JOC The Journal of Organic Chemistry

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Synthesis of 1,3,6-Trisubstituted Azulenes

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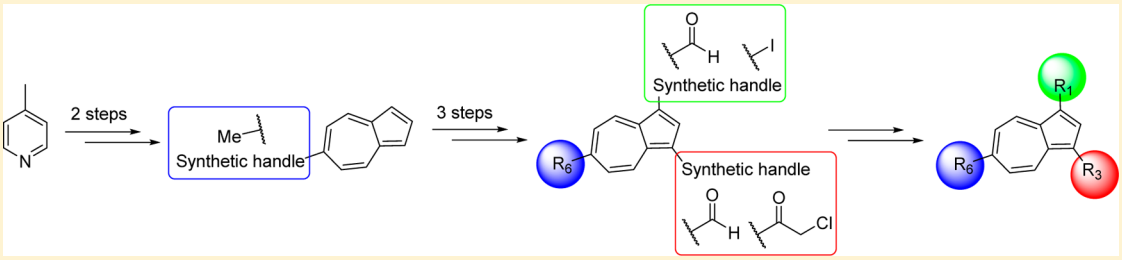
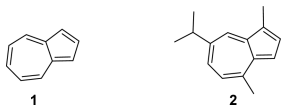
Supporting Information



ABSTRACT: We have developed a short, general synthetic route to 1,3,6-trisubstituted azulenes. The key intermediate, 6-methylazulene, was synthesized from readily available and inexpensive starting materials in 63% yield over two steps. The methyl group of 6-methylazulene was then used as a synthetic handle to introduce different substituents at the 6-position via two different methods. Subsequently, the 1- and 3-positions were substituted with additional functional handles, such as formyl, chloromethylketone, and iodide. The efficiency of the synthetic route was demonstrated by preparing a collection of three different products with the best demonstrated yield 33% over seven steps.

INTRODUCTION

Bicyclic aromatics such as naphthalene and indole are commonly encountered structures in drug molecules. Azulene (**1**), which is a nonbenzenoid isomer of naphthalene, has a similar dipole moment[1] to indole. Azulene can therefore be considered as an isostere to indole since both aromatic structures have an electron-rich five-membered ring fused to an electron deficient larger ring.



Azulene is commercially available, but its use in synthetic chemistry is limited by its rather unreactive seven-membered ring, which is difficult to substitute without a suitable synthetic handle such as a halogen or methyl group. The natural product guaiazulene (**2**) is a commonly used starting material in synthesis of azulene derivatives because it is inexpensive and readily available, unlike azulene itself (typical prices for azulene and guaiazulene are $40 and $1 per mmol, respectively). Even though the isopropyl and methyl groups of guaiazulene enable functionalization of the seven-membered ring,[2] the existing substituents in 1-, 4-, and 7-positions limit the substitution pattern of the final products.

Several synthetic routes to access the azulene scaffold have been developed.[3−6] Typically, they yield an azulene derivative with an unsubstituted seven-membered ring and/or have low overall yields due to the length of the synthetic route. Currently, there are only a few limited synthetic routes to access azulenes possessing three or more substituents, which has hindered the exploitation of azulene-based compounds in medicinal chemistry. This is emphasized by the fact that the antiulcer agent egualen sodium[7] is the only azulene-based drug on the market.

In our efforts to study the azulene scaffold for medicinal chemistry applications, we required a general synthetic route to access 1,3,6-trisubstituted azulenes. 6-Methylazulene (**3**) was chosen as a key intermediate for the synthetic route, as it can be synthesized from common and inexpensive starting materials in two steps.[8] The methyl group of 6-methylazulene can be easily converted to many different functionalized substituents.[9] In addition, other useful synthetic handles were planned to be introduced in the 1- and 3-positions of azulene (Figure 1). The electron-rich five-membered ring of azulene readily reacts with electrophiles at its 1- and 3-positions.[10] For example, Vilsmeier−Haack formylation[8,11] and iodination with *N*-iodosuccinimide (NIS)[12] result in formyl and iodine sub-

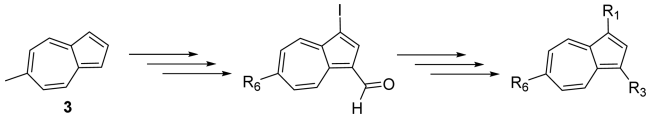


Figure 1. Proposed route to functionalize azulene scaffold at 1-, 3-, and 6-positions utilizing synthetic handles.

Received: September 29, 2015
Published: November 3, 2015

DOI: 10.1021/acs.joc.5b02271
J. Org. Chem. 2015, 80, 11513−11520

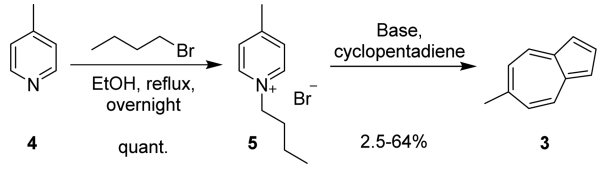
stituents, respectively, installing versatile synthetic handles. For example, the formyl group can be used in further reactions with nucleophiles or in redox reactions, and iodine enables a wide variety of coupling reactions.

RESULTS AND DISCUSSION

Optimization of the 6-Methylazulene Synthesis. The preparative two-step synthetic route to 6-methylazulene (**3**) is shown in Scheme 1. The pyridinium salt **5** was prepared in quantitative yield following a known literature method.[13] In the second step, the pyridinium salt was reacted with sodium cyclopentadienide prepared from cyclopentadiene and NaH in DMF.[8] The yield of the reaction was 23%, which is comparable to the 27% yield reported in the literature. In addition, several side products were formed in the reaction, which proved difficult to separate from the product. Due to these problems, an attempt to further optimize the reaction was made by varying concentration, solvent, base, temperature, reaction time, and heating regime using both conventional and microwave heating (Table 1). The yield decreased if NaH was changed to another base such as NaOH, NaOMe, or *n*-BuLi, or if the DMF was substituted with another solvent such as THF. This decrease is suggested to result from the incomplete deprotonation of the cyclopentadiene and reduced solubility of the pyridinium salt. Beneficially, a lower concentration of the reagents as well as the use of higher temperature and rapid heating in a microwave cavity gave improved yields. Increasing the temperature also significantly shortened the processing time from 240 to 35 min.

Having derived significantly enhanced reaction conditions leading to an isolated yield of 64%, we evaluated the scaled synthesis of this key intermediate. A 50 mmol scale-up of 6-methylazulene synthesis was conducted based on the conditions of entry 9 (Table 1), in which 0.25 M of reaction mixture was microwave irradiated at 200 °C for 30 min. Generally, the scale-up of microwave heated reactions is limited by the volume of microwave vials. This was partially circumvented by dividing the reaction mixture into ten separate microwave vials (10−20 mL) and running them sequentially using the robotic instrumentation. The processed vials could postreaction be combined into two batches for workup and condensed further to a single batch for final flash chromatography. This scale-up to 50 mmol gave an overall yield of 63%, which corresponds to 4.5 g of pure 6-methylazulene (**3**). Furthermore, we noticed that it is possible to further shorten the individual heated reaction time to 15 min without effecting purity or yield.

Scheme 1. Two-Step Synthesis of 6-Methylazulene (3)



Functionalization of the Methyl Group of 6-Methylazulene. The methyl group in the 6-position of 6-methylazulene (**3**) was systematically functionalized. 6-Formylazulene (**7**) was obtained by applying a previously described method for 1-methoxycarbonyl-4-formylazulene.[14] In this method, the enamine product **6** was obtained by heating 6-methylazulene (**3**) and *N*,*N*-dimethylformamide dimethyl acetal in DMF at 140 °C (Scheme 2). The crude enamine **6** was then reacted with sodium periodate at room temperature to furnish 6-formylazulene (**7**) in a good yield (68%) over two steps. The 6-formylazulene thus prepared was consistent with

Scheme 2. Functionalization of the Methyl Group of 6-Methylazulene (3) Via a Formyl Group

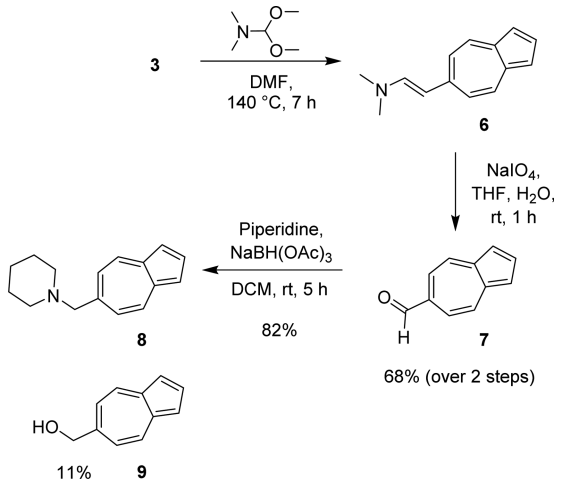
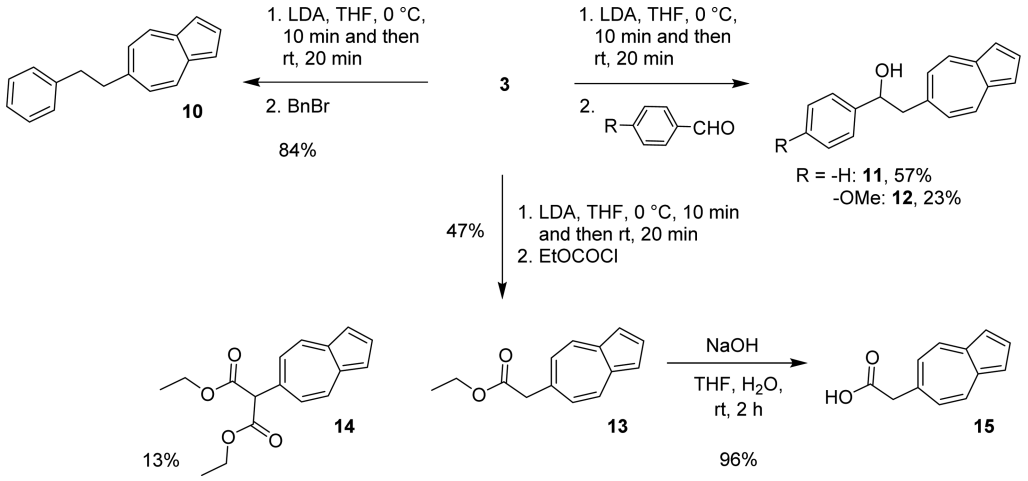


Table 1. Conditions Used in the Optimization of 6-Methylazulene Synthesis

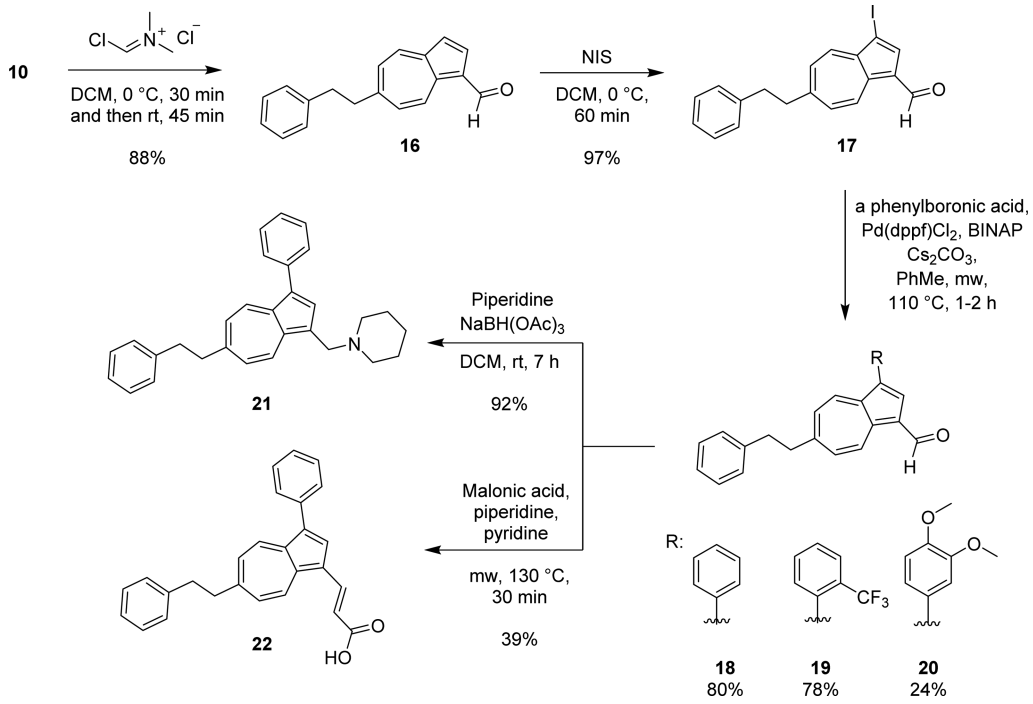
	temperature/time	base	solvents	concentration	scale	yield
1	rt, 1h + reflux, 3 h	NaH	DMF	1.0 M	10 mmol	23%
2	rt, 1h + reflux, 3 h	NaOH	MeOH/THF 1:20	1.0 M	10 mmol	3.5%
3	rt, 1h + reflux, overnight	NaOMe	MeOH	1.0 M	10 mmol	2.5%
4	rt, 1h + reflux, 3 h	NaH	THF	1.0 M	10 mmol	6.0%
5	rt, 1h + reflux, 3 h	NaH	EtOH/THF 1:4	0.80 M	10 mmol	2.5%
6	rt, 1h + reflux, 3 h	NaH	DMF	0.50 M	10 mmol	44%
7	rt, 5 min + mw, 170 °C, 30 min	NaH	DMF	0.25 M	2.5 mmol	57%
8	rt, 5 min + mw, 152 °C, 30 min	NaH	DMF	0.25 M	2.5 mmol	45%
9	rt, 5 min + mw, 200 °C, 30 min	NaH	DMF	0.25 M	2.5 mmol	59%
10	rt, 5 min + mw, 170 °C, 30 min	NaH	DMF	0.10 M	1.0 mmol	64%
11	rt, 5 min + mw, 170 °C, 30 min	NaH	DMF	0.050 M	0.50 mmol	52%
12	rt, 10 min + mw, 170 °C, 30 min	*n*-BuLi	Hex/THF/DMF 1:1:2	0.25 M	2.5 mmol	25%
13	rt, 15 min + mw, 170 °C, 30 min	*n*-BuLi	Hex/DMF 2.5:7.5	0.25 M	2.5 mmol	38%
14	rt, 15 min + mw, 170 °C, 30 min	*n*-BuLi	Hex/DMF 1:9	0.10 M	1.0 mmol	60%

DOI: 10.1021/acs.joc.5b02271
J. Org. Chem. 2015, 80, 11513−11520

Scheme 3. Deprotonation of 6-Methylazulene (3) Followed by Reactions with Electrophiles



Scheme 4. Synthesis of 1,3,6-Trisubstituted Azulenes Utilizing Iodine and a Formyl Group As Synthetic Handles

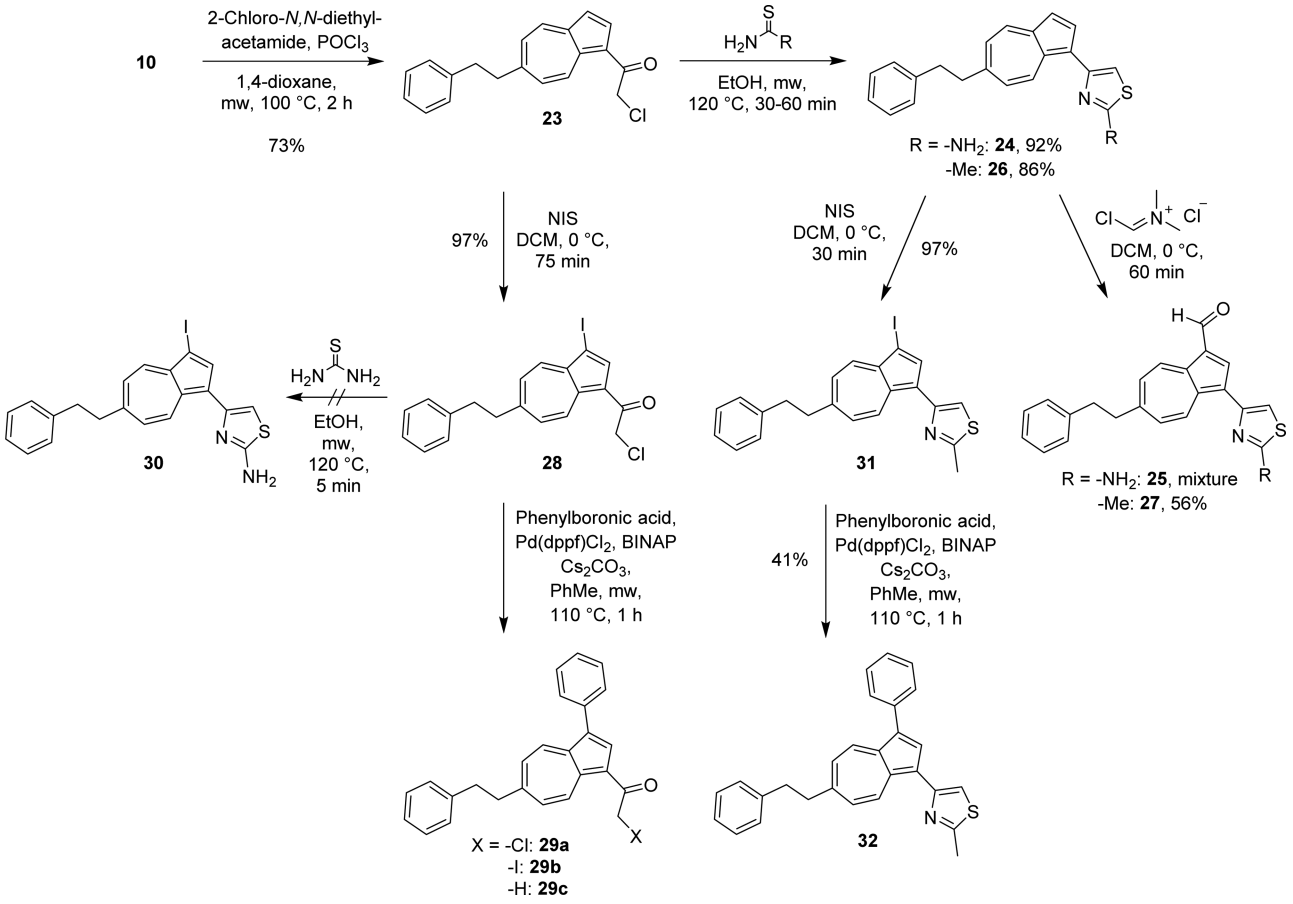


previously described literature material, which had been synthesized from an acetal-protected 4-formylpyridine in an overall yield of 18%.[15] Our method has the same number of synthetic steps, but an overall yield of 43%, and furthermore, our method does not require the use of protecting groups. The versatility of 6-formylazulene was demonstrated by a reductive amination reaction to obtain an amino functionality: the reaction with piperidine and sodium triacetoxyborohydride at room temperature gave **8** in 82% yield. The only observed side product was the corresponding alcohol **9**, which was additionally isolated in 11% yield.

The methyl group of 6-methylazulene (**3**) can also be deprotonated through the action of a strong base.[16] *n*-BuLi proved to be too strong of a base, resulting in the azulene scaffold's decomposition. We had better success with LDA which produced a dark red solution of the anion, which was then reacted directly with various electrophiles (Scheme 3). The reaction with benzyl bromide gave the 6-phenethylazulene (**10**) in 84% yield. The alcohols **11** and **12** were obtained with benzaldehyde and 4-methoxybenzaldehyde in 57% and 23% yields, respectively. The ester **13** was obtained from ethyl chloroformate in 47% yield. This azulenylacetic acid ester is also very prone to deprotonation allowing the anion to react a second time with ethyl chloroformate. Consequently, the corresponding diester **14** was also isolated in 13% yield from this reaction. A small amount of unreacted 6-methylazulene (**3**) was detected in all of the above-mentioned reactions (≤16%). Hydrolysis of the ester **13** with an aqueous solution of NaOH gave the corresponding carboxylic acid **15** in 96% yield. The carboxylic acid derivative **15** has been previously synthesized in good yield by deprotonating 6-methylazulene and reacting it with carbon dioxide.[16] Although our method requires an additional step, it does provide access to the protected ester product **13**, which alternatively saves an additional synthetic step for introducing a protecting group, if required in the following reactions.

DOI: 10.1021/acs.joc.5b02271
J. Org. Chem. 2015, 80, 11513−11520

Scheme 5. Synthesis of 1,3,6-Trisubstituted Azulenes Exploiting the Chloromethylketone Functionality



Functionalization of the Five-Membered Ring. After modification of the 6-position, functionalization of the 1- and 3-positions of the azulene scaffold were investigated (Scheme 4). 6-Phenethylazulene (**10**) was used as a test substance for scoping out the reactions. The 1-position of the azulene ring was first formylated using a fast Vilsmeier–Haack reaction performed at room temperature and resulting in the monoformylated product **16** being isolated in 88% yield. After a 1 h reaction at 0 °C with NIS the 1,3,6-trisubstituted azulene **17** was obtained in 97% yield. Compound **17** is a key intermediate with two useful synthetic handles, a formyl group and iodide. It should be noted that the compound is preferably synthesized by first performing the Vilsmeier–Haack reaction; reversing the order by conducting the iodination reaction first results in a mixture of mono- and di-iodinated compounds as well as unreacted starting material. Additionally, the mono-iodinated product without a 3-substituent was highly unstable and all our attempts to isolate it failed.

The use of the intermediate **17** as a viable substrate for Suzuki cross coupling reactions was demonstrated with three electronically differentiated phenylboronic acids. Compound **17**, the boronic acid, and palladium catalyst in toluene were irradiated with microwave heating at 110 °C for 1–2 h applying a previously reported method.[17] The isolated yields for the products **18**, **19**, and **20** were 80%, 78%, and 24%, respectively. Reductive amination of **18** with piperidine and sodium triacetoxyborohydride in DCM gave the corresponding amine **21** in 92% yield. The carboxylic acid derivative **22** was obtained through a Knoevenagel condensation in 39% yield by reacting **18**, malonic acid and piperidine in pyridine with heating under microwave irradiation at 130 °C for 30 min.

A modified Vilsmeier–Haack reaction described by Dragu[18] was applied to the introduction of a chloromethylketone to the five-membered ring (Scheme 5). 6-Phenethylazulene (**10**), 2-chloro-*N*,*N*-diethylacetamide and $POCl_3$ in 1,4-dioxane were heated in a microwave reactor at 100 °C to give **23** in 73% yield. Chloromethylketones could also be synthesized via a Friedel–Crafts acylation reaction using chloroacetyl chloride and $AlCl_3$; however, the isolated yields were much lower. In three attempts with 6-methylazulene, we obtained the product in a variable yield of 2–25%.

Chloromethylketone **23** was next reacted with thiourea to form the aminothiazole derivative **24** in an excellent 92% yield. In this procedure, a solution of azulene and thiourea in ethanol was heated using microwave irradiation at 120 °C for 30 min. The introduction of the aminothiazole, an electron-rich ring, caused selectivity problems, in the formylation of the 3-position of azulene that was tried in the next reaction step. Furthermore, aminothiazole derivative **24** was found to be relatively unstable. Alternatively when thiourea was replaced with thioacetamide, methylthiazole **26** was obtained in 86% yield. The 3-position on the azulene ring in **26** could then be formylated selectively in 56% yield; however, approximately one-third of the starting material remained unreacted in the reaction.

Chloromethylketone intermediate **23** was iodinated using the same method as the corresponding aldehyde derivative **16**, and in both cases the yield was 97%. The subsequent Suzuki reaction with phenylboronic acid gave a mixture of products, from which two fractions were separated. The first fraction

DOI: 10.1021/acs.joc.5b02271
J. Org. Chem. 2015, 80, 11513–11520

contained two compounds, the desired product **29a** and the product **29b** in which chlorine had been replaced by iodine (combined yield 25−30%). It would be possible to use the mixture of compounds in the next step, since both are expected to result in the same heterocyclic derivative. The other fraction contained dehalogenated compound **29c** isolated in 16% yield. Due to the mixture of products and low yield, the order of reactions was changed to first synthesize the aminothiazole **30**. Unfortunately, the reaction gave a mixture of compounds, from which the desired product could not be isolated.

Eventually, it was established that the best method was to first synthesize the thiazole heterocycle from the chloromethylketone and then to iodinate the resulting compound and perform a Suzuki reaction. The synthetic route was demonstrated with the methylthiazole derivative **26**. The iodination of the 3-position of the azulene ring in **26** with NIS was selective and gave a 97% yield. In the next step, the iodo compound **31** reacted with phenylboronic acid to give the desired product **32** in 41% yield.

CONCLUSIONS

In summary, we have developed an efficient and robust synthetic route for accessing 1,3,6-trisubstituted azulenes starting from 4-methylpyridine with 6-methylazulene as a key intermediate. We have synthesized amine derivative **21** and methylthiazole derivative **32** in seven synthetic steps in overall yields of 33% and 13%, respectively, demonstrating the efficiency of the developed synthetic approach. The developed synthetic route is short, has a good overall yield, and allows the substituents to be easily varied. Finally, the starting materials and reagents are readily available and inexpensive.

EXPERIMENTAL SECTION

General Information. All synthesized compounds were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy using $CDCl_3$ or acetone-d_6 as solvent. NMR spectra are reported in chemical shifts in parts per million (ppm) relative to the residual solvents: $CDCl_3$ 7.26 and 77.16 ppm, acetone-d_6 2.05 and 29.84 ppm for ^{1}H and ^{13}C NMR, respectively. The reactions at 0 °C were cooled in an ice bath and reactions at −78 °C were cooled in acetone/liquid nitrogen or acetone/dry ice baths by following the temperature with a thermometer. The progress of the reactions was monitored by thin-layer chromatography on silica gel 60-F_{254} plates. When the product was purified by flash chromatography, silica gel (SiO_2) 60 (230−400 mesh) was used. Microwave reactions were conducted in sealed reaction vessels using a Biotage Initiator$^+$ instrument equipped with an external IR-sensor to detect the reaction temperature.

*Butyl-4-picolinium Bromide (**5**).* 4-Methylpyridine (19.5 mL, 0.200 mol) and 1-bromobutane (36.5 mL, 0.340 mol) were dissolved in EtOH (100 mL). The resulting colorless solution was heated at reflux for 21 h. The yellow solution was allowed to cool to room temperature before solvent and excess 1-bromobutane were evaporated to afford a yellow oil. *n*-Hexane (100 mL) was added to the residue resulting in formation of white crystals. The *n*-hexane was evaporated and the product was dried in vacuo to give **5** as white crystals (45.6 g, quant). The product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (d, J = 6.7, 2H), 7.86 (d, J = 6.1 Hz, 2H), 4.85 (t, J = 7.4 Hz, 2H), 2.61 (s, 3H), 1.99−1.92 (m, 2H), 1.40−1.31 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 144.4, 128.9, 60.9, 33.7, 22.3, 19.3, 13.6.

*6-Methylazulene (**3**).* Cyclopentadiene (5.05 mL, 60.0 mmol) was added dropwise over 15 min to a suspension of NaH (60% in mineral oil, 2.00 g, 50.0 mmol) in anhydrous DMF (100 mL) at 0 °C under N_2. The red suspension was stirred at room temperature for an additional 45 min to give a dark red solution. The solution was divided into ten separate microwave vials (10−20 mL) charged with a solution of **5** (1.15 g, 5.00 mmol) in anhydrous DMF (10 mL). The solutions were stirred at room temperature for 5 min followed by microwave irradiation at 200 °C for 15 min. Five portions were combined and filtered through a pad of silica gel with *n*-hexane (100 mL). The *n*-hexane phase was decanted and the DMF phase was stirred with fresh *n*-hexane (50 mL) and decanted. This was repeated six times. Combined *n*-hexane phases were washed with water (2 × 100 mL) and brine (100 mL). *n*-Hexane (200 mL) was added to the DMF residue (from decantation) and it was washed with water (300 mL + 2 × 100 mL) and brine (100 mL). All *n*-hexane fractions were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated to give a dark blue solid. The same workup procedure was repeated to the remaining five portions. The crude products were combined and purified by flash chromatography (*n*-hexane) to give **3** as a blue, amorphous solid (4.47 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 10.5 Hz, 2H), 7.80 (t, J = 3.7 Hz, 1H), 7.33 (d, J = 3.7 Hz, 2H), 7.09 (d, J = 10.0 Hz, 2H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 138.9, 135.9, 135.6, 124.4, 118.1, 28.3. The ^{1}H NMR data is in accordance with the literature.[8]

*2-(Azulen-6-yl)-N,N-dimethylethen-1-amine (**6**).* Compound **3** (0.213 g, 1.50 mmol) was dissolved in anhydrous DMF (1.5 mL) under argon. *N*,*N*-Dimethylformamide dimethyl acetal (0.259 mL, 1.95 mmol) was added, and the resulting blue solution was heated at 140 °C for 7 h. EtOAc (50 mL) was added to the reaction mixture, and it was washed with water (4 × 25 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to give **6** as a dark gray, amorphous solid (0.29 g, 98%). The product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 10.8 Hz, 2H), 7.50 (t, J = 3.7 Hz, 1H), 7.16−7.12 (m, 3H), 7.00 (d, J = 11.0 Hz, 2H), 5.33 (d, J = 13.4 Hz, 1H), 2.96 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 144.1, 136.5, 136.1, 131.9, 118.7, 117.6, 102.4, 41.0.

*6-Formylazulene (**7**).* Compound **6** (0.28 g, 1.4 mmol) and $NaIO_4$ (0.90 g, 4.2 mmol) in a mixture of THF (3.5 mL) and H_2O (3.5 mL) was stirred at room temperature for 1 h. The precipitate was removed by filtration and washed with EtOAc (70 mL). The green organic phase was washed with saturated aqueous solution of $NaHCO_3$ (3 × 30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a green solid. The crude product was purified by flash chromatography (EtOAc/*n*-hexane 1:9) to give **7** as a green, amorphous solid (0.15 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.53 (d, J = 10.2 Hz, 2H), 8.11 (t, J = 3.8 Hz, 1H), 7.73 (d, J = 10.3 Hz, 2H), 7.51 (d, J = 3.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 141.8, 141.5, 140.3, 135.4, 123.9, 119.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_9O$ 157.0653; Found 157.0655. The NMR data is in accordance with the literature.[15]

*1-(Azulen-6-ylmethyl)piperidine (**8**).* Piperidine (0.059 mL, 0.60 mmol) was added to a suspension of **7** (0.047 g, 0.30 mmol) and $NaBH(OAc)_3$ (0.13 g, 0.60 mmol) in anhydrous DCM (1.5 mL). The reaction mixture was stirred at room temperature for 5 h. The blue mixture was treated with a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with DCM (20 + 5 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a blue solid. The crude product was purified by flash chromatography (EtOAc/*n*-hexane 1:4) to give **8** as a blue, amorphous solid (0.056 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, J = 10.5 Hz, 2H), 7.85 (t, J = 3.8 Hz, 1H), 7.35 (d, J = 3.9 Hz, 2H), 7.29 (d, J = 10.5 Hz, 2H), 3.62 (s, 2H), 2.46−2.43 (m, 4H), 1.65−1.57 (m, 4H), 1.50−1.42 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 139.5, 136.3, 135.9, 124.1, 117.9, 68.7, 54.8, 26.2, 24.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{20}N$ 226.1596; Found 226.1596.

*6-Phenethylazulene (**10**).* Compound **3** (0.71 g, 5.0 mmol) was dissolved in anhydrous THF (20 mL) under argon. LDA (1 M in hexane/THF, 5.5 mL, 5.5 mmol) was added to the blue solution at 0 °C over a period of 5 min. The solution immediately turned dark red and was stirred at 0 °C for 10 min and at room temperature for 20 min. The solution was cooled to −78 °C and benzyl bromide (0.60 mL, 5.0 mmol) was added over 1−2 min. The solution was stirred at −78 °C for 10 min and it was allowed to warm to room temperature over 30 min. The color of the reaction mixture turned back to blue. The reaction mixture was stirred at room temperature for 30 min. The

DOI: 10.1021/acs.joc.5b02271
J. Org. Chem. 2015, 80, 11513−11520

reaction was quenched with 1 M aqueous solution of HCl (10 mL) and extracted with Et_2O (100 mL). The organic phase was washed with 1 M aqueous solution of HCl (2 × 50 mL), saturated aqueous solution of $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a blue solid. The crude product was purified by flash chromatography (*n*-hexane/DCM 85:15) to give **10** as a blue, amorphous solid (0.97 g, 84%). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.30 (d, J = 10.5 Hz, 2H), 7.78 (t, J = 3.8 Hz, 1H), 7.33 (d, J = 3.9 Hz, 2H), 7.28−7.24 (m, 4H), 7.21−7.15 (m, 3H), 3.17−3.01 (m, 4H). ^{13}C NMR (75 MHz, acetone-d_6) δ 153.5, 142.2, 140.0, 136.7, 136.4, 129.4, 129.2, 126.8, 124.9, 118.7, 44.9, 39.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}$ 233.1330; Found 233.1336.

*2-(Azulen-6-yl)-1-phenylethan-1-ol (**11**).* Diisopropylamine (0.084 mL, 0.60 mmol) was dissolved in anhydrous THF (1 mL) under N_2. The solution was cooled to −78 °C and *n*-BuLi (1.1 M in hexane, 0.50 mL, 0.55 mmol) was added dropwise over 10 min. The solution was allowed to warm to −10 °C over a period of 50 min and was then added to the blue solution of **3** (0.071 g, 0.50 mmol) in anhydrous THF (1 mL) at 0 °C. The solution immediately turned dark red and was stirred at 0 °C for 10 min and then at room temperature for a further 20 min. The solution was again cooled to 0 °C and benzaldehyde (0.061 mL, 0.60 mmol) was added. The color of the solution turned back to blue. The solution was first stirred at 0 °C for 10 min and then at room temperature for 1.5 h. The reaction was quenched with water (2 mL) and extracted with EtOAc (15 mL). The organic phase was washed with 1 M aqueous solution of HCl (7.5 mL) and water (3 × 7.5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a dark blue solid. The crude product was purified by flash chromatography (*n*-hexane/DCM 4:1) to give **11** as a blue, amorphous solid (0.071 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 10.5 Hz, 2H), 7.86 (t, J = 3.7 Hz, 1H), 7.39−7.28 (m, 7H), 7.08 (d, J = 10.5 Hz, 2H), 5.02 (dd, J = 7.8, 5.5 Hz, 1H), 3.24−3.16 (m, 2H), 1.97 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 143.6, 139.2, 136.5, 135.9, 128.7, 128.0, 126.0, 124.9, 118.3, 76.2, 52.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}O$ 249.1279; Found 249.1281.

*2-(Azulen-6-yl)-1-(4-methoxyphenyl)ethan-1-ol (**12**).* The same procedure as described above was repeated with 4-methoxybenzaldehyde (0.073 mL, 0.60 mmol) to give **12** as a blue, amorphous solid (0.032 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 10.5 Hz, 2H), 7.86 (t, J = 3.7 Hz, 1H), 7.36 (d, J = 3.7 Hz, 2H), 7.30−7.26 (m, 2H), 7.06 (d, J = 10.5 Hz, 2H), 6.90−6.86 (m, 2H), 4.96 (t, J = 6.8 Hz, 1H), 3.81 (s, 3H), 3.23−3.15 (m, 2H), 1.99 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 148.5, 139.2, 136.4, 135.9, 135.8, 127.3, 124.9, 118.2, 114.0, 75.8, 55.4, 52.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}O_2$ 279.1385; Found 279.1382.

*Ethyl 2-(azulen-6-yl)acetate (**13**).* Compound **3** (0.11 g, 0.75 mmol) was dissolved in anhydrous THF (3 mL) under argon. LDA (1 M in hexane/THF, 0.83 mL, 0.83 mmol) was added to the blue solution at 0 °C. The solution turned dark red and was first stirred at 0 °C for 10 min and then at room temperature for 20 min. The solution was cooled to −78 °C and ethyl chloroformate (0.072 mL, 0.75 mmol) was added. The solution was stirred at −78 °C for 10 min and then allowed to warm to 0 °C over a period of 45 min. The mixture was quenched with 1 M aqueous solution of HCl (2 mL) and it was extracted with EtOAc (20 mL). The organic phase was washed with 1 M aqueous solution of HCl (2 × 10 mL), saturated aqueous solution of $NaHCO_3$ (2 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a blue oil. The crude product was purified by flash chromatography (manual gradient of *n*-hexane/DCM 4:1 → 2:3) to give **13** as a blue, amorphous solid (0.075 g, 47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 10.5 Hz, 2H), 7.88 (t, J = 3.8 Hz, 1H), 7.38 (d, J = 3.6 Hz, 2H), 7.15 (d, J = 10.5 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.79 (s, 2H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 143.8, 139.5, 137.0, 135.8, 124.5, 118.6, 61.3, 47.3, 14.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{15}O_2$ 215.1072; Found 215.1074.

*Diethyl 2-(azulen-6-yl)malonate (**14**).* The above-described reaction gave the side product **14** as a blue, amorphous solid (0.029 g, 13%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 10.5 Hz, 2H), 7.92 (t, J = 3.8 Hz, 1H), 7.41 (d, J = 3.6 Hz, 2H), 7.24 (d, J = 10.5 Hz, 2H), 4.75 (s, 1H), 4.32−4.17 (m, 4H), 1.27 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 141.7, 139.8, 137.9, 135.6, 124.3, 118.8, 62.4, 62.2, 14.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{18}O_4Na$ 309.1103; Found 309.1103.

*2-(Azulen-6-yl)acetic Acid (**15**).* Compound **14** (0.032 g, 0.15 mmol) was dissolved in a mixture of THF (1.5 mL) and water (0.75 mL). A 0.2 M aqueous solution of NaOH (0.75 mL) was added to the resulting blue solution, and the reaction mixture was stirred at room temperature for 2 h. A 1 M aqueous solution of HCl (20 mL) was then added to the reaction mixture. The aqueous phase was extracted with DCM (2 × 10 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a blue solid. The crude product was purified by flash chromatography (DCM/MeOH/AcOH 90:9:1) to give **15** as a blue, amorphous solid (0.027 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 10.5 Hz, 2H), 7.89 (t, J = 3.8 Hz, 1H), 7.39 (d, J = 3.9 Hz, 2H), 7.12 (d, J = 10.2 Hz, 2H), 3.82 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 142.7, 139.5, 137.3, 135.8, 124.5, 118.9, 46.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}O_2$ 187.0759; Found 187.0759.

*6-Phenethylazulene-1-carbaldehyde (**16**).* The yellow solution of (chloromethylene)dimethyliminium chloride (0.56 g, 4.4 mmol) in anhydrous DCM (60 mL) was added to the blue solution of **10** (0.93 g, 4.0 mmol) in anhydrous DCM (20 mL) at 0 °C over 30 min under argon. The solution turned dark red, and it was stirred at room temperature for 45 min. The reaction mixture was treated with 1 M aqueous solution of NaOH (100 mL). The organic phase and the water phase were separated and the water phase was extracted with DCM (50 mL). The organic phases were combined, washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a dark red solid. The crude product was purified by flash chromatography (DCM/EtOAc 97:3) to give **16** a red, amorphous solid (0.91 g, 88%). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.37 (s, 1H), 9.46 (d, J = 9.9 Hz, 1H), 8.56 (d, J = 10.2 Hz, 1H), 8.22 (d, J = 4.2 Hz, 1H), 7.67 (dd, J = 10.1, 1.7 Hz, 1H), 7.60 (dd, J = 10.2, 1.8 Hz, 1H), 7.35 (d, J = 4.2 Hz, 1H), 7.30−7.16 (m, 5H), 3.31−3.26 (m, 2H), 3.13−3.07 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 186.6, 157.2, 145.5, 141.8, 141.1, 139.7, 139.5, 137.4, 131.4, 130.8, 129.4, 129.2, 127.2, 127.0, 119.7, 44.7, 39.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{17}O$ 261.1279; Found 261.1279.

*3-Iodo-6-phenethylazulene-1-carbaldehyde (**17**).* Compound **16** (0.39 g, 1.5 mmol) was dissolved in anhydrous DCM (15 mL) under argon. The red solution was cooled to 0 °C and NIS (0.34 g, 1.5 mmol) was added. The solution was stirred at 0 °C for 30 min, an additional 1 equiv of NIS (0.34 g, 1.5 mmol) was added, and stirring was continued for 30 min at 0 °C. The reaction mixture was eluted through a pad of neutral alumina with DCM and concentrated in vacuo to provide **17** as a brown, amorphous solid (0.56 g, 97%). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.30 (s, 1H), 9.42 (d, J = 10.5 Hz, 1H), 8.40−8.37 (m, 2H), 7.81−7.74 (m, 2H), 7.30−7.15 (m, 5H), 3.35−3.30 (m, 2H), 3.15−3.09 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 185.9, 158.8, 148.0, 144.2, 141.6, 141.1, 139.5, 137.3, 132.6, 131.7, 129.5, 129.3, 128.4, 127.1, 76.4, 44.6, 39.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{15}ONaI$ 409.0065; Found 409.0066.

General Procedure for Suzuki Reactions of 18, 19, 20, 32. A mixture of the appropriate iodo derivative (1 equiv), boronic acid derivative (2 equiv), $Pd(dppf)Cl_2$ (0.05 equiv), BINAP (0.05 equiv), Cs_2CO_3 (4 equiv), and anhydrous toluene was irradiated with microwaves at 110 °C for 1 h under argon. The resulting mixture was filtered through a small pad of diatomaceous earth with DCM (10−30 mL) and diluted with DCM (10−100 mL). The organic phase was washed with water (2 × 10−50 mL) and brine (10−50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a crude product, which was purified by flash chromatography.

*6-Phenethyl-3-phenylazulene-1-carbaldehyde (**18**).* Compound **17** (0.50 g, 1.3 mmol) and phenylboronic acid gave a reddish brown tar, which after flash chromatography (DCM) afforded **18** as a purple-brown sticky oil (0.35 g, 80%). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.42 (s, 1H), 9.50 (d, J = 9.9 Hz, 1H), 8.64 (d, J = 10.5 Hz, 1H), 8.33

DOI: 10.1021/acs.joc.5b02271
J. Org. Chem. 2015, 80, 11513−11520

(s, 1H), 7.68−7.61 (m, 4H), 7.56−7.51 (m, 2H), 7.44−7.38 (m, 1H), 7.28−7.16 (m, 5H), 3.30−3.25 (m, 2H), 3.13−3.08 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 186.7, 158.1, 141.7, 140.9, 140.63, 140.58, 138.0, 137.9, 137.2, 132.7, 131.5, 131.1, 130.4, 129.7, 129.4, 129.3, 127.9, 127.0, 126.1, 44.5, 39.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{25}H_{21}O$ 337.1592; Found 337.1597.

*6-Phenethyl-3-[2-(trifluoromethyl)phenyl]azulene-1-carbaldehyde (**19**).* Compound **17** (0.077 g, 0.20 mmol) and 2-(trifluoromethyl)phenylboronic acid gave a purple oil, which after flash chromatography (DCM) afforded **19** as a purple, amorphous solid (0.063 g, 78%). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.42 (s, 1H), 9.56 (d, J = 10.2 Hz, 1H), 8.22 (s, 1H), 8.09 (d, J = 10.2 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.80−7.66 (m, 3H), 7.58 (d, J = 10.5 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.30−7.13 (m, 5H), 3.29−3.24 (m, 2H), 3.11−3.05 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 186.7, 158.0, 142.7, 141.8 (q, $^4J_{C,F}$ = 1.9 Hz), 141.7, 139.8, 138.1, 138.0, 136.1 (q, $^3J_{C,F}$ = 2.2 Hz), 134.6, 132.7, 131.9, 131.1, 130.6 (q, $^2J_{C,F}$ = 28.9 Hz), 129.4, 129.2, 129.1, 129.0, 127.1 (q, $^3J_{C,F}$ = 5.5 Hz), 127.0, 125.5, 125.3 (q, $^1J_{C,F}$ = 271.4 Hz), 44.6, 39.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{26}H_{20}OF_3$ 405.1466; Found 405.1464.

*3-(3,4-Dimethoxyphenyl)-6-phenethylazulene-1-carbaldehyde (**20**).* Compound **17** (0.077 g, 0.20 mmol) and 3,4-dimethoxyphenylboronic acid with 2 h heating gave a brown oil, which after flash chromatography (DCM) afforded **20** as a purple-brown oil (0.019 g, 24%). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.41 (s, 1H), 9.45 (d, J = 10.2 Hz, 1H), 8.65 (d, J = 10.2 Hz, 1H), 8.29 (s, 1H), 7.61 (dd, J = 10.2, 1.5 Hz, 1H), 7.55 (dd, J = 10.4, 1.4 Hz, 1H), 7.30−7.08 (m, 8H), 3.90 (s, 3H), 3.89 (s, 3H), 3.28−3.22 (m, 2H), 3.11−3.06 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 186.6, 157.8, 150.8, 149.9, 141.8, 140.7, 140.6, 140.5, 138.1, 137.6, 133.0, 131.2, 130.8, 129.9, 129.4, 129.2, 127.0, 125.9, 122.6, 114.4, 113.3, 56.30, 56.29, 44.5, 39.2. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{27}H_{24}O_3Na$ 419.1623; Found 419.1624.

*2-Methyl-4-(6-phenethyl-3-phenylazulen-1-yl)thiazole (**32**).* Compound **31** (0.046 g, 0.10 mmol) and phenylboronic acid gave a brown oil, which after flash chromatography (n-hexane/DCM 1:1) afforded **32** as a green, amorphous solid (0.017 g, 41%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.50 (d, J = 10.5 Hz, 1H), 8.40 (d, J = 10.2 Hz, 1H), 8.32 (s, 1H), 7.66−7.61 (m, 3H), 7.54−7.48 (m, 2H), 7.39−7.33 (m, 1H), 7.30−7.13 (m, 7H), 3.15−3.02 (m, 4H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, acetone-d_6) δ 165.7, 155.7, 153.5, 142.2, 138.4, 138.0, 137.1, 136.18, 136.16, 135.8, 131.6, 130.5, 129.5, 129.4, 129.2, 127.3, 126.9, 126.2, 126.1, 123.7, 113.3, 44.5, 39.2, 19.4. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{28}H_{24}NS$ 406.1629; Found 406.1629.

*1-[(6-Phenethyl-3-phenylazulen-1-yl)methyl]piperidine (**21**).* Compound **18** (0.034 g, 0.10 mmol) and NaBH(OAc)$_3$ (0.042 g, 0.20 mmol) were suspended in anhydrous DCM (2 mL) and piperidine (0.020 mL, 0.20 mmol) was added. After 7 h stirring at room temperature, the purple reaction mixture had turned blue. The reaction mixture was first treated with a saturated aqueous solution of $NaHCO_3$ (10 mL) and then extracted with DCM (20 + 5 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a blue oil. The crude product was purified by flash chromatography (DCM/MeOH 9:1) to give **21** as a sticky blue oil (0.038 g, 92%). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.55 (d, J = 10.2 Hz, 1H), 8.41 (d, J = 10.2 Hz, 1H), 7.93 (s, 1H), 7.62−7.58 (m, 2H), 7.51−7.45 (m, 2H), 7.35−7.11 (m, 8H), 3.99 (s, 2H), 3.14−3.00 (m, 4H), 2.52−2.45 (m, 4H), 1.61−1.54 (m, 4H), 1.47−1.40 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 154.7, 142.2, 138.5, 138.3, 135.8, 135.5, 135.2, 130.33, 130.28, 129.5, 129.4, 129.2, 126.95, 126.86, 125.4, 124.7, 56.6, 55.2, 44.7, 39.4, 26.6, 25.1.[19] HRMS (ASAP-TOF)[20] m/z: [M + H]$^+$ Calcd for $C_{30}H_{32}N$ 406.2529; Found 406.2518.

*3-(6-Phenethyl-3-phenylazulen-1-yl)acrylic Acid (**22**).* Piperidine (0.025 mL) was added to a solution of **18** (0.034 g, 0.10 mmol) and malonic acid (0.013 g, 0.12 mmol) in pyridine (0.50 mL). The resulting purple solution was heated under microwave irradiation at 130 °C for 30 min. EtOAc (20 mL) was added, and the organic phase was washed with 1 M aqueous solution of HCl (3 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a brown solid. The crude product was purified by flash chromatography (DCM/MeOH/AcOH 96:3:1) to produce a greenish brown solid, which was washed with toluene to give **22** as a green, amorphous solid (0.015 g, 39%). ^{1}H NMR (300 MHz, acetone-d_6) δ 8.64 (d, J = 10.2 Hz, 1H), 8.43 (d, J = 10.2 Hz, 1H), 8.37 (s, 1H), 8.22 (d, J = 15.9 Hz, 1H), 7.66−7.61 (m, 2H), 7.55−7.49 (m, 2H), 7.42−7.15 (m, 8H), 6.59 (d, J = 15.6 Hz, 1H), 3.20−3.04 (m, 4H). ^{13}C NMR (75 MHz, acetone-d_6) δ 168.8, 156.5, 141.9, 139.4, 139.1, 137.4, 136.7, 136.6, 134.7, 134.3, 133.6, 130.5, 129.6, 129.4, 129.2, 128.2, 127.73, 127.69, 126.9, 124.2, 115.2, 44.5, 39.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{27}H_{23}O_2$ 379.1698; Found 379.1692.

*2-Chloro-1-(6-phenethylazulen-1-yl)ethan-1-one (**23**).* Compound **10** (0.23 g, 1.0 mmol) was dissolved in anhydrous 1,4-dioxane (4 mL) under argon. 2-Chloro-*N*,*N*-diethylacetamide (0.59 mL, 4.3 mmol) and $POCl_3$ (0.37 mL, 4.0 mmol) were added. The resulting blue solution was heated under microwave irradiation at 100 °C for 2 h. The red reaction mixture was poured into 1 M aqueous solution of NaOH (75 mL) on ice bath and extracted with DCM (50 + 25 mL). The organic phases were combined, washed with water (50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a red oil. The crude product was purified by flash chromatography (manual gradient of n-hexane/DCM 1:1 → DCM) to give **23** as a red, amorphous solid (0.23 g, 73%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.67 (d, J = 10.2 Hz, 1H), 8.54 (d, J = 9.9 Hz, 1H), 8.35 (d, J = 4.2 Hz, 1H), 7.69 (dd, J = 10.4, 1.7 Hz, 1H), 7.60 (dd, J = 10.1, 1.4 Hz, 1H), 7.31−7.13 (m, 6H), 4.90 (s, 2H), 3.30−3.22 (m, 2H), 3.12−3.07 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 188.1, 157.4, 145.2, 141.8, 140.6, 139.6, 139.2, 139.1, 138.1, 130.8, 129.4, 129.2, 127.0, 122.6, 119.0, 48.3, 44.6, 39.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{20}H_{18}OCl$ 309.1046; Found 309.1043.

*4-(6-Phenethylazulen-1-yl)thiazol-2-amine (**24**).* Compound **23** (0.062 g, 0.20 mmol) and thiourea (0.015 g, 0.20 mmol) were suspended in EtOH (2.5 mL) under argon. The resulting red suspension was irradiated with microwaves at 120 °C for 30 min. The black solution was poured into 1 M aqueous solution of NaOH (25 mL) and extracted with DCM (15 mL + 2 × 10 mL). The organic phases were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a green solid. The crude product was purified by flash chromatography (manual gradient of DCM → DCM/MeOH 24:1) to give **24** as a green, amorphous solid (0.061 g, 92%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.50 (d, J = 10.2 Hz, 1H), 8.18 (d, J = 9.6 Hz, 1H), 8.10 (d, J = 3.9 Hz, 1H), 7.30−7.15 (m, 6H), 7.13−7.05 (m, 2H), 6.82 (s, 1H), 6.38 (s, 2H), 3.13−3.00 (m, 4H). ^{13}C NMR (75 MHz, acetone-d_6) δ 168.6, 154.4, 150.0, 142.2, 142.1, 138.0, 137.1, 135.8, 134.1, 129.4, 129.2, 126.8, 125.4, 125.2, 125.1, 118.6, 102.1, 44.7, 39.4. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{21}H_{19}N_2S$ 331.1269; Found 331.1269.

*2-Methyl-4-(6-phenethylazulen-1-yl)thiazole (**26**).* Compound **23** (0.062 g, 0.20 mmol) and thioacetamide (0.015 g, 0.20 mmol) were suspended in EtOH (2.5 mL) under argon. The resulting red suspension was irradiated with microwaves at 120 °C for 30 min. A further portion of thioacetamide (0.015 g, 0.20 mmol) was added, followed by an additional irradiation with microwaves at 120 °C for 30 min. The blue solution was poured into 1 M aqueous solution of NaOH (25 mL) and extracted with DCM (15 mL + 2 × 10 mL). The organic phases were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to provide a blue solid. The crude product was purified by flash chromatography (n-hexane/DCM 1:1) to give **26** as a blue, amorphous solid (0.057 g, 86%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.47 (d, J = 10.5 Hz, 1H), 8.25 (d, J = 9.9 Hz, 1H), 8.19 (d, J = 3.9 Hz, 1H), 7.57 (s, 1H), 7.33 (d, J = 4.2 Hz, 1H), 7.30−7.12 (m, 7H), 3.16−3.02 (m, 4H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, acetone-d_6) δ 165.6, 154.7, 153.9, 142.23, 142.19, 137.7, 137.5, 136.1, 134.4, 129.4, 129.2, 126.9, 125.9, 125.6, 124.4, 118.8, 112.7, 44.7, 39.4, 19.4. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{22}H_{20}NS$ 330.1316; Found 330.1320.

*3-(2-Methylthiazol-4-yl)-6-phenethylazulene-1-carbaldehyde (**27**).* The yellow solution of (chloromethylene)dimethyliminium chloride (0.014 g, 0.11 mmol) in anhydrous DCM (1.5 mL) was

DOI: 10.1021/acs.joc.5b02271
J. Org. Chem. 2015, 80, 11513−11520

added to the blue solution of **26** (0.033 g, 0.10 mmol) in anhydrous DCM (0.5 mL) at 0 °C under argon. The blue solution turned dark red, and it was stirred at 0 °C for 60 min. The reaction mixture was treated with 1 M aqueous solution of NaOH (20 mL) and extracted with DCM (2 × 10 mL). The organic phases were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a dark brown oil. The crude product was purified by flash chromatography (DCM → DCM/EtOAc 19:1) to give **27** as a red, amorphous solid (0.020 g, 56%). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.38 (s, 1H), 9.66 (d, J = 11.1 Hz, 1H), 9.44 (d, J = 10.5 Hz, 1H), 8.59 (s, 1H), 7.73 (s, 1H), 7.63−7.58 (m, 2H), 7.30−7.14 (m, 5H), 3.28−3.22 (m, 2H), 3.12−3.06 (m, 2H), 2.81 (s, 3H). ^{13}C NMR (75 MHz, acetone-d_6) δ 186.7, 166.1, 158.2, 152.4, 141.8, 140.82, 140.79, 140.1, 137.7, 131.6, 131.2, 129.4, 129.2, 127.0, 126.2, 125.1, 114.4, 44.5, 39.1, 19.3.[21] HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{23}H_{19}NONaS$ 380.1085; Found 380.1081.

*2-Chloro-1-(3-iodo-6-phenethylazulen-1-yl)ethan-1-one (**28**).* Compound **23** (0.062 g, 0.20 mmol) was dissolved in anhydrous DCM (2 mL) under argon. The red solution was cooled to 0 °C and NIS (0.045 g, 0.20 mmol) was added. The resulting solution was stirred at 0 °C. More NIS was added after 25 min (0.045 g, 0.20 mmol) and 50 min (0.023 g, 0.10 mmol) of stirring. After 75 min of stirring at 0 °C, the reaction mixture was eluted through a pad of neutral alumina with DCM and concentrated in vacuo to provide **28** as a brown, amorphous solid (0.084 g, 97%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.62 (d, J = 10.5 Hz, 1H), 8.50 (s, 1H), 8.36 (d, J = 10.5 Hz, 1H), 7.80−7.75 (m, 2H), 7.30−7.15 (m, 5H), 4.94 (s, 2H), 3.35−3.29 (m, 2H), 3.15−3.09 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 187.5, 158.9, 146.5, 144.0, 141.6, 140.8, 140.5, 138.9, 133.0, 131.7, 129.5, 129.3, 127.0, 124.0, 75.7, 48.3, 44.6, 39.1. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{20}H_{16}ONaClI$ 456.9832; Found 456.9834.

*4-(3-Iodo-6-phenethylazulen-1-yl)-2-methylthiazole (**31**).* Compound **26** (0.049 g, 0.15 mmol) was dissolved in anhydrous DCM (1.5 mL) under argon. The blue solution was cooled to 0 °C and NIS (0.034 g, 0.15 mmol) was added. After 30 min stirring at 0 °C, the reaction mixture was eluted through a pad of neutral alumina with DCM and evaporated to provide **31** as a green-blue oil (0.066 g, 97%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.44 (d, J = 10.5 Hz, 1H), 8.31 (s, 1H), 8.09 (d, J = 10.2 Hz, 1H), 7.66 (s, 1H), 7.33−7.14 (m, 7H), 3.19−3.03 (m, 4H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, acetone-d_6) δ 166.0, 156.4, 152.5, 142.7, 142.0, 140.8, 139.4, 137.9, 135.2, 129.4, 129.2, 127.2, 126.9, 126.6, 126.0, 113.8, 75.2, 44.6, 39.1, 19.4. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{22}H_{19}NSI$ 456.0283; Found 456.0281.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02271.

^{1}H and ^{13}C NMR spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was financially supported by The Finnish Pharmacists' Society, FinPharma Doctoral Program—Section of Pharmacy and the Doctoral Program in Drug Research of the University of Helsinki (T.O.L.). M.B. and I.R.B. thank The Royal Society for financial support. We also thank Dr. Ingo Aumüller for helpful discussions regarding azulene chemistry.

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(19) On the basis of 2D NMR experiments, we noticed that there are two carbon resonances at the chemical shift of 135.8 ppm and therefore only one signal is reported for these two carbons. We were not able to identify the other missing C resonance during these experiments even if longer relaxation time was applied and solvent changed from acetone-d_6 to $CDCl_3$.
(20) The compound **21** mainly fragmented during the HRMS analysis with ESI.
(21) We were not able to identify the missing carbon resonance with further NMR experiments such as using longer relaxation time or changing the solvent from acetone-d_6 to $CDCl_3$. We suspect it is overlapping with another signal.

DOI: 10.1021/acs.joc.5b02271
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