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# Total Synthsis of (+)-Ambuic Acid: α-Bromination with 1,2-Dibromotetrachloroethane

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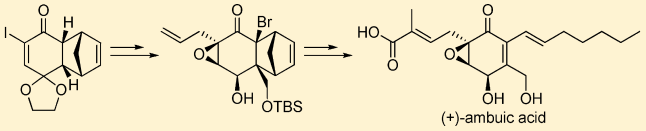
Supporting Information

**ABSTRACT:** Total synthesis of (+)-ambuic acid has been accomplished from the readily available stereocontrolled Diels–Alder adduct of cyclopentadiene and iodo-1,4-benzoquinone monoketal through an efficient series of steps. A new method for the highly commendable synthesis of α-brominated Diels–Alder adduct is described.




Chiral cyclohexenone epoxide compounds are frequently found in natural products and exhibit a wide range of interesting biologically active properties, including antibiotic, antimicotic, and antitumoral activities.[1] Among these compounds is the highly functionalized (+)-ambuic acid **1**, which has antifungal activity. This compound was isolated from the rainforest endophytic fungi, *Pestalotiopsis* spp. and *Monochaetia* sp., by Strobel and co-workers in 2001.[2] The structure of **1** was confirmed from solid NMR studies and more recently from the combined data of synchrotron X-ray powder diffraction and $^{13}C$ NMR shift tensor data.[3] Che and co-workers isolated (+)-ambuic acid **1** derivatives, including the acetylated derivative **2**, which displayed antimicrobial activity against the Gram-positive bacterium *Staphylococcus aureus* (Figure 1).[4]

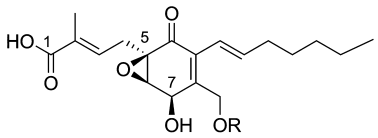


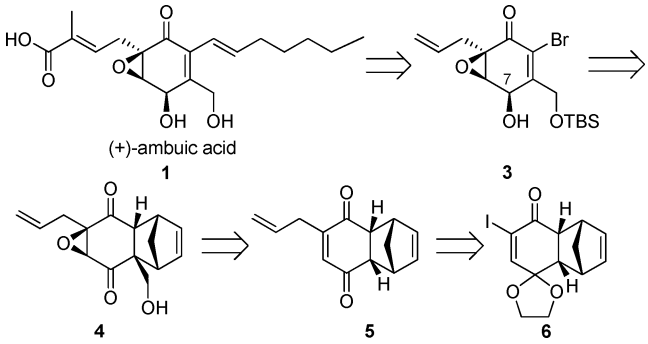

**Figure 1.** Structures of natural ambuic acid **1** and its acetate **2**.

Recent studies have shown that **1** is a novel quorum-sensing inhibitor, suggesting that it could be a lead compound for antipathogenic drugs targeting cyclic peptide quormone-mediated quorum sensing in a wide range of Gram-positive bacteria.[5] To develop a more potent inhibitor based on **1**, it is necessary to develop an efficient and flexible total synthesis methodology.

The first total synthesis of **1** was accomplished by Porco and co-workers in 2003, and the absolute configuration was determined based on their synthesis. However, the regioselective reduction of quinone for the introduction of the 7β-hydroxy group of **1** results in a 1.2:1 diastereomeric ratio of a mixture of interemediates.[6] The Mehta group developed an approach for the total synthesis of ambuic acid in racemic form using the Diels–Alder adducts of cyclopentadiene and 2-allyl-*p*-benzoquinone.[7] In recent years, our group has been interested in developing a general approach for the synthesis of natural cyclohexenone epoxide products.[8] Herein, we report first efficient method for the total synthesis of (+)-ambuic acid **1**, which requires the easily available Diels–Alder adduct **6**, prepared from the catalytic enantioselective Diels–Alder reaction with a chiral oxazaborolidinium ion.[9]

The retrosynthetic strategy for (+)-ambuic acid **1** is delineated in Scheme 1. (+)-Ambuic acid **1** could be accessed

**Scheme 1. Retrosynthetic Analysis of (+)-Ambuic Acid**




from epoxyquinone derivative **3**, which could be generated by bromination and the introduction of a β-hydroxy group from **4**. Access to **4** could be achieved through regioselective epoxidation and hydroxymethylation of **5**. Chiral quinone **5** could be obtained from chiral Diels–Alder adduct **6**, which was chosen as the starting point for the synthesis of (+)-ambuic acid **1**.

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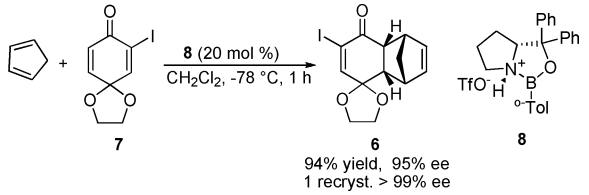
Optically pure Diels–Alder adduct **6** was obtained through the highly enantioseletive Diels–Alder reaction of cyclopentadiene and 2-iodo-1,4-quinone monoketal **7**, as we recently described (Scheme 2).[8,10] The reaction was carried out at −78 °C by stirring 2-iodo-1,4-quinone monoketal **7** and cyclopentadiene in the presence of chiral (*R*)-oxazaborolidium catalyst **8** (20 mol %) in dichloromethane under nitrogen.

**Scheme 2. Synthesis of Diels–Alder Adduct 6**

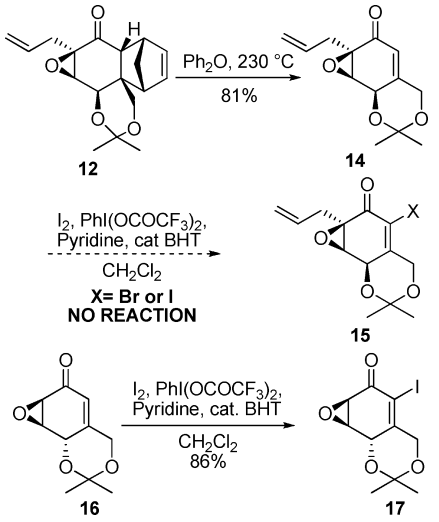



The attachment of the allyl chain was accomplished by Stille coupling with tributyl allyl stannane.[11] Exposing **9** to acidic conditions resulted in the deprotected ketone **5**. The hydrogen peroxide-mediated epoxidation of **5** in the presence of base was both regio- and stereoselective, providing only the *exo*-epoxide **10** in 93% yield. The monohydroxymethylation of **10** with aqueous HCHO in the presence of DBU followed the efficient and regioselective protocol of Metha et al. (Scheme 3).[12]

Several reduction conditions were studied to introduce a 7*β*-hydroxy group to the tricyclic hydroxy dione **4**. The DIBAL-H reduction, which employs 2 equiv of the reagent, furnished the *exo*-hydroxy product **11** in a remarkably regio- and stereocontrolled operation.[13] The diol in **11** was protected as the acetonide **12** in 98% yield. The primary hydroxyl group of **11** was protected as its TBS derivative to produce **13** in a 95% yield.

After the retro-Diels–Alder reaction of **12**, various *α*-halogenation reactions for **14** were attempted (Scheme 4). However, the desired product **15** was not obtained when **14** was treated with $Br_2/NaHCO_3$,[8b] $I_2$/DMAP,[14] or $I_2/TMSN_3$.[15] Iodinated cyclohexenone **17** can be prepared from **16** in high yield,[8a,16] but iodinated **15** could not be isolated under similar reaction conditions. Before the retro-Diels–Alder reactions of ketones **12** and **13**, *α*-bromination reactions were performed.

**Scheme 4. *α*-Halogenation of 14**




1,2-Dibromotetrachloroethane[17] was found to be an excellent brominating agent compared to $Br_2$ and NBS (Table 1).

Solvent effects were tested using substrate **18**,[18] and dichloromethane was confirmed as the best solvent (Table 1, entries 1 and 2). 1,8-Diazabicycloundec-7-ene (DBU) was the most effective base for this reaction, producing the bromination adduct **19** at room temperature with 90% yield (Table 1, entry 2). *N*-Bromosuccinimide was not as effective as 1,2-dibromotetrachloroethane and resulted in a lower yield (Table 1, entry 3). After optimizing a new *α*-bromination protocol, the scope of this methodology was investigated with a range of Diels–Alder adducts (**6**, **11**–**13**). Although other functional groups, such as hydroxy and epoxide groups, exist in the substrates, *α*-bromination adducts were obtained in excellent yields, as summarized in Table 2.

Treating **13** with 1,2-dibromotetrachloroethane and DBU at ambient temperature produced **20** in 98% yield (Table 2, entry 4). The retro-Diels–Alder reaction of **20** disengaged the cyclopentadiene and led to epoxyquinone derivative **3**, which has all the necessary functional elements for further transformation to the target natural (+)-ambuic acid (Scheme 5).

**Scheme 3. Syntheses of Intermediates 12 and 13**

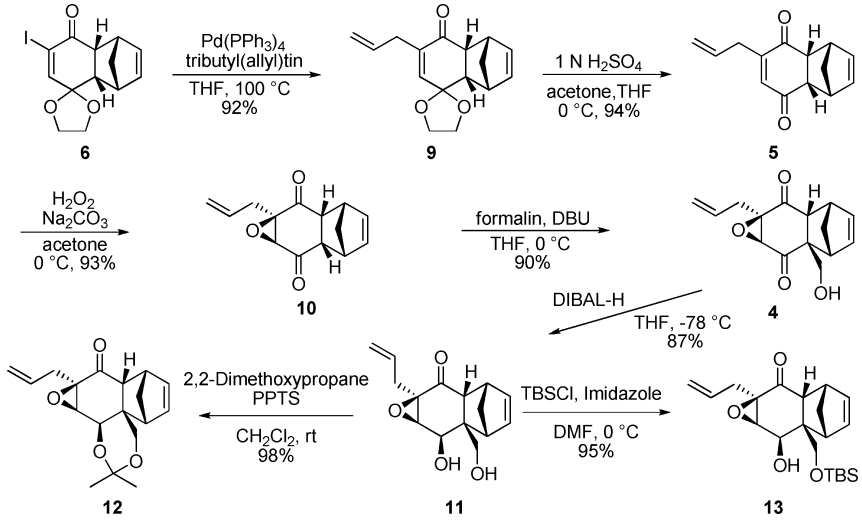




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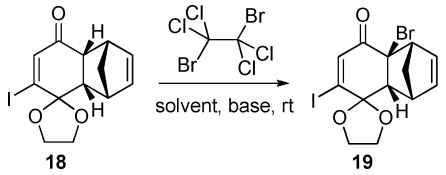
**Table 1. Optimization of the α-Bromination Conditions**

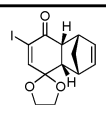
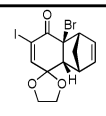
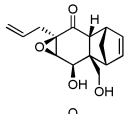
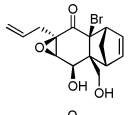
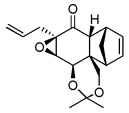
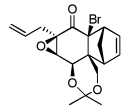
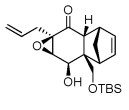
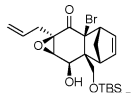



18 19

| entry | solvent | base | time (h) | yield[a] (%) |
|---|---|---|---|---|
| 1 | THF | DBU | 48 | 78 |
| 2 | $CH_2Cl_2$ | DBU | 2 | 90 |
| 3[b] | $CH_2Cl_2$ | DBU | 24 | 50 |
| 4 | $CH_2Cl_2$ | | 24 | |
| 5 | $CH_2Cl_2$ | imidazole | 24 | |
| 6 | $CH_2Cl_2$ | $Cs_2CO_3$ | 24 | 5 |
| 7 | $CH_2Cl_2$ | 1,1,3,3-tetramethyl guanidine | 24 | 30 |

[a]Isolated yield after column chromatography. [b]NBS was used instead of 1,2-dibromotetrachloroethane.

**Table 2. α-Bromination Reaction of the Various Diels–Alder Adducts with 1,2-Dibromotetrachloroethane**

| entry[a] | substrate | product | time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | 3 | 95 |
| 2 |  |  | 24 | 90 |
| 3 |  |  | 7 | 98 |
| 4 |  |  | 10 | 98 |

[a]All reactions were performed with 2.0 equiv of 1,2-dibromotetrachloroethane and 2.0 equiv of DBU under $CH_2Cl_2$ solvent at ambient temperature. [b]Isolated yield after column chromatography.

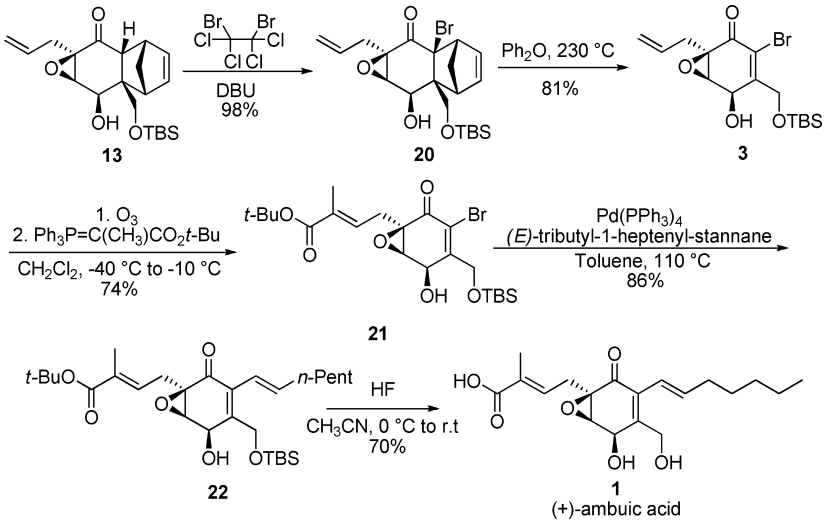
Ozonolysis of the allyl group of **3** and a subsequent Wittig reaction using $Ph_3P{=}C(CH_3)CO_2t$-Bu provided **21** in 74% yield in two steps. Finally, Stille cross-coupling with (*E*)-tributyl-1-heptenyl-stannane[6] followed by deprotection of **22** with $HF/CH_3CN$ produced the natural product (+)-ambuic acid **1**. The identity of the synthetic material has been fully established through comparison of the $^1H$ and $^{13}C$ NMR spectra and specific rotation, $[\alpha]_D^{25}$ = +92.7 (*c* = 0.83, MeOH) [lit. $[\alpha]_D^{25}$ = +92.1 (*c* = 1, MeOH)].[2,6]

In summary, we have achieved an efficient process for the enantioselective synthesis of (+)-ambuic acid **1** in 20% overall yield using 12 steps starting with chiral *endo*-Diels–Alder adduct **6**. A new α-bromination protocol for Diels–Alder adduct **13** provided α-bromoenone intermediate **3** in excellent yield. The synthetic approach delineated here can be altered to provide analogues for biological evaluations.

## EXPERIMENTAL SECTION

**(1′*R*,4′*S*,4′a*S*,8′a*R*)-7′-Iodo-1′,4′,4′a,8′a-tetrahydro-5′-((spiro-1,3-dioxolane)-1′,4′-methanonaphthalene)-8′-one (6).** To a solution of the freshly prepared catalyst **8** (0.72 mmol, 20 mol %)[9] at −78 °C were added a solution of **7** (1.0 g, 3.6 mmol) in $CH_2Cl_2$ (5 mL) and cyclopentadiene (2.27 mL, 27 mmol). The reaction mixture was stirred for 30 min at the same temperature and then

**Scheme 5. Synthesis of (+)-Ambuic Acid from 13**




13 20 3 21 22 1 (+)-ambuic acid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quenched by addition of 0.3 mL of $Et_3N$. After the mixture was warmed to room temperature, the solvent was removed by rotary evaporation. Flash chromatography purification afforded the **6** as yellow solid (1.16 g, 94% yield, 95% ee, endo). Recrystallization from hexane/$CH_2Cl_2$ afforded the desired product as yellow solid, >99% ee. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OJ-H, hexanes/2-propanol = 9:1, 1.0 mL/min, $t_R$ = 23.4 min (major) and $t_R$ = 26.3 min (minor)). Characterization data: $[\alpha]_D^{25}$ −84.67 (*c* 1.0, acetone); mp 77−79 °C; IR (ATR) $\nu_{max}$ 2994, 2887, 1673, 1607, 1336, 1137, 1114, 1055, 1013, 949, 768 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.07 (d, $J$ = 1.2 Hz, 1H), 6.09 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 2.7 Hz, 1H), 5.85 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 2.7 Hz, 1H), 4.19−4.05 (m, 2H), 4.04−3.93 (m, 2H), 3.35−3.25 (m, 2H), 3.24−3.21 (m, 1H), 2.88−2.81 (m, 1H), 1.44−1.37 (m, 1H), 1.36−1.31 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 193.4, 153.8, 135.8, 133.2, 108.6, 105.2, 65.4, 64.4, 50.7, 48.4, 46.5, 46.4, 46.3; HRMS (FAB$^+$) Exact mass calcd for $C_{13}H_{13}IO_3$ $[M]^+$ 343.9909, found 343.9909.

**(1′*R*,4′*S*,4′a*S*,8′a*R*)-7′-Allyl-1′,4′,4′a,8′a-tetrahydro-5′-((spiro-1,3-dioxolane)-1′,4′-methanonaphthalene)-8′-one (9).** To a solution of **6** (5.57 g, 16.2 mmol) in degassed THF (20 mL) was added $Pd(PPh_3)_4$ (1.4 g, 1.2 mmol) and tributyl(allyl)tin (7.5 mL, 24.3 mmol). The reaction mixture was stirred at 100 °C for 4 h and then quenched with 10% KF aqueous solution. The aqueous phase was extracted with diethyl ether (3 × 30 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography (hexane/ethyl acetate = 10:1) to afford **9** as yellow oil (3.84 g, 92%): $[\alpha]_D^{25}$ = −59.13 (*c* 0.3, $CHCl_3$); IR (ATR) $\nu_{max}$ 2947, 2831, 1665, 1338, 1224, 1147, 1072, 1026, 946, 724 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.06−6.01 (m, 2H), 5.89 (dd, $J$ = 5.4, 2.7 Hz, 1H), 5.76−5.64 (m, 1H), 5.09−5.07 (m, 1H), 5.06−5.02 (m, 1H), 4.13−3.96 (m, 4H), 3.31−3.30 (m, 1H), 3.17 (s, 1H), 3.06 (dd, $J_{AB}$ = 8.7 Hz, $J_{AC}$ = 4.5 Hz, 1H), 2.88−2.80 (m, 3H), 1.44−1.39 (m, 1H), 1.34−1.27 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 199.5, 141.8, 140.7, 135.5, 134.4, 133.4, 117.3, 104.5, 65.4, 64.1, 50.3, 48.8, 47.8, 46.6, 46.0, 33.1; HRMS (FAB$^+$) Exact mass calcd for $C_{16}H_{19}O_3$ $[M + H]^+$ 259.1334, found 259.1338.

**(1′*R*,4′*S*,4′a*S*,8′a*R*)-7′-Allyl-1′,4′,4′a,8′a-tetrahydro-(1′,4′-methanonaphthalene)-5′,8′-dione (5).** To a solution of **9** (955 mg, 3.7 mmol) in THF (5 mL) was added acetone (5 mL) and 1 N $H_2SO_{4\ (aq)}$ (5 mL). The reaction mixture was stirred at room temperature for 30 min and then quenched with saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure to furnish adduct **5** as yellow oil (745 mg, 94%), which is pure enough for next step without further purification: $[\alpha]_D^{25}$ = +26.3 (*c* 1.0, $CHCl_3$); IR (ATR) $\nu_{max}$ 2995, 1665, 1618, 1335, 1295, 1261, 1216, 1026, 916, 724 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.44 (t, $J$ = 1.2 Hz, 1H), 6.07−6.00 (m, 2H), 5.79−5.66 (m, 1H), 5.16−5.07 (m, 2H), 3.53 (br s, 2H), 3.22 (t, $J$ = 1.6 Hz, 2H), 3.06 (d, $J$ = 1.2 Hz, 1H), 3.04 (d, $J$ = 1.5 Hz, 1H), 1.55−1.51 (m, 1H), 1.43 (d, $J$ = 9.0 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 199.4, 199.0, 153.4, 139.2, 135.5, 135.1, 132.9, 118.8, 49.1, 49.0, 48.9, 48.7, 48.6, 33.4; HRMS (FAB$^+$) Exact mass calcd for $C_{14}H_{15}O_2$ $[M + H]^+$ 215.1072, found 215.1072.

**(1′*R*,4′*S*,4′a*S*,6′*S*,7′*R*,8′a*R*)-7′-Allyl-1′,4′,4′a,8′a-tetrahydro-(1′,4′-methanonaphtho-6′,7′-epoxy)-5′,8′-dione (10).** To a stirred solution of **5** (745 mg, 3.48 mmol) in acetone (10 mL) at 0 °C was added 10% $Na_2CO_3$ (2.5 mL) and 30% $H_2O_2$ (5 mL) dropwise. The reaction mixture was stirred at 0 °C for 30 min and then quenched with saturated aqueous solution of $NH_4Cl$. The aqueous phase was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography (hexane/ethyl acetate = 10:1) to afford **10** as white solid (745 mg, 93%): $[\alpha]_D^{25}$ = −35.60 (*c* 0.3, $CHCl_3$); mp 54−56 °C; IR (ATR) $\nu_{max}$ 2994, 1706, 1646, 1425, 1319, 1240, 930, 912, 847, 725 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.06 (t, $J$ = 1.6 Hz, 2H), 5.70−5.56 (m, 1H), 5.15−5.09 (m, 2H), 3.47 (t, $J$ = 2.7 Hz, 2H), 3.40 (s, 1H), 3.30−3.28 (m, 2H), 2.76−2.69 (m, 1H), 2.56 (dd, $J_{AB}$ = 15.3 Hz, $J_{AC}$ = 7.8 Hz, 1H), 1.51−1,47 (m, 1H), 1.31 (d, $J$ = 8.7 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 205.0, 136.7, 136.7, 130.2, 120.1, 66.3, 62.0, 50.5, 50.0, 46.7, 43.4, 43.2, 31.7; HRMS (FAB$^+$) Exact mass calcd for $C_{14}H_{15}O_3$ $[M + H]^+$ 231.1021, found 231.1021.

**(1′*R*,4′*S*,4′a*S*,6′*S*,7′*R*,8′a*R*)-7′-Allyl-4′a-hydroxymethyl-1′,4′,8′a-trihydro-(1′,4′-methanonaphtho-6′,7′-epoxy)-5′,8′-dione (4).** To a solution of **10** (2.29 g, 10.6 mmol) in dry THF (30 mL) at 0 °C were added DBU (0.3 mL, 2 mmol) and 37 wt % formaldehyde (4 mL, 53 mmol). The reaction mixture was stirred at 0 °C for 30 min and then quenched with saturated aqueous solution of $NH_4Cl$. The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography (hexane/ethyl acetate = 5:1) to afford **4** as white solid (2.48 g, 90%): $[\alpha]_D^{25}$ = −127.8 (*c* 0.22, $CHCl_3$); mp 104−106 °C; IR (ATR) $\nu_{max}$ 3482, 1713, 1699, 1397, 1204, 1069, 1038, 934, 823, 742 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.07 (t, $J$ = 1.6 Hz, 2H), 5.69−5.55 (m, 1H), 5.16−5.08 (m, 2H), 4.37 (dd, $J_{AB}$ = 11.4 Hz, $J_{AC}$ = 6.3 Hz, 1H), 3.81 (dd, $J_{AB}$ = 11.4 Hz, $J_{AC}$ = 6.0 Hz, 1H), 3.47 (s, 1H), 3.34−3.30 (m, 2H), 2.87 (d, $J$ = 3.6 Hz, 1H), 2.72−2.56 (m, 2H), 2.11 (t, $J$ = 6.3 Hz, 1H), 1.53 (d, $J$ = 9.3 Hz, 1H), 1.48−1.43 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 205.5, 204.4, 138.3, 138.2, 130.1, 120.4, 68.4, 67.3, 62.1, 61.8, 54.0, 46.0, 44.5, 43.6, 31.9; HRMS (FAB$^+$) Exact mass calcd for $C_{15}H_{17}O_4$ $[M + H]^+$ 261.1127, found 261.1128.

**(1′*R*,4′*S*,4′a*S*,5′*R*,6′*S*,7′*R*,8′a*R*)-7′-Allyl-5′-hydroxy-4′a-hydroxymethyl-1′,4′,8′a-trihydro-(1′,4′-methanonaphtho-6′,7′-epoxy)-8′-one (11).** To a solution of **4** (2.37 g, 9.62 mmol) in dry THF (20 mL) was added DIBAL-H (1.5 M solution in toluene, 19.2 mL, 28.8 mmol) at −78 °C, and the mixture was stirred for 30 min at that same temperature. The reaction mixture was quenched with MeOH (5 mL), saturated $NH_4Cl$ (aq) (3 mL), and 1 M HCl (aq) (15 mL). The aqueous phase was extracted with ethyl acetate (5 × 20 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography (hexane/ethyl acetate = 2:1) to afford **11** as white solid (2.19 g, 87%): $[\alpha]_D^{25}$ = −59.9 (*c* 1.0, $CHCl_3$); mp 70−72 °C; IR (ATR) $\nu_{max}$ 3459, 2988, 1707, 1416, 1329, 1086, 1044, 1030, 933, 705 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.30 (dd, $J_{AB}$ = 5.7 Hz, $J_{AC}$ = 3.0 Hz, 1H), 6.12 (dd, $J_{AB}$ = 5.7 Hz, $J_{AC}$ = 3.3 Hz, 1H), 5.72−5.58 (m, 1H), 5.12 (s, 1H), 5.07 (d, $J$ = 4.8 Hz, 1H), 4.84 (d, $J$ = 6.0 Hz, 1H), 4.72 (d, $J$ = 8.4 Hz, 1H), 3.99 (d, $J$ = 6.0 Hz, 1H), 3.18−3.72 (m, 2H), 3.47 (s, 1H), 3.34(s, 1H), 3.23(s, 1H), 2.65 (dd, $J$ = 6.3, 15.0 Hz, 1H), 2.51−2.44 (m, 2H), 1.61 (d, $J$ = 9.3 Hz, 1H), 1.48 (d, $J$ = 9.3 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 208.0, 140.4, 136.3, 131.3, 119.4, 73.2, 69.8, 66.6, 63.6, 55.2, 51.2, 46.3, 44.6, 44.2, 31.9; HRMS (FAB$^+$) Exact mass calcd for $C_{15}H_{19}O_4$ $[M + H]^+$ 263.1283, found 263.1286.

**(4a*S*,5*S*,6*S*,7a*R*,8*R*,11*S*,11[1]*S*)-6-Allyl-3,3-dimethyl-4a,7a,8,11-hexahydro-(8,11-methanonaphthonaphtho-5,6-epoxy)-[1-d]-[1,3]dioxin-7(1*H*)-one (12).** To a solution of **11** (1.1 g, 4.2 mmol) in $CH_2Cl_2$ (20 mL) at 0 °C were added pyridinium *p*-toluenesulfonate (0.211 g, 0.84 mmol) and 2,2-dimethoxy propane (3 mL, 25.2 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography (hexane/ethyl acetate = 10:1) to afford **12** as colorless oil (1.24 g, 98%): IR (ATR) $\nu_{max}$ 2993, 2955, 1704, 1378, 1158, 1197, 1068, 733, 672 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.26 (dd, $J_{AB}$ = 5.7 Hz, $J_{AC}$ = 3.0 Hz, 1H), 6.13 (dd, $J_{AB}$ = 5.7 Hz, $J_{AC}$ = 3.3 Hz, 1H), 5.75−5.61 (m, 1H), 5.13−5.06 (m, 2H), 4.71 (d, $J$ = 12 Hz, 1H), 3.93 (s, 1H), 3.62 (d, $J$ = 12 Hz, 1H), 3.49 (s, 1H), 3.37 (s, 1H), 3.17 (s, 1H),


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2.67 (dd, $J$ = 6.6, 15.3 Hz, 1H), 2.47 (dd, $J_{AB}$ = 15.0 Hz, $J_{AC}$ = 7.2 Hz Hz, 1H), 2.33 (d, $J$ = 3.3 Hz, 1H), 1.68 (s, 3H), 1.51 (s, 2H), 1.45 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 207.6, 140.0, 136.6, 131.54, 119.4, 97.5, 72.5, 66.3, 66.0, 65.8, 54.5, 47.4, 45.1, 44.2, 43.9, 32.4, 30.5, 22.4; HRMS (FAB$^+$) Exact mass calcd for $C_{18}H_{23}O_4$ [M + H]$^+$ 303.1596, found 303.1595.

**(1′*R*,4′*S*,4′a*S*,5′*R*,6′*S*,7′*R*,8′a*R*)-7′-Allyl-5′-hydroxy-4′a-*tert*-butyldimethylsiloxymethyl-1′,4′,8′a-trihydro-(1′,4′-methanonaphtho-6′,7′-epoxy)-8′-one (13).** To a solution of **11** (260 mg, 1 mmol) in DMF (5 mL) was added the imidazole (340 mg, 5 mmol). After 30 min at room temperature, TBSCl (376 mg, 2.5 mmol) was added to the mixture at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and then quenched with distilled water. The aqueous phase was extracted with hexane (5 × 10 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography (hexane/ethyl acetate = 15:1) to afford **13** as white solid (357 mg, 95%): $[\alpha]_D^{25}$ = −34.9 (*c* 0.3, $CHCl_3$); mp 72−74 °C; IR (ATR) $\nu_{max}$ 3434, 2856, 1705, 1466, 1258, 1098, 1066, 837, 830, 776 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.26 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 3.0 Hz, 1H), 6.13 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 3.0 Hz, 1H), 5.72−5.58 (m, 1H), 5.42 (d, $J$ = 5.7 Hz, 1H), 5.11−5.06 (m, 2H), 4.89 (d, $J$ = 10.5 Hz, 1H), 3.89 (d, $J$ = 5.7 Hz, 1H), 3.72 (d, $J$ = 10.5 Hz, 1H), 3.53 (s, 1H), 3.34 (s, 1H), 3.18 (s, 1H), 2.67 (dd, $J_{AB}$ = 15.0 Hz, $J_{AC}$ = 6.3 Hz, 1H), 2.44 (dd, $J_{AB}$ = 15.0 Hz, $J_{AC}$ = 7.5 Hz, 1H), 2.30 (d, $J$ = 3.3 Hz, 1H), 1.53 (d, $J$ = 9.0 Hz, 1H), 1.46 (d, $J$ = 9.0 Hz, 1H), 0.94 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 207.8, 139.4, 136.3, 131.2, 118.9, 72.7, 69.9, 67.1, 63.2, 54.3, 50.4, 45.5, 43.9, 43.7, 31.7, 25.7, 18.0, −5.6, −5.7; HRMS (FAB$^+$) Exact mass calcd for $C_{21}H_{33}O_4Si$ [M + H]$^+$ 377.2148; found 377.2151.

**(1′*S*,4′*S*,4′a*S*,5′*R*,6′*S*,7′*R*,8′a*S*)-7′-Allyl-8′a-bromo-5′-hydroxy-4′a-*tert*-butyldimethylsiloxymethyl-1′,4′-dihydro-(1′,4′-methanonaphtho-6′,7′-epoxy)-8′-one (20).** To a solution of **13** (233 mg, 0.62 mmol) in dry $CH_2Cl_2$ (3 mL) was added DBU (111 $\mu$L, 0.74 mmol) and 1,2-dibromotetrachloroethane (242 mg, 0.74 mmol). The reaction mixture was stirred at room temperature for 10 h and then quenched with saturated aqueous solution of $NH_4Cl$. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography (hexane/ethyl acetate = 10:1) to afford **8** as white solid (276 mg, 98%): $[\alpha]_D^{25}$ = +52.8 (*c* 1.0, $CHCl_3$); mp 50−52 °C; IR (ATR) $\nu_{max}$ 3404, 2931, 1709, 1254, 1106, 1062, 1003, 946, 836, 778 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.26 (dd, $J_{AB}$ = 5.7 Hz, $J_{AC}$ = 3.3 Hz, 1H), 6.15 (dd, $J_{AB}$ = 4.8 Hz, $J_{AC}$ = 3.0 Hz, 1H), 5.96 (d, $J$ = 6.0 Hz, 1H), 5.78−5.64 (m, 1H), 5.21−5.12 (m, 2H), 4.72 (d, $J$ = 10.8 Hz, 1H), 4.05 (d, $J$ = 10.5 Hz, 1H), 3.88 (d, $J$ = 6.0 Hz, 1H), 3.63(s, 1H), 3.43−3.39(m, 2H), 2.85 (dd, $J_{AB}$ = 15.0 Hz, $J_{AC}$ = 6.3 Hz, 1H), 2.42 (dd, $J_{AB}$ = 15.0 Hz, $J_{AC}$ = 7.5 Hz, 1H), 2.10 (d, $J$ = 9.6 Hz, 1H), 1.82−1.77 (m, 1H), 0.95 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 198.3, 138.8, 137.0, 130.6, 119.2, 74.0, 71.2, 70.2, 67.9, 61.9, 55.3, 50.2, 47.2, 43.8, 32.1, 25.7, 18.0, −5.6, −5.7; HRMS (FAB$^+$) Exact mass calcd for $C_{21}H_{32}BrO_4Si$ [M + H]$^+$ 455.1253; found 455.1255.

**(1*R*,5*R*,6*R*)-1-Allyl-3-bromo-4-((*tert*-butyldimethylsilyloxy)-methyl)-5-hydroxy-7-oxabicyclo[4.1.0]hept-3-en-2-one (3).** A solution of **20** (100 mg, 0.22 mmol) in $Ph_2O$ (5 mL) was heated to 230 °C. The reaction mixture was stirred for 2 h at that same temperature and then cooled to rt. The reaction mixture was purified by flash column chromatography (hexane/ethyl acetate = 10:1) to afford **3** as colorless oil (69 mg, 81%): $[\alpha]_D^{25}$ = −13.8 (*c* 1.0, $CHCl_3$); IR (ATR) $\nu_{max}$ 2953, 2930, 2857, 1696, 1471, 1255, 1087, 836, 814, 781 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.79−5.65 (m, 1H), 5.19−5.12 (m, 2H), 4.91−4.88 (m, 1H), 4.75 (dd, $J_{AB}$ = 16.5 Hz, $J_{AC}$ = 0.9 Hz, 1H), 4.61 (dd, $J_{AB}$ = 16.5 Hz, $J_{AC}$ = 1.8 Hz, 1H), 4.21 (d, $J$ = 3.9 Hz, 1H), 3.79 (d, $J$ = 3.0 Hz, 1H), 2.89 (dd, $J_{AB}$ = 14.7 Hz, $J_{AC}$ = 7.5 Hz, 1H), 2.63−2.55 (m, 1H), 0.93 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 186.5, 153.7, 130.8, 119.6, 116.8, 67.3, 66.6, 59.0, 57.9, 32.6, 25.6, 18.0, −5.5; HRMS (FAB$^+$) Exact mass calcd for $C_{16}H_{26}BrO_4Si$ [M + H]$^+$ 389.0784; found 389.0781.

**(*E*)-*tert*-Butyl 4-((1*R*,5*R*,6*R*)-3-bromo-4-((*tert*-butyldimethylsilyloxy)methyl)-5-hydroxy-2-oxo-7-oxabicyclo-[4.1.0]hept-3-en-1-yl)-2-methylbut-2-enoate (21).** A solution of **3** (292 mg, 0.75 mmol) in MeOH (3 mL) was cooled to −78 °C and ozonolyzed for 3 min. The resulting solution was treated with methyl sulfide (1 mL), warmed to room temperature, and stirred for 30 min prior to dilution with water and extraction with $CH_2Cl_2$ (3 × 10 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered and concentrated in vacuo to afford an oil. The crude aldehyde was used in the next step directly. A solution of *tert*-butyl 2-(triphenylphosphoranylidene) propionate (351 mg, 0.9 mmol) in $CH_2Cl_2$ (3 mL) was cooled to −40 °C. The crude aldehyde in $CH_2Cl_2$ (3 mL) was added dropwise. The reaction mixture was slowly warmed to −10 °C over 2 h, when all the starting material was consumed. Then, directly, the mixture was subjected to flash column chromatography (hexane/ethyl acetate = 15:1) to afford **21** as yellow oil (279 mg, 74%): $[\alpha]_D^{25}$ = −8.7 (*c* 1.0, $CHCl_3$); IR (ATR) $\nu_{max}$ 2955, 2931, 2858, 1699, 1367, 1254, 1172, 1129, 1089, 838 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.51−6.45 (m, 1H), 4.91−4.90 (m, 1H), 4.74(dd, $J_{AB}$ = 16.5 Hz, $J_{AC}$ = 0.9 Hz, 1H), 4.61(dd, $J_{AB}$ = 16.2 Hz, $J_{AC}$ = 1.5 Hz, 1H), 4.26 (d, $J$ = 3.6 Hz, 1H), 3.78 (d, $J$ = 3.0 Hz, 1H), 3.01 (dd, $J_{AB}$ = 15.6 Hz, $J_{AC}$ = 8.1 Hz, 1H), 2.66 (dd, $J_{AB}$ = 15.9 Hz, $J_{AC}$ = 7.2 Hz, 1H), 1.83 (s, 3H), 1.46 (s, 9H), 0.93 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 186.2, 166.7, 153.9, 133.2, 131.8, 116.6, 80.5, 67.2, 66.68, 58.74, 58.10, 28.0, 27.7, 25.6, 18.0, 12.8, −5.5; HRMS (FAB$^+$) Exact mass calcd for $C_{22}H_{36}BrO_6Si$ [M + H]$^+$ 503.1465, found 503.1464.

**(*E*)-*tert*-Butyl-4-((1*R*,5*R*,6*R*)-4-((*tert*-butyldimethylsilyloxy)-methyl)-3-((*E*)-hept-1-enyl)-5-hydroxy-2-oxo-7-oxabicyclo-[4.1.0]hept-3-en-1-yl)-2-methylbut-2-enoate (22).** To a solution of **21** (25 mg, 0.05 mmol) in degassed toluene (2 mL) were added $Pd(PPh_3)_4$ (11 mg, 0.01 mmol) and (*E*)-tributyl-1-heptenyl-stannane (25 mg, 0.05 mmol). The reaction mixture was stirred at 110 °C for 1 h and then quenched with 10% KF aqueous solution. The aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography (hexanes/ethyl acetate = 10:1) to afford **22** as pale yellow oil (22.5 mg, 86%): $[\alpha]_D^{25}$ = +54.26 (*c* 1.0, $CHCl_3$); IR (ATR) $\nu_{max}$ 2956, 2930, 2856, 1707, 1683, 1367, 1255, 1081, 836, 780 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.55−6.50 (m, 1H), 6.05 (d, $J$ = 15.9 Hz, 1H), 5.76−5.66(m, 1H), 4.87 (s, 1H), 4.69 (d, $J$ = 14.4 Hz, 1H), 4.59 (d, $J$ = 14.4 Hz, 1H), 3.77 (d, $J$ = 4.8 Hz, 1H), 3.74 (d, $J$ = 2.7 Hz, 1H), 2.93 (dd, $J_{AB}$ = 15.9 Hz, $J_{AC}$ = 8.1 Hz, 1H), 2.67 (dd, $J_{AB}$ = 15.9 Hz, $J_{AC}$ = 7.2 Hz, 1H), 2.18−2.11 (m, 2H), 1.83 (s, 3H), 1.47 (s, 9H), 1.44−1.22 (m, 6H), 0.91−0.88 (m, 12H), 0.11 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 194.1, 166.9, 147.9, 139.8, 132.8, 132.6, 129.2, 120.9, 80.3, 66.2, 62.5, 59.5, 58.3, 33.4, 33.1, 28.8, 28.0, 27.4, 25.7, 22.4, 18.1, 13.9, 12.7, −5.5; HRMS (FAB$^+$) Exact mass calcd for $C_{29}H_{47}O_6Si$ [M−H]$^+$ 519.3142, found 519.3143.

**(+)-Ambuic Acid.** To a solution of **22** (83.5 mg, 10.6 mmol) in dry $CH_3CN$ (3 mL) at 0 °C were added 2 drops of 48% aqueous HF. The reaction mixture was stirred at room temperature for 5 h and then quenched with saturated aqueous solution of $NH_4Cl$. The aqueous phase was extracted with ethyl acetate (5 × 10 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography (dichloromethane/methanol = 9:1) to afford **1** as white solid (39 mg, 70%): $[\alpha]_D^{25}$ = +92.7 (*c* 0.83, MeOH); IR (ATR) $\nu_{max}$ 3407, 2954, 2925, 2869, 1648, 1647, 1415, 1279, 1033, 982 cm$^{-1}$; $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 6.69 (t, $J$ = 7.9 Hz, 1H), 6.14 (d, $J$ = 17.1 Hz, 1H), 5.89−5.79 (m, 1H), 4.89 (s, 1H), 4.52 (d, $J$ = 12.9 Hz, 1H), 4.40 (d, $J$ = 12.9 Hz, 1H), 3.75 (d, $J$ = 2.7 Hz, 1H), 2.87−2.71 (m, 2H), 2.16 (q, $J$ = 6.9 Hz, 2H), 1.86 (s, 3H), 1.47−1.40 (m, 2H), 1.35−1.29 (m, 4H), 0.91 (t, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 196.0, 171.1, 150.6, 140.1, 136.5, 131.9, 131.8, 122.7, 65.8, 61.1, 61.0,


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60.3, 34.4, 32.5, 29.9, 28.7, 23.5, 14.4, 12.7; HRMS (FAB$^+$) Exact mass calcd for $C_{19}H_{26}NaO_6$ $[M + Na]^+$ 373.1627; found 373.1625.

**General Procedure for the α-Bromination.** To a solution of Diels–Alder adduct (0.3 mmol, 1.0 equiv) in $CH_2Cl_2$ (3 mL) were added DBU (0.6 mmol, 0.089 mL, 2.0 equiv) and 1,2-dibromotetrachloroethane (0.6 mmol, 0.19 g, 2.0 equiv). The reaction mixture was stirred at room temperature and monitored by TLC. After the reaction time indicated in Table 2, it was quenched with saturated aqueous solution of $NH_4Cl$. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried over anhydrous $Na_2SO_4$. The mixture was filtered, and the solvent was evaporated under reduced pressure. The concentrated crude product was purified by flash column chromatography to afford the pure α-brominated product.

**(1′*R*,4′*S*,4′a*S*,8′a*R*)-4′a-Bromo-6′-iodo-1′,4′,8′a-trihydro-5′-((spiro-1,3-dioxolane)-1′,4′-methanonaphthalene)-8′-one (19) (Table 1).** Spectral data: IR (ATR) $\nu_{max}$ 2984, 2899, 1678, 1592, 1253, 1164, 1085, 1014, 950, 889, 760 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.89 (s, 1H), 6.16 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 2.7 Hz, 1H), 5.89 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 3.0 Hz, 1H), 4.33–4.07 (m, 4H), 3.48–3.45 (m, 2H), 3.13 (s, 1H), 2.05 (d, $J$ = 9.0 Hz, 1H), 1.75–1.71 (m, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 189.0, 142.7, 137.3, 133.4, 131.7, 104.8, 66.8, 65.7, 62.8, 58.9, 56.9, 47.6, 47.3; HRMS (FAB$^+$) Exact mass calcd for $C_{13}H_{13}BrIO_3$ $[M + H]^+$ 422.9093, found 422.9093.

**(1′*R*,4′*S*,4′a*S*,8′a*R*)-4′a-Bromo-7′-iodo-1′,4′,8′a-trihydro-5′-((spiro-1,3-dioxolane)-1′,4′-methanonaphthalene)-8′-one (Entry 1 in Table 2).** Spectral data: IR (ATR) $\nu_{max}$ 2987, 2949, 2885, 1687, 1599, 1465, 1330, 1155, 1080, 1039, 1012, 956, 761, 672, 643 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.14 (d, $J$ = 0.6 Hz, 1H), 6.22 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 2.7 Hz, 1H), 5.88 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 3.0 Hz, 1H), 4.15–4.0 (m, 4H), 3.53–3.49 (m, 2H), 3.17 (s, 1H), 2.08–2.04 (m, 1H), 1.77–1.73 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 186.5, 153.6, 138.4, 132.5, 104.7, 104.2, 65.4, 64.9, 60.8, 60.4, 56.7, 47.2, 46.4; HRMS (FAB$^+$) Exact mass calcd for $C_{13}H_{13}BrIO_3$ $[M + H]^+$ 422.9093, found 422.9092.

**(1′*S*,4′*R*,4′a*S*,5′*R*,6′*S*,7′*R*,8′a*S*)-7′-Allyl-8′a-bromo-5′-hydroxy-4′a-hydroxymethyl-1′,4′-dihydro-(1′,4′-methanonaphtho-6′,7′-epoxy)-8′-one (Entry 2 in Table 2).** Spectral data: IR (ATR) $\nu_{max}$ 3728, 3628, 3231, 2991, 1711, 1425, 1248, 1099, 1040, 919, 695 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.27 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 3.0 Hz, 1H), 6.19 (dd, $J_{AB}$ = 5.4 Hz, $J_{AC}$ = 3.0 Hz, 1H), 577–5.63 (m, 1H), 5.21–5.13 (m, 2H), 4.51 (d, $J$ = 12.0 Hz, 1H), 4.29 (d, $J$ = 10.2 Hz, 1H), 4.13 (t, $J$ = 10.2 Hz, 1H), 3.89 (d, $J$ = 9.9 Hz, 1H), 3.57 (s, 1H), 3.48–3.42 (m, 2H), 3.07 (s, 1H), 2.87–2.78 (m, 1H), 2.52–2.44 (m, 1H), 2.05–2.01 (m, 1H), 1.76–1.71 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 197.9, 138.4, 138.3, 130.4, 119.5, 73.8, 70.57, 70.51, 67.1, 62.4, 55.5, 54.2, 50.4, 44.2, 32.0; HRMS (FAB$^+$) Exact mass calcd for $C_{15}H_{17}BrO_4Na$ $[M + Na]^+$ 363.0208, found 363.0209.

**(4a*S*,5*S*,6*S*,7a*S*,8*S*,11*R*,11′*S*)-6-Allyl-7a-bromo-3,3-dimethyl-4a,8,11-trihydro-(8,11-methanonaphthonaphtho-5,6-epoxy)-[1-d][1,3]dioxin-7(1*H*)-one (Entry 3 in Table 2).** Spectral data: IR (ATR) $\nu_{max}$ 3727, 2989, 1712, 1378, 1255, 1131, 1058, 913, 736, 663 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.28–6.25(m, 1H), 6.14–6.10 (m, 1H), 5.79–5.66 (m, 1H), 5.21–5.13 (m, 2H), 4.67 (d, $J$ = 12 Hz, 1H), 3.87 (d, $J$ = 1.5 Hz, 1H), 3.63 (dd, $J_{AB}$ = 12.0 Hz, $J_{AC}$ = 1.2 Hz, 1H), 3.57 (s, 1H), 3.43 (t, $J$ = 1.5 Hz, 2H), 2.88–2.81 (m, 1H), 2.49–2.41 (m, 1H), 2.13 (d, $J$ = 9.9 Hz, 1H), 1.86–1.81 (m, 1H), 1.66 (s, 3H), 1.45 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 198.1, 139.1, 136.9, 130.6, 119.3, 97.2, 73.4, 69.2, 66.9, 66.7, 64.3, 55.3, 48.6, 44.9, 44.6, 32.3, 30.0, 21.8; HRMS (FAB$^+$) Exact mass calcd for $C_{18}H_{22}BrO_4$ $[M + H]^+$ 381.0701, found 381.0703.

## ■ ASSOCIATED CONTENT

### Supporting Information

$^1$H and $^{13}$C NMR spectra for all intermediates **3**–**7**, **9**–**13**, **19**–**22**, (+)-ambuic acid **1**, and α-brominated products in Tables 1 and 2. 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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