, 2 H), 4.43 (t, *J* = 7.0 Hz, 2 H), 3.14 (t, *J* = 7.0 Hz, 2 H), 2.08 (s, 3 H). ^{13}C NMR (500 MHz): 170.7, 147.7, 138.9, 136.3, 135.7, 123.9, 118.1, 65.0, 40.8, 20.7. The ^{1}H NMR data were consistent with those reported previously.[14]

2-(Azulen-6-yl)ethyl 5-bromopentanoate (AzulE 5-bromovalerate), 1g. 5-Bromovaleric acid (70 mg, 0.39 mmol, 1.0 eq.), 6-(2-hydroxyethyl)azulene (74 mg, 0.43 mmol, 1.1 eq.), DCC (100 mg, 0.48 mmol, 1.3 eq.) and DMAP (9 mg, 0.07 mmol, 0.2 eq.) were dissolved in

dry DCM (10 mL) and stirred overnight at room temperature under an atmosphere of N_2. The reaction mixture was then diluted with DCM and washed with brine followed by water. The solvent was removed under reduced pressure. Chromatographic purification (dichloromethane) yielded the protected carboxylic acid **1g** as an indigo oil (104 mg, 0.31 mmol, 80%). λ_{max}: 570 nm. IR (ATR): ν_{max} 3080, 2955, 1729, 1579, 1395, 1168, 836, 751 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J*=10.0 Hz, 2H, H-4,8), 7.86 (t, *J*=3.5 Hz, 1H, H-2), 7.37 (d, *J*=3.5 Hz, 2H, H-1,3), 7.10 (d, *J*=10.0 Hz, 2H, H-5,7), 4.40 (t, *J*=7.0 Hz, 2H, H-10), 3.33 (t, *J*=6.5 Hz, 2H, H-15), 3.13 (d, *J*=7.0 Hz, 2H, H-9), 2.32 (t, *J*=7.0 Hz, 2H, H-12), 1.85-1.78 (m, 2H, H-14), 1.77-1.69 (m, 2H, H-13). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0 (C, C-11), 147.9 (C, C-6), 139.1 (C, C-3a,8a), 136.5 (CH, C-2), 135.8 (CH, C-4,8), 124.1 (CH, C-5,7), 118.3 (CH, C-1,3), 65.2 (CH_2, C-10), 41.1 (CH_2, C-9), 33.2 (CH_2, C-12), 33.0 (CH_2, C-15), 31.9 (CH_2, C-14), 23.4 (CH_2, C-13). HRMS: *m/z* $C_{17}H_{20}O_2Br^+$ $[M+H]^+$ Calculated 335.0641, found 335.06501.

2-(Azulen-6-yl)ethyl (benzyloxy)acetate (AzulE benzyloxyacetate), 1h. 2-Benzyloxyacetic acid (0.060 mL, 0.42 mmol, 1.0 eq.), 6-(2-hydroxyethyl)azulene (79 mg, 0.46 mmol, 1.1 eq.), DCC (103 mg, 0.50 mmol, 1.2 eq.) and DMAP (15 mg, 0.12 mmol, 0.3 eq.) were dissolved in dry DCM (10 mL) and stirred overnight at room temperature under an atmosphere of N_2. The reaction mixture was then diluted with DCM and washed with brine followed by water. The solvent was removed under reduced pressure. Chromatographic purification (petroleum ether/ethyl acetate, 5:1) yielded the protected carboxylic acid **1h** as an indigo oil (98 mg, 0.31 mmol, 73%). λ_{max}: 569 nm. IR (ATR): ν_{max} 3065, 3029, 2954, 2892, 1750, 1579, 1452, 1395, 1190, 1118, 836, 746, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J*=10.0 Hz 2H, H-4,8), 7.87 (t, *J* = 4.0 Hz, 1H, H-2), 7.37 (d, *J* = 4.0 Hz, 2H, H-1,3), 7.36-7.28 (complex m, 5H, H-15,16,17,18,19), 7.08 (d, *J* = 10.0 Hz, 2H, H-5,7), 4.58 (s, 2H), 4.49 (t, *J* = 7.0 Hz, 2H, H-10), 4.08 (s, 2H, H-12), 3.15 (t, *J* = 7.0 Hz, 2H, H-9). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.3 (C, C-11), 147.5 (C, C-6), 139.1 (C, C-3a,8a), 137.0 (C, C-14), 136.5 (CH, C-2), 135.8 (CH, C-4,8), 128.5 (CH, C-15,19 or C-16,18 or C-17), 127.99 (CH, C-15,19 or C-16,18 or C-17), 127.96 (CH, C-15,19 or C-16,18 or C-17), 124.1 (CH, C-5,7), 118.3 (CH, C-1,3), 73.3 (CH_2, C-13), 67.1 (CH_2, C-12), 65.5 (CH_2, C-10), 41.0 (CH_2, C-9). HRMS: *m/z* $C_{21}H_{21}O_3^+$ $[M+H]^+$ Calculated 321.1485, found 321.1491.

***N*-Fluorenylmethyloxycarbonyl glycine 2-(azulen-6-yl)ethyl ester (Fmoc-Gly-OazulE), 1i.** Fmoc-Gly-OH (159 mg, 0.5 mmol, 1 eq.), **2** (99 mg, 0.57 mmol, 1.07 eq.), DCC (149 mg, 0.72 mmol, 1.35 eq.) and DMAP (26 mg, 0.21 mmol, 0.39 eq.) were added to a RBF and dissolved in CH_2Cl_2 (10 mL). After 3 hours, a separation was performed with CH_2Cl_2/H_2O, and the organic fraction was purified by column chromatography using 9:1 CH_2Cl_2/Et_2O to obtain AzulE-protected glycine **1i** (225 mg, 93% yield) as an indigo-coloured gummy oil. λ_{max}: 568 nm. IR (ATR): ν_{max} 3336, 3065, 3013, 2950, 1703, 1578, 1515, 1447, 1395, 1181, 1048, 1001, 737 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J*=10.0 Hz, 2H, H-4,8), 7.89 (t, *J*=3.5 Hz, 1H, H-2), 7.79 (d, *J*=7.5 Hz, 2H, H-20), 7.62 (d, *J*=8.0 Hz, 2H, H-17), 7.47 (t, *J*=8.0 Hz, 2H, H-19), 7.39 (d, *J*=4.0 Hz, 2H, H-1,3), 7.34 (t, *J*=7.0 Hz, 2H, H-18), 7.07 (d, *J*=10.0 Hz, 2H, H-5,7), 5.30 (br. s, 1H, N-H), 4.48 (t, *J*=7.0 Hz, 2H, H-10), 4.43 (d, *J*=7.0 Hz, 2H, H-14), 4.25 (t, *J*=7.0 Hz, 1H, H-15), 3.98 (d, *J*=5.5 Hz, 2H, H-12), 3.14 (t, *J*=7.0 Hz, 2H,

H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9 (C, C-11), 156.2 (C, C-13), 147.3 (C, C-6), 143.8 (C, C-16), 141.3 (C, C-21), 139.1 (C, C-3a,8a), 136.6 (CH, C-2), 135.9 (CH, C-4,8), 127.7 (CH, C-19), 127.1 (CH, C-18), 125.0 (CH, C-17), 124.1 (CH, C-5,7), 120.0 (CH, C-20), 118.4 (CH, C-1,3), 67.2 (CH_2, C-14), 66.1 (CH_2, C-10), 47.1 (CH, C-15), 42.7 (CH_2, C-12), 41.0 (CH_2, C-9). HRMS: *m/z* $C_{29}H_{26}NO_4^+$ $[M+H]^+$ Calculated 452.1856, found 452.1875.

2-(Azulen-6-yl)ethyl cyclohexanecarboxylate (AzulE cyclohexanecarboxylate), 1j. Cyclohexanecarboxylic acid (41 mg, 0.32 mmol, 1 eq., heated to 32 ^{0}C and added as liquid), **2** (57 mg, 0.33 mmol, 1.02 eq.), DCC (73 mg, 0.35 mmol, 1.1 eq.) and DMAP (12 mg, 0.1 mmol, 0.3 eq.) were added together in a RBF and dissolved in CH_2Cl_2 (6 mL). The reaction was stirred overnight. A separation was performed in CH_2Cl_2/H_2O and the organic fraction was concentrated by rotary evaporation. The crude mixture was subjected to column chromatography using CH_2Cl_2 to afford **1j** (70 mg, 77% yield) as an indigo crystalline solid. mp 85.4-85.9 ^{0}C. λ_{max}: 571 nm. IR (ATR): ν_{max} 3079, 2930, 2849, 1723, 1578, 1395, 1167, 1130, 839, 743 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J*=10.5 Hz, 2H, H-4,8), 7.87 (t, *J*=3.5 Hz, 1H, H-2), 7.38 (d, *J*=3.5 Hz, 2H, H-1,3), 7.11 (d, *J*=10.0 Hz, 2H, H-5,7), 4.39 (t, *J*=7.0 Hz, 2H, H-10), 3.12 (t, *J*=7.0 Hz, 2H, H-9), 2.28 (tt, *J*=11.5, 3.5 Hz, 1H, H-12), 1.87 (dd, *J*=13.5, 2.5 Hz, 2H, H-13a), 1.74 (m, 2H, H-14a), 1.63 (m, 1H, H-15a), 1.42 (qd, *J*=12.0, 3.5 Hz, 2H, H-13b), 1.25 (m, 3H, H-14b, 15b). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0 (C, C-11), 148.2 (C, C-6), 139.1 (C, C-3a,8a), 136.4 (CH, C-2), 135.8 (CH, C-4,8), 124.2 (CH, C-5,7), 118.2 (CH, C-1,3), 64.9 (CH_2, C-10), 43.2 (CH, C-12), 41.2 (CH_2, C-9), 29.0 (CH_2, C-13), 25.7 (CH_2, C-15), 25.4 (CH_2, C-14). HRMS: *m/z* $C_{19}H_{23}O_2^+$ $[M+H]^+$ Calculated 283.1693, found 283.1700.

2-(Azulen-6-yl)ethyl trichloroacetate (AzulE trichloroacetate), 1k. 6-(2-Hydroxyethyl)azulene (21.8 mg, 0.12 mmol, 1 eq.) was dissolved in CH_2Cl_2 (5 mL) and trichloroacetyl chloride (0.07 mL, 0.62 mmol, 5 eq.) was added, followed by pyridine (0.2 mL, 2.5 mmol, 20 eq.). After 3 hours a colour change towards maroon was observed. A separation was performed with CH_2Cl_2/H_2O and the organic fraction was concentrated by rotary evaporation. The crude mixture was purified by column chromatography with 1:1 pet. ether/CH_2Cl_2 to afford **1k** (22 mg, 53% yield) as an indigo oil. λ_{max}: 568 nm. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J*=10.5 Hz, 2H, H-4,8), 7.88 (t, *J*=3.5 Hz, 1H, H-2), 7.39 (d, *J*=3.5 Hz, 2H, H-1,3), 7.12 (d, *J*=10.5 Hz, 2H, H-5,7), 4.66 (t, *J*=7.0 Hz, 2H, H-10), 3.25 (t, *J*=7.0 Hz, 2H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (C, C-11), 146.2 (C, C-6), 139.2 (C, C-3a,8a), 136.8 (CH, C-2), 135.9 (CH, C-4,8), 124.1 (CH, C-5,7), 118.5 (CH, C-1,3), 89.7 (C, CCl3), 69.8 (CH2, C-10), 40.7 (CH2, C-9). HRMS: *m/z* $C_{14}H_{12}Cl_3O_2^+$ $[M+H]^+$ Calculated 316.9897, found 316.9885.

2-(Azulen-6-yl)ethyl azulene-1-carboxylate (AzulE azulenecarboxylate), 1l. Azulene-1-carboxylic acid (**SI2**) (43 mg, 0.25 mmol), **2** (43 mg, 0.25 mmol, 1 eq.), DCC (76 mg, 0.37 mmol, 1.5 eq.) and DMAP (9 mg, 0.08 mmol, 0.3 eq.) were added to a RBF and dissolved in CH_2Cl_2 (6 mL). After 3 hours, further DMAP (41 mg, 0.34 mmol, 1.3 eq.) was added and the reaction was heated at reflux overnight. A separation was performed in CH_2Cl_2/H_2O and the organic fraction was concentrated by rotary evaporation. The crude mixture was subjected to column chromatography using CH_2Cl_2 to afford **1l** (64 mg, 78% yield) as a purple solid. mp

116.5-117.4 ^{0}C. λ_{max}: 514, 530 nm. IR (ATR): ν_{max} 3068, 2956, 2928, 2850, 1660, 1574, 1392, 1224, 1136, 1006, 120, 754 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (d, *J*=10.0 Hz, 1H, H-19), 8.45 (d, *J*=10.0 Hz, 1H, H-15), 8.35 (d, *J*=4.0 Hz, 1H, H-13), 8.32 (d, *J*=10.0 Hz, 2H, H-4,8), 7.87 (t, *J*=4.0 Hz, 1H, H-2), 7.70 (t, *J*=10.0 Hz, 1H, H-17), 7.47 (t, *J*=10.0 Hz, 1H, H-18), 7.44 (t, *J*=10.0 Hz, 1H, H-16), 7.39 (d, *J*=3.5 Hz, 2H, H-1,3), 7.29 (d, *J*=4.0 Hz, 1H, H-14), 7.24 (d, *J*=10.0 Hz, 2H, H-5,7), 4.71 (t, *J*=6.5 Hz, 2H, H-10), 3.32 (t, *J*=7.0 Hz, 2H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2 (C, C-11), 148.7 (C, C-6), 144.8 (C, C-14a), 140.8 (C, C-19a), 140.2 (CH, C-13), 139.1 (C, C-3a,8a), 139.0 (CH, C-17), 138.2 (CH, C-15), 137.8 (CH, C-19), 136.3 (CH, C-2), 135.9 (CH, C-4,8), 127.7 (CH, C-18), 126.8 (CH, C-16), 124.4 (CH, C-5,7), 118.2 (CH, C-1,3), 117.7 (CH, C-14), 116.6 (C, C-12), 64.7 (CH_2, C-10), 41.6 (CH_2, C-9). HRMS: *m/z* $C_{23}H_{19}O_2^+$ $[M+H]^+$ Calculated 327.1380, found 327.1387.

Deprotection studies on AzulE cinnamate (general procedure). AzulE (*E*)-cinnamate (10 mg, 0.03 mmol) was dissolved in solvent (3 mL) under open air, and base (approx. 0.1 mL) was added. The reaction was performed either at r.t. or reflux. The extent of reaction was monitored qualitatively through observed colour change and by TLC analysis and the reaction was stopped once no evidence of SM remained, or otherwise after overnight reaction. If the solvent and base were low boiling, the reaction mixture was concentrated by rotary evaporation was employed to give the crude reaction residue. Otherwise, an aqueous separation was employed using CH_2Cl_2 and 10% aqueous HCl, followed by concentration of the organic fraction by rotary evaporation to give the crude residue. This residue was subjected to quantitative ^{1}H NMR analysis and the principal peaks integrated to determine the extent of reaction (see details in Supporting Information). The results are shown in Table 2. In most deprotections, 6-vinylazulene (**4**) was generated as the by-product, but when using piperidine as the base, piperidine adduct **5** was obtained.

6-Vinylazulene, 4.[14] A blue crystalline solid was obtained as a by-product of AzulE ester deprotection, typically in yields corresponding to the extent of deprotection, and identified as 6-vinylazulene. λ_{max}: 608 nm. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J*=10.5 Hz, 2H, H-4,8), 7.85 (t, *J*=3.5 Hz, 1H, H-2), 7.36 (d, *J*=3.5 Hz, 2H, H-1,3), 7.31 (d, *J*=10.0 Hz, 2H, H-5,7), 6.92 (dd, *J*=17.5, 10.5 Hz, 1H, H-9), 5.97 (d, *J*=17.5 Hz, 1H, H-10b), 5.47 (d, *J*=10.5 Hz, 1H, H-10a). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7 (C, C-6), 141.3 (CH, C-9), 139.3 (C, C-3a,8a), 136.8 (CH, C-2), 135.6 (CH, C-4,8), 121.4 (CH, C-5,7), 118.4 (CH, C-1,3), 117.6 (CH_2, C-10). HRMS: *m/z* $C_{12}H_{11}^+$ $[M+H]^+$ Calculated 155.0855, found 155.0857. ^{1}H NMR data are consistent with those reported previously.[14]

***N*-2-(Azulen-6-yl)ethylpiperidine, 5.** An indigo oil, formed in Azul deprotections involving the use of piperidine, was obtained in quantities concordant with the extent of deprotection and identified as the title compound. This material was contaminated with a small amount of piperidine that was identifiable in the NMR spectra. λ_{max}: 562 nm. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J*=10.5 Hz, 2H, H-4,8), 7.83 (t, *J*=4.0 Hz, 1H, H-2), 7.35 (d, *J*=4.0 Hz, 2H, H-1,3), 7.09 (d, *J*=10.0 Hz, 2H, H-5,7), 3.00 (m, 2H, H-9), 2.67 (m, 2H, H-10), 2.50 (broad s, 4H, H-11), 1.64 (quin, *J*=6.0 Hz, 4H, H-12), 1.50-1.45 (m, 2H, H-13). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4 (C, C-6), 138.9 (C, C-3a,8a), 135.9 (CH, C-4,8), 135.8 (CH, C-2), 124.2 (CH, C-5,7), 117.9 (CH, C-1,3), 62.1 (CH_2, C-10), 54.5 (CH_2, C-11), 39.9 (CH_2, C-9), 26.0 (CH_2,

C-12), 24.3 (CH_2, C-13). HRMS: *m/z* $C_{17}H_{22}N^+$ $[M+H]^+$ Calculated 240.1747, found 240.1751.

Deprotection of AzulE esters (optimised procedure). The AzulE ester (0.5 mmol) was dissolved in MeCN (3 mL), DBU (0.2 mL) was added and the reaction mixture stirred, open to the air, for the time shown in Table 3. After this time, a colour change from indigo to blue was observed. Then HCl (2 mL, 10% in H_2O) was added and a phase separation was performed using CH_2Cl_2 and H_2O. The aqueous layer was washed three times with CH_2Cl_2 then twice with EtOAc. The organic phase was then concentrated by rotary evaporation. The crude mixture was purified by gradient column chromatography whereby 6-vinylazulene eluted with pet. ether and the deprotected carboxylic acid was obtained by elution with a mixture of pet. ether/ethyl acetate (typically 2:1 v/v). Occasionally a green tint remained in the product from degraded azulene material; this was a very minor impurity and could be removed by filtering through a silica plug. The yields of the carboxylic acids are shown in Table 3; all of these (and δ-valerolactone) are commercially available.

2-(1-(2-Methoxy-2-oxoacetyl)azulen-6-yl)ethyl (*E*)-cinnamate, 6. AzulE cinnamate (**1a**) (79 mg, 0.26 mmol, 1 eq.) was dissolved in CH_2Cl_2 (3 mL). Oxalyl chloride (0.1 mL, 1.16 mol, 4.5 eq.) was added, followed 20 seconds later by methanol (0.3 mL, 7.4 mmol, 28 eq.) and after another 40 seconds by pyridine (0.4 mL, 5 mmol, 19 eq.). Immediately, this reaction mixture was subjected to workup using CH_2Cl_2/H_2O and the organic fraction was concentrated by rotary evaporation and purified by column chromatography in 2:1 pet. ether/ethyl acetate to give activated species **6** as an orange-red oil (99 mg, 98% yield). λ_{max}: 505 nm. IR (ATR): ν_{max} 3002, 2950, 1732, 1710, 1623, 1409, 1305, 1174, 850, 769 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (d, *J*=10.5 Hz, 1H, H-8), 8.45 (d, *J*=10.0 Hz, 1H, H-4), 8.40 (d, *J*=4.0 Hz, 1H, H-2), 7.70 (d, *J*=10.0 Hz, 1H, H-7), 7.66 (d, *J*=16.0 Hz, 1H, H-13), 7.58 (d, *J*=10.5 Hz, 1H, H-5), 7.50 (m, 2H, H-15), 7.39-7.37 (m, 3H, H-16, H-17), 7.26 (d, *J*=4.0 Hz, 1H, H-3), 6.39 (d, *J*=16.0 Hz, 1H, H-12), 4.56 (t, *J*=7.0 Hz, 2H, H-10), 3.99 (s, 3H, O-Me), 3.31 (t, *J*=6.5 Hz, 2H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6 (C, C-18), 166.7 (C, C-19), 164.8 (C, C-11), 152.1 (C, C-6), 146.1 (C, C-3a), 145.5 (CH, C-13), 142.3 (CH, C-2), 141.8 (C, C-8a), 138.9 (CH, C-8), 138.1 (CH, C-4), 134.1 (C, C-14), 132.4 (CH, C-7), 131.0 (CH, C-5), 130.5 (CH, C-17), 128.9 (CH, C-16), 128.2 (CH, C-15), 120.9 (C, C-1), 119.4 (CH, C-3), 117.4 (CH, C-12), 64.7 (CH_2, C-10), 52.6 (CH_3, O-Me), 41.1 (CH_2, C-9). HRMS: *m/z* $C_{24}H_{21}O_5^+$ $[M+H]^+$ Calculated 389.1384, found 389.1386.

Deprotection of activated AzulE cinnamate (general procedure). Deprotection of activated AzulE cinnamate **6** was conducted in acetonitrile with bases as described in Table 5. Reaction completion was determined by NMR spectroscopic analysis of the crude reaction mixture (see details in Supporting Information).

Deprotection of activated AzulE cinnamate (optimised procedure). Activated AzulE cinnamate **6** (16 mg, 0.041 mmol) was dissolved in acetonitrile (3 ml) and treated with morpholine (0.1 mL, 1.2 mmol). The reaction mixture was stirred for 19 hours before evaporation under reduced pressure to afford the crude product mixture as an orange oil.

Column chromatography (DCM) provided cinnamic acid as a pale orange oil (6 mg, 0.04 mmol, 99%).

AzulE – O-TBS competitive deprotection studies. Cyclohexanemethyl *tert*-butyldimethylsilyl ether (**7**) and AzulE cinnamate were used in the following experiments. The extent of reaction was measured through comparison of ^{1}H NMR integration of the starting materials and the products (see details in Supporting Information).

Selective O-TBS deprotection in the presence of AzulE ester. 11 mg of a mixture of AzulE cinnamate (**1d**) and TBS-protected cyclohexanemethanol[19] was added to a flask [equivalent to AzulE cinnamate (**1d**) (0.029 mmol, 1.4 eq.) and **7 (**0.021 mmol, 1 eq.)], PPTS (85 mg, 0.33 mmol, 16 eq.) was added and the reaction was dissolved in MeCN (3 mL) and heated at reflux overnight open to air. A separation was performed with CH_2Cl_2/H_2O and the organic phase was concentrated by rotary evaporation (taking care not to subject the mixture to prolonged vacuum to avoid loss of cyclohexanemethanol) and this mixture was subjected to NMR analysis (see details in Supporting Information). This indicated that the deprotection of the TBS-ether proceeded to completion without interference of the AzulE ester.

Selective AzulE deprotection in the presence of O-TBS. AzulE cinnamate (**1d**) (10.1 mg, 0.033 mmol, 1 eq.) and TBS-protected cyclohexanemethanol (**7**)[19] (8.4 mg, 0.037 mmol, 1.07 eq.) were dissolved in THF (3 mL), and DBU (0.1 mL, 0.67 mmol, 18.5 eq.) was added. After stirring overnight, a phase separation was performed using H_2O/Et_2O and the separated organic phase was washed four times with H_2O. The organic phase was reduced via rotary evaporation under low vacuum. The aqueous phase was treated with 3 mL HCl (10% aq.) and washed twice with CH_2Cl_2. This organic fraction was concentrated by rotary evaporation. NMR analysis of these fractions indicated the deprotection of AzulE cinnamate proceeded cleanly to completion without interference from the TBS-ether (see details in Supporting Information).

Deprotection of TBS ether and AzulE Ester. AzulE cinnamate (**1d**) (8.3 mg, 0.027 mmol, 1 eq.) and TBS-protected cyclohexanemethanol (**7**)[19] (6.2 mg, 0.027 mmol, 1 eq.) were dissolved in THF (3 mL), and TBAF (0.4 mL of a 1 M solution in THF, 0.4 mmol, 15 eq.) was added. A colour change was visible after 10 minutes. After 70 minutes, 1 mL of 10% aq. HCl was added and a phase separation was performed with CH_2Cl_2/H_2O. The organic fraction was concentrated by rotary evaporation and the crude mixture submitted for NMR analysis. This indicated that full deprotection had occurred (see details in Supporting Information).

AzulE – O-MOM competitive deprotection studies. A standardised mixture of AzulE cinnamate (**1d**) (69.7 mg, 1 eq.) and MOM-protected cetyl alcohol **8**[20] (71 mg, 1.07 eq.), was made for use in the following experiments. The extent of reaction was measured through comparison of ^{1}H NMR integration of the starting materials [AzulE cinnamate (**1d**) and cetyl MOM ether **8**] and the products [6-vinylazulene (**4**), cinnamic acid and cetyl alcohol].

Selective O-MOM deprotection in the presence of AzulE ester. The standardised MOM deprotection mixture [43 mg, equivalent to 0.070 mmol AzulE cinnamate (**1d**) and 0.076 mmol MOM-protected cetyl alcohol (**8**)[20]] and PPTS (73 mg, 0.29 mmol, 4.1 eq.) were added

to a RBF fitted with condenser and dissolved in ethanol (3 mL) and MeCN (1 mL). The reaction was heated at reflux overnight. A separation was performed using CH_2Cl_2/sat. aq. $NaHCO_3$ and the organic layer was submitted for NMR analysis (see details in Supporting Information). This indicated that the deprotection of the MOM ether proceeded to completion without interference from the AzulE ester.

Selective AzulE deprotection in the presence of O-MOM. The standardised MOM deprotection mixture [16 mg, equivalent to 0.025 mmol AzulE cinnamate (**1d**) and 0.027 mmol MOM-protected cetyl alcohol (**8**)[20]] was dissolved in THF (3 mL), and DBU (0.1 mL, 0.66 mmol) was added under open air. The reaction was stirred for 19 hours. 10 drops of 10% HCl (aq.) were added to the reaction mixture, and a separation was performed in CH_2Cl_2/H_2O. The organic layer was concentrated by rotary evaporation and submitted for NMR analysis. This indicated that the deprotection of AzulE cinnamate proceeded cleanly to completion without interference from the MOM ether (see details in Supporting Information).

AzulE – Fmoc competitive deprotection studies. Extent of reaction was measured through comparison of ^{1}H NMR integration of the starting material, Fmoc-Gly-OAzulE (**1i**), and the products, 6-vinylazulene (**4**), H-Gly-OAzulE, dibenzofulvene, 1-(fluoren-9-ylmethyl)piperidine.[16]

Deprotection of NH-Fmoc and AzulE Ester. Fmoc-Gly-OAzulE (**1i**) (23 mg, 0.05 mmol, 1 eq.) was dissolved in THF (3 mL) and DBU (0.1 mL, 0.66 mmol, 13 eq.) was added. After 9 hours, the reaction mixture had changed colour from indigo to blue. HCl (1 mL, 10% aqueous solution) was added and a phase separation was performed with CH_2Cl_2/H_2O, followed by rotary evaporation of the organic fraction. The crude mixture was submitted for quantitative NMR analysis (see details in Supporting Information). This indicated that complete deprotection of both the Fmoc and the AzulE group occurred.

Selective NH-Fmoc deprotection in the presence of AzulE ester. Fmoc-Gly-OAzulE (**1i**) (36 mg, 0.079 mmol, 1 eq.) was dissolved in MeCN (3 mL) and piperidine (0.1 mL, 1 mmol, 13 eq.) was added to this mixture. After 30 minutes, the reaction was complete by TLC. The reaction mixture was concentrated by rotary evaporation and the crude mixture submitted for quantitative NMR analysis (see details in Supporting Information). This indicated that complete and selective Fmoc deprotection was achieved.

AzulE deprotection in the presence of NH-Fmoc. AzulE-protected Fmoc glycine **1i** (189 mg, 0.42 mmol, 1 eq.) was dissolved in CH_2Cl_2 (4 mL) and oxalyl chloride (0.2 mL, 2.3 mmol, 5.5 eq.) was added at 0 ^{0}C, followed 20 seconds later by MeOH (0.4 mL, 9.9 mmol, 23 eq.) and another 30 seconds later by pyridine (0.5 mL, 6.2 mmol, 15 eq.). A phase separation was performed using CH_2Cl_2/H_2O, and the organic fraction was concentrated by rotary evaporation. The crude material was purified by column chromatography in ethyl acetate to afford activated species **9** as an orange-red solid (209 mg, 92%). mp 63.6-65.7 ^{0}C. λ_{max}: 507 nm. IR (ATR): ν_{max} 3355, 3040, 2951, 1720, 1621, 1395, 1255, 1182, 1048, 783 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (d, *J*=10.0 Hz, 1H, H-8), 8.42 (d, *J*=10.5 Hz, 1H, H-4), 8.40 (d, *J*=4.5 Hz, 1H, H-2), 7.76 (d, *J*=7.5 Hz, 2H, H-20), 7.63 (d, *J*=10.0 Hz, 1H, H-7), 7.58

(d, *J*=7.5 Hz, 2H, H-17), 7.51 (d, *J*=10.0 Hz, 1H, H-5), 7.40 (t, *J*=7.5 Hz, 2H H-19), 7.31 (t, *J*=7.5 Hz, 2H, H-18), 7.25 (d, *J*=4.5 Hz, 1H, H-3), 5.22 (t, *J*=5.5 Hz, 1H, N-H), 4.51 (d, *J*=7.0 Hz, 2H, H-10), 4.40 (d, *J*=7.0 Hz, 2H, H-14), 4.22 (t, *J*=7.0 Hz, 1H, H-15), 3.99 (s, 3H, O-Me), 3.96 (d, *J*=5.5 Hz, 2H, H-12), 3.26 (t, *J*=7.0 Hz, H, H-9). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6 (C, C-22), 169.8 (C, C-11), 164.7 (C, C-23), 156.2 (C, C-13), 151.3 (C, C-6), 146.0 (C, C-3a or 8a), 143.7 (C, C-16), 142.4 (CH, C-2), 141.8 (C, C-3a or 8a), 141.3 (C, C-21), 138.8 (CH, C-8), 138.1 (CH, C-4), 132.2 (CH, C-7), 130.9 (CH, C-5), 127.7 (CH, C-19), 127.1 (CH, C-18), 125.0 (CH, C-17), 120.9 (C, C-1), 120.0 (CH, C-20), 119.6 (CH, C-3), 67.2 (CH_2, C-14), 65.6 (CH_2, C-10), 52.6 (CH_3, O-Me), 47.1 (CH, C-15), 42.7 (CH_2, C-12), 40.8 (CH_2, C-9). HRMS: *m/z* $C_{32}H_{28}NO_7^+$ $[M+H]^+$ Calculated 538.1860, found 538.1876.

Activated ketoester compound **9** (38 mg, 0.07 mmol, 1 eq.) was dissolved in MeCN (3 mL) at 0 ^{0}C. NEt_3 (0.1 mL, 0.7 mmol, 10 eq.) was added and the reaction left to stir for 3 hours at 0 ^{0}C. The reaction mixture was concentrated by rotary evaporation at r.t. and the crude mixture was submitted for quantitative NMR analysis (see details in Supporting Information). This indicated full AzulE deprotection, accompanied by partial (25%) Fmoc deprotection.

Compatibility of AzulE with strong base. KHMDS (0.79 mL of a 0.5 M in toluene solution, 0.40 mmol, 3 eq.) was added dropwise to a stirred solution of AzulE cinnamate (40 mg, 0.13 mmol, 1.0 eq.) in dry THF (6 mL) at -78 °C under an atmosphere of argon. Aliquots (0.25 mL) were taken at 0 minutes (before KHMDS addition), and subsequently at 6, 31, 61, 90 and 180 minutes. Each aliquot was treated with 10% aqueous HCl solution and extracted with ethyl acetate before concentrating to dryness under reduced pressure and analysing by NMR spectroscopy (see details in Supporting Information). This indicated that the conversion of AzulE cinnamate into cinnamic acid and 6-vinylazulene was complete within 6 minutes.

Compatibility of AzulE with Suzuki cross-coupling at reflux. Phenylboronic acid (69 mg), palladium tetrakis[triphenylphosphine] (65 mg), and potassium carbonate (131 mg) were added together and the powders mixed thoroughly with a spatula. This mixture was partitioned into two portions – the control (135 mg) and the AzulE benzoate-containing sample (129 mg). To the control sample (containing a calculated 1.2 eq. phenylboronic acid, 0.11 eq. $Pd(PPh_3)_4$ and 2 eq. K_2CO_3), toluene (3.2 mL) and 2-bromoanisole (0.03 mL, 0.24 mmol, 1 eq.) were added, and the reaction vessel was fitted with a reflux condenser and heated at reflux for 2 hours, during which time the reaction mixture changed colour from yellow to red to brown. A phase separation was performed with CH_2Cl_2/H_2O and the organic fraction was concentrated by rotary evaporation and subjected to NMR analysis (see details in Supporting Information and results in Table 7). For the spiked reaction, to a flask containing AzulE benzoate (**1a**) (71 mg, 0.25 mmol, 1.06 eq.) and the powdered mixture described above (containing a calculated 1.15 eq. phenylboronic acid, 0.11 eq. $Pd(PPh_3)_4$, and 1.9 eq. K_2CO_3), toluene (3.2 mL) and 2-bromoanisole (0.03 mL, 1 eq.) were added, and the reaction vessel was fitted with a reflux condenser and heated at reflux for 2 hours, during which time a colour change from indigo to purple and back to indigo was observed. A phase separation was performed with CH_2Cl_2/H_2O, and the organic fraction was concentrated by rotary evaporation and subjected to NMR analysis (see details in Supporting Information and

results in Table 7). These indicated that this reaction is not compatible with AzulE protection.

Compatibility of AzulE with Suzuki cross-coupling at ambient temperature. Phenylboronic acid (72 mg), palladium acetate (16 mg), *p*-iodonitrobenzene (108.6 mg) and potassium carbonate (158 mg) were added together and mixed as powders with a spatula. This mixture was partitioned into two portions, the control (185 mg) and the AzulE benzoate-spiked sample (168 mg). To the control sample (containing a calculated 1.34 eq. phenylboronic acid, 0.16 eq. palladium acetate, 1 eq. *p*-iodonitrobenzene, and 2.6 eq. potassium carbonate), methanol (3 mL) was added and the reaction was left to stir at r.t. under open air for three days. A separation was performed using CH_2Cl_2/H_2O, and the organic layer was concentrated by rotary evaporation and submitted for NMR analysis. For the spiked reaction, to a RBF containing AzulE benzoate (**1a**) (75 mg, 0.27 mmol, 1.3 eq.) and the powdered mixture described above (containing a calculated 1.34 eq. phenylboronic acid, 0.16 eq. palladium acetate, 1 eq. *p*-iodonitrobenzene and 2.61 eq. potassium carbonate), methanol (3 mL) was added and the reaction was left to stir at r.t. under open air for three days. A separation was performed using CH_2Cl_2/H_2O, and the organic layer was submitted for NMR analysis (see details in Supporting Information and results in Table 7). These indicated that this reaction is compatible with AzulE protection.

Compatibility of AzulE with Masamune-Roush reaction. A solution of triethylphosphonoacetate (0.2 mL), triethylamine (0.28 mL) in THF (4 mL) was prepared and divided into two portions. For the control reaction, 2 mL of the above solution (containing a calculated 1 eq. triethylphosphonoacetate and 2 eq. NEt_3) was added to a RBF containing LiBr (108 mg, 1.24 mmol, 2.5 eq) and left to stir for 30 minutes. Anisaldehyde (0.24 mL, 0.98 mmol, 2 eq.) was then added and the reaction was left to proceed overnight. A separation was performed using CH_2Cl_2/H_2O, and the organic layer was submitted for NMR analysis. For the AzulE benzoate-spiked reaction, 2 mL of the above solution (containing a calculated 1 eq. triethylphosphonoacetate and 2 eq. NEt_3) was added to a RBF containing LiBr (102 mg, 1.18 mmol, 2.4 eq.) and AzulE benzoate (105 mg, 0.38 mmol, 0.32 eq.) and left to stir for 30 minutes. Anisaldehyde (0.24 mL, 0.98 mmol, 2 eq.) was then added and the reaction was left to proceed overnight. A separation was performed using CH_2Cl_2/H_2O, and the organic layer was submitted for NMR analysis (see details in Supporting Information and results in Table 7). These indicated that this reaction is compatible with AzulE protection.

Compatibility of AzulE with $NaBH_4$ reduction. Benzophenone (146 mg) and $NaBH_4$ (86 mg) were added together and mixed as solids. This mixture was partitioned into two portions, the control (112 mg) and the AzulE benzoate-spiked sample (120 mg). To the control sample (containing a calculated 1 eq. benzophenone and 2.8 eq. $NaBH_4$), methanol (2 mL) was added and the reaction was allowed to stir for 5 hours. A separation was performed using CH_2Cl_2/H_2O, and the organic layer was submitted for NMR analysis. For the spiked reaction, to a sample containing AzulE benzoate (**1a**) (112 mg, 1.04 eq.) and the mixture described above (containing a calculated 1 eq. benzophenone and 2.8 eq. $NaBH_4$), methanol (2 mL) was added and the reaction was allowed to stir for 5 hours. A separation was performed using CH_2Cl_2/H_2O, and the organic layer was submitted for NMR analysis (see details in

Supporting Information and results in Table 7). These indicated that this reaction is compatible with AzulE protection

Compatibility of AzulE with Swern oxidation. DMSO (0.5 mL), $(COCl)_2$ (0.2 mL) and CH_2Cl_2 (5 mL) were added together at -78 ^{0}C and left for 30 minutes. For the control reaction, cetyl alcohol (54 mg, 0.22 mmol, 1 eq.) was dissolved in THF (4 mL) at -78 ^{0}C, and the above oxidising mixture (2 mL, containing a calculated 4.2 eq. chlorodimethylsulfonium chloride) was added. The solution became cloudy. After two hours, NEt_3 (0.3 mL, 2.15 mmol, 9.7 eq.) was added and the reaction was maintained at -78 ^{0}C for a further 30 minutes before allowing it to warm up to r.t. over an hour. 1 mL 10% HCl (aq.) was added to the reaction mixture, followed by water and a separation was performed using CH_2Cl_2/H_2O, and the organic layer was submitted for NMR analysis. For the AzulE benzoate-spiked reaction, AzulE benzoate (**1a**) (52 mg, 0.19 mmol, 0.94 eq.) and cetyl alcohol (49 mg, 0.2 mmol, 1 eq.) were mixed in THF (4 mL) at -78 ^{0}C, and the above oxidising mixture (2 mL, containing a calculated 4.6 eq. chlorodimethylsulfonium chloride) was added. The indigo reaction mixture rapidly became magenta. Triethylamine (0.3 mL, 2.15 mmol, 10.8 eq.) was added after 130 minutes, and the reaction was kept at -78 ^{0}C for a further 30 minutes before being allowed to warm up to r.t. over an hour. 1 mL 10% HCl (aq.) was added, followed by water and a separation was performed using CH_2Cl_2/H_2O, and the organic layer was submitted for NMR analysis (see details in Supporting Information and results in Table 7). These indicated that this reaction is not compatible with AzulE protection: there was evident degradation of the AzulE protecting group and most of the colour (azulene material) remained in the aqueous layer during phase separation.

Compatibility of AzulE with Dess-Martin oxidation. Cetyl alcohol (18 mg, 0.072 mmol, 1.0 eq.) was dissolved in dry DCM (2 mL) and added to a solution of DMP (38 mg, 0.089 mmol, 1.2 eq.) in dry DCM (2 mL) under argon gas and left to stir. After 4 hours the reaction mixture was diluted with diethyl ether (4 mL) and poured into a solution of saturated aqueous $NaHCO_3$ (6 mL) containing $Na_2S_2O_3.5H_2O$ (180 mg, 0.72 mmol, 10 eq.). The organic layer was separated and extracted with saturated aqueous $NaHCO_3$ (6 mL), then distilled water (6 mL), before drying over $MgSO_4$. The organic layer was concentrated to dryness under reduced pressure and the white solid reaction product subjected to ^{1}H NMR analysis (see details in Supporting Information and results in Table 7). These indicated that this reaction is not compatible with AzulE protection.

Compatibility of AzulE with pyridinium chlorochromate oxidation. For the control reaction, cetyl alcohol (18 mg, 0.072 mmol, 1.0 eq.) was dissolved in dry DCM (2.5 mL) and added quickly to an orange solution of PCC (25 mg, 0.116 mmol, 1.6 eq.) dissolved in dry DCM (2.5 mL) under argon gas. The reaction was left to stir and the colour changed to brown over time. At 2 hours, the reaction mixture was diluted with DCM (10 mL) and filtered through a sintered funnel containing a Celite pad, followed by washing with diethyl ether. The reaction mixture was concentrated to dryness under reduced pressure to recover a crude mass of 16.5 mg, as an off-white solid, which was submitted for NMR analysis. For the spiked reaction, cetyl alcohol (18 mg, 0.074 mmol, 1.0 eq.) and AzulE benzoate (20 mg, 0.073 mmol, 1.0 eq.) were dissolved in dry DCM (2.5 mL) and added quickly to an orange

solution of PCC (25 mg, 0.116 mmol, 1.6 eq.) in dry DCM (2.5 mL) under argon gas. The reaction turned to a dark murky brown colour and was left to stir for 2 hours, by which time it had changed to a dark muddy green. The reaction mixture was diluted with DCM (10 mL) and filtered through a sinter funnel containing a Celite pad, washing with diethyl ether. The filtrate was concentrated to dryness under reduced pressure to afford a dark green solid. This was submitted to NMR analysis (see details in Supporting Information and results in Table 7). These indicated that the PCC oxidation is not compatible with the AzulE protecting group.

Compatibility of AzulE with TEMPO/BAIB oxidation. Cetyl alcohol (18 mg, 0.072 mmol, 1.0 eq.), BAIB (26 mg, 0.080 mmol, 1.1 eq.) and TEMPO (1 mg, 0.0072 mmol, 0.1 eq.) were dissolved in dry DCM (2 mL) and left to stir open to the atmosphere. After 3.5 hours the reaction mixture was diluted with DCM (5 mL) and to this a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) was added. The mixture was stirred for 5 min before extracting with DCM (4x5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), then brine (5 mL) before being dried over Na_2SO_4 and concentrated to dryness under reduced pressure to recover a crude mass of 17.9 mg, as a white solid. The same experimental procedure was followed for the spiked reaction but AzulE benzoate (20 mg, 0.072 mmol, 1 eq.) was additionally dissolved with cetyl alcohol, TEMPO and BAIB in dry DCM (2 mL) to produce an indigo solution. After dilution, work-up and concentration to dryness under reduced pressure an indigo solid was obtained. NMR analysis of both reaction mixtures (see details in Supporting Information and results in Table 7) indicated that the TEMPO-BAIB oxidation is not compatible with the AzulE protecting group.

Compatibility of AzulE with activated MnO_2. For the control reaction, *E*-non-2-en-1-ol (21 mg, 0.148 mmol, 1.0 eq.) in dry DCM (2 mL) was added to activated MnO_2 (129 mg, 1.484 mmol, 10.0 eq.) in dry DCM under argon gas and left to stir. After 23 hours the reaction mixture was filtered through a sinter funnel with a Celite pad before being concentrated to dryness under reduced pressure to recover a crude mass of 21 mg, as a yellow oil. For the spiked reaction, the same experimental procedure was followed but AzulE benzoate (40 mg, 0.145 mmol, 1 eq.) was additionally dissolved with *E*-non-2-en-1-ol in dry DCM (2 mL). After filtration and concentration to dryness under reduced pressure a crude mass of 59 mg, as an indigo solid, was recovered. NMR analysis of both reaction mixtures (see details in Supporting Information and results in Table 7) indicated that manganese dioxide oxidations of allylic alcohols are compatible with the AzulE protecting group.

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Supporting Information available: General experimental procedures and conditions, synthetic methods and analytical data for deprotection of AzulE esters, data on colour change during deprotection, kinetic studies on deprotection, details of protecting group and reaction compatibility studies, synthesis of azulene-1-carboxylic acid, ^{1}H and ^{13}C NMR spectra for all new compounds.

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