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# 2-Hydroxy-1,2,3,6-tetrahydro-azulen-6-carboxylic Acid Ethyl Ester—A Novel Precursor for a New Class of Liquid Crystalline Materials

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**Abstract:** A novel approach for the syntheses of carbene adduct **4** is reported. A ring-enlargement strategy was employed for the synthesis of precursors **5** and **6** and established the mechanism of the formation of azulene derivative **6**. Synthesis of target precursor **13**, a novel precursor for the synthesis of new mesogenic materials, and its various halogenated derivatives (**14**–**16**) was carried out.

**Keywords:** Birch reduction, carbene addition, liquid crystals, ring enlargement

## INTRODUCTION

A wide range of property changes affecting the liquid crystal (LC) behavior of the materials can be produced by simply modifying the basic structure of the core units. The core unit presently used in most of the calamitic LC is cyclohexane and phenylcyclohexane, and various modifications in the basic

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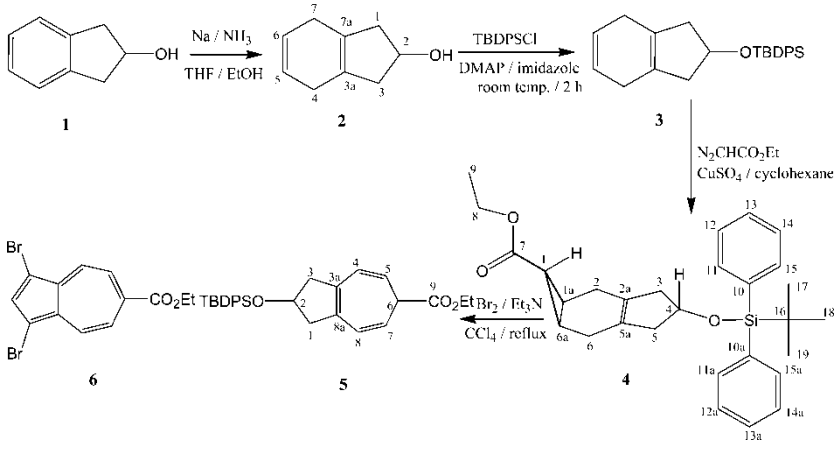
cyclohexyl, bicyclohexyl, and phenyl bicyclohexyl structures have been made recently to overcome problems of electrooptic and viscoelastic parameters.[1,2] We developed a completely new core unit—the perhydroazulene unit.[3] It is flat and allows introduction of numerous substituents. Its stereochemistry can be affected by the central junction as well as the relative orientation of the substituents. Our experience on the synthesis of a variety of similar materials showed the novelty of such core units for mesogenic materials. However, previous synthetic approaches lead to the core units with the possibility of extending the system in only one side. Therefore, a new approach that could result in precursors with the possibility of extending the core units in both directions was desirable. We here report the first synthesis of a core unit (**13**) as a novel precursor for a variety of new mesogenic materials.

## RESULTS AND DISCUSSION

To get a partially reduced azulene system with the possibility of derivatizable or replaceable group such as OH or any halogen at position 2, the new synthetic route outlined in Scheme 1 was developed. This new strategy resulted in compounds such as **5**, which is a potential intermediate for a large variety of new materials, and **6**, which is a new azulene derivative formed during the course of the reaction. Starting from inexpensive and readily available 2-indanol **1** it was possible to prepare 4,7-dihydro-2-indanol **2** by Birch reduction in almost quantitative yield. The hydroxy function of **1** was protected by tertiary butyl diphenyl silyl chloride in the



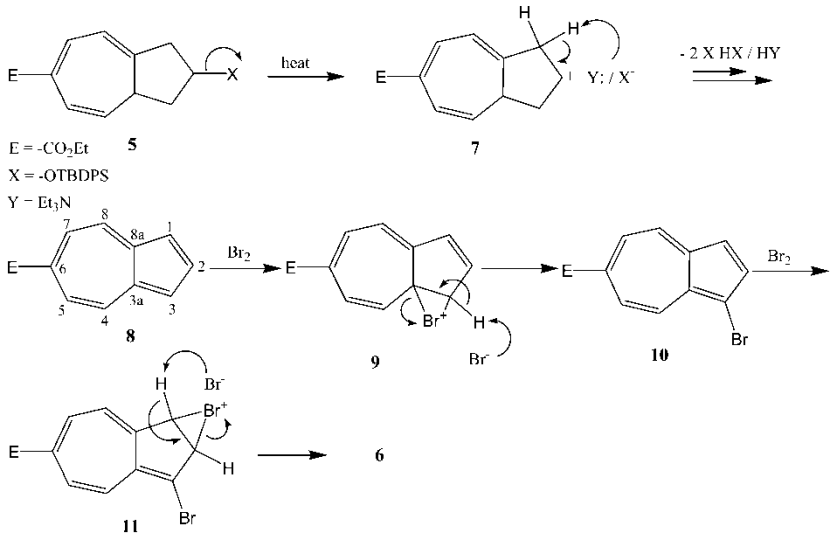

***Scheme 1.*** Synthesis of 1,3-dibromo azulene derivative **6** and a 2,6-disubstituted tetrahydroazulene derivative **5**.

presence of dimethyl amino pyridine and imidazole[4] at room temperature, also in quantitative yield. The protection of the hydroxy function was carried out to direct the carbene addition to the external double bond in the next step. The protected 4,7-dihydro-2-indanol **3** was subjected to carbene addition in the presence of ethyldiazoacetate and dried copper sulfate in dried cyclohexane to yield the carbene adduct **4** in 75% yield while some of the diethyl fumarate, which was formed during the reaction, was also isolated as well as some unreacted starting material. The yield in this reaction was improved by increasing the carbene addition time and using thoroughly dried copper sulfate and cyclohexane as the solvents. Ring expansion of compound **4** was performed in the presence of bromine and triethyl amine with carbon tetrachloride as solvent. In this reaction bromine was added first to the double bond and later removed as a hydrobromide salt by adding triethylamine and refluxing the mixture for several hours. This resulted in cyclopropane ring opening to provide **5** as the major product in 52% yield and **6** as a minor component in 10% yield. The formation of **5** was expected during the reaction, and **6** formed by rearrangement and bromination of **5**. It is important to note that the yield of **6** can be increased by merely prolonging the reflux time, which might be due to the rearrangement of **6**, which forms first. The new adducts were characterized by the usual spectroscopic data, which are summarized in the experimental section.

A triplet at 1.40 ppm in $^1$H NMR for **4** with coupling constants of 4.3 Hz between the protons on the cyclopropyl ring indicates a *trans* configuration between the carbethoxy group and the cyclohexene ring. Furthermore, a triplet at 2.53 ppm ($^3J = 5.6$ Hz) in the $^1$H NMR for 6-H in **5** and the presence of two doublets at 6.04 ($^3J = 9.4$ Hz) for 4/8-H in **5** indicates the formation of a seven-membered skeleton in compound **5**. The formation of compound **6** was confirmed by the presence of an AB quartet at 8.01 ppm in $^1$H NMR ($^3J = 10.3$ Hz) for 4,8/5,7-H and further confirmation of the skeleton from its single-crystal X-ray structure.

A plausible mechanism for the formation of **6** could involve the following steps (Scheme 2). On refluxing the mixture for a longer time, the side chain from the rearranged **5**, which is too bulky, can be cleaved off, leaving behind a secondary carbocation **7**, which can be stabilized by a proton abstraction with a negatively charged oxygen atom of the leaving group or triethylamine present in the mixture.

Very likely the driving force of the transformation is the formation of more stable aromatic azulene nucleus. Positions 1 and 3 of azulene are more susceptible to electrophilic attack,[5] and the presence of bromine results in the formation of brominated product **6**. First bromine adds to the double bond at 1 and 8a, which results in the formation of bromonium **9**, while the bromide ion abstracts a proton, resulting the formation of the mono-substituted product **10** instead of the addition product, thus restoring the aromaticity of the molecule. The abstraction of a proton from **11**,

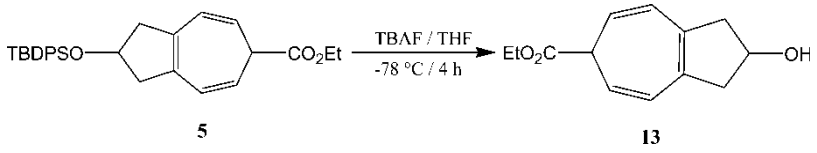



***Scheme 2.*** Mechanism of formation of dibromide **6**.

when a second bromine molecule adds at the double bond between position 2 and 3, is more likely to take place from position 3, which is more accessable to bromide. This results in the formation of **6**.

Compound **6** was obtained as a dark blue solid, which was recrystallized from dichloromethane and hexane to yield dark green needles suitable for X-ray analysis. X-ray data[6] showed the presence of two crystallographically independent molecules in the asymmetric unit. The azulene frameworks of both the molecules were planar with mean deviations of 0.01 and 0.02 Å out of the calculated ring planes. Planes defined by the atoms of the ethyl ester groups were twisted from the ring planes by 4.3(4)° and 3.3(4)°. The bond lengths of the azulene systems, from 1.374(8) Å to 1.410(8) Å, did not show significant differences within their standard deviations in both the molecules. This is the same order of magnitudes as found by Kaftory et al.[7] for other substituted azulene derivatives.

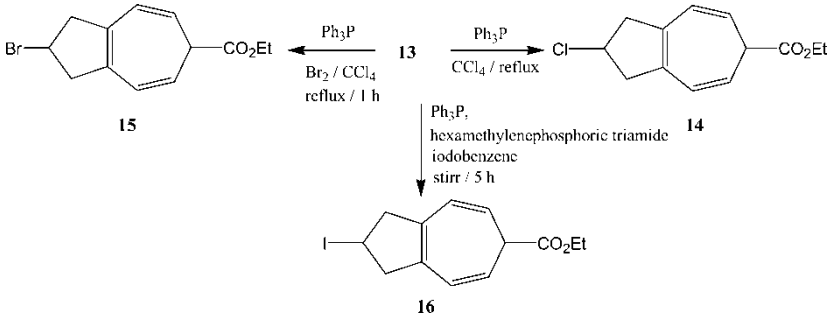
Considering compound **13** as an intermediate for further coupling reactions, it was thought desirable to remove the TBDPS group without damaging the rest of the molecule. After trying various approaches,[8] the method reported by Overman and Rishton[9] was found to be the method of choice where a more expensive but effective commercially available catalyst, tetrabutylammonium fluoride (TBAF) in THF, was used, resulting in acceptable to good yield (62–65%) of **13** from **5**. The disappearance of aromatic signals at 7.69–7.41 ppm and signals at 1.07 ppm due to *t*-butyl protons in $^1$H NMR spectrum indicates the formation of **13** (Scheme 3).




***Scheme 3.*** Synthetic route to cycloheptatriene **13**.

Compound **13** is a novel precursor for the synthesis of a variety of new materials. It gives the possibility to extend the system in both 2 and 6 positions. It further allows getting the fully reduced core unit—a perhydroazulene system—which could be an alternate to cyclohexyl or phenyl cyclohexyl core units for the synthesis of novel materials as calamitic liquid crystals.

Derivative **13** is therefore, in principle an important candidate for various coupling reactions. However, most of such reactions are successful only for activated molecules,[10] and the most promising results were obtained with an intermediate that had halogen substituents. Therefore, halogen derivatives of **13** are more important intermediates, and the method of choice for the conversion of the alcohol to halogen derivatives utilizes $Ph_3P$ and corresponding halogen.[11] Alcohol **13** was converted to the halogenated derivatives **14**–**16** (Scheme 4). It is important to note that the reaction in the cases of chloride and iodide resulted in ~60% yield but in the case of bromide only ~30% of the purified product **15** could be isolated. Direct conversion[12] of the protected alcohol **5** to bromide derivative **15** did not yield any product at all. All of these derivatives showed similar $^{13}C$ NMR spectra; however, signals corresponding to 2-H in the $^{1}H$ NMR spectra appeared to have slightly different ppm values ($\delta = 4.57$ ppm for the bromo derivative, $\delta = 4.60$ ppm for the chloro derivative, and $\delta = 4.76$ ppm for **16**). All of these derivatives were fully characterized further by their usual mass spectrometric and other analytical data, which are given separately in the experimental section.




***Scheme 4.*** Halogenation reactions of the alcohol **13**.

## EXPERIMENTAL

Thin-layer chromatography was performed by using precoated plastic plates, PolyGram Sil $G/UV_{254}$. Column chromatography was performed on silica gel 60 (70–230 mesh) from Merck (Darmstadt). Measurements below 200°C were determined on a Büchi 510 melting-point apparatus and above 200°C were carried out on a Kofler-Heiztischmikroskop apparatus. They are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were recorded on the following spectrometers: Bruker AC 200, $^{1}H$ NMR (200.1 MHz) and $^{13}C$ NMR (50.3 MHz); Bruker DRX-400, $^{1}H$ NMR (400.1 MHz) and $^{13}C$ NMR (100.6 MHz). Chemical shifts ($\delta$) are expressed in parts per million (ppm) downfield from tetramethylsilane or using the residual non-deuterated solvent as internal standard ($CDCl_3$: $^{1}H$: $\delta = 7.26$; $^{13}C$: $\delta = 77.00$). Coupling constants are expressed in Hertz. IR spectra were recorded using a Nicolet 320 FT-IR and a Bruker Tensor 27 spectrometer. Samples were prepared either as KBr pellets or as thin films. UV spectra were recorded in acetonitrile and methanol using a Beckman UV 5230 and HP 8452 A diode array spectrophotometer. Mass spectra were recorded using a Finnigan MAT 8430 spectrometer using the electron ionization method (EI, 70 eV). GC/MS spectra were recorded on a Finnigan MAT 4515 (EI, 40 eV) mass spectrometer attached to a Carlo-Erba HRGC 5160 (DB 1–0.25 μm fused silica capillary column; 30 m × 0.31 mm ID; carrier gas Argon) gas chromatograph. Elemental analyses were carried out at the Institut für Pharmazeutische Chemie, TU Braunschweig. $CH_2Cl_2$ and $Et_3N$ were distilled from $CaH_2$ under nitrogen prior to use, and THF and $Et_2O$ were distilled from Na and benzophenone under nitrogen prior to use. All other chemicals were of reagent quality and used as obtained from the manufacturers. Reactions were carried out in dry $N_2$ when necessary.

### Synthesis of 4-7-Dihydro-2-indanol (2)

2-Indanol (**1**, 5.0 g; 37.26 mmol), liquid $NH_3$ (30 mL), EtOH (30 mL), and THF (20 mL, anhydrous) were placed in a 500-mL, three-necked flask fitted with a mechanical stirrer, and the temperature was maintained at −75°C with a methanol–liquid nitrogen bath. Sodium metal was added until the blue color persisted for 20 min. The $NH_3$ was allowed to evaporate overnight. The remaining residue was partitioned between ether and water. The ether layer was evaporated, and the resulting liquid was again partitioned between ether and water. The ether layer was dried with $MgSO_4$ and the ether evaporated to give crude 4,7-dihydro-2-indanol (4.91 g, 97%) as a colorless solid, which melted above room temperature. The product was rather unstable and on standing slowly reoxidized to 2-indanol; it was thus readily used for further reaction.

$R_F$ ($SiO_2$; ether/pentane, 1 : 2) = 0.3; mp = 36°C (lit.[13]); $^1$H NMR (400.1 MHz, $CDCl_3$): $\delta$ = 2.23–2.64 (m, 4H, 1/3-H), 2.64–2.75 (m, 4H, 4/7-H), 4.51–4.55 (m, 1H, 2-H), 5.77 (s, 2H, 5/6-H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ = 27.57 (t, C-4/7), 46.02 (t, C-1/3), 70.83 (d, C-2), 124.75 (d, C-5/6), 129.77 (s, C-3a/7a); IR (film): $\tilde{\nu} = 3330\,cm^{-1}$ (s, OH), 2912, 2818 (s, CH-stretching), 1430, 1291 (m); UV/Vis ($CH_3CN$): $\lambda_{max}$ (lg $\varepsilon$) = 194 nm (4.06), 204 (3.65), 212 (3.48), 218 (3.31), 224 (2.90), 266 (2.50), 274 (2.49); MS (EI, 70 eV): $m/z$ (%) = 136 [$M^+$] (35), 119 [$M^+$-OH] (5), 117 [119-$H_2$] (77), 92 [$M^+$-$C_2H_4O$] (70), 91[92-H] (100), 79 [92-CH] (30), 77 [91-$CH_2$] (23); Anal. calcd. for $C_9H_{12}O$ (136.19): C, 79.37%; H, 8.88%; O, 11.75%. Found C, 79.57%; H, 9.02%.

## Synthesis of 2-(tert-Butyl-diphenyl-silanyloxy)-4,7-dihydro-indane (3)

4,7-Dihydro-2-indanol (**2**, 4 g; 29.41 mmol) in anhydrous dichloromethan (100 mL) was added in a flame-dried flask kept under a stream of nitrogen, and the mixture was stirred for a few min. DMAP (359 mg, 2.94 mmol) and imidazole (4.40 g, 64.70 mmol) were added, and the mixture cooled to 0°C with an ice bath. TBDPSCl (8.892 g, 32.35 mmol) dissolved in dichloromethan (10 mL) was then added dropwise at 0°C with stirring. After complete addition, the mixture was stirred further for 3 h at room temperature, the solvent evaporated, and the product purified by passing through a small column of silica gel with pentane to provide 10 g (90%) of pure **3** as colorless viscous oil.

$R_F$ ($SiO_2$; pentane) = 0.2; $^1$H NMR (400.1 MHz, $CDCl_3$): $\delta$ = 1.11 (s, 9 H, tert-butyl-H), 2.43–2.45 (m, 4H, 1/3-H), 2.60-2.67 (m, 4H, 4/7-H), 4.61–4.64 (m, 1H, 2-H), 5.77 (s, 2H, 5/6-H), 7.42–7.47 (m, 6H, 10-12/10a-12a-H), 7.73–7.75 (dd, $^3J_1$ = 7.85 Hz, $^4J_2$ = 1.57 Hz, 4H, 9, 13/9a-13a-H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ = 19.11 (s, tert-butyl), 26.91 (q, tert-butyl), 27.18 (t, C-4/7), 45.45 (t, C-1/3), 72.32 (d, C-2), 124.56 (d, C-5/6), 127.49 (d, C-10, 12/10a, 12a), 129.39 (s, C-3a/7a), 129.44 (d, C-11/11a), 134.59 (s, C-8/8a), 135.71 (d, C-9, 13/9a, 13a); IR (film): $\tilde{\nu} = 2930\,cm^{-1}$, 2885, 2856 (s, CH-stretching), 1428 (m), 111 (m), 1074 (m); UV/Vis ($CH_3CN$): $\lambda_{max}$ (lg $\varepsilon$) = 196 nm (4.73), 204 (4.44), 214 (4.24), 224 (4.09), 256 (2.92), 266 (2.99); MS (EI, 70 eV): $m/z$ (%) = 317 [$M^+$-tert-butyl] (91), 240 [317-$C_6H_5$] (10), 239 [240-H] (52), 227 [240-CH] (99), 199 [239-$C_3H_4$] (100), 135 [$M^+$-TBDPS] (10).

## Synthesis of 4-(tert-Butyl-diphenyl-silanyloxy)-1,1a,2,3,4,5,6,6a-octahydrocyclopropa [*f*] indene-1-carboxylic Acid Ethyl Ester (4)

A solution of ethyl diazoacetate (6.73 g, 58.99 mmol) in 30 mL of anhydrous cyclohexane was added dropwise with stirring over a 5 h period, with a

dropping funnel to a refluxing mixture of **3** (6.5 g, 17.37 mmol), $CuSO_4$ (anhydrous, 1.45 g), and cyclohexane (anhydrous, 60 mL). The mixture was refluxed for another 60 min and filtered to remove $CuSO_4$. The solution was concentrated, and the product was separated by column chromatography on silica gel using pentane as the solvent, increasing its polarity with dichloromethane (1–10%). Some unreacted starting material was recovered as it eluted from the column first, followed by the product (6.0 g, 75%) and by diethyl fumarate as a side product. The product was obtained as colorless viscous oil. $R_F$ ($SiO_2$; pentane/$CH_2Cl_2$; 3 : 2) = 0.6; $^1$H NMR (200.1 MHz, $CDCl_3$): $\delta = 1.07$ (s, 9H, tert-butyl), 1.22–1.24 (t, $^3J = 7.1$ Hz, 3H, 9-H), 2.26–2.35 (m, 4H, 3/5-H), 1.33–1.38 (m, 2H, 1a, 6a-H), 1.40 (t, $^3J = 4.3$ Hz, 1H, 1-H), 2.40 (br. s, 4H, 2/6-H), 4.16-4.19 (q, $^3J = 7.0$ Hz, 2H, 8-H), 4.50–4.52 (m, 1H, 4-H), 7.69–7.41 (m, 10H, aromatic rings protons); $^{13}$C NMR (50.3 MHz, $CDCl_3$): $\delta = 14.26$ (q, C-9), 19.06 (s, tert-butyl), 26.89 [q, $(-CH_3)_3$], 21.88 (d, C-1a/6a), 23.44 (d, C-1), 23.78 (t, C-2/6), 45.68 (t, C-3/5), 60.26 (t, C-8), 71.90 (d, C-4), 127.50 (d, C-12, 14/12a, 14a), 127.53 (d, C-13/13a), 135.65 (d, C-11, 15/11a, 15a), 135.58 (s, C-10/10a), 129.45 (s, C-2a/5a), 175.02 (s, C-7); IR (film): $\tilde{\nu} = 3071\ cm^{-1}$, 3049 (m, CH-stretching), 2959, 2930, 2898, 2875, 2858 (s, CH-aromatic), 1723 (s, C=O), 1463, 1428 (m), 1287, 1173, 112, 1076 (s), 1063 (s); UV/Vis ($CH_3CN$): $\lambda_{max}$ (lg $\varepsilon$) = 194 nm (4.96), 208 (4.46), 214 (4.33), 222 (4.22), 228 (3.92), 266 (2.86); MS (EI, 70 eV): $m/z$ (%) = 460 [$M^+$] (25), 459 [$M^+$-H] (36), 445 [$M^+$-$CH_3$] (95), 403 [$M^+$-tert-butyl] (8), 326 [403-$C_6H_5$] (1), 297 [326-$C_2H_5$] (2), 199 [$C_{13}H_{11}O_2$] (100), 183 [199-O] (29); Anal. calcd. for $C_{29}H_{36}O_3Si$ (460.24): C, 75.61%; H, 7.88%; found C, 75.48%; H, 8.09%.

### Synthesis of Ethyl 2-(tert-Butyl-diphenyl-silanyloxy)-1, 2, 3, 6-tetrahydro-6-azulen-carboxylate (5)

Reactant **4** (6.0 g, 13.39 mmol) was dissolved in $CCl_4$ (300 mL) and the mixture cooled with an ice bath under stirring. Bromine (2.139 g, 13.39 mmol) dissolved in $CCl_4$ (20 mL) was added dropwise with stirring. When the addition was complete, triethylamine (6.62 g, 65.64 mmol) was added. Triethylamine hydrobromide began to form immediately. The mixture was refluxed for 18 h. The HBr salt was filtered off, and the solvent was evaporated. The resulting oil was washed with water, dried with $MgSO_4$, and filtered to get the crude product (5 g) containing ethyl 1,3-dibromo-6-azulenecarboxylate and ethyl 2-(tert-butyl-diphenyl-silanyloxy)-1,2,3,6-tetrahydro-6-azulenecarboxylate. The mixture was purified by column chromatography on silica gel using pentane as an eluent, increasing its polarity with dichloromethan (1–10%). Ethyl 1,3-dibromo-6-azulenecarboxylate **6** (0.5 g, 10%), being less polar, eluted first (dark blue material) followed by ethyl 2-(tert-butyl-diphenyl-silanyloxy)-1,2,3,6-tetrahydro-6-azulenecarboxylate.

**Compound 5:** 3.2 g, 52%, bluish oil. $R_F$ ($SiO_2$; pentane/dichloromethane; 3 : 2 = 0.7; bp = >200°C/5 torr; $^1$H NMR (400.1 MHz, $CDCl_3$): $\delta = 0.98$ (s, 9 H, tert-butyl), 1.24 (t, $^3J = 7.1$ Hz, 3H, 11-H), 2.53 (t, $^3J = 5.6$ Hz, 1H, 6-H), 2.71 (m, 4H, 1/3-H), 4.15–4.19 (q, $^3J = 7.1$ Hz, 2H, 10-H), 4.45–4.54 (m, 1H, 2-H), 5.19–5.24 (m, 2H, 5/7-H), 6.04-6.08 (2 × d, $^3J = 9.4$, 9.3 Hz, 4/8-H), 7.08–7.28 (m, 6H, 14–16/14a-16a-H), 7.49–7.52 (m, 4H, 13, 17/13a, 17a-H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.20$ (q, C-11), 19.08 (s, tert-butyl), 26.87 [q, $(-CH_3)_3$], 45.06 (d, C-6), 45.73 (t, C-1/3), 60.99 (t, C-10), 72.73 (d, C-2), 117.13 (d, C-5/7), 125.07 (d, C-15/15a), 127.57 (d, C-14, 16/14a, 16a), 129.57 (d, C-4/8), 134.29 (s, C-3a/8a), 135.67 (d, C-13, 17/13a, 17a), 139.52 (s, C-12/12a), 173.08 (s, C-9); IR (film): $\tilde{\nu} = 2959\,cm^{-1}$, 2932 (w, CH-stretching), 1737 (s, C=O), 1428 (m), 1199, 1161, 1111, 1086 (m), 702 (s); UV/Vis ($CH_3CN$): $\lambda_{max}$ (lg $\varepsilon$) = 196 nm (4.91), 266 (3.75), 202 (4.79), 296 (3.46), 312 (3.27); MS (EI, 70 eV): $m/z$ (%) = 458 [$M^+$] (10), 429 [$M^+$-$C_2H_5$] (1.6), 401 [$M^+$-tert-But.] (58), 385 [$M^+$-$C_3H_5O_2$] (98), 323 [401-$C_6H_6$] (30), 295 [323-$C_2H_4$] (8), 199 [$C_{13}H_{11}O_2$] (100); HRMS ($C_{29}H_{34}O_3Si$): calcd. 458.22772; found 458.22788 ± 4 ppm.

**Ethyl 1,3-dibromo-6-azulen-carboxylate (6):** $R_F$ ($SiO_2$; pentane/dichloromethane; 8:2 = 0.7; mp = 115–116°C; $^1$H NMR (400.1 MHz, $CDCl_3$): $\delta = 1.37$–$1.40$ (t, $^3J = 7.12$ Hz, 3H, 11-H), 4.36–4.41 (q, $^3J = 7.12$ Hz, 2H, 10-H), 7.83 (s, 1H, 2-H), 8.01–8.28 (AB q, $^3J = 10.30$ Hz, 4H, 4, 8/5, 7-H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.25$ (q, C-11), 76.68 (t, C-10), 103.86 (2 × s, C-1/3), 124.18 (d, C-5/7), 135.14 (d, C-4/8), 136.87 (2 × s, C-3a/8a), 138.98 (s, C-6), 140.81 (d, C-2), 167.26 (s, C-9).

IR (KBr): $\tilde{\nu} = 2991\,cm^{-1}$, 2974 (w, CH-stretching), 1721 (s, C=O), 1480, 1386 (m, C=C stretching), 1292, 1270 (s), 1211 (m); UV/Vis ($CH_3CN$): $\lambda_{max}$ (lg $\varepsilon$) = 206 nm (4.27), 222 (4.32), 246 (4.28), 298 (4.81), 344 (3.74), 358 (3.84), 366 (3.32); MS (EI, 70 eV): $m/z$ (%) = 358 [$M^+$] (87), 330 [$M^+$-$C_2H_4$] (100), 313 [$M^+$-$C_2H_5O$] (4), 285 [$M^+$-$C_3H_5O_2$] (10), 206 [285-Br] (29); anal. calcd. for $C_{13}H_{10}O_2Br_2$ (358.02): C, 43.61%; H, 2.82%; found C, 43.86%; H, 2.53%.

## Synthesis of 2-Hydroxy-1,2,3,6-tetrahydro-azulen-6-carboxylic Acid Ethyl Ester (13)

In a 1-L, three-necked flask, compound **5** (5.66 g, 12.35 mmol) was dissolved in 650 mL of dry THF. The solution was cooled to −78°C with an acetone–liquid nitrogen bath and tetrabutylammoniumfluoride (TBAF) (68 mL, 68.00 mmol) was added in one portion. Cooling was removed, and the solution was stirred for 4 h at room temperature. When the reaction was complete, 200 mL of saturated $NH_4Cl$ solution was added. The THF was evaporated, and the resulting mixture extracted thrice with ethyl acetate. The

combined organic phase was washed three times with brine and dried with $MgSO_4$, and the solvent was evaporated to give the crude product. The new material was purified by using silica-gel column chromatography with a mixture of ether and pentane (1 : 3). When all the impurities had emerged from the column, the column was washed with ether to yield the desired product in 62.5% (1.72 g) yield. The product was isolated as a bluish viscous liquid, which solidified in the refrigerator.

$R_F$ (ether/pentane, 3 : 2) = 0.32; $^1$H NMR (200.1 MHz, $CDCl_3$): $\delta = 6.23$ (d, $^3J = 9.26$ Hz, 2H, 4/8-H), 5.42 (m, 2H, 5/7-H), 4.54 (m, 1H, 2-H), 4.24 (q, $^3J = 7.15$ Hz, 2H, 10-H), 3.06/2.72 (m, 4H, 1/3-H), 2.60 (t, $^3J = 5.4$ Hz, 1H, 6-H), 1.30 (t, $^3J = 7.14$ Hz, 3H, 11-H); $^{13}$C NMR (50.3 MHz, $CDCl_3$): $\delta = 173.0$ (s, C-9), 139.3 (s, C-3a/8a), 125.00 (d, C-4/8), 117.01 (d, C-5/7), 70.84 (d, C-2), 61.01 (t, C-10), 45.05 (d, C-6), 46.36 (t, C-1/3), 14.2 (q, C-11); IR (film): $\tilde{\nu} = 3427\,cm^{-1}$ (m), 2980, 2930, 2907 (m, CH-stretching), 1736 (s, C=O), 1368 (m), 1297 (m), 1263 (m), 1194 (m), 1174 (m), 1040 (m); UV/Vis ($CH_3CN$): $\lambda_{max}$ (lg $\varepsilon$) = 194 nm (4.00), 206 (4.10), 274 (3.43), 294 (3.18), 310 (2.84), 330 (2.44); MS (EI, 70 eV): $m/z$ (%) = 220 [$M^+$] (12), 211 (3), 200 (3), 191 [$M^+$-$CH_3CH_2$] (4), 173 [191-$H_2O$] (9), 147 [$M^+$-EtOOC] (100), 129 [147–$H_2O$] (49), 115 (11); HRMS ($C_{13}H_{16}O_3$): calcd. 220.1099; found 220.10964 $\pm$ 4 ppm.

## Synthesis of 2-Chloro-1,2,3,6-tetrahydro-azulen-6-carboxylic Acid Ethyl Ester (14)

Alcohol **13** (100 mg, 0.45 mmol) dissolved in 10 mL of $CCl_4$ was placed in a 50-mL, three-necked flask. Then $Ph_3P$ (132 mg, 1.1 eq) was added, and the mixture was refluxed overnight. When the reaction was complete the mixture was filtered to remove unreacted $Ph_3P$. The product was purified by silica-gel column chromatography using a mixture of $CH_2Cl_2$ and pentane (1 : 3) as the eluent. The first compound to elute was unreacted $Ph_3P$; then the product started eluting. The last fraction to emerge was unreacted starting material. The product was isolated as a light bluish liquid in 60% yield (64.5 mg).

$R_F$ ($CH_2Cl_2$) = 0.73; bp = 120–123°C/5 torr; $^1$H NMR (200.1 MHz, $CDCl_3$): $\delta = 6.22$ (m, 2H, 4/8-H), 5.47 (m, 2H, 5/7-H), 4.60 (m, 1H, 2-H), 4.25 (q, $^3J = 7.14$ Hz, 2H, 10-H), 3.01–3.32 (m, 4H, 1/3-H), 2.68 (t, $^3J = 5.61$ Hz, 1H, 6-H), 1.30 (t, $^3J = 7.14$ Hz, 3H, 11-H); $^{13}$C NMR (50.3 MHz, $CDCl_3$): $\delta = 173.0$ (s, C-9), 134.8 (s, C-3a/8a), 124.4 (d, C-4/8), 117.5 (d, C-5/7), 61.2 (t, C-10), 47.1 (t, C-1/3), 45.1 (d, C-2), 44.2 (d, C-6), 14.2 (q, C-11). IR (film): $\tilde{\nu} = 3450\,cm^{-1}$ (w), 3026 (w), 2981 (m), 2938 (m), 2906 (w), 2852 (w), 1737 (s), 1368 (m), 1303 (s), 1258 (s), 1196 (s), 1176 (s), 1166 (m), 1117 (w), 751 (w), 712 (m); UV/Vis ($CH_3CN$): $\lambda_{max}$ (lg $\varepsilon$): 206 nm (4.26), 272 (3.56); MS (EI, 70 eV): $m/z$

(%) = 240 [$M^+(^{37}Cl)$] (3), 238 [$M^+(^{35}Cl)$] (7), 212 [$M^+$-HCl] (1), 209 [$^{35}M^+$-$CH_3CH_2$] (6), 200 (6), 173 [$M^+$-$CH_3CH_2$–HCl] (8), 167 [$^{37}M^+$-EtOOC] (29), 165 [$^{35}M^+$-EtOOC] (100), 129 [167/165-HCl] (86); anal. calcd. for $C_{13}H_{15}O_2Cl$ (238.71): C, 65.41%; H, 6.33%; found C, 65.52%; H, 6.27%.

## Synthesis of 2-Bromo-1,2,3,6-tetrahydro-azulen-6-carboxylic Acid Ethyl Ester (15)

In a 250-mL, three-necked flask $PPh_3$ (1.25 g, 4.77 mmol) was dissolved in 50 mL of $CCl_4$ under nitrogen. The solution was cooled with an ice bath and $Br_2$ (762 mg, 4.77 mmol) in 20 mL of $CCl_4$ was added dropwise to the solution from a dropping funnel. When the addition was complete the ice bath was removed, and the mixture was left to stir at room temperature. After 15 min alcohol **13** (1.0 g, 4.54 mmol) in 20 mL of $CCl_4$ was added from a dropping funnel in one portion. When the addition was complete the mixture was refluxed for 1 h. Water was added, and the organic layer was extracted with diethyl ether. The organic layer was again washed with water, separated, and dried with $MgSO_4$. The solvent was evaporated and the product purified by silica-gel column chromatography using a mixture of $CH_2Cl_2$ and pentane as the eluent. The purification yielded 390 mg (30%) of the product as a light blue liquid.

$R_F$ ($CH_2Cl_2$/pentane, 1 : 1) = 0.6; bp. = 134–136°C/5 Torr (distilled as a colorless liquid but also visibly decomposed simultaneously; $^1$H NMR (200.1 MHz, $CDCl_3$): $\delta = 6.17$ (m, 2H, 4/8-H), 5.40 (m, 2H, 5/7-H), 4.57 (m, 1H, 2-H), 4.19 (q, $^3J = 7.14$ Hz, 2H, 10-H), 3.36–3.02 (m, 4H, 1/3-H), 2.68 (t, $^3J = 5.63$ Hz, 1H, 6-H), 1.24 (t, $^3J = 7.13$ Hz, 3H, 11-H); $^{13}$C NMR (50.3 MHz, $CDCl_3$): $\delta = 173.2$ (s, C-9), 139.1 (s, C-3a/8a), 124.3 (d, C-4/8), 118.1 (d, C-5/7), 61.1 (t, C-10), 47.8 (t, C-1/3), 47.5 (d, C-6), 45.1 (d, C-2), 14.2 (q, C-11). IR (film): $\tilde{\nu} = 3452\,cm^{-1}$ (w), 3025 (w), 2980, 2938 (m, CH-stretching), 2873, 2824 (w), 1736 (s, C=O), 1368 (m), 1302 (s), 1226 (s), 1196 (s), 1173 (s), 1040 (m); UV/Vis ($CH_3CN$): $\lambda_{max}$ (lg $\varepsilon$): 206 nm (4.31), 270 (3.55), 312 (2.79), 320 (2.69), 340 (2.60); MS (EI, 70 eV): $m/z$ (%) = 284 [($^{81}$Br)$M^+$] (2), 282 [($^{79}$Br)$M^+$] (2), 253 [$^{79}M^+$-$CH_3CH_2$] (1), 211 [$^{81}M^+$-EtOOC] (26), 209 [$^{79}M^+$-EtOOC] (26), 202 [$M^+$-HBr] (12), 185(12), 172 [$M^+$-HBr–$CH_3CH_2$] (14), 129 [$M^+$-EtOOC–HBr] (100); anal. calcd. for $C_{13}H_{15}O_2Br$ (283.16): C, 55.14%; H, 5.34%; found C, 55.46%; H, 5.44%.

## Synthesis of 2-Iodo-1,2,3,6-tetrahydro-azulen-6-carboxylic Acid Ethyl Ester (16)

To a mixture of alcohol **13** (200 mg, 0.91 mmol) in 10 mL of iodobenzene (461 mg, 1.82 mmol) were added $PPh_3$ (476 mg, 1.82 mmol) and

hexamethylphosphorous triamide (651 mg, 3.63 mmol) in one portion. The dark mixture was stirred at room temperature for 5 h until TLC analysis showed consumption of all starting material. The mixture was diluted with ether (40 mL) and quenched with an ice-cold saturated solution of sodium bicarbonate. The organic layer was separated and washed consecutively with 1M $H_2SO_4$, water, and finally a saturated solution of $NaHCO_3$. The organic phase was dried with $MgSO_4$. The product was purified by silica-gel column chromatography using a mixture of $CH_2Cl_2$ and pentane (1 : 2) as the eluent. The product was isolated as a colorless liquid (180 mg) in 60% yield. The product can be preserved for a few days in deep freeze but the colorless liquid turns gradually dark brown, decomposing.

$R_F$ ($CH_2Cl_2$/pentane, 1 : 2) = 0.42; bp = decomposed on heating; $^1$H NMR (200.1 MHz, $CDCl_3$): $\delta = 6.22$ (m, 2H, 4/8-H), 5.43 (m, 2H, 5/7-H), 4.76 (m, 1H, 2-H), 4.25 (q, $^3J = 7.16$ Hz, 2H, 10-H), 3.38–3.12 (m, 4H, 1/3-H), 2.74 (t, $^3J = 5.58$ Hz, 1H, 6-H), 1.30 (t, $^3J = 7.13$ Hz, 3H, 11-H); $^{13}$C NMR (50.3 MHz, $CDCl_3$): $\delta = 173.0$ (s, C-9), 134.8 (s, C-3a/8a), 124.3 (d, C-4/8), 118.0 (d, C-5/7), 61.1 (t, C-10), 49.8 (t, C-1/3), 49.9 (d, C-6), 45.1 (d, C-2), 14.2 (q, C-11); UV/Vis ($CH_3CN$): $\lambda_{max}$ (lg $\varepsilon$): 198 nm (4.32), 264 (3.60); MS (EI, 70 eV): $m/z$ (%) = 330 [$M^+$] (0.5), 257 [$M^+$-EtOOC] (4), 202 [$M^+$-HI] (13), 173 [202—$CH_3CH_2$] (6), 129 [$M^+$-HI–EtOOC] (100); anal. calcd. for $C_{13}H_{15}O_2I$ (330.17): C, 47.29%; H, 4.58%; found C, 47.68%; H, 4.57%.

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