Tetrahedron Letters 53 (2012) 5019–5022

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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# Efficient synthesis and applications of 2-substituted azulene derivatives: towards highly functionalized carbo- and heterocyclic molecules

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ARTICLE INFO

*Article history:*
Received 23 May 2012
Revised 3 July 2012
Accepted 10 July 2012
Available online 15 July 2012

Dedicated to Professor Chun-Chen Liao on the occasion of his 70th birthday

*Keywords:*
Azulenes
Electrophilic substitution reactions
Aldol reactions
Paal–Knorr furan synthesis
Carbo- and heterocyclic molecules

ABSTRACT

An efficient synthesis of 2-substituted azulene derivatives (**3**–**6**) was accomplished from ethyl 2-oxo-*2H*-cyclohepta[*b*]furan-3-carboxylate **1** and its derivative **2**, which in turn were prepared from readily available tropolone. Compounds **1** and **2** were utilized to construct densely functionalized benz[*a*]azulene and azulene-furan frameworks (**16**–**25**, **29**–**34**, **37**, **38**).



Azulene and benz[*a*]azulene derivatives constitute the best known class of typical non-benzenoid polycyclic aromatic hydrocarbons and have long fascinated chemists with their beautiful colors from red, blue, purple to green.[1] The significance of these derivatives is demonstrated by the presence of azulene frameworks in various bioactive natural products such as phorbol,[2a] gnidilatin,[2a] aconitine,[2a] cephalotaxine,[2a] frondosin C,[2b] guanacastepene A, C, E, N,[2c] linderazulene,[2d] and hamigeran C, D.[2e] Several azulene derivatives, in fact, have been known to exhibit various biological activities such as non-prostanoid thromboxane $A_2$ receptor antagonists,[3a] cytotoxicity,[3b] anti-neoplastic,[3c] multi-receptor tyrosine kinase inhibitors,[3d] antigastric ulcer,[3e] photomutagenicity, and photogenotoxicity.[3f] Interestingly, these derivatives also play a key role in cosmetics, dyes, pigments, co-polymers, and nonlinear optical devices.[4]

Several research groups have reported fascinating syntheses of azulene[5] and benz[*a*]azulene derivatives.[6] Tung and co-workers have developed a convenient synthesis of substituted bicyclo-[5.3.0]azulene derivatives.[7a] Recently, Iwama et al., have reported a simple and efficient synthesis of 2-alkylazulenes from tropolone *p*-toluenesulfonate.[7b] Very recently, we have developed highly efficient intramolecular Friedel–Crafts type cyclization on azulene derivatives, and their applications toward thermal and photochemical reactions.[7c]

In continuation of our ongoing research program[7c,8] on azulene derivatives of carbo- and heterocyclic molecules, we herein report a highly efficient synthesis of 2-substituted azulene derivatives and their applications toward the syntheses of benz[*a*]azulene and multisubstituted furan derivatives. Therefore, it occurred to us that the azulene frameworks, derived from tropolone, could, in principle, serve as potential precursors to provide densely functionalized benz[*a*]azulene and furan derivatives via Vilsmeier–Haack, Friedel–Crafts, Michael, aldol, Knoevenagel, and Paal–Knorr reactions.[9] To the best of our knowledge, syntheses of benz[*a*]azulene and azulene-furan frameworks derived from 2-substituted azulene derivatives have not been reported in the literature.

Ethyl 2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (**1**) was prepared from commercially available tropolone in 2 steps.[8] Compound **1** was treated with 2-methylfuran in toluene at 190 °C in a sealed tube for 60 h to obtain ethyl 2-(2-oxopropyl)azulene-1-carboxylate (**3**) in 56%,[10] similarly ethoxy derivative (**4**) in 60% isolated yield from their precursor (**2**). For further generalization, compounds **1** and **2** were treated with 2,5-dimethoxy-2,5-dihydrofuran to obtain 2-substituted azulene derivatives **5** (60%) and **6** (80%), respectively. All the products were well characterized with their spectral data (Scheme 1).

After successful syntheses of 2-substituted azulene derivatives (**3**–**6**), we treated compounds **3–6** with Vilsmeier–Haack formylation ($DMF/POCl_3$), Friedel–Crafts acylation (acetyl chloride with $AlCl_3$), and Michael addition reaction (methyl vinyl ketone (MVK)

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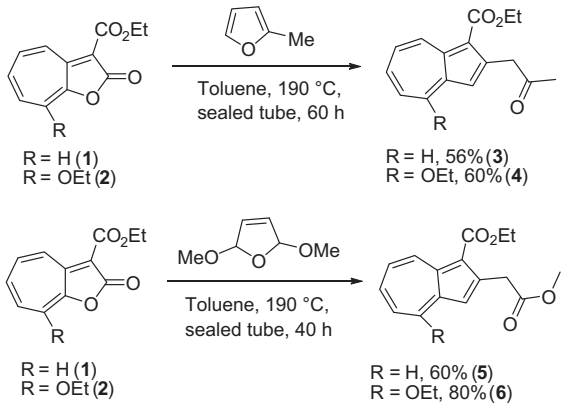
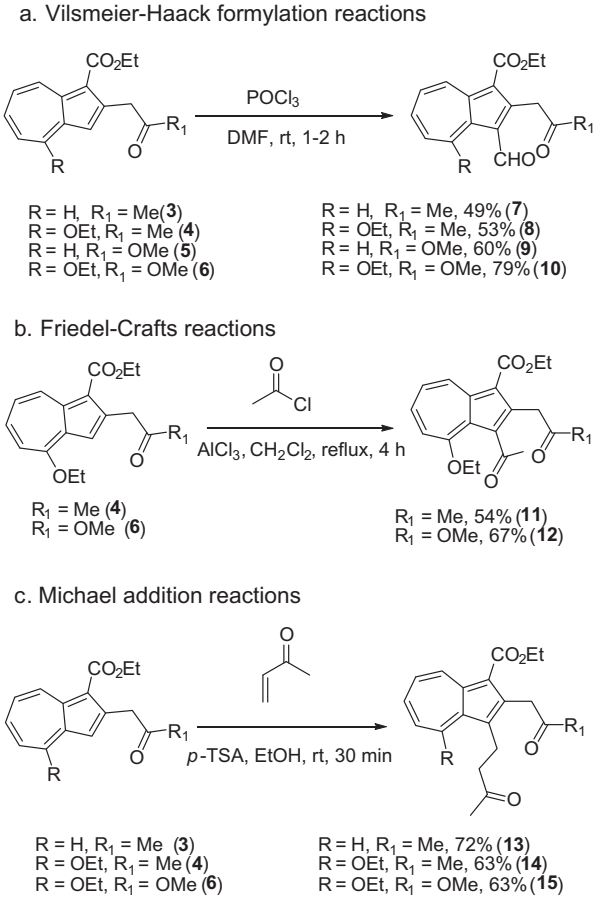
http://dx.doi.org/10.1016/j.tetlet.2012.07.040



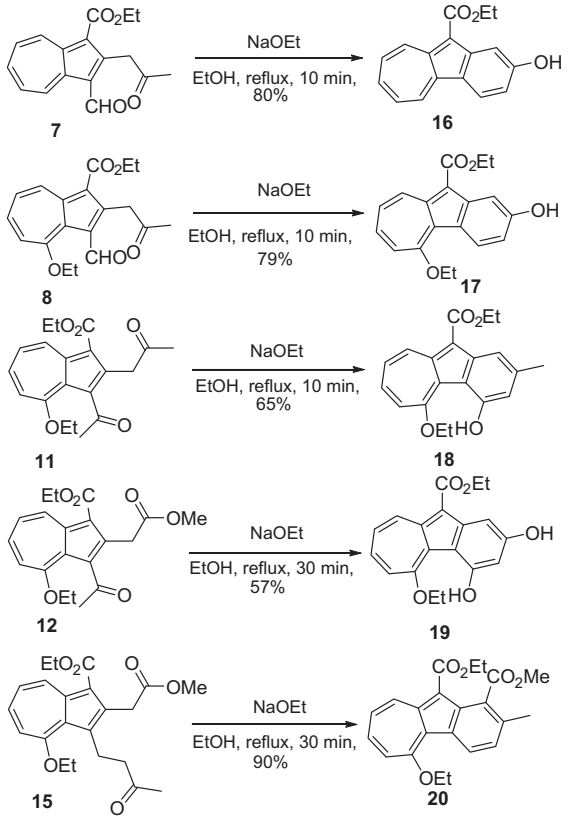

**Scheme 1.** Syntheses of 2-substituted azulene derivatives.

in the presence of *p*-TSA) to provide 3-substituted azulene derivatives (**7–15**, Scheme 2) in moderate to good yields; all the products were characterized with their spectral data (IR, $^{1}H$, $^{13}C$ NMR). Encouraged by these results, 3-substituted azulene derivatives (**7**, **8**, **11**, **12**, and **15**) were further transformed into the desired densely functionalized benz[*a*]-azulene derivatives (**16–20**) under various conditions. The best results were obtained via intramolecular aldol pathway in the presence of NaOEt in refluxing ethanol (Scheme 3).[11]

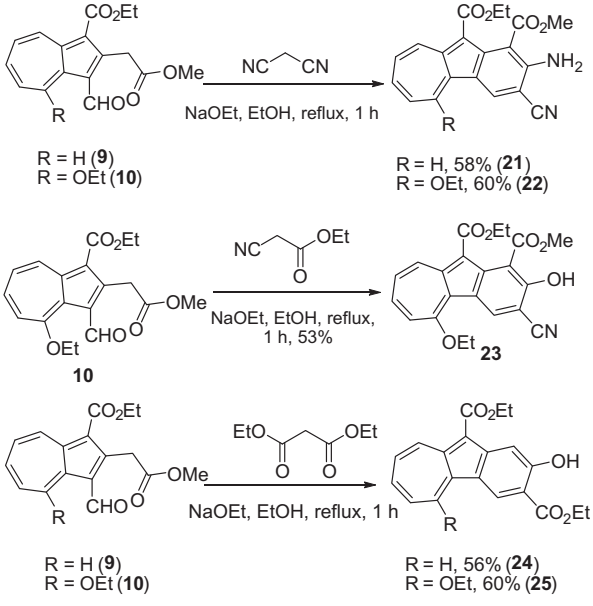
After developing a simple one-pot methodology for the construction of multifunctionalized benz[*a*]azulene derivatives with an aldol condensation, further applications were made on Vilsmeier–Haack products (**9** and **10**), with malononitrile under various conditions. The optimized results were obtained in the presence of NaOEt in EtOH under reflux for 1 h to provide diethyl 2-amino-3-cyanobenz[*a*]azulene-1,10-dicarboxylate (**21**) in 58% isolated yield[12] via Knoevenagel condensation, aldimine formation, and further cyclization. Similarly, 5-ethoxy derivative **22** was obtained in



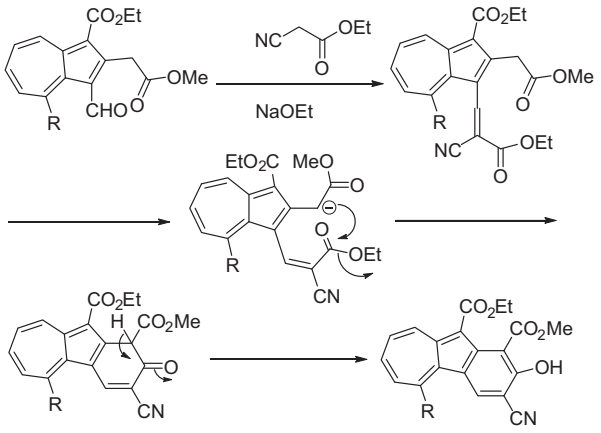

**Scheme 2.** Applications of 2-substituted azulene derivatives.




**Scheme 3.** One-pot synthesis of benzo-fused azulenes from 2-substituted azulene derivatives via aldol condensation.



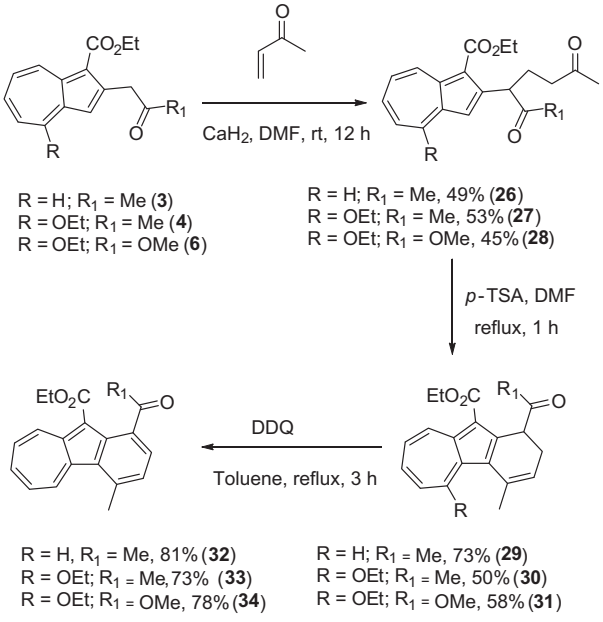

**Scheme 4.** One-pot synthesis of benz[*a*]azulenes via Knoevenagel condensation followed by cyclization.



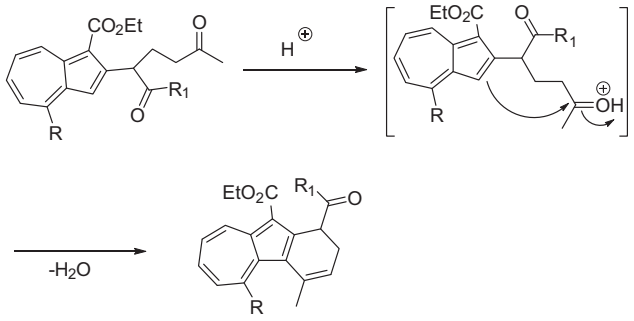
**Scheme 5.** Plausible mechanism for the synthesis of benz[*a*]azulenes.

60% yield (Scheme 4). We also extended this standard synthetic strategy to ethyl 2-cynoacetate, and diethyl malonate to provide various benz[*a*]azulene derivatives (**23**–**25**) in 53–60% yields (Scheme 4). Although the yields are not high, this one-pot methodology demonstrates the potential in construction of multifunctionalized benz[*a*]azulene derivatives. A plausible mechanism for the formation of benzo-fused azulene derivatives is depicted in Scheme 5.

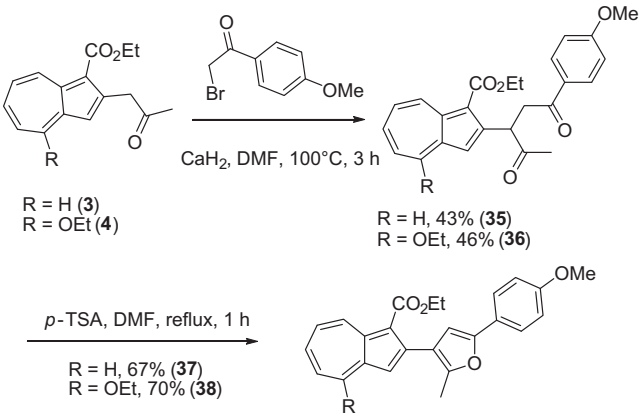
Next, we focused our attention toward the intramolecular Friedel–Crafts reaction pathway to obtain new types of benzo-fused azulene derivatives. For these studies we selected ethyl 2-(2,6-dioxoheptan-3-yl)azulene-1-carboxylate (**26**), which was prepared via the Michael addition of ethyl 2-(2-oxopropyl)azulene-1-carboxylate (**3**) to MVK with $CaH_2$ in DMF at room temperature for 12 h. With compound **26** in hand, we screened several acids and solvent systems to find the best result to obtain ethyl 1-acetyl-4-methyl-1,2-dihydrobenz[*a*]azulene-10-carboxylate (**29**) in 73% isolated yield.[13] The subsequent oxidization with DDQ gave fully aromatized benz[*a*]azulene derivative **32** in 81%.[14] All the products were well characterized with their spectral



**Scheme 6.** Synthesis of benz[*a*]azulenes from 2-substituted azulene derivatives via intramolecular Friedel–Crafts reaction.



**Scheme 7.** Plausible mechanism for the intramolecular Friedel–Crafts reaction.



**Scheme 8.** Synthesis of azulene-furan frameworks via Paal–Knorr reaction.

data. We also generalized the reactions with various derivatives in good to excellent yields (Scheme 6). A plausible mechanism for the intramolecular Friedel–Crafts reaction of azulene derivatives is presented in Scheme 7.

Finally, we focused our attention on the construction of azulene-furan frameworks. For these studies, we selected ethyl 2-(1-(4-methoxyphenyl)-1,4-dioxopentan-3-yl)azulene-1-carboxylate (**35**) which was prepared from compound **3** and 2-bromo-1-(4-methoxyphenyl)ethanone with $CaH_2$ in DMF at 100 °C for 3 h. Compound **35** was further treated with *p*-TSA in DMF under reflux for 1 h to provide ethyl 2-(5-(4-methoxy-phenyl)-2-methyl furan-3-yl)azulene-1-carboxylate (**37**) in 67%, isolated yield.[15] Similarly, ethoxy derivative **38** was obtained in 70% (Scheme 8) via Paal–Knorr reaction.

In summary, we have successfully synthesized 2-substituted azulene derivatives (**3–6**) from ethyl 2-oxo-2*H*-cyclohepta[*b*]-furan-3-carboxylate **1** and its derivative **2**. These derivatives were effectively applied in the syntheses of densely functionalized benz[*a*]azulene and multisubstituted azulene-furan derivatives by using aldol, Knoevenagel, intramolecular Friedel–Crafts, and Paal–Knorr reactions. Utilization of these methodologies for the syntheses of biologically important heterocyclic molecules is in progress.

## Acknowledgments

We gratefully acknowledge Professor Chun-Chen Liao for helpful discussions. The financial support is from the CYCU distinctive research area project as grant CYCU-99-CR-CH and National Science Council (NSC) of Taiwan (Grant No.: NSC 100-2119-M-033-001). B.D. thanks NSC of Taiwan (Grant No.: NSC 100-2811-M-033-008) for a postdoctoral fellowship.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.040.

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10. General procedure for the preparation of **3**: To a stirred solution of ethyl 2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate **1** (1 mmol, 0.218 g) in toluene (3 mL) was added 2-methylfuran (2 mL), and the mixture was refluxed at 190 °C for 60 h. The mixture was allowed to cool to room temperature, diluted with water (10 mL), and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and stripped off the solvent to give a crude product, which was purified by silica gel column chromatography (hexane/EtOAc = 9:1) to afford the compound **3** (0.143 g) as solids (mp: 51-52 °C) in 56% yield. $^1H$ NMR ($CDCl_3$, 300 $MH_Z$): $\delta$ 1.40 (t, 3H, $J$ = 7.2 Hz), 2.19 (s, 3H), 4.29 (s, 2H), 4.39 (q, 2H, $J$ = 7.2 Hz), 7.12 (s, 1H), 7.37 (t, 1H, $J$ = 10.0 Hz), 7.48 (t, 1H, $J$ = 10.0 Hz), 7.70 (t, 1H, $J$ = 10.0 Hz), 8.29 (d, 1H, $J$ = 10.0 Hz), 9.53 (d, 1H, $J$ = 10.0 Hz); $^{13}C$ NMR ($CDCl_3$, 75 $MH_Z$): $\delta$ 14.4, 29.8, 46.5, 59.7, 114.8, 120.4, 127.1, 127.8, 137.1, 137.2, 138.3, 141.6, 143.0, 148.6, 165.5, 205.8; IR (KBr): $\nu$ 1702, 1670, 1420, 1402, 1220, 1058 $cm^{-1}$.
11. General procedure for the preparation of **16**: To a solution of ethyl 3- formyl-2-(2-oxopropyl)azulene-1-carboxylate **7** (1 mmol, 0.284 g) in EtOH (3 mL) at room temperature was added NaOEt (1.2 mmol, 0.081 g). The mixture was heated at 100 °C under reflux for 10 min. Then the reaction mixture was allowed to cool to room temperature, diluted with water (10 mL), and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column chromatography (hexane/EtOAc = 1:1) to afford the compound **16** (0.212 g) as solids (mp: 218–219 °C) in 80% yield. $^1H$ NMR ($CDCl_3$, 300 $MH_Z$): $\delta$ 1.44 (t, 3H, $J$ = 7.1 Hz), 4.40 (q, 2H, $J$ = 7.1 Hz), 6.99 (dd, 1H, $J$ = 2.18, 8.6 Hz), 7.58–7.66 (m, 3H), 7.82 (s, 1H), 8.44 (d, 1H, $J$ = 8.6 Hz), 8.86 (dd, 1H, $J$ = 1.0, 8.5 Hz), 9.05 (d, 1H, $J$ = 10.0 Hz), 10.18 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 $MH_Z$): $\delta$ 14.5, 59.3, 106.0, 109.6, 113.5, 123.1, 123.2, 129.6, 130.1, 130.4, 134.5, 136.1, 141.2, 143.0, 144.3, 160.1, 165.6; IR (KBr): $\nu$ 3200, 1620, 1588, 1420, 1350, 1290, 1120 $cm^{-1}$; LC–MS ($m/z$): 266 (100), 254 (26.0), 238 (29.1), 225 (11.9), 210 (11.6), 197 (24.9), 181 (34.8), 152 (27.3), 139 (12.6), 126 (11.1).
12. General procedure for the preparation of **21**: To a stirred solution of ethyl 3-formyl-2-(methoxy carbonylmethyl)azulene-1-carboxylate **9** (1 mmol, 0.3 g) in EtOH (3 mL) were added malononitrile (1.5 mmol, 0.1 mL), and NaOEt (1.2 mmol, 0.081 g) at room temperature. The mixture was heated at 100 °C under reflux for 1 h. Then the reaction mixture was allowed to cool to room temperature, diluted with water (10 mL), and extracted with EtOAc. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and stripped off the solvent to give crude product **21**, which was isolated by silica gel column chromatography (hexane/EtOAc = 1:1) to afford compound **21** (0.202 g) as solids (mp: 180–181 °C) in 58% yield. $^1H$ NMR ($CDCl_3$, 300 $MH_Z$): $\delta$ 1.36 (t, 3H, $J$ = 7.1 Hz), 1.38 (s, 3H), 4.38 (q, 2H, $J$ = 7.2 Hz), 6.40 (s, 2H), 7.39–7.57 (m, 3H), 8.39 (dd, 1H, $J$ = 8.4, 10.0 Hz), 8.46 (s, 1H), 8.87 (dd, 1H, $J$ = 0.9, 11.2 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 14.3, 51.5, 60.8, 94.3, 103.7, 117.8, 121.5, 129.9, 130.0, 130.1, 131.1, 134.4, 136.7, 139.6, 140.2, 142.8, 145.4, 150.7, 166.5, 168.6; IR (KBr): $\nu$ 3400, 2200, 1680, 1610, 1420, 1160 $cm^{-1}$; LC–MS ($m/z$): 348 (18.10), 319 (13.95), 288 (10.39), 270 (16.32), 244 (15.43), 190 (12.46), 188 (62.31), 135 (18.99), 111 (24.63), 100 (27.30), 59 (100).
13. General procedure for the preparation of **29**: To a solution of ethyl 2-(2, 6-dioxoheptan-3-yl)azulene-1-carboxylate **26** (1 mmol, 0.326 g) in DMF (3 mL) at room temperature was added *p*-TSA (2 mmol, 0.344 g) the mixture was heated at 170 °C under reflux for 1 h. Then the reaction mixture was allowed to cool to room temperature, diluted with water (10 mL), and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column chromatography (hexane/EtOAc = 4:1) to afford compound **29** (0.225 g) as a viscous liquid in 73% yield. $^1H$ NMR ($CDCl_3$, 300 $MH_Z$): $\delta$ 1.38 (t, 3H, $J$ = 7.2 Hz), 1.95 (s, 3H), 2.40 (s, 3H), 2.49-2.59 (m, 1H), 2.83 (dd, 1H, $J$ = 6.6, 16.8 Hz), 4.38 (q, 2H, $J$ = 7.2 Hz), 4.59 (dd, 1H, $J$ = 1.7, 8.1 Hz), 5.66 (brs, 1H), 7.23 (t, 1H, $J$ = 10.0 Hz), 7.34 (t, 1H, $J$ = 10.0 Hz), 7.58 (t, 1H, $J$ = 10.0 Hz), 8.72 (d, 1H, $J$ = 10.0 Hz), 9.45 (d, 1H, $J$ = 10.0 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 14.5, 22.7, 26.7, 28.9, 48.4, 60.1, 113.9, 122.9, 126.0, 126.4, 127.9, 131.0, 135.9, 136.6, 137.1, 138.7, 142.5, 151.0, 165.5, 208.8; IR (KBr): $\nu$ 2925, 1686, 1573, 1430, 1260, 1192, 1092, 1031, 799 $cm^{-1}$; GC–MS ($m/z$): 308 ($M^+$, 24), 265 (63), 236 (38), 219 (100), 192 (56), 178 (47), 95 (87), 81 (47).
14. General procedure for the preparation of **32**: To a solution of ethyl 1- acetyl-4-methyl-1,2-dihydrobenz[*a*]azulene-10-carboxylate **29** (1 mmol, 0.308 g) in toluene (3 mL) at room temperature was added DDQ (2 mmol, 0.454 g). The mixture was heated at 120 °C under reflux for 3 h. Then the reaction mixture was allowed to cool to room temperature, diluted with water (10 mL), and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column chromatography (hexane/EtOAc = 2:1) to afford compound **32** (0.248 g) as a solid (mp: 115–116 °C) in 81% yield. $^1H$ NMR ($CDCl_3$, 300 $MH_Z$): $\delta$ 1.37 (t, 3H, $J$ = 7.2 Hz), 2.65 (s, 3H), 2.99 (s, 3H), 4.42 (q, 2H, $J$ = 7.2 Hz), 7.23 (dd, 1H, $J$ = 0.6, 9.6 Hz), 7.25 (ddd, 1H, $J$ = 1.1, 11.0, 11.0 Hz), 7.29 (dd, 1H, $J$ = 0.6, 7.5 Hz), 7.46 (dd, 1H, $J$ = 9.6, 11.0 Hz), 7.82 (d, 1H, $J$ = 7.5 Hz), 8.74 (d, 1H, $J$ = 9.6 Hz), 8.90 (d, 1H, $J$ = 11.0 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 14.3, 23.5, 29.0, 60.3, 116.4, 125.5, 128.0, 128.3, 128.5, 128.7, 131.5, 135.0, 135.2, 136.9, 137.2, 138.2, 141.4, 142.1, 166.7, 201.5; IR (KBr): $\nu$ 2970, 1698, 1681, 1455, 1403, 1254, 1197, 1085, 1033, 798; GC–MS ($m/z$): 306 ($M^+$, 100), 261 (70), 234 (26), 189 (42), 178 (20).
15. General procedure for the preparation of **37**: To a solution of ethyl 2-(1- (4-methoxyphenyl)-1,4-dioxopentan-3-yl)azulene-1-carboxylate **35** (1 mmol, 0.404 g) in DMF (3 mL) at room temperature was added *p*-TSA (2 mmol, 0.344 g). The mixture was heated at 170 °C under reflux for 1 h. Then the reaction mixture was allowed to cool to room temperature, diluted with water (10 mL), and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column chromatography (hexane/EtOAc = 3:1) to afford compound **37** (0.259 g) as a viscous liquid in 67% yield. $^1H$ NMR ($CDCl_3$, 300 $MH_Z$): $\delta$ 1.26 (t, 3H, $J$ = 7.2 Hz), 2.48 (s, 3H), 3.81 (s, 3H), 4.35 (q, 2H, $J$ = 7.2 Hz), 6.70 (s, 1H), 6.92 (d, 2H, $J$ = 6.9 Hz), 7.24 (s, 1H), 7.37 (t, 1H, $J$ = 10.0 Hz), 7.51 (t, 1H, $J$ = 10.0 Hz), 7.59 (d, 2H, $J$ = 6.9 Hz), 7.64 (t, 1H, $J$ = 10.0 Hz), 8.31 (d, 1H, $J$ = 10.0 Hz), 9.40 (d, 1H, $J$ = 10.0 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MzH): $\delta$ 13.1, 14.3, 55.2, 60.0, 107.1, 114.1, 115.1, 119.2, 119.8, 124.7, 126.8, 127.7, 136.5, 136.7, 137.7, 141.9, 142.6, 145.6, 149.1, 151.1, 158.7, 166.1; IR (KBr): $\nu$ 2900, 1687, 1608, 1502, 1417, 1248, 1205, 1031, 805; GC–MS ($m/z$): 386 ($M^+$, 100), 340 (29), 325 (28), 313 (13), 135 (66).