Articles

Asymmetric Reductive Cyclization. Total Synthesis of (−)-C_{10}-Desmethyl Arteannuin B

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An efficient total synthesis of (−)-C_{10}-desmethyl arteannuin B (**5**) has been achieved. The sequence features the use of a chiral auxiliary to introduce absolute asymmetry at an early stage and a stereoselective, chelation-controlled reductive cyclization of **8**, using samarium diiodide as the reducing agent. The methodology promises to be applicable to the synthesis of a wide range of analogs capable of being converted to potent antimalarial agents related to artemisinin (**1**).

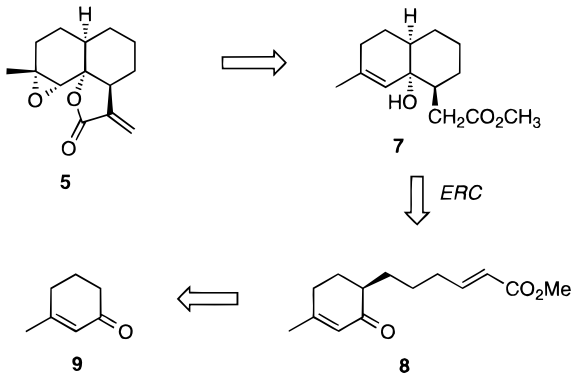
Malaria continues to be a scourge to millions of people throughout the world. Unfortunately, drug-resistant strains have developed. Consequently, several of the previously used antimalarial agents are no longer efficacious.[1,2] One of the more effective materials in the treatment of the disease is artemisinin (qinghaosu, **1**), a tetracyclic sesquiterpene lactone possessing an interesting 1,2,4-trioxane unit.[3] Mechanistic studies have shed light upon the importance of this subunit and its interaction with iron-rich parasites, in the expression of biological activity.[4]

A number of syntheses of artemisinin (**1**), and its structural analogs, have been developed.[5] Several rely upon the use of artemisinic acid (**6**) and arteannuin B (**4**) as precursors.[6,7] Like the natural product, the analog 10,11-didesmethyl artemisinin (**3**), displays significant antimalarial activity against strains of *Plasmodium falciparum*.[8] We report the total synthesis of (−)-C_{10}-desmethyl arteannuin B (**5**), a substance that could be converted to **2** using known methodology.[6] Our approach, illustrated in Scheme 1, is highlighted by its simplicity and efficiency (17% overall yield).

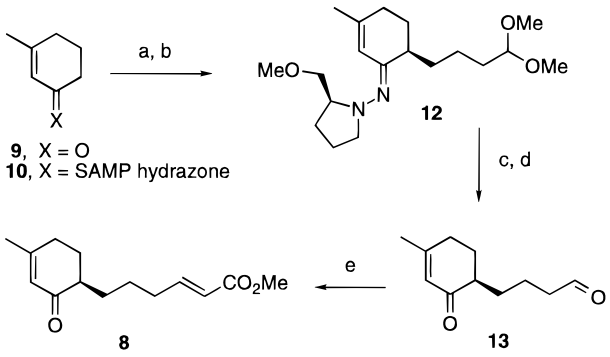
The key step in the sequence is the reductive cyclization designed to convert enone **8** to the bicyclic hydroxy ester **7**. Our previous studies utilizing the electroreductive cyclization (ERC) reaction *en route* to natural products suggested that it would be ideally suited to achieving this objective.[9−12]

As shown in Scheme 2, the sequence begins with the conversion of 3-methylcyclohexenone (**9**) to the corresponding (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine

Scheme 1



Scheme 2[a]



[a] Key: (a) SAMP, PhH , 97%; (b) LDA, $(MeO)_2CH(CH_2)_3I$, **11**, 78%, (>95% ee); (c) O_3, CH_2Cl_2, -78 °C, 86%; (d) TFA, CH_2Cl_2/H_2O, 98%; (e) NHMDS, THF, $(MeO)_2POCH_2CO_2Me$, 95%, (7:1 E/Z)

(SAMP) hydrazone (as a 1.4:1 mixture of *E*/*Z* isomers) **10**,[13] thereby introducing absolute asymmetry at an early stage of the sequence. Formation of the carbanion of **10** at −78 °C, followed by treatment with iodide **11** afforded a mixture of regioisomers resulting from alkylation at the α- and α′-positions.[14] The selectivity and yield improved significantly when 10 mol % lithium chloride,[15] premixed with diisopropylamine in THF, was used in the

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

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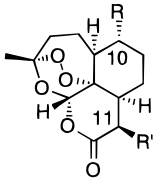
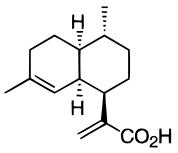
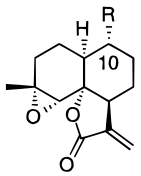
S0022-3263(96)00041-2 CCC: $12.00



1, artemisinin (R = R' = CH_3)
2, R = H, R' = CH_3
3, R = R' = H



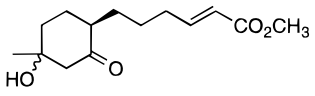
6, artemisinic acid



4, R = CH_3, arteannuin B
5, R = H, C_{10}-desmethyl arteannuin B

preparation of LDA. In this manner, the time needed for carbanion formation was reduced from 8 h at −78 °C to 4 h at −95 °C. Alkylation then proceeded cleanly to afford a single diastereomer, **12**, in 78% yield. Oxidative cleavage of the chiral auxiliary and removal of the acetal was achieved using ozone followed by treatment with trifluoroacetic acid in methylene chloride/water.[16] Olefination of the resulting keto aldehyde **13** proceeded routinely, to afford enoate **8** in a 95% yield as a 7:1 mixture of *E*/*Z* isomers. Once separated, the stage was set to attempt reductive cyclization.

Both electrochemical and reagent-induced cyclizations were explored.[10,17] The need to form a σ-bond between the β-carbon of the enoate and the ketone carbonyl carbon calls for either the selective 1,4-reduction of the unsaturated ester, or 1,2-reduction of the enone. However, the α,β-unsaturated ester is more difficult to reduce than the enone (E_p −2.45 *vs* −2.2 V),[18] and reduction of the enone promised to lead to saturation of the C=C π-bond which is needed to permit introduction of the epoxide. On the other hand, reduction of the epoxy ketone **14** illustrated in eq 1 (E_p −2.1 V), promised to afford the β-hydroxy ketone **15** as an intermediate,[19] a system that maintains functionality in the form of the hydroxyl group, that can be converted to the double bond. This intermediate could then undergo a second two-electron reduction forming the cyclized material **16.** Consequently, we first elected to examine the electroreductive cyclization of epoxy ketone **14**, rather than enone **8**.



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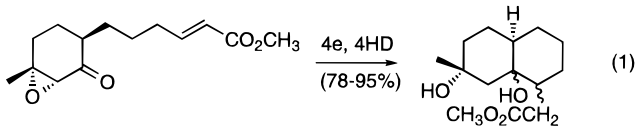
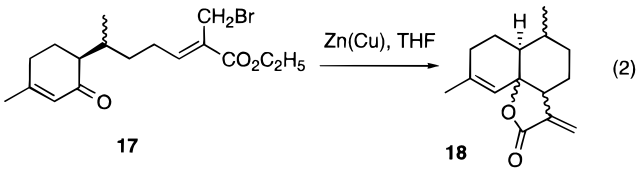
While the cyclization proceeded in a respectable 78−95% yield, it was not a stereoselective process (see eq 1). This observation is similar to that of Dreiding and coworkers,[20] whose attempts to effect cyclization of **17** using a zinc−copper couple, culminated in the formation of stereoisomers **18**, none of which corresponded to an adduct that could be converted to arteannuin B (**4**).



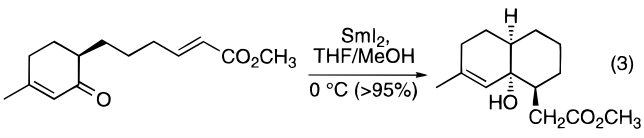
14 **16** (1)



17 **18** (2)

We were delighted to discover that in contrast to both of the transformations illustrated above, samarium diiodide proved to be a very effective reagent in promoting the cyclization of enone **8** (see eq 3).[21] Careful attention to several experimental parameters proved critical. For example, it was important to thoroughly de-gas the solution containing the substrate prior to use (N_2 stream). In this manner, it was possible to use only 2.5 equiv of the reducing agent instead of the customary large excess. To obviate simple reduction of the enone to the corresponding allylic alcohol, and to promote the desired cyclization required the simultaneous, but separate, addition of a dilute solution of the proton donor (MeOH) and samarium diiodide to the substrate. Even then, it proved important to carry out the reduction at 0 °C, rather than at −78 °C. At the lower temperature, only reduction to the allylic alcohol was observed, whereas at 0 °C, cyclization proved fast enough to compete effectively.

Under the conditions just described, the samarium diiodide-promoted reductive cyclization of **8** afforded the bicyclic γ-hydroxy ester **7** in greater than 95% yield. Within the limits of detection by 200 MHz ^{1}H NMR spectroscopy, no stereoisomer was produced. Given the instability of the product to even trace amounts of acid, a standard workup proved unsatisfactory, leading to low yields and poor mass balance. The workup was simplified and the yield improved significantly by using Rochelle's salt in an aqueous medium containing 10% potassium carbonate. Rather than the insoluble salts which normally accompany a basic workup, the aqueous layer was homogeneous and clear. To the best of our knowledge, this procedure has not been employed previously. We recommend its use in the isolation of acid-sensitive materials.



8 **7** (3)

Determination of the stereochemical outcome was facilitated by comparing the coupling constants, J_{ab} and J_{ac}, in structure **7** with values reported by Dreiding for the corresponding protons in arteannuin B (**4**).[20] As illustrated, the agreement is striking, leaving little doubt concerning the accuracy of the assignment.

We attribute the stereoselectivity of the cyclization to the formation of a transition state similar to **19**, one with

(16) Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, 499.
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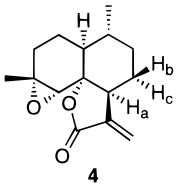
(21) Molander, G. A. In *Organic Reactions*; Wiley: New York, 1995; Vol. 46, p v.



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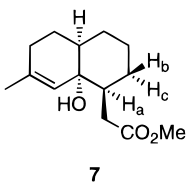
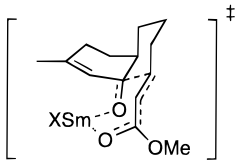


7

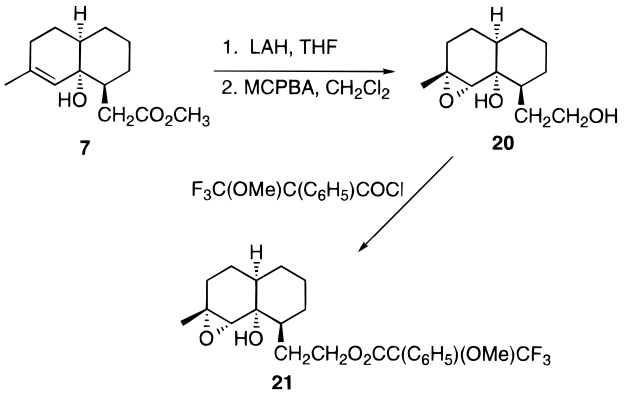
the side chain oriented axially so that *re*-face attack on the enone carbonyl carbon is achieved. There are many examples suggesting the formation of medium to large ring transition structures involving samarium chelates.[22,23] Clearly, the high oxophilicity of samarium is advantageous in this context to the extent that its positioning between the two oxygens promotes stereocontrol.



19

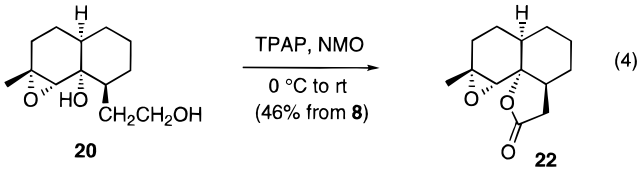
In principle, one could complete the synthesis of desmethyl arteannuin B (**5**) in any of a number of ways. However, given the acid lability of many of the intermediates, the sequence of events proved critical. A satisfactory solution was initiated by reduction of **7** to the diol. Hydroxyl-directed epoxidation (MCPBA, 20 mol % K_2CO_3) afforded epoxide **20**[24] (Scheme 3), the first substance after the cyclization that did not display exceptional acid lability. At this stage, we assessed the diastereoselectivity of the initial alkylation, cyclization, and epoxidation events. To do so, we converted **20** to the corresponding Mosher's ester **21**. The ^{1}H NMR spectrum displayed a 27/1 ratio of signals corresponding to the methyl groups of the diastereomeric methyl ethers, *i.e.*, to a diastereomeric excess of >93%.[25,28]

Scheme 3



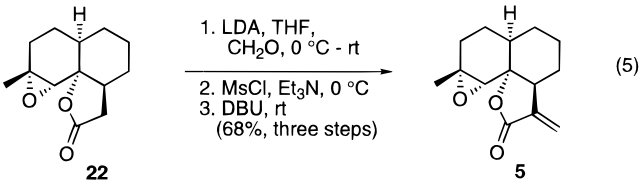
7 **20** **21**

Lactonization was conveniently accomplished using 5 mol % of tetra-*N*-propylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) as the cooxidant.[26] This exceptionally fine method afforded the epoxy lactone **22** in a 46% yield, over four steps (**8** → **22**) without the need to purify labile intermediates. When purification was attempted, significant material loss was experienced.



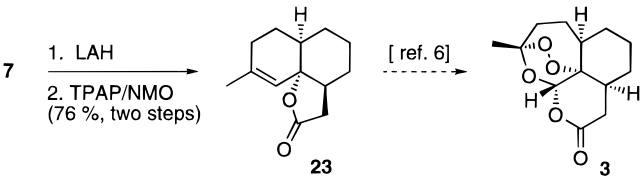
20 **22** (4)

Treatment of **22** with 3 equiv of LDA and formalin afforded the desired β-hydroxy lactone.[27] This material was most efficiently used directly in the subsequent mesylation-elimination processes to deliver enantiomerically pure desmethyl arteannuin B (**5**) in a 68% yield over the final three steps. The structure of **5** was confirmed via X-ray crystallographic analysis; an ORTEP representation has been provided as supporting information.[29]



22 **5** (5)

Finally, we note that treatment of the initially formed cyclized material, **7**, with LAH followed by 5 mol % of TPAP and NMO as the cooxidant affords lactone **23** in 76% yield (two steps).[26] This material is the 10,11-didesmethyl analog of an intermediate which has been converted to artemisinin (**1**).[6] We anticipate that the same methodology could be used to convert lactone **23** to **3**, the 10,11-didesmethyl analog of artemisinin that displays potent antimalarial activity against resistant strains of *Plasmodium falciparum*.[8]



23 **3**

In summary, we have developed an efficient total synthesis of (−)-C_{10}-desmethyl arteannuin B (**5**) beginning with readily available starting materials. The route features a stereoselective, chelation-controlled reductive cyclization to convert **8** to **7**. The methodology appears to be sufficiently general to allow the construction of a

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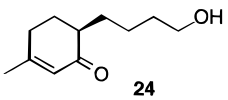
(28) This value is consistent with that obtained earlier from an examination of the Mosher ester of alcohol **24**, prepared from the alkylation of SAMP hydrazone **10** with the corresponding silyl-protected iodide. Within the limits of detection of 200 MHz NMR, no other diastereomer was observed.



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(29) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

great many analogs of the potent antimalarial agent, artemisinin (**1**).

Experimental Section

General. Melting points are uncorrected. Specific rotations were measured with the use of a 10 cm cell. ^{1}H NMR spectra were recorded at 200 or at 500 MHz, and ^{13}C NMR spectra were recorded at 200 MHz. All spectra were recorded in $CDCl_3$ as the solvent, and chemical shifts are reported in δ relative to TMS. IR spectra of solid compounds were obtained as solutions in $CDCl_3$ (NaCl plates). Solvents were dried (drying agent in parentheses) and distilled prior to use: Et_2O and THF (Na/benzophenone) CH_2Cl_2 and Et_3N (CaH_2). Samarium diiodide was purchased from Aldrich (0.1 M in THF) and used as is. Thin-layer chromatography (TLC) was performed with precoated glass plates; Kieselgel 60 GF_{254} (Merck). Column chromatography was performed using ICN (32−63, 60A) silica gel and the indicated solvents reported by volume (v/v). Capillary gas chromatography was performed on a Hewlett-Packard 5890 gas chromatograph. All compounds were purified. Those which were unstable to purification were used in subsequent reactions as crude products. All reactions were conducted under an argon atmosphere

(*S*)-(+)-[(3-Methylcyclohex-2-en-1-yidine)amino]-2-(methoxymethyl)pyrrolidine (10). To a solution of 3-methylcyclohex-2-en-1-one (10.23 g, 92.9 mmol) dissolved in 100 mL of benzene was added (*S*)-(−)-1-amino-2-(methoxymethyl)-pyrrolidine (SAMP) (12.50 g, 96.0 mmol), and the solution was refluxed with azeotropic removal of water. After 72 h, the reaction mixture was allowed to cool, and the solvent was removed under reduced pressure, affording the crude product as a yellow oil. Distillation under vacuum afforded 20.05 g (90.3 mmol, 97%) of the hydrazone in a 1.4:1 ratio of isomers as a yellow oil (bp 104−106°C, 0.4 mmHg): IR (neat) 2932, 2859, 1720, 1664, 1432 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.49 (s, 1H), 5.98 (s, 1H), 3.46 (dd, J = 2, 7 Hz, 1H), 3.43 (dd, J = 3.5, 9 Hz, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.16−3.27 (m, 8H), 2.79 (ddd, J = 4.5, 9, 16 Hz, 1H), 2.54 (dd, J = 8, 17 Hz, 1H), 2.42 (dd, J = 8.5, 17 Hz, 1H), 2.34 (m, 1H), 2.1−2.17 (m, 4H), 1.98−2.07 (m, 4H), 1.86 (s, 3H), 1.81 (s, 3H), 1.78 (m, 4H), 1.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 161.83, 161.18, 148.98, 145.76, 123.99, 117.51, 75.35, 75.35, 66.45, 66.33, 59.05, 59.05, 56.01, 54.28, 31.35, 31.13, 30.31, 26.58, 26.58, 26.36, 24.24, 23.97, 22.61, 22.31, 22.05, 22.05; HRMS calcd for $C_{13}H_{22}N_2O$ 222.1732; found 222.1726; σ = 2.8 ppm.

(2*S*,5*R*)-(−)-[[5-(4′,4′-Dimethoxybutyl)-3-methylcyclohex-2-en-1-ylidine]amino]-2-(methoxymethyl)pyrrolidine (12). To a solution of diisopropylamine (3.9L mL, 29.8 mmol) and LiCl (85 mg, 2 mmol) in 20 mL of freshly distilled THF was added *n*-butyllithium (2.98 mL of 10M, 29.8 mmol) at −78 °C. The mixture was allowed to warm to 0 °C over 20 min. The solution was cooled to −95 °C and the SAMP hydrazone **10** (4.41 g, 19.9 mmol) was added dropwise. The reaction mixture was stirred at −95 °C for an additional 4 h. After enolate formation was complete (usually 4 h), 4-iodobutyraldehyde dimethyl acetal (7.27 g, 29.8 mmol) was added dropwise, and the reaction mixture, after warming to 0 °C over 30 min, was quenched with a saturated ammonium chloride solution (30 mL). The aqueous layer was extracted twice with 20 mL portions of methylene chloride and the combined organic layers were washed with brine (2 × 30 mL), dried over magnesium sulfate, and concentrated under reduced pressure to afford a yellow oil. The crude product was chromatographed on silica gel (hexane/EtOAc/NEt_3, 80:28:2) to yield **12** as a pale yellow oil (5.29 g, 15.7 mmol, 79%): IR (neat) 2942, 2871, 2830, 1646, 1455, 1367, 1189, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (s, 1H), 4.38 (t, J = 5.5 Hz, 1H), 3.43 (dd, J = 4, 9 Hz, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 3.24 (m, 2H), 3.20 (dd, J = 8, 16.5 Hz, 1H), 3.14 (ddd, 1H), 3.07 (m, 2H), 2.45 (dd, J = 8.5, 17 Hz, 1H), 2.20 (m, 1H), 2.05 (ddd, J = 7.5, 13.5, 19.5 Hz, 1H), 1.97 (dd, J = 5, 18.5 Hz, 1H) 1.88 (ddd, J = 2.5, 5, 13.5 Hz, 1H), 1.81 (s, 3H), 1.81 (m, 1H), 1.62 (m, 4H), 1.45 (m, 2H), 1.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 164.98, 142.45, 120.48, 101.76, 73.55, 66.05, 58.87, 55.51, 52.63, 52.40, 33.72, 32.31, 29.02, 27.11, 26.47, 24.48, 23.70, 22.25, 22.25; MS *m*/*z* (relative intensity) 338 (8), 307 (12), 294 (20), 293 (100), 192 (9), 84 (10), 75 (24), 71 (23), 70 (19), 45 (15); HRMS calcd for $C_{19}H_{34}N_2O_3$ 338.2569; found 338.2569; σ = 0.1 ppm.

(*R*)-(−)-4-(4′-Methyl-2′-oxocyclohex-3′-en-1′-yl)butyraldehyde Dimethyl Acetal (12a). The alkylated SAMP hydrazone **12** (4.82 g, 14.3 mmol) was dissolved in 50 mL of methylene chloride and cooled to -78 °C. Ozone was bubbled into the solution until TLC analysis indicated that the reaction was complete. The mixture was degassed with nitrogen and allowed to warm to room temperature with continuous degassing. The solvent was removed under vacuum, and the resulting brown oil was chromatographed on silica gel (hexanes/EtOAc, 5:1) yielding the enone as a colorless oil (2.77 g, 12.3 mmol, 86%): $[\alpha]^{25}_D$ = −68.1° (*c*, 0.010, CH_2Cl_2); IR (neat) 2942, 2871, 2830, 1646, 1455, 1367, 1189 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.80 (q, J = 1.5 Hz, 1H), 4.34 (dt, J = 1.5, 6 Hz, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 2.29 (t, J = 6 Hz, 2H), 2.17 (dddd, J = 5, 7, 10.5, 12 Hz, 1H), 2.08 (dq, J = 5, 13.5 Hz, 1H), 1.90 (s, 3H), 1.84 (m, 1H), 1.71 (dddd, J = 7, 10.5, 13.5, 17.5 Hz, 1H), 1.60 (m, 2H), 1.43 (m, 1H), 1.35 (ddd, J = 3.5, 7.5, 11.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 201.69, 161.52, 126.43, 104.57, 52.95, 52.86, 45.47, 32.75, 30.32, 29.08, 27.65, 24.30, 22.20; MS *m*/*z* (relative intensity) 196 (13, $M^+ - CH_3O$), 195 (100, $M - CH_3O$), 194 (6), 180 (8), 136 (10), 135 (76), 75 (25); HRMS calcd for $C_{12}H_{18}O_2$ ($M - CH_3OH$) 194.1307; found 194.1302; σ = 2.7 ppm.

(*R*)-(−)-4-(4′-Methyl-2′-oxocyclohex-3′-en-1′-yl)butyraldehyde (13). To 2 mL (26 mmol) of trifluoroacetic acid in 30 mL of water was added the dimethyl acetal **12a** (1.35 g, 5.97 mmol) in 30 mL of methylene chloride. The mixture was stirred at room temperature until TLC analysis indicated that the reaction was complete (usually 2−4 h). The reaction mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layers were washed with a saturated bicarbonate solution (20 mL) and brine (2 × 20 mL), dried over magnesium sulfate, and concentrated in vacuo. The resulting oil was chromatographed on silica gel (hexanes/EtOAc, 5:1) to give the aldehyde as a colorless oil (1.05 g, 5 83 mmol, 98%): $[\alpha]^{25}_D$ = −32.9° (*c*, 0.033, CH_2Cl_2); IR (neat) 3029, 2928, 2865, 2724, 1724, 1673, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.75 (t, J = 1.5 Hz, 1H), 5.79 (q, J = 1.5 Hz, 1H), 2.45 (t, J = 7.5 Hz, 2H), 2.30 (ddd, J = 4.5, 10 Hz, 1H), 2.17 (dddd, J = 5, 7, 11, 12 Hz, 1H), 2.08 (ddd, J = 4.5, 9.5, 13 Hz, 1H), 1.92 (s, 3H), 1.82 (dddd, J = 5.5, 11, 13.5, 16.5 Hz, 1H), 1.61−1.77 (m, 4H), 1.38 (dddd, J = 5.5, 7.5, 11.5, 13 Hz, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 202.67, 201.29, 161.76, 126.37, 45.34, 44.12, 30.42, 28.91, 27.80, 24.30, 19.75; HRMS calcd for $C_{11}H_{17}O_2$ $(P + H)^+$ 181.1229; found 181.1230; σ = 0.9 ppm.

^{1}H NMR data for (1′*R*, 3′*R*, 4′*R*)-methyl (2*E*)-6-(3′,4′-epoxy-4′-methyl-2′-oxocyclohex-1′-yl)hexenoate (14): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.95 (dt, J = 6.5, 15 Hz, 1H), 5.78 (dt, J = 1.5, 15 Hz, 1H), 3.69 (s, 3H), 3.04 (s, 1H), 2.13 (m, 3H), 1.86 (m, 2H), 1.72 (m, 1H), 1.63 (m, 3H), 1.45 (m, 2H), 1.41 (s, 3H).

(*R*)-(+)-Methyl (2*E*)-6-(4′-Methyl-2′-oxocyclohex-3′-en-1′-yl)hexenoate (8). To a solution of sodium bis(trimethylsilyl)amide (1.53 mL, 1.53 mmol) in 10 mL of THF, was added dropwise via a precooled (−78 °C) cannula, trimethyl phosphonoacetate (0.28 g, 1.5 mmol) at −78 °C. The mixture was allowed to stir for 15 min, and then the aldehyde **13** (0.25 g, 1.39 mmol) was diluted in 5 mL of THF and added dropwise via the precooled cannula. The reaction mixture was allowed to warm to 0 °C and was quenched with brine. The aqueous layer was extracted with ether (2 × 20 mL), and the combined organic layers were washed with brine (20 mL) and dried over magnesium sulfate, and the solvent was removed in vacuo. The resulting oil was chromatographed on silica gel (hexanes/EtOAc, 5:1) to give the unsaturated ester as a colorless oil (0.27 g, 1.15 mmol, 83%, *E* isomer): $[\alpha]^{25}_D$ = +40.9° (*c*, 0.029, CH_2Cl_2); IR (neat) 2932, 2859, 1719, 1664, 1432 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.95 (dt, J = 6.5, 15 Hz, 1H), 5.83 (s, 1H), 5.82 (d, J = 15 Hz, 1H), 3.71 (s, 3H), 2.30 (m, 2H), 2.14−2.24 (m, 2H), 2.07 (ddd, J = 5, 10, 13.5 Hz, 1H), 1.93 (s, 3H), 1.83 (m, 1H), 1.71 (m, 1H), 1.51 (m, 3H), 1.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 201.74, 161.87, 149.68, 126.71, 121.53,

51.84, 45.68, 32.74, 30.67, 30.66, 29.30, 28.14, 25.98, 24.58; HRMS calcd for $C_{14}H_{20}O_3$ 236.1412; found 236.1409; $\sigma = 1.5$ ppm.

Methyl (1′*S*,4a′*R*,8a′*S*)-2-(8a′-Hydroxy-7′-methyl-1′,2′,3′,4′,4a′,5′,6′,8a′-octahydro-1′-naphthyl)acetate (7). The unsaturated ester **8** (0.51 g, 2.16 mmol) was dissolved in 50 mL of dry THF and degassed with argon for 10 min. The solution was then chilled to 0 °C and SmI_2 (0.1 M in THF, 80 mL, 8 mmol) was added slowly via cannula. While the SmI_2 was being introduced, methanol (0.41 mL dissolved in 10 mL THF, 10 mmol) was also added slowly. When TLC analysis indicated that the reaction was complete (usually under 15 min, the reaction mixture was still dark blue), a saturated solution of sodium−potassium tartrate containing 10% potassium carbonate was added. The aqueous layer was extracted with methylene chloride (3 × 30 mL) and the combined organic layers were washed with brine (2 × 20 mL) and dried over magnesium sulfate. The solution was then filtered through a short pad of silica and concentrated in vacuo to yield the cyclized product (0.53 g): IR (neat) 3494 br, 2927, 2851, 1733, 1717, 1652, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.36 (s, 1H), 3.66 (s, 3H), 2.87 (dd, $J = 5$, 15 Hz, 1H), 2.14 (dd, $J = 9$, 15 Hz, 1H), 2.12 (m, 1H), 1.98 (m, 2H), 1.86 (m, 2H), 1.68 (s, 3H), 1.62 (m, 4H), 1.44 (m, 2H), 1.35 (dddd, $J = 4$, 8, 13.5, 17 Hz, 1H), 1.24 (ddd, $J = 3.5$, 12.5, 15 Hz, 1H), 0.98 (ddd, $J = 3.5$, 12.5, 16 Hz, 1H).

(1′*S*,4′*R*,7′*R*,8′*R*,8a′*S*)-2-(7′,8′-Epoxy-8a′-hydroxy-7′-methylperhydro-1′-naphthyl)ethanol (20). Lithium aluminum hydride (123 mg, 3.24 mmol) was added to 20 mL of dry THF at 0 °C. To this was added the γ-hydroxy ester **7** (0.53 g, 2.16 mmol) dissolved in 5 mL of THF; stirring continued until TLC analysis indicated that the reaction was complete (usually under 15 min). The reaction was quenched with 0.12 mL of water followed by 0.12 mL of 1 N NaOH and then 0.36 mL of water. The mixture was then filtered over a bed of sodium sulfate and concentrated in vacuo to yield the crude product as a colorless oil. To the crude diol (0.5 g, 2.16 mmol) in 15 mL of methylene chloride and 15 mL of hexanes was added solid potassium carbonate (0.30 g, 2.17 mmol) and *m*-chloroperbenzoic acid (0.75 g, 4.35 mmol) at room temperature. The mixture was stirred until TLC analysis indicated that the reaction was complete (2−4 h). The white slurry was diluted with 30 mL of methylene chloride, filtered, and washed with 10% sodium bisulfite (30 mL), followed by saturated sodium bicarbonate (20 mL), and brine (20 mL). The aqueous layers were sequentially back-extracted with methylene chloride (2 × 20 mL), and the resulting extracts were washed with saturated sodium bicarbonate solution and brine. The organic extracts were combined, and the solvent was removed in vacuo to yield the crude epoxide as a viscous colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 5.29 (s, 1H), 3.79 (ddd, $J = 6$, 11, 16.5 Hz, 1H), 3.64 (ddd, $J = 5$, 8, 11 Hz, 1H), 2.08 (dddd, $J = 5.5$, 8, 11, 13.5 Hz, 1H), 1.88 (dd, $J = 5.5$, 15 Hz, 1H), 1.65−1.81 (m, 6H), 1.25−1.50 (m, 2H), 1.36 (s, 3H), 1.06−1.19 (m, 2H).

(−)-(1′*S*,4′*R*,7′*R*,8′*R*,8a′*S*)-2-(7′,8′-Epoxy-8a′-hydroxy-7′-methylperhydro-1′-naphthyl)ethan-8a′-olide (22). To the crude epoxide **20** (0.5 g, 2.16 mmol), dissolved in 20 mL of methylene chloride, was added crushed 4 Å molecular sieves (1 g), 4-methylmorpholine *N*-oxide (0.38 g, 3.25 mmol), and tetrapropylammonium perruthenate(VII) (35 mg, 0.1 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature with constant stirring. When the reaction was complete, as indicated by TLC analysis, the mixture was diluted with 20 mL of methylene chloride and filtered through a short pad of silica. The solvent was removed in vacuo, and the resulting crude oil was chromatographed on silica gel (hexanes/EtOAc/NEt_3, 88:10:2), yielding a white crystalline solid. Recrystallization from Et_2O yielded the lactone **22** (0.22 g, 1.0 mmol, 46% over 4 steps). $[\alpha]^{25}_D = -10.2°$ (*c*, 0.024, CH_2Cl_2); mp 144−146 °C; IR (dissolved in $CDCl_3$) 2936, 1781, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.83 (s, 1H), 2.60 (dd, $J =$ 14.5, 16.5 Hz, 1H), 2.49 (dd, $J = 7$, 16.5 Hz, 1H), 2.21 (m, 1H), 1.75−1.95 (m, 6H), 1.59 (m, 2H), 1.42 (dddd, $J = 3.5$, 7, 8.5, 12 Hz, 1H), 1.38 (s, 3H), 1.34 (m, 1H), 1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 175.44, 82.99, 57.87, 56.88, 47.14, 37.64, 32.75, 26.22, 25.23, 24.42, 24.07, 22.98, 19.46; HRMS calcd for $C_{13}H_{18}O_3$ $(M + H)^+$ 223.1334; found 223.1342; $\sigma = 3.8$ ppm. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found C, 70.19; H, 8.11.

(−)-(1′*S*,4′*R*,7′*R*,8′*R*,8a′*S*)-2-(7′,8′-Epoxy-8a′-hydroxy-7′-methylperhydro-1′-naphthyl)propen-8a′-olide (5). To a solution of butyllithium (0.90 mL, 2.25 mmol) in 5 mL of dry THF at −78 °C was added diisopropylamine (0.30 mL, 2.3 mmol); the reaction mixture was warmed to 0 °C over 15 min. The solution was cooled to −78 °C and the lactone **22** (0.140 g, 0.63 mmol) in 5 mL of THF was added and stirred for 1 h. Then, 5 mL of a freshly prepared formaldehyde solution in THF (generated from 0.20 g of paraformaldehyde, 7 mL of THF and 0.3 mL of BF_3·OEt, Schlosser procedure) was added. The reaction mixture, maintained at −78 °C for 15 min, was allowed to warm to 0 °C over 30 min and quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with methylene chloride (2 × 10 mL), washed with 0.1 N HCl (10 mL) and then with a 10% bicarbonate solution, and brine, and dried over magnesium sulfate. The solvent was removed in vacuo; the resulting crude mixture was dissolved in methylene chloride, and cooled to 0 °C. Triethylamine (0.50 mL, 3.6 mmol) was added, followed by a dropwise addition of mesyl chloride (0.20 mL, 2.6 mmol). The reaction mixture was allowed to stir for 12 h. The reaction was quenched with a saturated bicarbonate solution (10 mL) and the aqueous layer was extracted with methylene chloride (2 × 10 mL). The combined organic layers were washed once with 0.1 M HCl (10 mL) brine and dried over magnesium sulfate. The solvent was removed in vacuo and replaced with benzene to which was added DBU (0.47 mL, 3.15 mmol). After 1 h, the reaction was quenched with a saturated ammonium chloride solution, dried with magnesium sulfate and chromatographed on silica gel (hexanes/EtOAc/NEt_3, 78:20:2). Recrystallization from Et_2O yielded C_{10}-desmethyl arteannuin B as a colorless crystalline solid (0.102g, 0.44 mmol, 69%): mp 147−149 °C; $[\alpha]^{25}_D = -68.09°$ (*c*, 0.010, CH_2Cl_2); IR (dissolved in $CDCl_3$) 3099, 2952, 2927, 2863, 1764, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.16 (d, $J = 4$ Hz, 1H), 5.42 (d, $J = 4$ Hz, 1H), 2.73 (dddd, $J = 3$, 6, 9.5, 12 Hz, 1H), 2.67 (s, 1H), 2.07 (dddd, $J = 1.5$, 3, 7, 8.5 Hz, 1H), 1.76−1.95 (m, 4H), 1.64 (ddddd, $J = 1.5$, 4.5, 8.5, 12, 13.5 Hz, 1H), 1.49 (dddd, $J = 4$, 8, 12.5, 17 Hz, 1H), 1.35, (m, 2H), 1.34 (s, 3H), 1.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 169.93, 138.44, 117.76, 81.26, 58.33, 58.10, 52.40, 37.01, 26.46, 24.72, 24.47, 22.90, 22.14, 19.52; HRMS calcd for $C_{14}H_{18}O_3$ $(M + H)^+$ 235.1334; found 235.1336; $\sigma = 0.9$ ppm. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found C, 71.72; H, 7.80.

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Supporting Information Available: Spectral data for compounds **5**, **7**, **8**, **10**, **12**, **12a**, **13**, **20**, and **22** and Figure 1 (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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