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Stereocontrolled Formal Synthesis of Platencin

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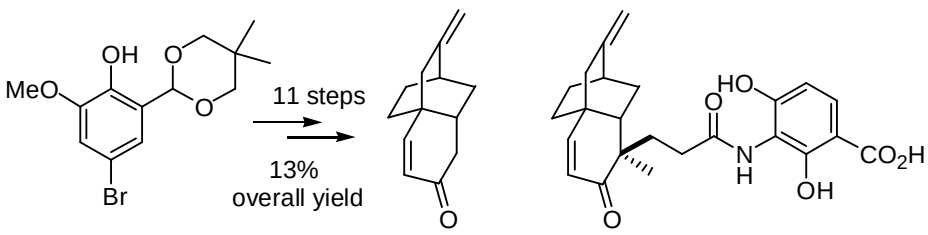
Keywords: Formal synthesis, intermolecular Diels-Alder, masked *o*-benzoquinone, platencin, stereocontrol



7 **3** platencin (**1**)

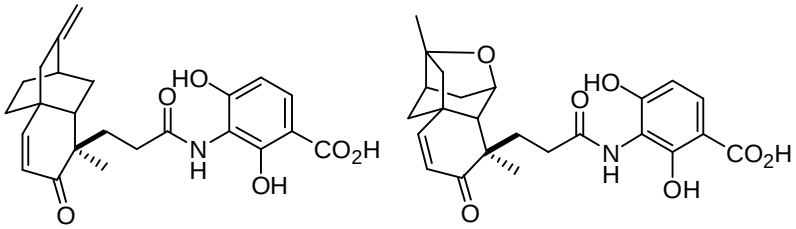
Abstract: A stereocontrolled formal synthesis of platencin was accomplished in 11 steps from bromophenol **7**, in 13% overall yield. The intermolecular Diels-Alder reaction of masked *o*-benzoquinone and aldol condensation were the key steps in the construction of the tricyclic core of platencin.

Introduction

The discovery of antibiotics was a huge step forward in sustaining human health, by preventing deadly infections caused by microorganisms. With the emergence of penicillin, millions of human lives could be saved from diseases for which there was previously no cure. With time, overuse and misuse of antibiotics resulted in drug resistance, or even multidrug resistance. Modification of certain types of

drug can help in preventing loss of efficacy. Methicillin is one of the frequently used drugs for the treatment of infections, but nowadays, the majority of infections are caused by the methicillin-resistant *Staphylococcus aureus* (MRSA)[1] in hospital facilities. Hence, there is an urgent need to develop new antibiotics.

By screening a large number of natural product extracts, Singh and coworkers discovered platencin[2] (**1**) and platensimycin[3] (**2**) (Figure 1), both of which showed highly potent and broad-spectrum activity against many multidrug-resistant pathogens. Platencin (**1**) inhibits fatty acid acyl carrier protein synthases II (FabF) and III (FabH),[4] which are essential for bacterial fatty acid biosynthesis, while platensimycin (**2**) selectively blocks FabF. Because **1** exhibits a broad range of antibacterial/biological properties, the development of new and efficient strategies to synthesize platencin has become a major focal point of synthetic chemistry. Hence, many total[5,6] and formal[7] syntheses of **1** have been reported to date, and different strategies have been adopted to construct its tricyclic core. Among these, Diels-Alder approaches for the construction of the bicyclo[2.2.2]octane skeleton were reported by several groups.[5e,7b,7d,e,i] One of these approaches involves an intramolecular Diels-Alder reaction of masked *o*-benzoquinone.[5e] Masked *o*-benzoquinones, which can be easily generated *in situ* by oxidation of the corresponding 2-methoxyphenols with hypervalent iodine in the presence of an appropriate alcohol, have been used to construct various carbon frameworks in organic synthesis,[8] especially the bicyclo[2.2.2]octane ring system.[9] Herein, we report a new approach for the formal synthesis of **1** via an intermolecular Diels-Alder reaction of masked *o*-benzoquinone.



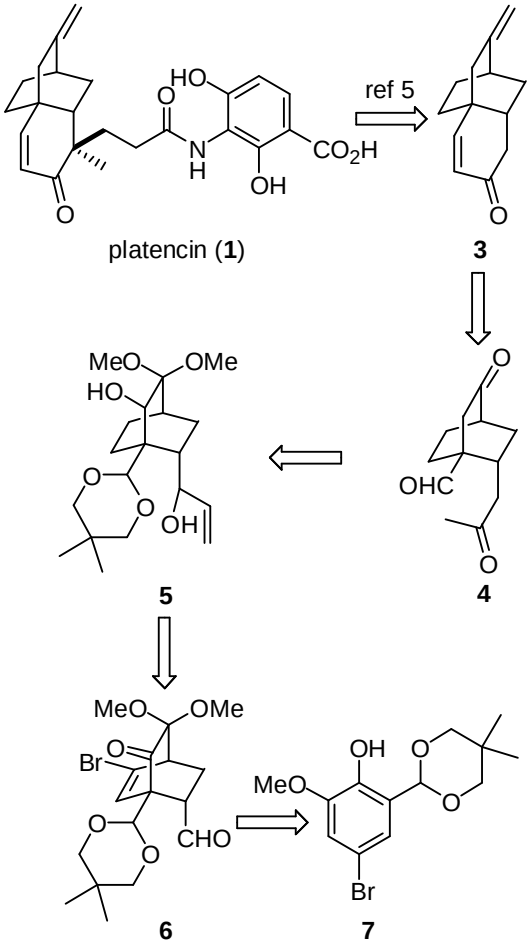
platencin (**1**) platensimycin (**2**)

Figure 1. Structures of platencin (**1**) and platensimycin (**2**)

The retrosynthetic analysis is outlined in Scheme 1. Since the installation of a methyl and an aromatic side chain on the tricyclic core **3** has been reported by several groups,[5] we focused on the

preparation of tricyclic enone **3**. We envisioned that the aldol condensation and regioselective olefination of **4** would be a potentially viable synthetic route to **3**. Aldol condensation precursor **4** would be obtained from diol **5** through dehydroxylation, deprotection, and double bond oxidation. Diol **5** could be derived from cycloadduct **6.** Cycloadduct **6** with the desired stereostructure would be obtained from the well-established Diels-Alder reaction of *in situ* generated masked *o*-benzoquinone and acrolein.

Scheme 1. Retrosynthetic analysis

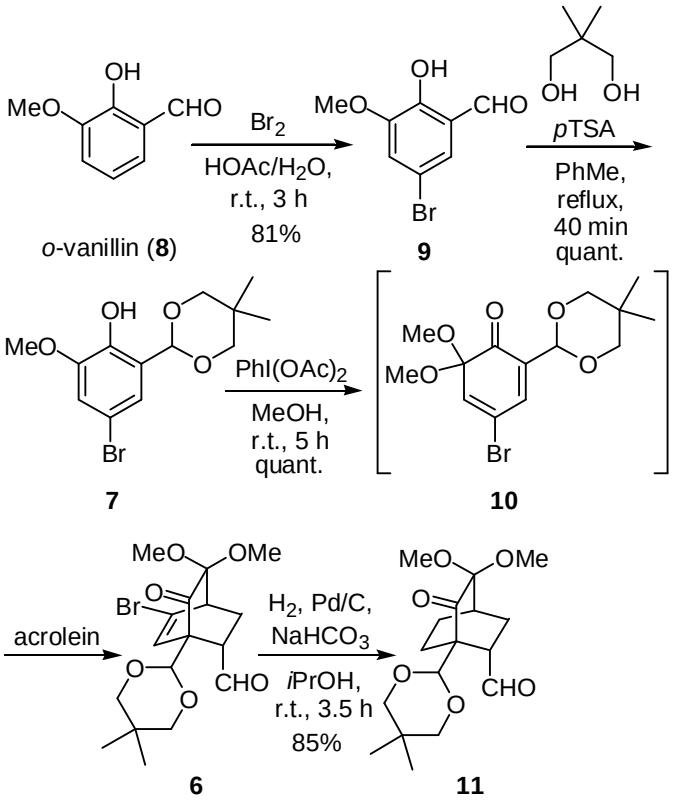


Results and Discussion

Bromophenol **7** used in this synthesis was prepared from commercially available *o*-vanillin (**8**) via bromination[10] and protection of the aldehyde with acetal (Scheme 2). The intermolecular Diels-Alder reaction of masked *o*-benzoquinone **10** (generated *in situ* by addition of a solution of diacetoxyiodobenzene (DAIB) in methanol to **7** in methanol) and acrolein afforded **6** in quantitative yield.[8f] The regiochemistry and stereochemistry of **6** were consistent with the literature precedents,[8f] and

this compound possessed the desired stereostructure for the tricyclic core of platencin. Debromination and reduction of the double bond proceeded simultaneously under the hydrogenation conditions in the presence of sodium bicarbonate to give ketoaldehyde **11**.[11]

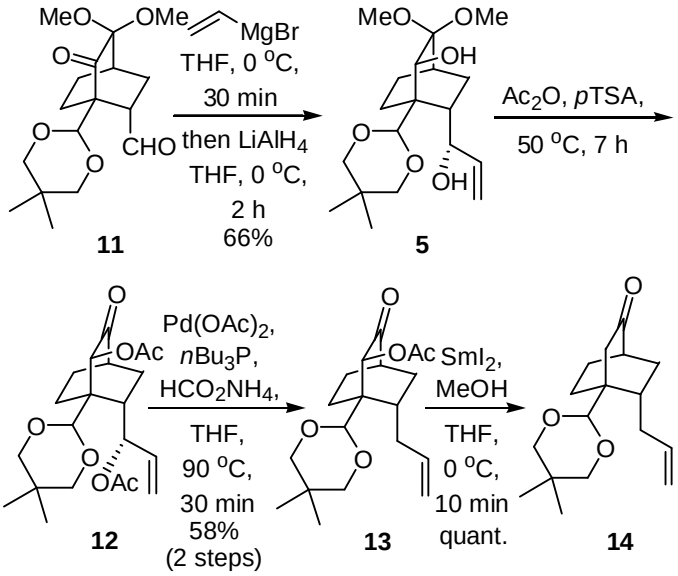
Scheme 2. Preparation of ketoaldehyde **11**



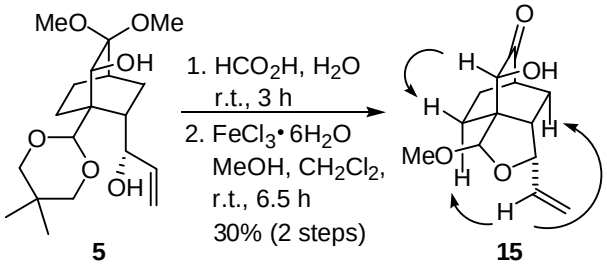
With ketoaldehyde **11** in hand, we attempted two-carbon elongation of the aldehyde. Selective addition of vinylmagnesium bromide to the aldehyde moiety on **11**, followed by reaction with lithium aluminum hydride to reduce the ketone afforded diol **5** as a single stereoisomer (Scheme 3). In order to determine its stereostructure, **5** was further subjected to acidic conditions[12] and subsequently treated with ferric chloride in methanol[13] to form tricyclic acetal **15**. The stereostructure of tricyclic acetal **15** was determined by a NOESY experiment, so that the stereochemistry of the allyl alcohol in **5** could be revealed (Scheme 4). Dehydroxylation of **5** was achieved in a three-step sequence. Conversion of hydroxyls to acetates was performed in neat acetic anhydride with a catalytic amount of *p*-toluenesulfonic acid at 50 ^{o}C for 7 h; under these conditions, the desired acetates were formed, and the dimethyl ketal moiety was hydrolyzed into ketone. The allylic acetate was then reduced with ammonium

formate in the presence of palladium catalyst[14] to form **13**. The remaining acetate was reduced by a reaction with samarium diiodide[15] to obtain bicyclo[2.2.2]octanone **14** in quantitative yield.

Scheme 3. Preparation of bicyclo[2.2.2]octanone **14**



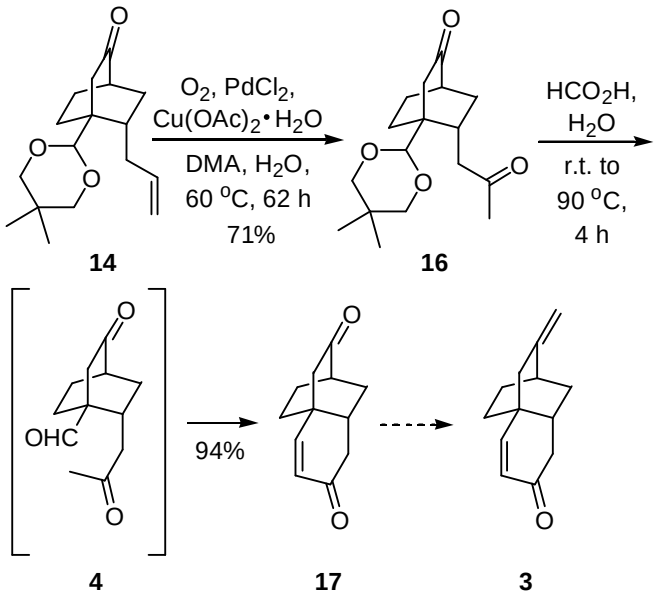
Scheme 4. Selected NOE correlations of tricyclic acetal **15**



With **14** in hand, we next focused on the formation of the cyclohexenone moiety to obtain the desired tricyclic core of platencin. To this end, Wacker oxidation[16] at the terminal double bond was performed to afford methyl ketone **16** in 71% yield (Scheme 5). Hydrolysis of the acetal moiety was first carried out with 5 M sulfuric acid[17] in 1,2-dichloroethane at room temperature; however, the reaction did not proceed under these conditions. We then employed aqueous formic acid which was previously used for the hydrolysis of acetal, for the transformation of **5** to **15**. To our delight, hydrolysis of the acetal proceeded smoothly at room temperature to form ketoaldehyde **4**, which was then heated to 90 °C, to furnish the intramolecular aldol condensation product (tricyclic compound) **17** in 94% yield. The final step was regioselective methylenation on the bicyclo[2.2.2]octanone moiety. Unfortunately, attempts to

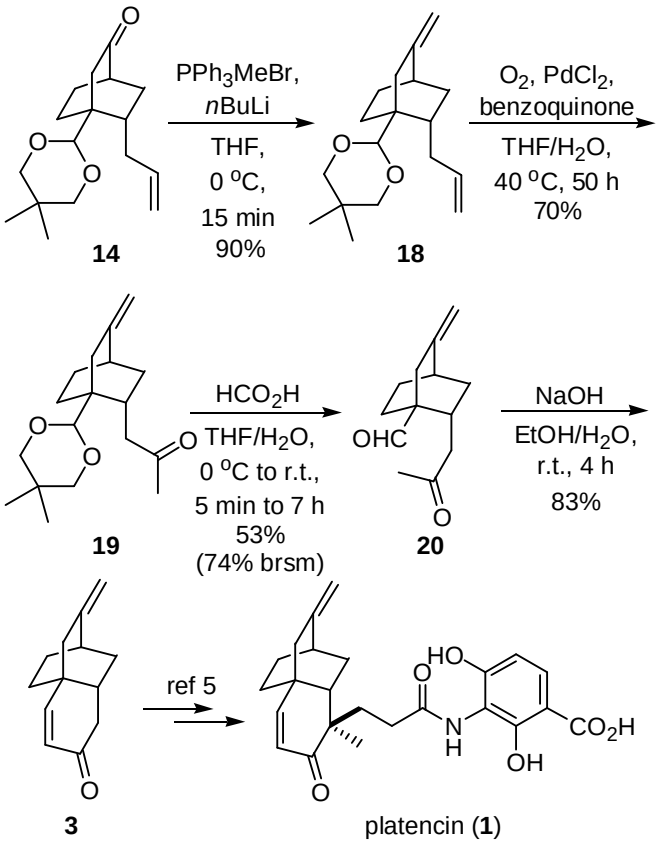
achieve selective methylenation by using various methylenation reagents, such as CH_2I_2/Zn/$TiCl_4$,[18a] Mg/$TiCl_4$,[18b] Petasis reagent,[18c] Al/$AlMe_3$,[18d] CH_2I_2/Zn/$AlMe_3$,[18a] and Wittig reagent,[18e] were unsuccessful and afforded a complicated mixture of products.

Scheme 5. Preparation of key intermediate **3**



Because the regioselective olefination of **17** to form key intermediate **3** was unsuccessful, we decided to install the exo double bond at an early stage of the synthesis, as per the modified procedure shown in Scheme 6. Methylenation of ketone **14** using the Wittig reagent, followed by Wacker oxidation[19] at the allyl side chain afforded **19**. Hydrolysis of the acetal moiety was first carried out at 0 °C in aqueous formic acid, and then, the reaction mixture was warmed to room temperature for 7 h to obtain ketoaldehyde **20** in 53% (74% brsm) yield. It is noteworthy that hydrolysis of the acetal moiety should be performed at room temperature, at higher temperatures led to the addition of water and formic acid to the exo double bond. Finally, ketoaldehyde **20** was allowed to react with a base to form the desired product **3**, which could be readily converted to platencin (**1**) according to the literature procedure.[5]

Scheme 6. Alternative procedure for the preparation of key intermediate **3**



Conclusion

In summary, a stereocontrolled formal synthesis of platencin, in 13% overall yield, was accomplished in 11 steps from bromophenol **7**. Dearomatization/Diels-Alder reaction allowed for the rapidly construction of bicyclo[2.2.2]octenone with the desired stereostructure. All the necessary stereogenic centers of the tricyclic core of platencin were established by the Diels-Alder reaction in one step. Further investigation in asymmetric formal synthesis of platencin using a carbohydrate-templated asymmetric Diles-Alder reaction of a masked *o*-benzoquinone[20] is currently underway.

Experimental Section

General Information. Unless stated otherwise, reagents were obtained from commercial sources and used without further purification. All reactions were performed under an argon or nitrogen atmosphere in anhydrous solvents, which were dried prior to use following standard procedures. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254) using 7% ethanolic phosphomolybdic acid as developing agent. Merck silica gel 60 (particle size 0.040–0.063 mm,

230–400 mesh) was employed for flash chromatography. Melting points are uncorrected. IR spectra were recorded as films on KBr plates. ^{1}H NMR spectra were obtained in $CDCl_3$ at 400 MHz (Bruker DPX-400). ^{13}C NMR spectra were obtained at 100 MHz. Chemical shifts were reported in δ (ppm) relative to the residual nondeuterated solvent signal for ^{1}H ($CHCl_3$: δ = 7.26 ppm) and relative to the deuterated solvent signal for ^{13}C ($CDCl_3$: δ = 77.0 ppm). High resolution mass spectra (HRMS) were obtained on a TOF MS instrument with an EI source.

5-Bromo-2-hydroxy-3-methoxybenzaldehyde (9).[10] To a stirred solution of *o*-vanillin (**8**) (5.00 g, 32.9 mmol) in AcOH (25 mL) and water (5 mL) was added bromine (1.7 ml, 33.0 mmol) slowly at room temperature. After stirred at room temperature for 3 h, the reaction mixture was diluted with water (75 mL). The solid was collected and washed with water. The solid was dissolved in EtOAc and then washed successively with saturated aqueous $Na_2S_2O_3$, brine, dried over $MgSO_4$, filtered, and concentrated to give phenol **9** (6.13 g, 81%) as yellow solid. Analytically pure **9** was obtained by crystallization from EtOAc: Mp 128–129.5 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.99 (s, 1H), 9.85 (s, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 3.91 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.3 (CH), 150.9 (C), 149.3 (C), 126.1 (CH), 121.4 (C), 120.8 (CH), 111.0 (C), 56.6 (CH_3).

4-Bromo-2-(5,5-dimethyl-1,3-dioxan-2-yl)-6-methoxyphenol (7). A mixture of phenol **9** (6.00 g, 26.0 mmol), 2,2-dimethyl-1,3-propanediol (4.05 g, 39.0 mmol) and *p*TSA (0.10 g, 0.53 mmol) in toluene (110 mL) was heated to reflux with a Dean-Stark apparatus for 40 min. The reaction mixture was cooled to room temperature and then washed successively with saturated aqueous $NaHCO_3$, water, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give phenol **7** (8.20 g, quantitative) as pale yellow solid. Analytically pure **7** was obtained by crystallization from EtOAc: Mp 96–97 ^{o}C; IR (KBr) ν 3293, 2952, 2867, 1572, 1488, 1382, 1254, 1213, 1077, 1023, 847, 782, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18 (d, J = 2.2 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 6.85 (br, 1H), 5.63 (s, 1H), 3.85 (s, 3H), 3.78 (d, J = 11.2 Hz, 2H), 3.66 (d, J = 11.2 Hz, 2H), 1.29 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.0 (C), 143.2 (C), 124.5 (C), 122.1 (CH), 115.0 (CH), 111.4 (C), 98.8 (CH), 77.7 (CH_2), 56.4 (CH_3), 30.3 (C), 22.9 (CH_3), 21.8 (CH_3); MS (EI) *m/z* (% base peak) 318 (25),

316 (M^+, 26), 232 (100), 231 (17), 230 (88), 186 (20), 184 (19); HRMS (EI) calcd for $C_{13}H_{17}{}^{79}BrO_4$ 316.0310, Found 316.0307; Anal. calcd for $C_{13}H_{17}BrO_4$: C, 49.23; H, 5.40. Found: C, 49.37; H, 5.28.

(1*S,2*R**,4*S**)-5-Bromo-1-(5,5-dimethyl-1,3-dioxan-2-yl)-8,8-dimethoxy-7-oxobicyclo[2.2.2]oct-5-ene-2-carbaldehyde (6).** To a mixture of phenol **7** (1.02 g, 3.2 mmol) and freshly distilled acrolein (5.2 mL, 77.8 mmol) in anhydrous MeOH (16 mL) was added dropwise a solution of diacetoxyiodobenzene (1.22 g, 3.8 mmol) in anhydrous MeOH (16 mL) through a dropping funnel under N_2 at room temperature over 1 h. Once the addition completed, dropping funnel was rinsed with anhydrous MeOH (2 mL), reaction mixture was stirred at room temperature for another 5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The solvent was evaporated in vacuo and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (hexane/EtOAc = 3:1) to give aldehyde **6** (1.30 g, quantitative) as pale yellow oil. IR (neat) *v* 2957, 2918, 2850, 1746, 1724, 1612, 1470, 1395, 1188, 1106, 1059, 1028, 909, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.46 (d, J = 4.3 Hz, 1H), 6.39 (d, J = 2.3 Hz, 1H), 4.96 (s, 1H), 3.67–3.61 (m, 2H), 3.54–3.46 (m, 2H), 3.38–3.33 (m, 1H), 3.36 (s, 3H), 3.33 (s, 3H), 3.07–2.99 (m, 1H), 2.23 (ddd, J = 13.6, 10.1, 3.1 Hz, 1H), 1.80 (ddd, J = 13.6, 5.6, 3.1 Hz, 1H), 1.11 (s, 3H), 0.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.2 (CH), 196.0 (C), 125.3 (CH), 124.4 (C), 98.9 (CH), 94.1 (C),77.7 (CH_2), 77.3 (CH_2), 60.3 (C), 50.8 (CH_3), 50.2 (CH_3), 48.7 (CH), 46.4 (CH), 30.1 (C), 23.3 (CH_3), 23.1 (CH_2), 21.8 (CH_3); MS (EI) *m/z* (% base peak) 402 (M^+, 0.1), 376 (100), 374 (99), 345 (54), 289 (38), 287 (35), 243 (46), 241 (46), 185 (30), 165 (27), 115 (41), 105 (50), 91 (47), 77 (91), 69 (100); HRMS (EI) calcd for $C_{17}H_{23}{}^{79}BrO_6$ 402.0678, Found 402.0681.

(1*R,2*R**,4*S**)-1-(5,5-Dimethyl-1,3-dioxan-2-yl)-5,5-dimethoxy-6-oxobicyclo[2.2.2]octane-2-carbaldehyde (11).** To a mixture of **6** (1.20 g, 3.0 mmol), 10% Pd/C (240 mg) and $NaHCO_3$ (599 mg, 7.1 mmol) was added *i*PrOH (50 mL). The mixture was stirred under a hydrogen balloon at room temperature for 3.5 h. The mixture was filtered through a short pad of celite and filtrate was concentrated in vacuo to give a residue. The residue was diluted with water, and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give

aldehyde **11** (826 mg, 85%) as white solid. Analytically pure **11** was obtained by crystallization from Et_2O: Mp 129–130 ^oC; IR (KBr) *v* 2949, 2882, 1738, 1717, 1466, 1392, 1194, 1139, 1062, 1035, 884, 790 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.97 (d, *J* = 2.8 Hz, 1H), 4.75 (s, 1H), 3.63–3.55 (m, 2H), 3.51 (d, *J* = 11.1 Hz, 1H), 3.40 (d, *J* = 11.1 Hz, 1H), 3.28 (s, 3H), 3.27 (s, 3H), 3.08–3.00 (m, 1H), 2.36–2.30 (m, 1H), 2.13–1.74 (m, 4H), 1.71–1.53 (m, 2H), 1.08 (s, 3H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.1 (C), 201.2 (CH), 101.0 (CH), 97.5 (C), 77.8 (CH_2), 77.4 (CH_2), 52.3 (C), 50.0 (CH_3), 49.6 (CH_3), 43.8 (CH), 32.6 (CH), 30.1 (C), 23.5 (CH_3), 21.9 (CH_3), 21.1 (CH_2), 20.9 (CH_2), 19.7 (CH_2); MS (EI) *m/z* (% base peak) 326 (M^+, 0.1), 298, (6), 269 (100), 255 (8), 212 (2), 183 (25), 169 (6), 115 (6), 101 (83), 69 (8); HRMS (EI) calcd for $C_{17}H_{26}O_6$ 326.1729, Found 326.1729; Anal. calcd for $C_{17}H_{26}O_6$: C, 62.56; H 8.03. Found: C, 62.40; H, 8.02.

(1*S,2*S**,4*S**,6*R**)-1-(5,5-Dimethyl-1,3-dioxan-2-yl)-6-((*R**)-1-hydroxyallyl)-3,3-dimethoxybicyclo[2.2.2]octan-2-ol (5).** To a stirred solution of aldehyde **11**(1.17 g, 3.6 mmol) in anhydrous THF (15 mL) was added vinylmagnesium bromide (0.7 M in THF, 12.8 mL, 9.0 mmol) slowly at 0 ^oC under Ar atmosphere. The reaction mixture was stirred at 0 ^oC for another 30 min. The mixture was transferred to a stirred solution of $LiAlH_4$ (221 mg, 5.8 mmol) in anhydrous THF (3 mL) through cannula at 0 ^oC under Ar atmosphere. The above residue was rinsed with anhydrous THF (2 x 4 mL). The reaction mixture was stirred for additional 2 h at 0 ^oC. The mixture was then quenched with brine (10 mL). Once reaction mixture separated into clear solution and white slurry, the solution was decanted, and the slurry was washed twice with EtOAc. The combined decantate was filtered and concentrated in vacuo. The crude product was purified by gradient silica-gel column chromatography (hexane/EtOAc = 5:1 to 3:1, containing 0.5 % v/v of Et_3N) to give diol **5** (811 mg, 66%) as colorless oil. IR (neat) *v* 3521, 2952, 2871, 1728, 1470, 1395, 1269, 1204, 1108, 1049, 1016, 919, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.80 (ddd, *J* = 17.2, 10.7, 4.2 Hz, 1H), 5.29 (ddd, *J* = 17.2, 1.9, 1.9 Hz, 1H), 5.11 (ddd, *J* = 10.7, 1.9, 1.9 Hz, 1H), 4.58 (s, 1H), 4.43–4.35 (m, 1H), 3.81 (d, *J* = 5.9 Hz, 1H), 3.73–3.59 (m, 2H), 3.56–3.41 (m, 2H), 3.44 (d, *J* = 5.9 Hz, 1H), 3.29 (s, 3H), 3.24 (s, 3H), 3.22 (d, *J* = 3.7 Hz, 1H), 2.07–1.88 (m, 3H), 1.68–1.61 (m, 2H), 1.56–1.47 (m, 1H), 1.44–1.36 (m, 2H), 1.18 (s, 3H), 0.72 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9 (CH), 113.6 (CH_2), 103.3 (CH), 100.9 (C), 77.4 (CH_2), 77.2 (CH_2),74.4 (CH), 71.8 (CH), 49.1 (CH3), 48.7 (CH3), 44.6 (C), 35.6 (CH), 32.2 (CH), 30.2 (C), 22.9 (CH3), 22.0 (CH_2), 21.6 (CH_3), 20.1 (CH_2), 19.0 (CH_2); MS (EI) *m/z* (% base peak) 356 (M^+, 0.3), 341 (38), 269 (11), 268 (43), 209 (6), 193 (6), 149 (7), 131 (8), 115 (100), 101 (63), 69 (33); HRMS (EI) calcd for $C_{19}H_{32}O_6$ 356.2199, Found 356.2197.

(1*S,2*S**,4*S**,6*R**)-6-Allyl-1-(5,5-dimethyl-1,3-dioxan-2-yl)-3-oxobicyclo[2.2.2]octan-2-yl acetate (13).** To a mixture of diol **5** (544 mg, 1.5 mmol) and Ac_2O (3.0 mL, 31.8 mmol) was added *p*TSA (29 mg, 0.15 mmol) and then heated to 50 ^oC for 7 h. The reaction mixture was then cooled to room temperature, and quenched with saturated aqueous $NaHCO_3$. After stirred for further 2 h, aqueous layer was extracted with EtOAc. The combined extracted were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a residue. A mixture of $Pd(OAc)_2$ (16 mg, 0.073 mmol) and ammonium formate (367 mg, 5.8 mmol) was added a solution of the above residue in dry THF (7 mL) under Ar atmosphere and the flask was rinsed with dry THF (3 mL). The mixture was added nBu$_3$P (0.18 mL, 0.73 mmol) and then heated to reflux at 90 ^oC for 30 min. The reaction mixture was cooled to room temperature and filtered through a short pad of celite. Filtrate was concentrated in vacuo to give a residue, which was purified by gradient silica-gel column chromatography (hexane/EtOAc = 7:1 to 4:1) to give ketone **13** (295 mg, 58%) as white solid. Mp 99–100.5 ^oC; IR (KBr) ν 2949, 2860, 1755, 1736, 1642, 1473, 1394, 1372, 1228, 1106, 1027, 923, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.82–5.63 (m, 1H), 5.42 (s, 1H), 5.15–4.94 (m, 2H), 4.27 (s, 1H), 3.68–3.52 (m, 2H), 3.35 (d, J = 11.1 Hz, 1H), 3.28 (d, J = 11.1 Hz, 1H), 2.52–2.41 (m, 1H), 2.41–2.34 (m, 1H), 2.27–2.15 (m, 1H), 2.13 (s, 3H), 2.07–1.89 (m, 3H), 1.89–1.71 (m, 3H), 1.40 (ddd, J = 13.4, 8.3, 2.0 Hz, 1H), 1.12 (s, 3H), 0.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.8 (C), 169.8 (C), 136.9 (CH), 116.3 (CH_2), 103.0 (CH), 77.6 (CH_2), 77.2 (CH_2), 75.7 (CH), 45.9 (C), 41.9 (CH), 36.1 (CH_2), 32.7 (CH_2), 31.3 (CH), 30.1 (C), 23.1 (CH_3), 21.8 (CH_3), 20.8 (CH_3), 20.5 (CH_2), 19.0 (CH_2); MS (EI) *m/z* (% base peak) 336 (M^+, 2), 293 (2), 249 (4), 227 (2), 180 (2), 155 (4), 141 (6), 115 (100), 91 (8), 69 (61); HRMS (EI) calcd for $C_{19}H_{28}O_5$ 336.1937, Found 336.1933; Anal. calcd for $C_{19}H_{28}O_5$: C, 67.83; H 8.39. Found: C, 67.62; H, 8.47.

(1*S,4*R**,5*R**)-5-Allyl-4-(5,5-dimethyl-1,3-dioxan-2-yl)bicyclo[2.2.2]octan-2-one (14).** To a stirred solution of ketone **13** (142 mg, 0.42 mmol) in anhydrous THF (1.0 mL) and MeOH (0.14 mL) at 0 ^{o}C under Ar atmosphere was added SmI_2 (0.1 M in THF, 13 mL, 1.3 mmol). The reaction mixture was stirred at 0 ^{o}C for 10 min and quenched with saturated aqueous NH_4Cl, saturated aqueous $Na_2S_2O_3$ and saturated aqueous Na_2CO_3. The solvent was removed under in vacuo and extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1) to give ketone **13** (117 mg, quantitative) as pale yellow oil. IR (neat) *v* 2952, 2869, 1728, 1640, 1472, 1395, 1364, 1343, 1185, 1105, 1023, 993 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78–5.65 (m, 1H), 5.09–4.96 (m, 2H), 4.24 (s, 1H), 3.57 (d, *J* = 11.0 Hz, 2H), 3.36 (d, *J* = 10.8 Hz, 1H), 3.34 (d, *J* = 10.8 Hz, 1H), 2.44 (d, *J* = 19.1 Hz, 1H), 2.41–2.35 (m, 1H), 2.31 (dd, *J* = 19.1, 2.0 Hz, 1H), 2.25–2.20 (m, 1H), 1.93–1.84 (m, 3H), 1.78–1.70 (m, 2H), 1.66–1.58 (m, 2H), 1.40–1.30 (m, 1H), 1.11 (s, 3H), 0.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 217.2 (C), 136.9 (CH), 116.0 (CH_2), 102.6 (CH), 77.2 (CH_2), 77.1 (CH_2), 43.8 (CH_2), 43.0 (CH), 42.2 (C), 35.7 (CH_2), 35.0 (CH), 30.2 (CH_2), 30.1 (C), 22.9 (CH_2), 22.7 (CH_3), 21.6 (CH_3), 20.6 (CH_2); MS (EI) *m/z* (% base peak) 278 (M^+, 30), 267 (15), 250 (36), 193 (27), 155 (56), 141 (76), 115 (100), 105 (41), 91 (81), 79 (90), 69 (100); HRMS (EI) calcd for $C_{17}H_{26}O_3$ 278.1882, Found 278.1881.

(1*R,3a*S**,4*S**,6*S**,7a*R**)-4-Hydroxy-3-methoxy-1-vinyltetrahydro-3*H*-3a,6-ethanoisobenzofuran-5(4*H*)-one (15).** A mixture of diol **5** (109 mg, 0.31 mmol), HCO_2H (1.0 mL) and water (0.1 mL) was stirred at room temperature under N_2 atmosphere for 3 h. The solvent was removed in vacuo to give a residue. To a stirred solution of the above residue in CH_2Cl_2 (2 mL) was added MeOH (19 mg, 0.58 mmol) and $FeCl_3{\cdot}6H_2O$ (118 mg, 0.43 mmol) under N_2 atmosphere and stirred at room temperature for 6.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 2:3, containing 1 % v/v of Et_3N) to give ketone **15** (22 mg, 30%) as colorless oil. IR (neat) *v* 3453, 2950, 2877, 1731, 1643, 1453, 1402, 1191, 1146, 1093, 1017, 928, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (ddd, *J* = 17.0, 10.3,

6.9 Hz, 1H), 5.36 (ddd, *J* = 17.0, 1.4, 1.4 Hz, 1H), 5.30 (ddd, *J* = 10.3, 1.4, 1.4 Hz, 1H), 4.79 (s, 1H), 4.78–4.72 (m, 1H), 4.52 (s, 1H), 4.11 (s, 1H), 3.44 (s, 3H), 3.13–2.99 (m, 1H), 2.39–2.33 (m, 1H), 2.08-1.91 (m, 2H), 1.80–1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.2 (C), 136.5 (CH), 117.6 (CH_2), 107.7 (CH), 80.3 (CH), 75.6 (CH), 54.8 (CH_3), 49.9 (C), 41.0 (CH), 34.6 (CH), 25.2 (CH_2), 24.2 (CH_2), 20.7 (CH_2); MS (EI) *m/z* (% base peak) 238 (M^+, 4), 206 (21), 178 (67), 121 (49), 115 (47), 96 (100), 91 (77), 79 (70), 58 (93); HRMS (EI) calcd for $C_{13}H_{18}O_4$ 238.1205, Found 238.1208.

(1*S,4*R**,5*S**)-4-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-(2-oxopropyl)bicyclo[2.2.2]octan-2-one (14).** To a stirred solution of ketone **14** (79 mg, 0.28 mmol) in DMA (1.05 mL) and water (0.15 mL) was added $PdCl_2$ (6 mg, 0.034 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (118 mg, 0.59 mmol). The mixture was stirred at 60 ^{o}C under an oxygen balloon for 48 h. Additional portion of $PdCl_2$ (5.4 mg, 0.030 mmol) and water (0.1 mL) was added to the above mixture and stirred additional 14 h at 60 ^{o}C under O_2. The reaction mixture was cooled to room temperature and diluted with EtOAc. The mixture was filtered through a short pad of celite and the solvent was removed in vacuo to give a residue. The residue was added 10% aqueous LiCl until color turned into yellowish brown and extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 4:1) to give dione **16** (59 mg, 71 %) as colorless oil. IR (neat) *v* 2953, 2869, 1726, 1470, 1395, 1361, 1166, 1106, 1027, 991 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.08 (s, 1H), 3.55–3.45 (m ,2H), 3.27 (d, *J* = 11.0 Hz, 1H), 3.26 (d, *J* = 11.0 Hz, 1H), 2.80 (dd, *J* = 15.5, 5.1 Hz, 1H), 2.40 (d, *J* = 19.1 Hz, 1H), 2.37–2.16 (m, 4H), 2.14–2.03 (m, 1H), 2.09 (s, 3H), 1.77–1.55 (m, 4H), 1.18 (ddd, *J* = 13.6, 6.8, 2.1 Hz, 1H), 1.08 (s, 3H), 0.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 216.3 (C), 207.7 (C), 102.7 (CH), 76.9 (CH_2), 76.8 (CH_2), 46.7 (CH_2), 44.6 (CH_2), 42.7 (CH), 42.1 (C), 31.8 (CH), 31.4 (CH_2), 30.1 (C), 29.7 (CH_3), 22.8 (CH_2), 22.8 (CH_3), 21.6 (CH_3), 19.6 (CH_2); MS (EI) *m/z* (% base peak) 294 (M^+, 5), 208 (4), 179 (5), 115 (100), 95 (7), 79 (17), 69 (60); HRMS (EI) calcd for $C_{17}H_{26}O_4$ 294.1831, Found 294.1828.

(2*S,4a*R**,8a*S**)-1,2,8,8a-Tetrahydro-7*H*-2,4a-ethanonaphthalene-3,7(4*H*)-dione (15).** A mixture of dione **14** (39 mg, 0.13 mmol), formic acid (1.5 mL) and water (0.15 mL) was stirred at room

temperature for 3 h under N_2 atmosphere and then heated to 90 °C for 4 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 2:1) to give enone **15** (24 mg, 94 %) as pale yellow oil. IR (neat) *v* 2945, 2871, 1725, 1683, 1455, 1404, 1275, 1157, 1106, 943, 851, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.59 (d, *J* = 10.1 Hz, 1H), 5.93 (d, *J* = 10.1 Hz, 1H), 2.56 (dd, *J* = 16.8, 4.1 Hz, 1H), 2.48–2.32 (m ,3H), 2.28–2.15 (m, 2H), 2.11 (dd, *J* = 18.4, 2.2 Hz, 1H), 1.99–1.85 (m, 3H), 1.73–1.60 (m, 1H), 1.46–1.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.3 (C), 198.6 (C), 153.8 (CH), 128.4 (CH), 49.1 (CH_2), 42.5 (CH), 41.2 (CH_2), 37.3 (C), 36.0 (CH), 31.4 (CH_2), 23.6 (CH_2), 23.5 (CH_2); MS (EI) *m/z* (% base peak) 190 (M^+, 40), 162 (14), 146 (22), 134 (13), 120 (26), 105 (29), 91 (100), 77 (81), 65, (25); HRMS (EI) calcd for $C_{12}H_{14}O_2$ 190.0994, Found 190.0992.

2-((1*R,2*R**,4*S**)-2-Allyl-5-methylenebicyclo[2.2.2]octan-1-yl)-5,5-dimethyl-1,3-dioxane (18).** To a stirred solution of methyltriphenylphosphonium bromide (985 mg, 2.8 mmol) in anhydrous THF (6 mL) at 0 °C under Ar atmosphere was added *n*BuLi (2.5 M in *n*Hexane, 1.1 mL, 2.8 mmol) dropwise. The resulting orange solution was stirred at 0 °C for 30 min. To this mixture was added dropwise a solution of ketone **14** (154 mg, 0.55 mmol) in anhydrous THF (3 mL), the flask was rinsed with anhydrous THF (3 mL). The mixture was stirred at 0 °C for 15 min. The Reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane) to give diene **18** (137 mg, 90 %) as pale yellow oil. IR (neat) *v* 3071, 2950, 2865, 1640, 1470, 1394, 1362, 1108, 1023, 993, 908, 872 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.82–5.66 (m, 1H), 5.07–4.93 (m, 2H), 4.71 (d, *J* = 2.1 Hz, 1H), 4.61 (d, *J* = 2.1 Hz, 1H), 4.17 (s, 1H), 3.64–3.55 (m, 2H), 2.41–3.30 (m, 2H), 3.48–2.27 (m, 3H), 2.21–2.14 (m, 1H), 1.91–1.65 (m, 3H), 1.65–1.43 (m, 4H), 1.22–1.15 (m, 1H), 1.17 (s, 3H), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.8 (C), 138.0 (CH), 115.3 (CH_2), 104.7 (CH_2), 104.5 (CH), 77.4 (CH_2), 77.3 (CH_2), 39.8 (C), 36.2 (CH), 35.9 (CH_2), 35.6 (CH), 34.9 (CH_2), 33.9 (CH_2), 30.2 (C), 26.1 (CH_2), 23.0 (CH_3), 21.8 (CH_3), 21.7 (CH_2); MS (EI) *m/z* (% base peak)

276 (M^+, 53), 233 (17), 205 (17), 190 (26), 155 (46), 141 (55), 115 (100), 91 (65), 69 (100); HRMS (EI) calcd for $C_{18}H_{28}O_2$ 276.2089, Found 276.2088.

1-((1*R,2*S**,4*S**)-1-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-methylenebicyclo[2.2.2]octan-2-yl)propan-2-one (19).** To a stirred solution of diene **18** (60 mg, 0.22 mmol) in THF (1.75 mL) and water (0.25 mL) was added freshly sublimated 1,4-benzoquinone (30 mg, 0.28 mmol) and $PdCl_2$ (6 mg, 0.034 mmol). The mixture was stirred at 40 ^oC under an oxygen balloon for 50 h. The reaction mixture was diluted with Et_2O, and filtered through a short pad of celite. Filtrate was concentrated in vacuo to give a residue, which was purified by gradient silica-gel column chromatography (hexane/Et_2O = 15:1 to 3:1) to give ketone **19** (44 mg, 70 %) as pale yellow oil. IR (neat) *v* 3066, 2950, 2865, 1715, 1650, 1470, 1394, 1362, 1164, 1103, 1027, 989, 872 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.71 (d, *J* = 1.9 Hz, 1H), 4.61 (d, *J* = 1.9 Hz, 1H), 4.02 (s, 1H), 3.57–3.47 (m, 2H), 3.28 (d, *J* = 11.0 Hz, 1H), 3.27 (d, *J* = 11.0 Hz, 1H), 2.78 (dd, *J* = 15.1, 6.7 Hz, 1H), 2.45–2.34 (m, 1H), 2.34–2.21 (m, 2H), 2.21–2.12 (m, 2H), 2.09 (s, 3H), 1.93–1.82 (m, 1H), 1.60–1.43 (m, 4H), 1.13 (s, 3H), 1.06 (ddd, *J* = 12.6, 6.9, 1.8 Hz, 1H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.8 (C), 150.9 (C), 105.1 (CH_2), 104.5 (CH), 77.1 (CH_2), 77.0 (CH_2), 47.3 (CH_2), 39.8 (C), 36.0 (CH), 35.8 (CH_2), 35.0 (CH_2), 32.5 (CH), 30.1 (C), 29.6 (CH_3), 25.9 (CH_2), 23.0 (CH_3), 21.7 (CH_3), 20.5 (CH_2); MS (EI) *m/z* (% base peak) 292 (M^+, 16), 234 (9), 205 (6), 188 (8), 148 (18), 115 (100), 105 (14), 91 (38), 69 (80); HRMS (EI) calcd fo $C_{18}H_{28}O_3$ 292.2038, Found 292.2038.

(1*R,2*S**,4*S**)-5-Methylene-2-(2-oxopropyl)bicyclo[2.2.2]octane-1-carbaldehyde (20).**[5c] To a stirred solution of ketone **19** (9 mg, 0.031 mmol) in THF (0.5 mL) was added a mixture of formic acid (0.4 mL) and water (0.05 mL) slowly at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 5 min and then stirred at room temperature for 7 h. The mixture was quenched carefully with saturated aqueous $NaCO_3$ and extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by gradient silica-gel column chromatography (hexane/EtOAc = 10:1 to 5:1) to give aldehyde **20** (3.4 mg, 53 %, 74 % brsm) as colorless oil and recovered ketone **19** (2.6 mg). IR (neat) *v* 3070, 2929, 2869, 2713, 1716, 1651, 1429, 1357, 1232, 1163,

1025, 881, 782, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.42 (s, 1H), 4.87–4.82 (m, 1H), 4.75–4.71 (m, 1H), 2.56–2.42 (m, 3H), 2.36 (dd, *J* = 17.8, 10.4 Hz, 1H), 2.31–2.24 (m, 2H), 2.12 (s, 3H), 2.10–2.02 (m, 1H), 1.86–1.75 (m, 1H), 1.69–1.47 (m, 3H), 1.14 (ddd, *J* = 13.3, 5.2, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.4 (C), 205.2 (CH), 147.5 (C), 107.1 (CH_2), 48.4 (C), 47.4 (CH_2), 36.4 (CH_2), 36.0 (CH), 34.4 (CH_2), 31.2 (CH), 30.3 (CH_3), 25.5 (CH_2), 20.2 (CH_2).

(2*S,4a*R**,8a*S**)-3-Methylene-1,2,3,4,8,8a-hexahydro-7*H*-2,4a-ethanonaphthalen-7-one (3).**[5c] To a stirred solution of ketoaldehyde **20** (15 mg, 0.073 mmol) in EtOH (1.0 mL) was added a solution of NaOH (6 mg, 0.15 mmol) in water (0.05 mL). The mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo and added saturated aqueous NH_4Cl. The mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 15:1) to give enone **3** (12 mg, 83 %) as colorless oil. IR (neat) *v* 2939, 2865, 1683, 1612, 1469, 1429, 1392, 1272, 1251, 1167, 877, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.56 (d, *J* = 10.1 Hz, 1H), 5.87 (d, *J* = 10.1 Hz, 1H), 4.83 (dd, *J* = 4.2, 1.8 Hz, 1H), 4.68 (dd, *J* = 3.8, 1.8 Hz, 1 H), 2.50–2.38 (m, 2H), 2.37–2.26 (m, 2H), 2.21–2.05 (m, 2H), 2.05–1.94 (m, 1H), 1.83–1.65 (m, 3H), 1.56–1.46 (m, 1H), 1.20 (ddd, *J* = 12.2, 7.5, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.1 (C), 156.7 (CH), 148.9 (C), 127.7 (CH), 106.9 (CH_2), 41.6 (CH_2), 40.8 (CH_2), 36.0 (CH), 35.6 (C), 35.5 (CH), 34.9 (CH_2), 26.4 (CH_2), 24.5 (CH_2).

Supporting Information Available: The comparison tables of the ^1H and ^{13}C NMR data between reported and synthetic **3**. Copies of ^1H and ^{13}C NMR for compounds **3**, **5**–**7**, **9**, **11**, and **13**–**20**.

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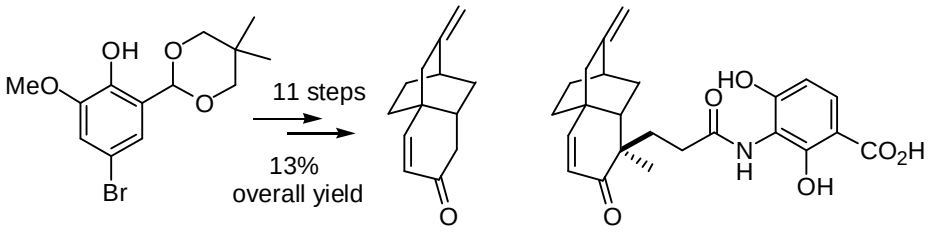
Key Topic：Formal Synthesis

A stereocontrolled construction of the tricyclic core of platencin was accomplished from bromophenol **7** in 11 steps via the dearomatization/Diels-Alder reaction and aldol condensation. All the necessary stereogenic centers of the tricyclic core of platencin were established by the Diels-Alder reaction in one step.



7 **3** platencin (**1**)