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Synthesizing the Tetracyclic Core of Nanolobatolide

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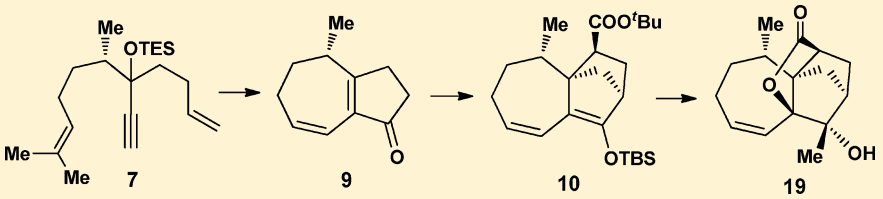
Supporting Information



ABSTRACT: A concise synthetic pathway that enables the stereoselective construction of the tetracyclic core of nanolobatolide has been developed by applying a tandem ring-closing metathesis (RCM) reaction of dienynes, a Eu(fod)$_3$-catalyzed intermolecular Diels–Alder reaction, and a biomimetic epoxide opening reaction as key steps.

Azulene-type sesquiterpenoids are a large group of natural products that exhibit various interesting biological activities.[1] Recently one member of this family, nanolobatolide (**1**),[2] that possesses a novel C_{18} terpenoid-related structure has been isolated from the soft coral *Sinularia nanolobata*. The structure of nanolobatolide (**1**) has been established by extensive spectroscopic studies and validated by X-ray diffraction analysis. Biological studies suggest that nanolobatolide (**1**) has promising anti-neuroinflammatory and neuroprotective activities.[2]

Alzheimer's disease and Parkinson's disease are classic neurodegenerative disorders, which have placed ever-increasing burdens on global healthcare and economy.[3] Nanolobatolide could possibly serve as a biological probe to investigate neurodegenerative disorders. Biologically important natural products are a major focus of our laboratory's research areas in a hope of identifying potential leading compounds for drug discovery.[4] Thus the scaffold of nanolobatolide naturally attracted our total synthetic interest.

Nanolobatolide (**1**) comprises an unprecedentedly complex tetracyclic ring system that carries six contiguous stereogenic centers, among which three are quaternary carbons placed at the C1, C7, and C8 positions. The structural complexity of nanolobatolide (**1**) presents a considerable challenge toward synthesis. Shen and co-workers proposed a biosynthetic pathway targeting **1** from a guaiane-type[5] precursor as shown in Figure 1. The hypothetical precursor guaiane **4**, which functioned as the diene of a Diels–Alder reaction, was intended to react with acrylic acid to afford the carboxylic acid **3**. The epoxidation of **3** in the double bond of the five-membered ring of **3** was expected to produce **2**. They proposed that the subsequent acid-catalyzed ring opening of the epoxide and finally the lactonization of **2** could lead to the formation of **1**.

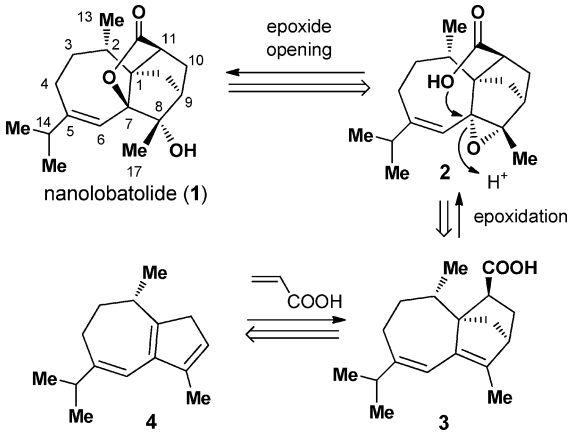


Figure 1. Proposed biosynthetic pathway for nanolobatolide (**1**).

The first biomimetic total synthesis of nanolobatolide (**1**) was achieved by Chen and co-workers in 2011.[6] Their synthetic strategy featured an oxidative ring expansion and a Nazarov cyclization to form the key intermediate **4**, and a biosynthetic pathway of intermolecular Diels–Alder reaction was also involved for the formation of tetracyclic core.

Our group was also involved in the synthetic study toward the total synthesis of nanolobatolide (**1**), and we designed a synthetic strategy that was a bit similar to the one utilized by Chen's group. In furtherance of our synthetic proposal, we herein report our establishment of a new entry to the tetracyclic core of nanolobatolide by applying a tandem ring-closing

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metathesis (RCM) reaction of dienynes,[7] a $Eu(fod)_3$-catalyzed intermolecular Diels–Alder reaction,[8] and a biomimetic epoxide opening reaction as key steps.[2]

As indicated in our above synthetic proposal for nanolobatolide (**1**), our objective was to identify a synthetic pathway that enables a rapid access to the tetracyclic skeleton of nanolobatolide (**1**). We intended such a pathway would lay a foundation to achieve the total synthesis of nanolobatolide (**1**) as well as for the modular construction of a library of its analogues, which in turn it was hoped would facilitate medicinal chemistry studies of these biologically active compounds.

Retrosynthetically, we anticipated that **B** would straightforwardly generate scaffold **A** by regio- and stereoselective nucleophilic addition (Figure 2). We further envisioned that

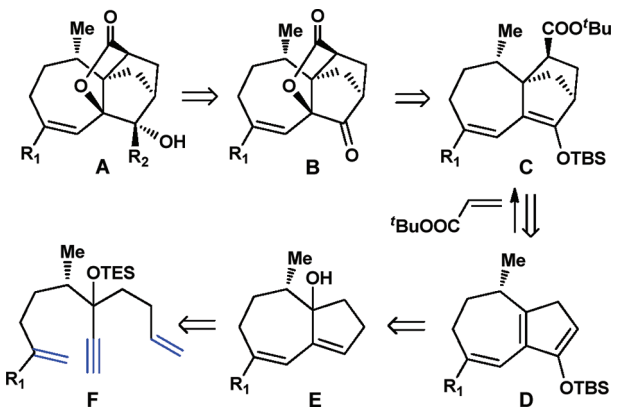
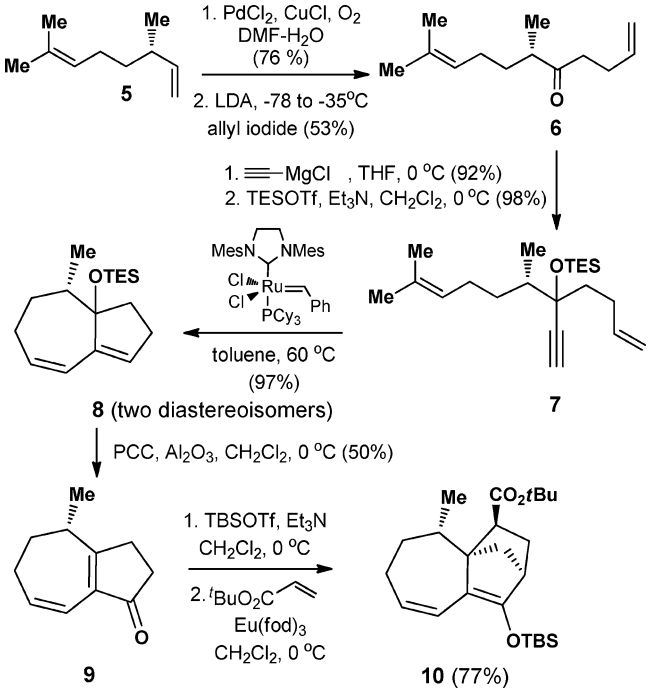


Figure 2. Retrosynthetic analysis of nanolobatolide (**1**).

B could easily arise from **C** via epoxidation/epoxide opening reaction, given that the vinyl silyl ether subunit could promote the epoxidation of olefin easily.[9] We also anticipated that the key intermediate **C** would be favorably formed via the intermolecular Diels–Alder reaction of silyl ether **D** and *tert*-butyl substituted acrylate in view of their favorable electronic and steric effects.[10] Thus, our retrosynthetic analysis could trace back to the construction of intermediate **D**, which was expected to derive from **E** via PCC oxidative rearrangement,[11] followed by silylation. The key intermediate **E** could be directly produced from **F** via a tandem dienyne RCM reaction, which is a powerful reaction utilized by Grubbs and co-workers for the preparation of fused bicyclic rings in 1994[12] and by many other groups for the construction of a number of complex scaffolds more recently.[13]

Our synthesis of the core structure of nanolobatolide (**1**) therefore targeted the construction of the (5,7)-bicyclic core **9** by way of a cascade RCM reaction starting from a functionalized dienyne such as **7**. To that end, the commercially available *β*-citronellene **5** was chosen as the substrate to go through the Wacker oxidation. The ketone generated thereof was first subjected to a LDA-mediated enolization, followed by the reaction with allyl iodide to afford ketone **6** in 40% overall yield. Ketone **6** was treated with the Grignard reagent ethynylmagnesium chloride to obtain enyne **7** (in 90% yield in two steps) after protection of the newly generated tertiary alcohol. Afterward under the typical conditions of a RCM reaction, dienyne **7** was treated with Grubbs' second-generation catalyst (2 mol %) in toluene at 60 °C for 48 h. The tandem RCM reaction was observed, which prepared the bicyclic conjugated diene **8** in almost quantitative yield (Scheme 1). Compound **8**, without purification, was to be utilized in the next step of our experiment.

Scheme 1. Synthesis of Intermediate 10



At this stage, we planned to prepare tetrahydroazulenone **9** directly from **8** by PCC-mediated oxidative allylic rearrangement.[11] Our initial attempt was to remove the silyl group of compound **8**, followed by PCC-mediated oxidative rearrangement. Unfortunately, the newly formed tertiary alcohol turned out to be unstable under the oxidative conditions.

We therefore tested the same reaction involving substrate **8** with the in situ deprotection of its silyl group. In that event, when **8** was subjected to oxidation in line with the literature reported procedure, the desired product **9** was obtained, albeit in low yield. By further optimization of the reaction conditions, we observed that the product yield was increased to 50% when the reaction was carried out in the presence of Al_2O_3 (PCC-Al_2O_3 = 1.0 mmol/g). The yield increase presumably was due to the fact that the formed oxidative product **9** could be more easily extracted from the reaction mixture.

To construct the tricyclic compound **10**, ketone **9** was first converted to its silyl ether, which was then reacted with *tert*-butyl acrylate in the presence of Lewis acids (such as $BF_3{\cdot}Et_2O$, $TiCl_4$, $EtAlCl_2$). Different from our expectation, the desired annulated product **10** was formed in less than 30% yield. In the course of optimizing the reaction, we identified $Eu(fod)_3$[14] (5 mol %) as an effective catalyst that capably promoted this intermolecular Diels–Alder reaction, and 77% yield of ketone **9** was obtained when the reaction was carried out in CH_2Cl_2 at 0 °C.

With the tricylic product **10** in hand, we next turn to constructing the tetracyclic core of nanolobatolide (**1**). Inspired by the biosynthetic pathway that Chen and co-workers had adopted for the formation of the oxo-bridged tetracyclic core of nanolobatolide, we attempted to establish the core structure **13** via the direct intramolecular epoxide-opening reaction involving the C11 carboxylate and the C7–C8 epoxide. With compound

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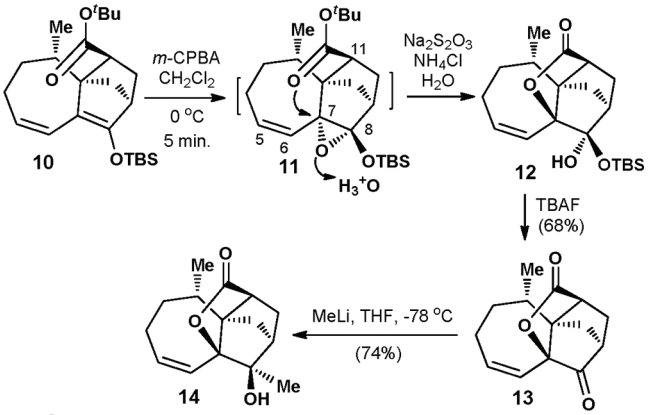
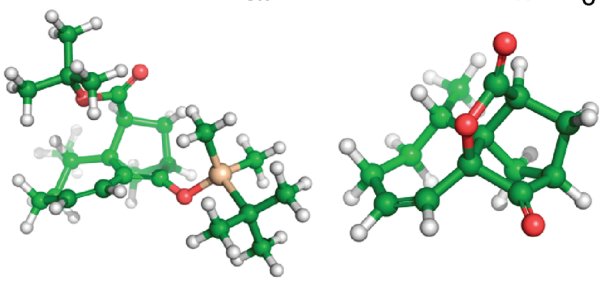
10 available, its ability to participate in *m*-CPBA-mediated direct intramolecular epoxide-opening reaction was thoroughly examined. We envisioned that the core structure **12** could be derived from **11** via the intramolecular epoxide-opening reaction involving the C11 carboxylate and the C7−C8 epoxide. After careful optimization, we found that the proposed transformation could be effectively achieved by reaction of substrate **10** with excess amount of *m*-CPBA (1.2 equiv) in CH_2Cl_2 within 5 min at 0 °C, and the formed product **12** was immediately removed from the reaction system by treatment of the reaction mixture with an ammonium chloride solution of $Na_2S_2O_3$ in order to avoid the further epoxidation of the C5/C6 double bond of product **12**. The regio- and stereoselective formation of the intermediate epoxide **11** as shown could be attributed to both the favorable electronic effect of OTBS and the conformation control of substrate **10**, as both led *m*-CPBA to approach from the bottom face of **10** (see 3D structure of **10** optimized by Gaussian 03 in Scheme 2).

Scheme 2. Synthesis of Compound 14





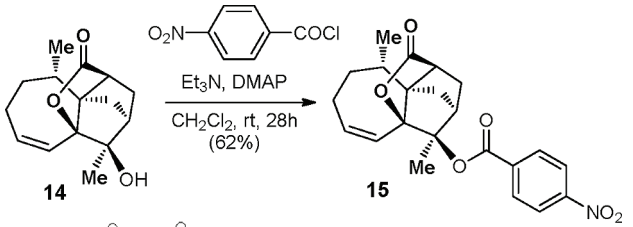
3D structure of **10** 3D structure of **13**

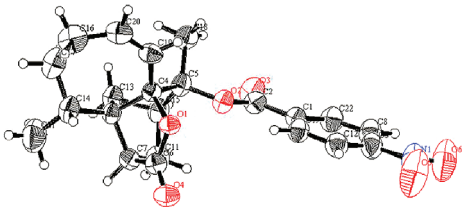
We then attempted to build up the model with the right relative stereochemistry of the natural product from ketone **12**. To this end, **12** was subjected to desilylation by TBAF, and the formed ketone **13** was treated with MeLi; however, product **14** with the wrong stereochemistry at C8 was obtained in 74% yield as a single diastereoisomer. To determine its relative stereochemistry, compound **14** was converted to its corresponding 4-nitrobenzoate **15**, and the structure of **15** has been confirmed by X-ray crystallographic analysis (Scheme 3).

While we attempted to change the reaction conditions by varying the solvents and adding the additives, as well as applied several other alkylating agents including MeMgBr in order to invert the stereochemical outcome, no improvement incurred.

We inferred from the above experiments especially those failures that the substrate conformation played a pivotal role in controlling the stereochemical outcome of epoxidation. Thus

Scheme 3. Synthesis of 4-Nitrobenzoate Ester 15



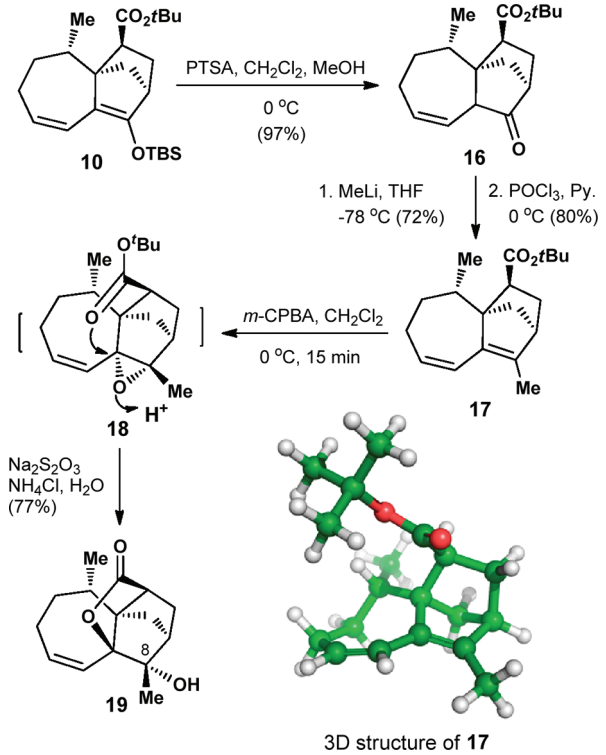


X-ray structure of compound **15**

we aimed to explore an alternative approach to stereoselectively install the tertiary alcohol at C8.

We envisioned that the bottom face of **17** was more accessible than its top face (see 3D structure of **17** optimized by Gaussian 03 in Scheme 4), thereby *m*-CPBA would approach

Scheme 4. Stereoselective Synthesis of Compound 18



3D structure of **17**

17 from its bottom face; as a result, product **18** would be formed predominately. To validate our analysis, substrate **10** was first subjected to the desilylation to afford ketone **16**, which was then methylated with MeLi, followed by the dehydration with $POCl_3$ in the presence of pyridine in CH_2Cl_2 at 0 °C to give diene **17** in 58% yield for two steps. Fortunately, with treatment of diene **17** with *m*-CPBA in CH_2Cl_2 at 0 °C for 15 min, the formed epoxide underwent *in situ* epoxide-opening reaction to afford the desired product **19** in 77% yield. The stereochemistry of **19** was determined by comparing the its

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NMR spectra with that of both natural product nanolobatolide and compound **14**. By then we were pleased to have developed two reaction pathways, both of which allowed for generating the chiral center of C8 of the nanolobatolide's scaffold.

In conclusion, in 11 steps we have successfully synthesized the tetricyclic core of nanolobatolide (**1**) starting from the commercially available *β*-citronellene. The key synthetic steps include (1) a tandem ring-closing metathesis (RCM) reaction of dienynes, (2) a $Eu(fod)_3$-catalyzed intermolecular Diels–Alder reaction;, and (3) a biomimetic epoxide opening reaction. Our current work will focus on developing an asymmetric version of the total synthesis of nanolobatolide (**1**) and its analogues.

EXPERIMENTAL SECTION

Synthesis of 6,10-Dimethylundeca-1,9-dien-5-one (6). $PdCl_2$ (3.54 g, 20 mmol) and CuCl (19.8 g, 200 mmol) were added to a solution of DMF (560 mL) and water (80 mL), and the mixture was stirred at room temperature for 3 h under an oxygen atmosphere. To this resultant solution was added a solution of *β*-citronellene **5** (27.6 g in DMF (42 mL) and H_2O (6 mL), 200 mmol) via a cannula. The formed mixture was stirred under balloon pressure of oxygen for 2 days. This reaction was worked up with the addition of a saturated aqueous NH_4Cl solution (500 mL) and extracted with Et_2O (3 × 1500 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The generated solvent thereof was removed *in vacuo* at 0 °C, and the residue was purified by flash column chromatography (pentane/Et_2O = 150/1) to give ketone product **5′** (23.4 g) as colorless oil in 76% yield: R_f = 0.3 (pentane/Et_2O = 10/1); IR (film) ν_{max} 2958, 2924, 2854, 1737, 1711, 1461, 1367, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.04–5.02 (m, 1H), 2.49–2.45 (m, 1H), 2.08 (s, 3H), 1.94–1.90 (m, 2H), 1.69–1.64 (m, 1H), 1.64 (s, 3H), 1.55 (s, 3H), 1.35–1.28 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 212.4, 132.0, 123.7, 46.5, 32.8, 27.8, 25.6, 25.5, 17.5, 16.0; HRMS-ESI calcd for $C_{10}H_{18}O$ [M + H^+] 155.1436, found 155.1424.

To a solution of LDA (72.0 mL, 2.0 M in THF, 144 mmol) was added a solution of **5′** (18.4 g, 120 mmol) in THF (200 mL) in a dropwise manner via a cannula at −78 °C, and the formed mixture was stirred at the same temperature for 30 min. To this solution was added allyl iodide (12.0 mL, 131 mmol) in a dropwise manner via a syringe, and the formed mixture was stirred at −35 °C for 4.5 h. This reaction was worked up with the addition of a saturated aqueous NH_4Cl solution (200 mL) and extracted with Et_2O (3 × 500 mL). The combined organic layer was washed by brine and dried over anhydrous Na_2SO_4. After the removal of the solvent *in vacuo* at 0 °C, the residue was purified by flash column chromatography (pentane/Et_2O = 150/1) to give product **6** (12.4 g) as colorless oil in 53% yield: R_f = 0.4 (pentane/Et_2O = 10/1); IR (film) ν_{max} 2969, 2930, 2859, 1712, 1458, 1377, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86–5.72 (m, 1H), 5.05–4.93 (m, 3H), 2.53–2.48 (m, 3H), 2.35–2.26 (m, 2H), 1.97–1.89 (m, 2H), 1.75–1.63 (m, 1H), 1.66 (s, 3H), 1.57 (s, 3H), 1.39–1.29 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 137.4, 132.2, 123.8, 115.1, 45.8, 40.2, 33.0, 27.7, 25.7, 17.7, 16.3; EI-MS m/z (%) 194 (92), 152 (100), 123 (58); HRMS-ESI calcd for $C_{13}H_{22}O$ [M + H^+] 195.1749, found 195.1744.

Synthesis of Enyne 7. To a solution of **6** (15.77 g, 81.3 mmol) in THF (300 mL) was added ethynylmagnesium chloride (366 mL, 0.6 M in THF/toluene, 244 mmol) at 0 °C, and the formed mixture thereof was stirred at 0 °C for 1.5 h. This reaction was worked up with the addition of saturated aqueous NH_4Cl solution (200 mL) and extracted with Et_2O (3 × 500 mL). The combined organic layer was washed by brine and dried over anhydrous Na_2SO_4. After the removal of the solvent *in vacuo* at 0 °C, the residue was purified by flash column chromatography (pentane/Et_2O = 20/1) to give tertiary alcohol **6′** (16.5 g) as colorless oil in 92% yield: R_f = 0.5 (pentane/Et_2O = 3/1); IR (film) ν_{max} 3466, 3307, 2966, 2927, 2859, 1641, 1452, 1377, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.93–5.85 (m, 1H), 5.13–5.12 (m, 1H), 5.09 (dd, J = 17.2, 1.7 Hz, 1H), 4.99 (d, J = 10.2 Hz, 1H), 2.44 (d, J = 2.0 Hz, 1H), 2.35–2.31 (m, 2H), 2.15–2.09 (m, 1H), 2.05(2.00) (s, 1H), 1.97–1.92 (m, 1H), 1.81–1.68 (m, 4H), 1.70 (s, 3H), 1.62 (s, 3H), 1.24–1.18 (m, 1H), 1.04 (1.02) (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 131.6, 131.5, 124.4, 124.3, 114.7, 86.0, 85.8, 74.4, 74.3, 73.1, 42.3, 42.2, 38.0, 31.5, 31.1, 28.6, 28.4, 26.1, 25.6, 17.6, 14.3, 13.5; EI-MS m/z (%) 220 (11), 165(42), 121 (27), 96 (100); HRMS-ESI calcd for $C_{15}H_{24}O$ [M + H^+] 221.1905, found 221.1925.

To a solution mixture of tertiary alcohol (7.76 g, 35.3 mmol) and Et_3N (14.8 mL, 105.8 mmol) in CH_2Cl_2 (300 mL) was added TESOTf (8.0 mL, 35.3 mmol) at 0 °C, and the resultant mixture was stirred at 0 °C for 4 h. The reaction was worked up with the addition of a saturated aqueous NH_4Cl solution (200 mL), and the formed mixture of was extracted with DCM (3 × 200 mL). The combined organic layer was washed by brine and dried over anhydrous Na_2SO_4. After the removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (pentane) to give product **7** (11.5 g) as colorless oil in 98% yield: R_f = 0.9 (pentane); IR (film) ν_{max} 3312, 2956, 2877, 1455, 1415, 1375, 1238, 1080, 1006, 910, 741, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88–5.83 (m, 1H), 5.16–5.14 (m, 1H), 5.04 (dd, J = 17.1, 1.3 Hz, 1 H), 4.96 (d, J = 10.2 Hz, 1H), 2.43 (d, J = 5.6 Hz, 1H), 2.23–2.19 (m, 2H), 2.15–2.05 (m, 1H), 1.94–1.90 (m, 1H), 1.75–1.66 (m, 2H), 1.71 (s, 3H), 1.63 (s, 3H), 1.15–1.12 (m, 1H), 0.99 (t, J = 7.8 Hz, 9H), 0.98 (d, J = 10.6 Hz, 3H), 0.71 (q, J = 7.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 131.3, 124.7, 114.1, 87.2, 75.2, 73.6, 73.5, 42.0, 41.8, 38.2, 38.0, 31.4, 31.0, 28.4, 28.2, 26.3, 25.6, 17.6, 14.1, 13.8, 7.0, 6.2; EI-MS m/z (%) 334 (62), 305 (81), 279 (100), 251 (57); HRMS-ESI calcd for $C_{21}H_{38}OSi$ [M + H^+] 335.2770, found 335.2766.

Synthesis of 4-Methyl-2,3,5,6-tetrahydroazulen-1(4*H*)-one (9). To a solution of Grubbs second generation catalyst[15] (81 mg, 0.095 mmol) in toluene (80 mL) was added a solution of **7** (2.121 g, 6.35 mmol in toluene (40 mL), and the formed mixture was stirred at 60 °C for 24 h. To this solution was added a solution of Grubbs second generation catalyst (27 mg, 0.032 mmol) in toluene (20 mL) via a cannula, and the mixture was stirred at 60 °C an additional 24 h. GC–MS (or ^1H NMR) monitored throughout the completion of this reaction. The reaction mixture was filtered through a short pad of aluminum oxide (neutral) and washed with toluene. The filtrate was concentrated *in vacuo* to give a crude ring-closed product **8** without further purification: R_f = 0.9 (pentane); IR (film) ν_{max} 3017, 2957, 2936, 2913, 2876, 1458, 1237, 1080, 1009, 868, 739, 723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.11–6.05 (m, 1H), 5.66–5.52 (m, 2H), 2.52–2.44 (m, 1H), 2.41–2.33 (m, 1H), 2.28–2.22 (m, 3H), 2.13–2.09 (m, 1H), 2.02–1.88 (m, 1H), 1.67–1.61 (m, 1H), 1.41–1.37 (m, 1H), 1.06 (d, J = 6.8 Hz, 1.5H), 0.94 (t, J = 8.0 Hz, 9H), 0.87 (d, J = 7.2 Hz, 1.5H), 0.57 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 145.8, 132.9, 130.3, 130.0, 125.1, 124.1, 90.8, 88.0, 45.1, 41.0, 40.5, 38.0, 30.3, 29.8, 29.0, 27.2, 27.0, 17.8, 14.1, 7.1, 6.2; HRMS-ESI calcd for $C_{17}H_{30}OSi$ [M + H^+] 279.2144, found 279.2148.

To a solution of the above intermediate in CH_2Cl_2 (150 mL) was added PCC-Al_2O_3 (19 g, 1 mol/g, 19 mmol) at 0 °C,[11] and the mixture was stirred at room temperature for 2 h. The reaction solution was filtered through a short aluminum oxide (neutral) layer. After removal of the solvent *in vacuo*, the residue was purified by a flash column chromatography (pentane/Et_2O = 50/1 then 5/1) to give **9** (525 mg) as a colorless oil in 49% yield for 2 steps: R_f = 0.2 (hexane/Et_2O = 5/1); IR (film) ν_{max} 2964, 2921, 2875, 1700, 1624, 1420, 1276, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (d, J = 11.6 Hz, 1H), 6.00–5.96 (m, 1H), 2.82–2.73 (m, 2H), 2.51–2.36 (m, 5 H), 1.84–1.81 (m, 2H), 1.18 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 178.1, 134.7, 134.6, 117.9, 38.0, 34.3, 29.9, 29.5, 27.4, 18.4; EI-MS m/z (%) 162 (100); HRMS-ESI calcd for $C_{11}H_{14}O$ [M + H^+] 163.1123, found 163.1122.

Synthesis of *tert*-Butyl 1-((*tert*-Butyldimethylsilyl)oxy)-5-methyl-2,3,4,5,6,7-hexahydro-2,4a-methanobenzo[7]-annulene-4-carboxylate (10). To a solution of **9** (390 mg, 2.4 mmol) in CH_2Cl_2 (20 mL) was sequentially added dry Et_3N (5.0 mL, 36 mmol) and TBSOTf (7.2 mL, 31.3 mmol) at 0 °C, and the formed

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mixture was stirred at room temperature for 15 min. To this solution was sequentially added a solution of $Eu(fod)_3$[14] (125 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) and *tert*-butyl acrylate (3.5 mL, 24.0 mmol) at room temperature. The formed mixture thereof was stirred at the same temperature for 10 min. The reaction mixture was worked up with the addition of a saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After the removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (hexane/EtOAc = 200/1) to give **10** (747 mg) as colorless oil in 77% yield: R_f = 0.9, (hexane/EtOAc = 8/1); IR (film) ν_{max} 2962, 2937, 2882, 1740, 1611, 1452, 1244, 1150, 851 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (d, J = 11.6 Hz, 1H), 5.26−5.23 (m, 1H), 2.74 (dd, J = 9.1, 4.4 Hz, 1H), 2.56 (brs, 1H), 2.54−2.47 (m, 1H), 2.42−2.37 (m, 1H), 2.29−2.22 (m, 1H), 1.92−1.87 (m, 1H), 1.85−1.80 (m, 2H), 1.49−1.45 (m, 2H), 1.39 (s, 9H), 0.96 (d, J = 6.9 Hz, 3H), 0.95 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 156.2, 125.9, 120.7, 117.3, 79.8, 66.4, 48.0, 46.3, 44.5, 33.6, 33.2, 32.1, 31.6, 28.1, 25.7, 18.1, 17.7, −3.8, −3.9; EI-MS m/z (%) 404 (100), 347 (11), 303 (8), 276 (48), 233 (23); HRMS-ESI calcd for $C_{24}H_{40}O_3Si$ [M + H^+] 405.2825, found 405.2818.

Synthesis of 10-Methyl-1,2,3,3a,9,10-hexahydro-2,5a-methanocyclohepta[*b*]cyclopenta[*c*]furan-4,11(8*H*)-dione (13). To a solution of **10** (295 mg, 0.73 mmol) in CH_2Cl_2 (10 mL) was added a solution of *m*-CPBA (202 mg, 0.87 mmol) at 0 °C, and the mixture was stirred at the same temperature for 15 min. The reaction was worked up by addition of a solution of $Na_2S_2O_3$ (5 mL) and NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ and brine and then dried over Na_2SO_4. The dried solution was concentrated to ca. 2 mL and diluted with THF (5 mL). To this solution was added TBAF (1.56 mL, 1,0 M in THF), and the formed mixture was stirred at room temperature for 3 h. The reaction was worked up by addition of a saturated solution of NH_4Cl (5 mL), and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (hexane/EtOAc = 10/1) to give lactone **13** (115 mg) as colorless solid in 68% yield: R_f = 0.2 (hexane/EtOAc = 8/1); mp 70−72 °C; IR (film) ν_{max} 2967, 2934, 2880, 1788, 1763, 1719, 1701, 1653, 1458, 1368, 1220, 1152, 976, 918 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.19−6.15 (m, 1H), 5.72 (dd, J = 2.5, 12.1 Hz, 1H), 2.90−2.86 (m, 2H), 2.44−2.39 (m, 1H), 2.34−2.27 (m, 2H), 2.23−2.19 (m, 1H), 2.15−2.12 (m, 1H), 1.94−1.92 (m, 1H), 1.82−1.78 (m, 2H), 1.73−1.64 (m, 1H), 1.11 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 177.5, 139.9, 119.2, 87.4, 62.9, 48.3, 45.8, 33.6, 32.0, 30.9, 29.7, 25.7, 18.5; EI-MS m/z (%) 232 (100), 171 (15); HRMS-ESI calcd for $C_{14}H_{17}O_3$ [M + H^+] 233.1178, found 233.1179.

Synthesis of 11-Hydroxy-10,11-dimethyl-1,2,3,3a,9,10-hexahydro-2,5a-methanocyclohepta[*b*]cyclopenta[*c*]furan-4(8*H*)-one (14). To a solution of **13** (38 mg, 0.16 mmol) in THF (5 mL) was added MeLi (160 μL, 0.16 mmol, 1 M in THF) at −78 °C, and the formed mixture was stirred at the same temperature for 1 h. The reaction was worked up with the addition of a saturated aqueous NH_4Cl solution (2 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (hexane/EtOAc = 10/1) to give **14** (29 mg) as colorless oil in 74% yield (86% yield based on starting material recovery): R_f = 0.1 (hexane/EtOAc = 4/1); IR (film) ν_{max} 3458, 2957, 2925, 2855, 1745, 1471, 1367, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86−5.81 (m, 1H), 5.55 (d, J = 12.4 Hz, 1H), 2.68 (d, J = 11.5 Hz, 1H), 2.41 (s, 1H), 2.33−2.18 (m, 3H), 2.08−2.03 (m, 1H), 1.93−1.87 (m, 1H), 1.82−1.73 (m, 2H), 1.65−1.56 (m, 1H), 1.52−1.45 (m, 2H), 1.28 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 131.2, 124.9, 93.9, 78.4, 64.4, 47.1, 45.9, 32.5, 32.2, 31.2, 30.9, 29.6, 28.1, 24.6, 18.8; EI-MS m/z (%) 248 (87), 220 (100), 191 (18); HRMS-ESI calcd for $C_{15}H_{20}O_3$ [M + H^+] 249.1491, found 249.1491.

Synthesis of 10,11-Dimethyl-4-oxo-1,2,3,3a,4,8,9,10-octahydro-2,5a-methanocyclohepta[*b*]cyclopenta[*c*]furan-11-yl-4-nitrobenzoate (15). To a solution of **14** (60 mg, 0.24 mmol) and 4-(dimethylamino)pyridine (15 mg, 0.12 mmol) in CH_2Cl_2 (4 mL) were added triethylamine (202 μL, 1.45 mmol) and then *p*-nitrobenzoylchloride (134 mg, 0.73 mmol) at room temperature, and the mixture was stirred at the same temperature for 28 h. The reaction was worked up by addition of CH_2Cl_2 (10 mL), and the mixture was washed with aqueous of saturated $NaHCO_3$ and brine. The solution was dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (hexane/EtOAc = 10/1) to give **15** (61 mg) as colorless solid in 62% yield: R_f = 0.6 (hexane/EtOAc = 2/1); mp 169−172 °C; IR (film) ν_{max} 3361, 3169, 2955, 2922, 2855, 2360, 2324, 1773, 1731, 1654, 1632, 1526, 1458, 1279, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 8.7 Hz, 2H), δ 8.18 (d, J = 8.7 Hz, 2H), δ 6.03 (d, J = 12.4 Hz, 1H), 5.95−5.91 (m, 1H), 2.83 (s, 1H), 2.74 (d, J = 11.5 Hz, 1H), 2.35−2.29 (m, 2H), 2.22 (d, J = 13.2 Hz, 1H), 2.13−2.10 (m, 1H), 2.03 (dd, J = 8.0 Hz, 1H), 1.98 (dd, J = 10.7 Hz, 1H), 1.87−1.81 (m, 1H), 1.68 (s, 1H), 1.65 (d, J = 11.5 Hz, 1H), 1.62−1.57 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 163.4, 150.7, 136.1, 131.5, 130.8, 126.4, 123.6, 93.3, 88.0, 64.1, 46.3, 45.9, 45.4, 32.3, 32.1, 30.5, 27.5, 21.1, 18.8; EI-MS m/z (%) 297 (9), 295 (100), 251 (13), 219 (16), 57 (67); HRMS-ESI calcd for $C_{15}H_{20}O_3$ [M + H^+] 398.1598, found 398.1584.

Synthesis of *tert*-Butyl 5-Methyl-1-oxo-1,2,3,4,5,6,7,9a-octahydro-2,4a-methanobenzo[7]annulene-4-carboxylate (16). To a solution mixture of **10** (50 mg, 0.12 mmol) in CH_2Cl_2 (1 mL) and MeOH (1 mL) was added one portion of PTSA·H_2O (23 mg, 0.12 mmol) at 0 °C, and the formed mixture was stirred at the same temperature. The reaction was worked up with the addition of a saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by a flash column chromatography (hexane/EtOAc = 10/1) to give **16** (35 mg) as a colorless oil in 97% yield: R_f = 0.2 (hexane/EtOAc = 5/1); IR (film) ν_{max} 2967, 2924, 2845, 1745, 1703, 1360, 1128, 931 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.63−5.60 (m, 1H), 5.53−5.49 (m, 1H), 3.28 (brs, 1H), 2.69 (brs, 1H), 2.63 (t, J = 7.8 Hz, 1H), 2.52−2.49 (m, 1H), 2.41−2.37 (m, 1H), 2.19−2.13 (m, 1H), 2.04−2.02 (m, 2H), 1.79−1.77 (m, 2H), 1.72 (d, J = 10.1 Hz, 1H), 1.51 (d, J = 10.1 Hz, 1H), 1.41 (s, 9H), 1.10 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.0, 173.2, 130.9, 124.2, 81.0, 61.6, 55.0, 49.8, 48.3, 47.3, 42.4, 35.1, 32.0, 30.8, 28.1, 17.8; EI-MS m/z (%) 290 (37), 248 (9), 218 (100); HRMS-ESI calcd for $C_{18}H_{26}O_3$ [M + H^+] 291.1960, found 291.1950.

Synthesis of *tert*-Butyl 1,5-Dimethyl-2,3,4,5,6,7-hexahydro-2,4a-methanobenzo[7]annulene-4-carboxylate (17). To a solution of **16** (40 mg, 0.138 mmol) in THF (5 mL) was added MeLi (150 μL, 1.0 M in THF, 0.150 mmol) at −78 °C, and the formed mixture was stirred at the same temperature for 1 h. The reaction mixture was worked up with the addition of saturated aqueous NH_4Cl solution (2 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (hexane/EtOAc = 10/1) to give a tertiary alcohol **16′** (30 mg) as colorless oil in 72% yield.

To the solution of the intermediate made above (30 mg, 0.099 mmol) in dry pyridine (0.5 mL) was added $POCl_3$ (0.1 mL) at 0 °C, and the reaction mixture was stirred at the same temperature for 5 h. The reaction mixture was diluted with hexane (20 mL) and worked up with the addition of cold water (5 mL) carefully. After being extracted with EtOAc (3 × 10 mL), the combined organic layer was washed by brine and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by flash column chromatography (hexane/EtOAc = 100/1) to give **17** (23 mg) as colorless oil in 80% yield: R_f = 0.8 (hexane/EtOAc = 8/1); IR (film) ν_{max} 2958, 2929, 2872, 1727, 1457, 1367, 1257, 1149 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (d, J = 11.8 Hz, 1H), 5.43−5.39 (m, 1H), 2.74 (dd, J = 9.2, 4.1 Hz, 1H), 2.59 (brs, 1H), 2.47−2.39 (m, 2H), 2.32−2.28 (m,

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1H), 1.87−1.80 (m, 2H), 1.77 (s, 3H), 1.47−1.42 (m, 3H), 1.39 (s, 9H), 1.15−1.12 (m, 1H), 0.99 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 142.0, 134.9, 128.9, 122.0, 79.7, 68.8, 47.4, 46.9, 46.3, 33.3, 33.1, 28.2, 18.2, 12.6; EI-MS m/z (%) 288 (20), 270 (35), 242 (10), 217 (100); HRMS-ESI calcd for $C_{19}H_{28}O_2$ [M + H$^+$] 289.2168, found 289.2180.

Synthesis of 11-Hydroxy-10,11-dimethyl-1,2,3,3a,9,10-hexahydro-2,5a-methanocyclohepta[*b*]cyclopenta[*c*]furan-4(8*H*)-one (19). To a solution of **17** (9 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added a solution of *m*-CPBA (8 mg, 0.87 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C, and the formed mixture was stirred at same temperature for 15 min. The reaction was worked up with the addition of a solution of $Na_2S_2O_3$ (3 mL) and NH_4Cl (3 mL) and extracted with DCM (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the residue was purified by flash column chromatography (hexane/EtOAc = 10/1 then 5/1) to give lactone **19** (6 mg) as a colorless oil in 77% yield: R_f = 0.1 (hexane/EtOAc = 8/1); IR (film) ν_{max} 3471, 2961, 2928, 2853, 1748, 1458, 1380, 1243, 981 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06−6.01 (m, 1H), 5.58 (d, J = 12.0 Hz, 1H), 2.64 (d, J = 11.5 Hz, 1H), 2.47−2.38 (m, 2H), 2.27−2.18 (m, 2H), 2.06−2.00 (m, 2H), 1.92−1.89 (m, 1H), 1.79−1.75 (m, 1H), 1.64−1.59 (m, 1H), 1.47−1.42 (m, 2H), 1.31 (s, 3H), 0.98 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 134.4, 123.5, 96.9, 80.6, 63.8, 47.0, 45.2, 33.4, 32.3, 32.1, 30.2, 27.4, 20.2, 19.0; EI-MS m/z (%) 248 (100); HRMS-ESI calcd for $C_{15}H_{20}O_3$ [M + H$^+$] 249.1491, found 249.1490.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra and X-ray data including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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