Total Synthesis of Eleutherobin and Eleuthosides A and B

K. C. Nicolaou,* T. Ohshima, S. Hosokawa, F. L. van Delft, D. Vourloumis, J. Y. Xu, J. Pfefferkorn, and S. Kim

Contribution from the Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego 9500 Gilman Drive, La Jolla, California 92093

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Abstract: The total synthesis of the cytotoxic marine natural products eleutherobin (**1**) and eleuthosides A (**2**) and B (**3**) is described. The strategy involves glycosidation of the (+)-carvone-derived intermediate **7** with the arabinose-derived trichloroacetimidate **9** followed by base-induced ring closure and elaboration to afford the dihydroxy eneynone **19**. Selective hydrogenation of **19** led to the generation and intramolecular collapse of dienone **20** furnishing **21** and thence **22** with the required structural framework of the target molecules. Finally, esterification with mixed anhydride **24** followed by deprotection gave eleutherobin (**1**) which served as a precursor to eleuthosides A (**2**) and B (**3**). The α-glycoside anomer of eleutherobin, compound **27**, was also synthesized by application of the developed chemistry, demonstrating the flexibility of the sequence in generating designed analogues for biological screening.

1. Introduction

In 1995, Fenical et al. disclosed in a patent[1] the isolation and structure of a marine natural product with potent cytotoxicity, which they called eleutherobin (**1**, Figure 1). In more detailed accounts in 1997, the Fenical group revealed further information about the cytotoxic properties of **1** and disclosed its Taxol-like mechanism of action.[2,3] This mechanism involves tubulin polymerization and microtubule stabilization.[4] Isolated from an *Eleutherobia* species of soft coral (possibly *E. albiflora* Alcynacea, Alcyoniidea collected from the Indian Ocean near Bennett's Shoal in Western Australia), eleutherobin (**1**) was structurally elucidated by spectroscopic means, even though its absolute stereochemistry remained unknown. In the meantime, Kashman and his group[5] reported in 1996 the isolation and structural elucidation of eleuthosides A (**2**) and B (**3**). Isolated from an *Eleutherobia aurea* species of soft coral (collected near the Kwazula-Natal coast of South Africa), these substances are closely related to eleutherobin (**1**) and differ only by the position of their acetate groups. Also related to eleutherobin (**1**) and the eleuthosides A (**2**) and B (**3**) are sarcodictyins A (**4**) and B (**5**), reported in 1987 by Pietra et al.,[6] and valdivone (**6**), first reported by Kennart and Watson in 1968[7] and, subsequently, by Faulkner and his group in 1993.[8] In the preceding paper,

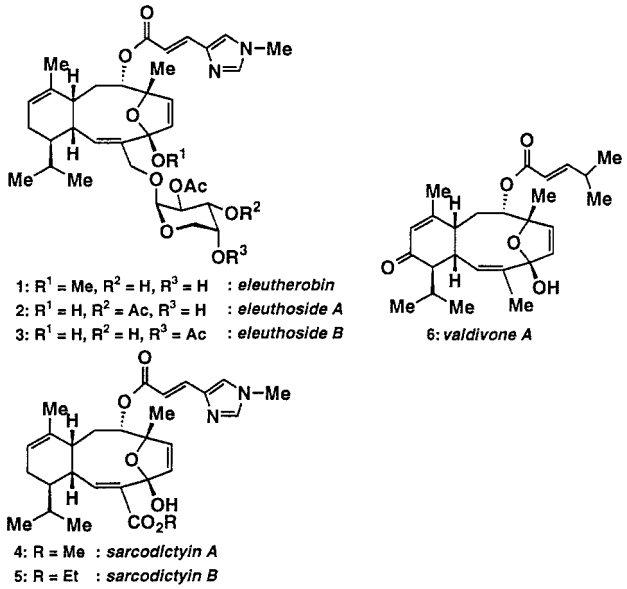

Figure 1. Molecular structures of eleutherobin (**1**), eleuthosides A (**2**) and B (**3**), and sarcodictyins A (**4**) and B (**5**) (Ac = acetyl).

we described the total synthesis of sarcodictyins A and B.[9] In this paper, we present the details of our total synthesis of eleutherobin (**1**)[10−12] and eleuthosides A (**2**) and B (**3**), the

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(11) For another total synthesis of eleutherobin, see: Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *110*, 835−838; Chen, X.-T.; Gutteridge, C. E.; Bhattacharya, S. K.; Zhou, B.; Pettus, T. R. R.; Hascall, T.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 185−187.

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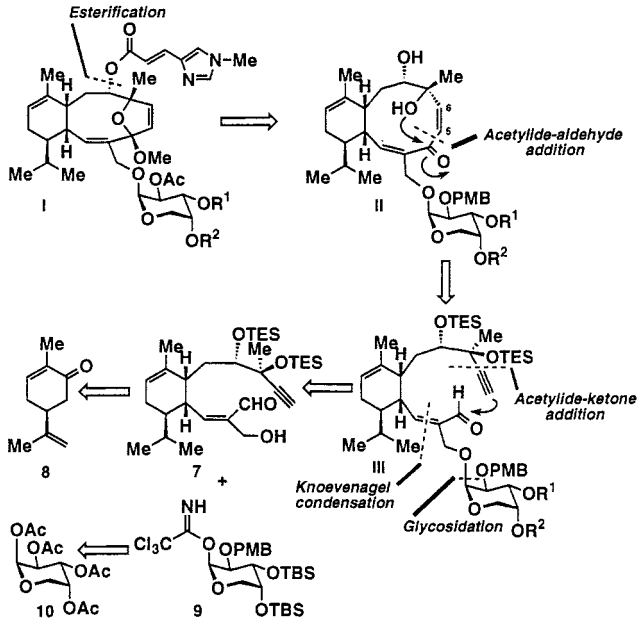


Figure 2. Retrosynthetic analysis of eleutherobin (**1**) and eleuthosides A (**2**) and B (**3**).

absolute stereochemistry of eleutherobin (**1**), and the construction of a number of analogues of these compounds.[12]

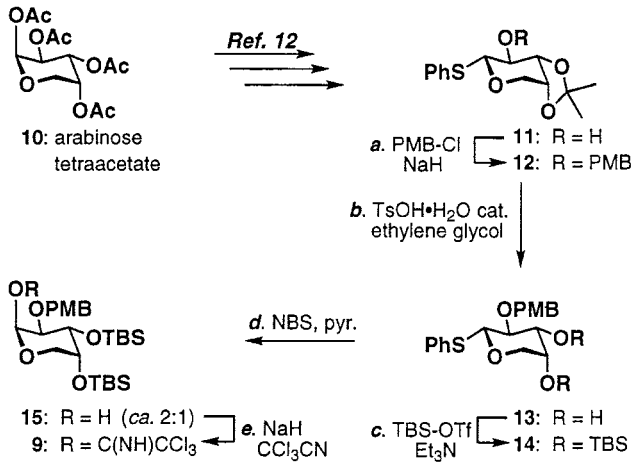
2. Retrosynthetic Analysis and Strategy

With the exception of the D-arabinopyranose moiety, the structural features of eleutherobin (**1**) and the eleuthosides A (**2**) and B (**3**) are similar to those of the sarcodictyins (**4** and **5**). Thus, the strategy for their total synthesis was devised from a similar retrosynthetic analysis with appropriate provisions for the introduction of the carbohydrate unit. Figure 2 outlines the retrosynthetic analysis for eleutherobin (**1**) and the eleuthosides (**2**, **3**). Thus, removal of the (*E*)-*N*(6′)-methylurocanic acid residue from the target structure (I) and dismantling of the oxygen bridge of the central bicyclic core leads to the 10-membered ring dihydroxy dienone II, whose origin can be traced to the open-chain acetylenic aldehyde III. Further carbon−carbon bond disconnections and retroglycosidation led to hydroxy acetylene **7**, whose relationship to (+)-carvone **8** was amply evident. It was comforting to know that, although the (+)-enantiomer of carvone was chosen as the initial starting material, the (−)-enantiomer was also available in case the absolute stereochemistry of the natural substances required it. The trichloroacetimidate **9** required for the projected total synthesis was traced to D-arabinose tetraacetate **10**. The execution of the total synthesis of eleutherobin (**1**) and eleuthosides A (**2**) and B (**3**) was carried out as described below.

3. Total Synthesis of Eleutherobin (1)

The construction of the (+)-carvone-derived hydroxy aldehyde fragment **7** (Scheme 2) has been described in the preceding paper.[9] We, therefore, begin here with the synthesis of the requisite fragment, trichloroacetimidate **9** (Scheme 1). Thus, arabinosetetraacetate (**10**) was efficiently converted to thioglycoside **11** by a sequence recently reported from these laboratories.[12] The hydroxyl group of **11** was then protected as a PMB ether by the action of PMB-Cl in the presence of NaH (93% yield), and the acetonide group of the resulting compound **12**

Scheme 1. Construction of Glycodise Donor 9[a]



[a] Reagents and conditions: (a) 1.1 equiv of NaH, DMF, 0 °C, 30 min; then 1.2 equiv of PMB-Cl, 2 h, 93%; (b) 0.1 equiv of $TsOH·H_2O$, ethylene glycol−MeOH (1:10), 25 °C, 6 h, 84%; (c) 4.0 equiv of TBSOTf, 10 equiv of Et_3N, CH_2Cl_2, 0 °C, 2 h, 97%; (d) 3.4 equiv of NBS, 11 equiv of pyridine, acetone−H_2O (93:7), 80% (ca. 2:1 ratio of anomers); (e) 0.2 equiv of NaH, 5.0 equiv of Cl_3CCN, CH_2Cl_2, 25 °C, 3.5 h, 93%. Ts = *p*-toluenesulfonyl. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate. NBS = *N*-bromosuccinimide. PMB = *p*-methoxybenzyl.

was removed by treatment with TsOH in ethylene glycol: methanol (1:10), furnishing diol **13** in 84% yield. Both hydroxyl groups in **13** were then silylated (TBSOTf−Et_3N, 97% yield of **14**), and the anomeric position was freed by the action of NBS-pyridine in aqueous acetone, affording lactol **15** (80% yield, ca. 2:1 mixture of anomers). Finally, treatment of **15** with NaH, followed by addition of Cl_3CCN gave the desired trichloroacetimidate **9** in 93% yield as the major isomer (greater than 95% purity).[13] Purification of this sensitive intermediate could be achieved by flash chromatography with a short column (silica, 10% ether in hexane containing 1% Et_3N). The next task was to define suitable conditions for the stereospecific glycosidation of hydroxyaldehyde **7** with the arabinose-derived carbohydrate donor **9**. To this end, the study in Table 1 was carried out. Indeed, it was possible to reverse the stereoselectivity of the formed glycoside bond by varying the experimental conditions. Thus, while reaction of **7** with **9** in hexane in the presence of TMSOTf as a catalyst at −78 °C gave a ca. 8:1 ratio of glycosides in favor of the α-anomer **26** (75% combined yield), the use of dioxane:toluene (2:1) as solvent at 0 °C led to a ca. 8:1 ratio of products in favor of the desired β-anomer **25** (75% yield after flash chromatography purification). Flash chromatography produced pure **25** ready for the next step.

Reaction of the pure β-anomer **25** with LiHMDS in THF at −30 °C caused smooth cyclization via acetylide formation and intramolecular attack on the aldehyde group affording an intermediate secondary alcohol (mixture of diastereomers) which was immediately oxidized with Dess−Martin reagent to dienone **16** (Scheme 2).[14]

It was now time to install the acetate group at the C-2 position of the pyranose ring. Selective removal of the PMB group from **16** with DDQ led to the formation of the corresponding hydroxy compound **17** (Scheme 2) in 91% yield. Standard acetylation then led to acetate **18** (95% yield). Both TES groups were then

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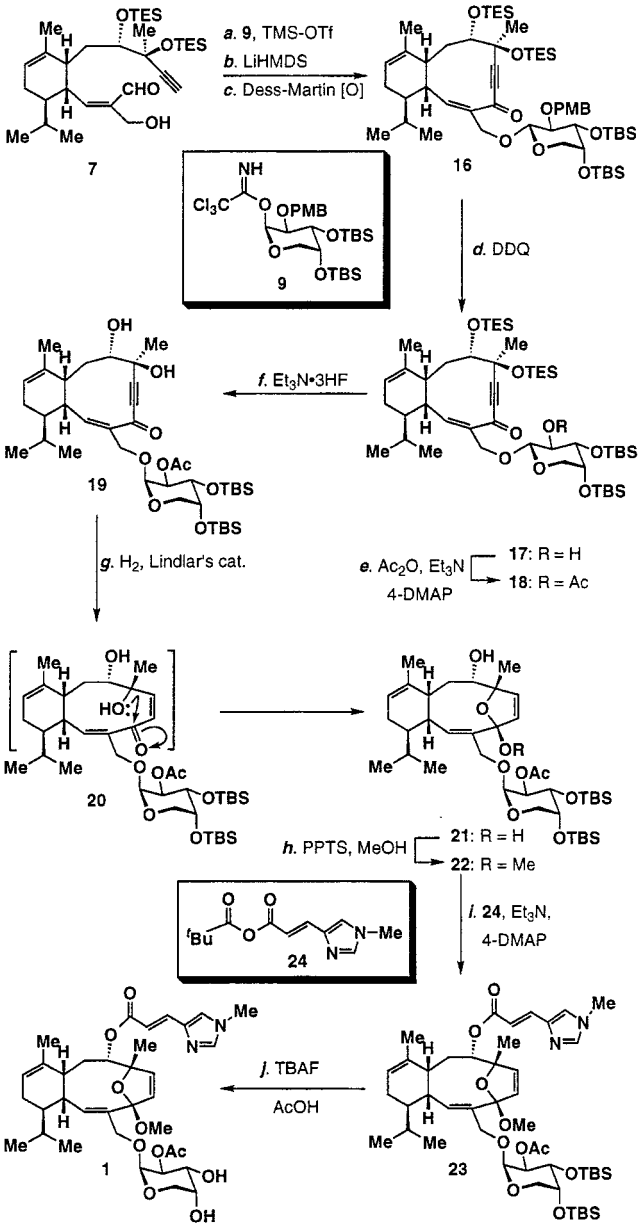
Scheme 2. Total Synthesis of Eleutherobin (**1**)[a]

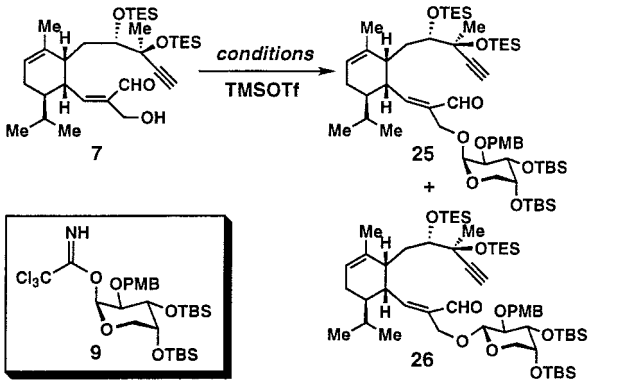


[a] Reagents and conditions: (a) **9**, TMSOTf, see Table 1; (b) 2.0 equiv of LiHMDS, THF, −30 °C, 20 min; (c) 2.0 equiv of Dess−Martin periodinane, 10 equiv of $NaHCO_3$, 10 equiv of pyridine, CH_2Cl_2, 0 °C, 15 min, 93% for two steps; (d) 2.2 equiv of DDQ, $CH_2Cl_2-H_2O$ (20:1), 25 °C, 91%; (e) 12 equiv of Ac_2O, 16 equiv of Et_3N, 0.5 equiv of DMAP, CH_2Cl_2, 25 °C, 1 h, 95%; (f) $Et_3N{\cdot}3HF-THF$ (1:7), 25 °C, 3 h, 81%; (g) H_2, 50 mol % Lindlar's catalyst, $PhCH_3$, 25 °C, 20 min; (h) 0.2 equiv of PPTS, MeOH, 25 °C, 20 min, 76% for two steps; (i) 10 equiv of **24**, 15 equiv of Et_3N, 2.0 equiv of DMAP, CH_2Cl_2, 25 °C, 18 h, 97%; (j) 17 equiv of TBAF, 4.0 equiv of AcOH, THF, 25 °C, 2.5 h, 96%. TMSOTf = trimethylsilyl trifluoromethanesulfonate. LiHMDS = lithium hexamethyldisilazane. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-(dimethylamino)pyridine. Lindlar's catalyst = Pd/$CaCO_3$/Pb. PPTS = pyridinium *p*-toluenesulfonate. TBAF = tetra-*n*-butylammonium fluoride.

removed from **18** without damage of the TBS group by the discriminating action of $Et_3N{\cdot}3HF$ in THF at 25 °C furnishing diol **19**.

The next objective in the synthesis was the generation of the key dienone **20**, the fleeting intermediate expected to readily collapse in favor of its bridged isomer **21** (Scheme 2). Indeed, upon selective hydrogenation of the acetylene moiety (Lindlar catalyst, H_2, toluene, 25 °C), compound **19** gave rise to the expected lactol **21**, whose conversion to the methoxy ketal **22** proved straightforward (MeOH, PPTS, 76% yield from **19**).

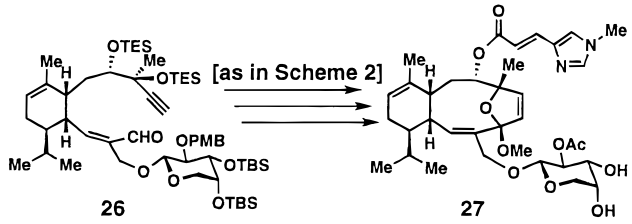
Table 1. Toward the Total Synthesis of Eleutherobin (1): Studies for the Attachment of the Sugar Moiety



conditions	products (**25**:**26**)[c]	yield (%)
CH_2Cl_2, −78 °C[a]	1:3	52 (mixture of **25** and **26**)
hexane, −78 °C[a]	1:8	34 (mixture of **25** and **26**)
MeCN, −35 °C[a]	1:4	62 (mixture of **25** and **26**)
Et_2O, −80 °C[a]	2:1	65 (mixture of **25** and **26**)
Et_2O, 0 °C[a]	2.5:1	54 (of **25**)
Et_2O, 25 °C[a]	3:1	60 (mixture of **25** and **26**)
dioxane−toluene (1:1), 0 °C[b]	7:1	67 (of **25**)
dioxane−toluene (2:1), 0 °C[b]	8:1	75 (of **25**)
dioxane−toluene (3:1), 0 °C[b]	7:1	70 (of **25**)

[a] Concentration of starting material is 0.1 M, TMSOTf (2−5%), 1.5 equiv of imidate. [b] Concentration of starting material is 0.07 M, TMSOTf (2−5%) 2.5 equiv of imidate. [c] The ratio of the two anomers was determined by NRM. TES = triethylsilyl, PMB = *p*-methoxybenzyl, TBS = *t*-butyldimethylsilyl, NIS = N-iodosuccinimide.

Scheme 3. Synthesis of the α-Anomer of Eleutherobin (**27**)



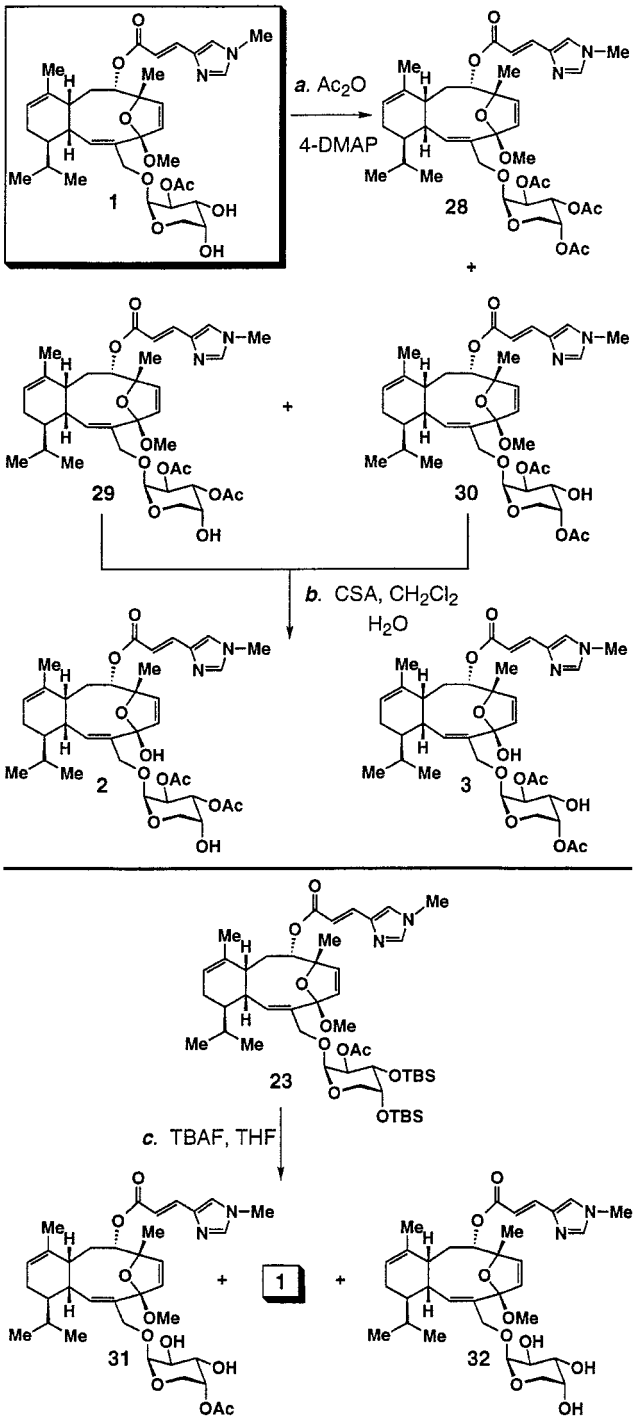
The attachment of the (*E*)-*N*(6′)-methylurocanic acid residue onto the main framework of the target molecule was accomplished by reaction of alcohol **22** with mixed anhydride **24**[9] in the presence of Et_3N and DMAP in CH_2Cl_2 at 25 °C, leading to esterified product **23** (97% yield). Finally, exposure of **23** to TBAF−AcOH in THF resulted in the cleavage of the TBS group and the liberation of eleutherobin (**1**) in 96% yield. Synthetic eleutherobin (**1**) exhibited identical physical data to those reported for the natural substance. Furthermore, the sign of its rotation $[\alpha]_D$ −67 (c = 0.2, MeOH) was the same as that reported for the natural eleutherobin, establishing the absolute stereochemistry of the latter as that corresponding to (+)-carvone (**6**) and structure **1**.

The α-glycoside analogue **27** of eleutherobin (Scheme 3) was synthesized from the α-anomer **26** (Table 1) by following the same route as for **1** (shown in Scheme 2). The yields for the steps involved in this construction were similar to those for the eleutherobin sequence.

4. Total Synthesis of Eleuthosides

The eleuthosides A (**2**) and B (**3**) were synthesized from eleutherobin (**1**) as indicated in Scheme 4. Thus, exposure of

Scheme 4. Synthesis of Eleuthosides A (**2**) and B (**3**)[a]



[a] Reagents and conditions: (1) 1.1 equiv of Ac_2O, 3.0 equiv of Et_3N, 0.2 equiv of DMAP, 0 °C, 1 h, 16% of **28** along with 73% of the mixture of **29** and **30** (2.2:1 by NMR); (b) 2.0 equiv of CSA, CH_2Cl_2−H_2O (10:1), 25 °C, 48 h, 80% of the mixture of **2** and **3** (based on 87% conversion of the starting material); (c) 4.0 equiv of TBAF, THF, 25 °C, 6 h, **1** (22%), **31** (60%) and **32** (8%). DMAP = 4-(dimethylamino)pyridine. CSA = 10-camphorsulfonic acid.

1 to 1.1 equiv of Ac_2O in the presence of excess Et_3N and 0.2 equiv of DMAP in CH_2Cl_2 at 0 °C resulted in the formation of triacetate **28** (12% yield) and diacetates **29** and **30** (75% yield as a ca. 1:2 mixture in favor of **29** by ^{1}H NMR), plus some unreacted starting material (13%). The inseparable mixture of diacetates (**29** and **30**) was exposed to CSA in moist CH_2Cl_2, furnishing a mixture of eleuthosides A and B (**2** + **3**). This mixture could not be separated by conventional chromatographic methods and was characterized as such, matching, in all respects, the data reported for the natural eleuthosides A (**2**) and B (**3**).[5] Exposure of bis-TBS ether **23** (or **1**) to TBAF in THF at 25 °C caused slow migration of the acetate group from the 2′-position to the 4′-hydroxyl group, leading to the isomeric eluetherobin **31** (60% yield) as well as deacylation leading to deacetoxyeleutherobin **32** (8% yield). The structure of **31** was established by NMR spectroscopic methods (^{1}H 1D and 2D COSY) and comparisons with **1** and **23**.

5. Conclusion

Following a strategy similar to that described for the sarcodictyins A and B in the preceding paper[9] and by incorporating the arabinose pyranoside moiety into the molecule prior to ring closure, the total synthesis of the marine natural products eleutherobin (**1**) and eleuthosides A (**2**) and B (**3**) has been accomplished. In addition, the chemical synthesis of the isomeric eleutherobin (**27**) in which the glycosidic bond is oriented in the α-position as well as the eleuthoside analogues **28**−**32** is described. The reported chemistry allows access not only to the rare naturally occurring substances but also to designed analogues and combinatorial libraries for biological screening purposes. Combined with their appealing mechanism of tubulin polymerization and microtubule stabilization, the described technology makes the eleutherobins and eleuthosides an attractive proposition as a new class of potential anticancer agents for further investigation.

6. Experimental Section

General Techniques. For general techniques, see the preceding paper.[9] Procedures and data for compounds **9** and **12**−**15** can be found in the Supporting Information accompanying this paper.

Enynone 16. A solution of LiHDMS (1.0 M in THF, 0.150 mL, 0.150 mmol, 2.0 equiv) was added dropwise to a solution of **25** (77.5 mg, 0.0742 mmol, 1.0 equiv) in THF (4.0 mL) at −30 °C and the reaction was stirred for 10 min at −30 °C. After the reaction was complete as indicated by TLC analysis, saturated NH_4Cl solution (5 mL) was added and the resulting biphasic mixture was extracted with ether (3 × 30 mL). The combined extracts were washed with brine, dried over over Na_2SO_4, and concentrated to give a crude residue which was was purified by short column chromatography (silica gel, 10% EtOAc in hexanes). The purified mixture of isomers was then used immediately for the next step. To a solution of this mixture in CH_2Cl_2 (4.0 mL) at 0 °C was added $NaHCO_3$ (62.3 mg, 0.742 mmol, 10.0 equiv) and pyridine (60 mL, 0.742 mmol, 10.0 equiv), and the resulting solution was chilled to 0 °C and stirred for 10 min. Dess−Martin reagent (63.0 mg, 0.149 mmol, 2.0 equiv) was added, and the reaction was stirred for an additional 15 min at 0 °C. After the reaction was complete as indicated by TLC analysis, it was quenched by addition of saturated $Na_2S_2O_3$ (2 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined extracts were dried over Na_2SO_4 and concentrated to provide a crude residue which was purified by flash chromatography (silica gel, 5% EtOAc in hexanes) to afford **16** (72.0 mg, 93% for two steps): R_f = 0.80 (silica, Et_2O−hexane,1:3); [α] −11.5 (*c* 0.46, $CHCl_3$); FT-IR (neat) ν_{max} 2954, 2878, 1663, 1512, 1462, 1250, 1115, 1037, 1004, 834, 777, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2 H), 6.82 (d, *J* = 8.5 Hz, 2 H), 6.28 (d, *J* = 11.8 Hz, 1 H, C-2), 5.38 (bs, 1 H, C-12), 4.64 (d, *J* = 2.3 Hz, 1 H, C-1″), 4.63−4.59 (m, 1 H, C-15), 4.48 (d, *J* = 12.5 Hz, 2 H), 3.96−3.87 (m, 2 H, C-14, C-4″ or C-5″), 3.80−3.73 (m, 1 H, C-4″ or C-5″), 3.78 (s, 3 H), 3.70−3.68 (m, 1 H, C-1), 3.58 (dd, *J* = 11.4, 2.3 hz, 1 H, C-2″) 3.55−3.48 (m, 2 H, C-8, C-3″), 3.45 (dd, *J* = 10.3, 5.3 Hz, 1 H, C-5″), 2.35 (bd, *J* = 9.1 Hz, 1 H, C-10), 2.20 (bd, *J* = 18.5 Hz, 1 H, C-13), 1.98 (bd, *J* = 18.5 Hz, 1 H, C-13), 1.87−1.76 (m, 2 H, C-9), 1.69 (s, 3 H, C-17), 1.56−1.45 (m, 2 H), 1.34 (s, 3 H, C-16), 0.96−0.89 (m, 24 H, C-19, C-20), 0.83−0.51 (m, 12 H), 0.86 (s, 9 H), 0.83 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 6 H), −0.02 (s, 3 H); ^{13}C NMR (125.7 MHz,

$CDCl_3$) δ 180.7, 159.1, 141.9, 139.7, 134.0, 130.9, 129.5, 121.6, 113.6, 103.8, 98.1, 87.7, 83.4, 73.0, 72.5, 68.6, 64.2, 39.0, 38.5, 36.1, 29.9, 25.9, 25.9, 25.8, 22.0, 21.5, 21.2, 20.2, 18.2, 7.0, 6.9, 5.8, 5.7, −4.5, −4.7, −4.8; HRMS (FAB) calcd for $C_{57}H_{100}O_9Si_4$ (M + Cs^+) 1173.5569, found 1173.5499.

Enynone Alcohol 17. To a solution of PMB-ether **16** (202 mg, 0.194 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) and water (0.35 mL) at 0 °C was added DDQ (98.0 mg, 0.432 mmol, 2.3 equiv), and the resulting solution was allowed to warm to 25 °C and stirred for 20 min. Once complete by TLC analysis, the reaction was quenched by addition of saturated $Na_2S_2O_3$ solution (2.0 mL) and saturated $NaHCO_3$ solution (2.0 mL). The reaction mixture was then extracted with CH_2Cl_2 (3 × 40 mL), and the combined extracts were dried over Na_2SO_4 and concentrated to afford a crude residue which was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to provide alcohol **17** (163 mg, 91%): R_f = 0.6 (silica gel, EtOAc−hexane, 1:5); [α] −0.176 (*c* 1.6, $CHCl_3$); FT-IR (neat) ν_{max} 2955, 2929, 2203, 1663, 1462, 1366, 1252, 1214, 1118, 1076, 1004, 835, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, *J* = 11.8 Hz, 1 H, C-2), 5.40 (bs, 1 H, C-12), 4.79 (d, *J* = 2.8 Hz, 1 H, C-1″), 4.57 (d, *J* = 11.8 Hz, 1 H, C-15), 3.89−3.83 (m, 2 H), 3.78 (m, 1 H, C-2″), 3.74 (dd, *J* = 8.3, 1.7 Hz, 1 H, C-3″), 3.69 (bs, 1 H), 3.62 (dd, *J* = 10.3, 1.4 Hz, 1 H, C-8), 3.51−3.45 (m, 2 H), 2.37−2.30 (m, 1 H, C-10), 2.14 (bd, *J* = 17.5 Hz, 1 H, C-13), 1.98 (bd, *J* = 17.5 Hz, 1 H, C-13), 1.85 (dd, *J* = 14.5, 3.3 Hz, 1 H, C-12), 1.76 (dd, *J* = 14.5, 2.1 Hz, 1 H, C-12), 1.70 (s, 3 H, C-17), 1.53−1.42 (m, 1 H, C-18), 1.37 (s, 3 H, C-16), 1.09−1.05 (m, 1 H, C-14), 0.97−0.86 (m, 2 H), 0.96−0.89 (m, 24 H, C-19, C-20), 0.89 (s, 9 H), 0.86 (s, 9 H), 0.80−0.54 (m, 12 H), 0.06 (s, 3 H), 0.05 (s, 6 H), 0.04 (s, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 180.7, 143.2, 139.5, 133.8, 125.5, 121.7, 104.6, 98.0, 87.7, 83.3, 72.5, 71.8, 70.4, 69.9, 69.0, 64.6, 44.8, 38.8, 38.6, 36.1, 30.3, 29.9, 29.7, 26.0, 25.8, 25.7, 22.0, 21.4, 21.2, 20.1, 18.3, 18.1, 7.0, 6.9, 5.8, 5.2, −4.2, −4.5, −4.6, −4.7; HRMS (FAB) calcd for $C_{49}H_{92}O_8Si_4$ (M + Cs^+): 1053.4924, found 1053.4974.

Enynone Acetate 18. To a solution of alcohol **17** (163 mg, 0.177 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL) at 0 °C were added Et_3N (400 μL, 2.86 mmol, 16.1 equiv), DMAP (10.0 mg, 0.0818 mmol, 0.46 equiv), and Ac_2O (0.2 mL, 2.12 mmol, 12.0 equiv), and the reaction was warmed to 25 °C and stirred for 1 h. After completion was established by TLC analysis, the reaction was quenched by addition of saturated $NaHCO_3$ solution (2.0 mL). The reaction mixture was then extracted with CH_2Cl_2 (3 × 40 mL), and the combined extracts were dried over Na_2SO_4 and concentrated to give a crude residue which was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to afford acetate **18** (162 mg, 95%): R_f = 0.57 (silica, Et_2O−hexane, 1:5); [α] −0.34 (*c* 1.4, $CHCl_3$); FT-IR (neat) ν_{max} 2956, 1746, 1661, 1461, 1371, 1237, 1119, 1004 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.18 (d, *J* = 11.8, Hz, 1 H, C-2), 5.40 (bs, 1 H, C-12), 4.98−4.94 (m, 2 H, C-1″, C-2″), 4.51 (dd *J* = 12.2, 1.2 hz, 1 H, C-15), 3.93 (dd, *J* = 8.4, 2.5 Hz, 1 H, C-3), 3.85 (bs, 2 H), 3.69 (bs, 1 H, C-1), 3.65 (d, *J* = 11.8 Hz, 1 H), 3.51−3.45 (m, 1 H), 3.48 (d, *J* = 11.7 Hz, 1 H), 2.36 (bd, *J* = 10.6 Hz, 1 H, C-10), 2.17−2.12 (m, 1 H, C-13), 2.03 (s, 3 H, C-2‴), 1.99 (bd, *J* = 16.4 Hz, 1 H, C-13), 1.84 (dd, *J* = 14.5, 3.4 Hz, 1 H, C-9), 1.76 (dd, *J* = 14.5, 2.0 hz, 1 H, C-9), 1.69 (s, 3 H, C-17), 1.63−1.44 (m, 1 H, C-18), 1.39 (s, 3 H, C-16),1.08−1.03 (m, 1 H, C-14), 0.96−0.88 (m, 24 H, C-19, C-20), 0.88 (s, 9 H), 0.86 (s, 9 H), 0.80−0.50 (m, 12 H), 0.06 (s, 3 H), 0.05 (s, 6 H), 0.04 (s, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 180.3, 170.2, 143.1, 139.3, 133.8, 121.7, 103.9, 95.3, 87.7, 83.4, 72.5, 71.3, 68.8, 68.2, 64.1, 44.8, 38.9, 38.6, 36.0, 29.9, 29.7, 25.8, 25.7, 21.9, 21.4, 21.1, 20.2, 18.1, 14.1, 7.0, 6.9, 5.8, 5.2, −4.1, −4.6, −4.7, −4.8; HRMS (FAB) calcd for $C_{51}H_{94}O_9Si_4$ (M + Cs^+) 1095.5030, found 1095.5088.

Enynone Diol 19. To a solution of silyl ether **18** (161 mg, 0.167 mmol, 1.0 equiv) in THF (4.2 mL) at 0 °C was added $Et_3N{\cdot}3HF$ (0.60 mL, 3.68 mmol, 22.0 equiv), and the reaction mixture was warmed to 25 °C and stirred for 4 h. After completion (TLC analysis), the reaction was quenched by addition of saturated $NaHCO_3$ solution (2.0 mL) at 0 °C. The biphasic mixture was then extracted with ether (3 × 40 mL), and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to produce a crude residue which was purified by flash chromatography (silica gel, 50% EtOAc in hexanes) to afford diol **19** (100 mg, 81%): R_f = 0.40 (silica gel, Et_2O−hexane, 3:1); [α] −53.5 (*c* 0.85, $CHCl_3$); FT-IR (neat) ν_{max} 3410, 2929, 2856, 1744, 1652, 1370, 1254, 1123, 1063, 1037, 837, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (d, *J* = 5.9 Hz, 1 H, C-2), 5.43 (bs, 1 H, C-12), 5.01−4.99 (m, 2 H, C-1″, C-2″), 4.89 (s, 1 H), 4.53 (dd, *J* = 12.5, 1.5 Hz, 1 H, C-15), 3.96−3.94 (m, 1 H, C-3″), 3.92 (dd, *J* = 5.9, 1.5 Hz, 1 H), 3.89−3.87 (m, 1 H, C-4″), 3.76−3.72 (m, 1 H, C-1), 3.67 (dd, *J* = 12.0, 1.4 Hz, 1 H, C-5″), 3.52 (dd, *J* = 12.0, 3.6 Hz, 1 H, C-5″), 3.46 (dt, *J* = 11.5, 2.9 Hz, 1 H, C-8), 2.55 (bs, 1 H, OH), 2.43 (bd, *J* = 10.3 Hz, 1 H, C-10), 2.28 (bs, 1 H, OH), 2.17 (bd, *J* = 18.4 Hz, 1 H, C-13), 2.06 (s, 3 H, C-2‴), 2.01 (bd, *J* = 18.4 Hz, 1 H, C-13), 1.95 (dd, *J* = 14.5, 4.5 Hz, 1 H, C-5), 1.75 (s, 3 H, C-17), 1.67−1.62 (m, 1 H, C-9), 1.57−1.51 (m, 1 H, C-18), 1.50 (s, 3 H, C-16), 1.12−1.07 (m, 1 H, C-14), 0.93−0.89 (m, 6 H, C-19, C-20), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 6 H), 0.07 (s, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 180.4, 170.4, 143.0, 139.9, 121.8, 102.8, 95.0, 87.7, 80.7, 71.3, 71.3, 68.1, 45.0, 38.9, 38.5, 33.2, 29.7, 29.5, 25.8, 25.5, 21.9, 21.5, 21.3, 20.4, 20.0, 18.1, 18.1, −4.1, −4.6, −4.6, −4.8; HRMS (FAB) calcd for $C_{39}H_{66}O_9Si_2$ (M + Cs^+) 867.3336, found 867.3300.

Tricyclic Core Compound 22. A heterogeneous mixture of eneynone **19** (103 mg, 0.140 mmol, 1.0 equiv) and Lindlar catalyst (148 mg, 0.069 mmol, 0.5 equiv) was treated with hydrogen (1 atm), and the reaction was stirred at 25 °C for 20 min. The reaction mixture was then filtered through a Celite pad eluting with ether and concentrated to give a crude residue which was used without further purification. This residue was dissolved in MeOH (4.0 mL), PPTS (7.0 mg, 0.028 mmol, 0.2 equiv) was added, and the reaction was stirred at 25 °C for 20 min. Once complete (TLC monitoring), the reaction was quenched by addition of saturated $NaHCO_3$ solution (2.0 mL). The reaction mixture was then extracted with ether (3 × 20 mL), and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to provide a crude residue which was purified by flash chromatography (silica gel, 50% EtOAc in hexanes) to afford methyl ketal **22** (80.1 mg, 76%): R_f = 0.74 (silica gel, Et_2O−hexane, 3:1); [α] −38.61 (*c* 0.65, $CHCl_3$); FT-IR (neat) ν_{max} 3448, 2929, 2856, 1748, 1254, 1144, 1038, 837, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (d, *J* = 5.9 Hz, 1 H, C-5), 6.02 (d, *J* = 5.9 Hz, 1 H, C-6), 5.52 (d, *J* = 9.5 Hz, 1 H, C-2), 5.27 (br, 1 H, C-12), 4.98 (dd, *J* = 8.4, 2.8 Hz, 1 H, C-2″), 4.89 (d, *J* = 2.8 Hz, 1 H, C-1″), 4.25 (d, *J* = 12.5 Hz, 1 H, C-15), 3.97 (dd, *J* = 8.4, 2.8 Hz, 1 H, C-3″), 3.90−3.87 (m, 1 H, C-4″), 3.86−3.84 (m, 1 H, C-1), 3.84 (d, *J* = 12.5 Hz, 1 H, C-15), 3.67 (d, *J* = 7.2 Hz, 1 H, C-8), 3.65 (d, *J* = 11.7 Hz, 1 H, C-5″), 3.48 (dd, *J* = 11.7, 4.5 Hz, 1 H, C-5″), 3.18 (s, 3 H, C-21), 2.38−2.32 (m, 2 H, C-10, C-13), 2.04 (s, 3 H, C-2‴), 1.95 (bd, *J* = 19.4 Hz, 1 H, C-13), 1.58 (s, 3 H, C-17), 1.52 (s, 3 H, C-16), 1.50−1.43 (m, 3 H, C-9, C-18), 1.20−1.17 (m, 1 H, C-14), 0.93−0.78 (m, 6 H, C-19, C-20), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 6 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.2, 134.6, 133.8, 133.5, 130.5, 121.6, 115.7, 95.0, 91.32, 80.7, 76.8, 76.8, 71.5, 69.4, 64.0, 49.6, 42.4, 39.2, 34.5, 33.8, 29.7, 29.2, 25.9, 24.9, 24.6, 24.5, 22.3, 22.1, 21.2, 20.4, 18.1, −4.2, −4.5, −4.7, −4.8; HRMS (FAB) calcd for $C_{40}H_{70}O_9Si_2$ (M + Cs^+) 883.3580, found 883.3613.

Eleutherobin bis-TBS Ether 23. To a solution of alcohol **22** (64 mg, 0.0871 mmol, 1.0 equiv) in CH_2Cl_2 (0.4 mL) were added Et_3N (0.177 mL, 1.27 mmol, 15.0 equiv) and DMAP (21 mg, 0.0017 mmol, 0.02 equiv). The solution was then chilled to 0 °C, and a 0.2 M CH_2Cl_2 solution of mixed anhydride **24**[9] was added (4.2 mL, 0.84 mmol, 9.6 equiv). The reaction mixture was then warmed to 25 °C and stirred for 18 h. After completion was established (TLC analysis), the reaction was quenched by addition of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to afford a crude residue which was purified by flash chromatography (silica gel, 67% EtOAc in hexanes) to produce urocanic ester **23** (73.0 mg, 97%): R_f = 0.35 (silica gel, EtOAc−hexane, 1:3); [α] −61.3 (*c* 0.6, $CHCl_3$); FT-IR (neat) ν_{max} 2929, 2856, 2362, 2338, 1746, 1707, 1639, 1468, 1367, 1296, 1253, 1150, 1062, 1038, 1001, 886, 837, 775 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 15.6 Hz, 1 H, C-3′), 7.44 (s, 1 H, C-7′), 7.07 (s, 1 H, C-5′), 6.55 (d, *J* = 15.6 Hz, 1 H, C-2′), 6.08−6.05 (m, 2 H, C-5, C-6), 5.55 (d, *J* = 9.5 Hz, 1 H, C-2), 5.24 (bs, 1 H, C-12), 4.99−4.96 (m, 1 H, C-2″), 4.88 (s, 1 H, C-1″), 4.79 (d, *J* = 7.4 Hz, 1 H, C-8), 4.25 (d,

J = 12.4 Hz, 1 H, C-15), 3.97 (dd, J = 8.3, 2.3 Hz, 1 H, C-3″), 3.95−3.92 (m, 1 H, C-1), 3.88−3.84 (m, 2 H, C-4″, C-15), 3.66 (d, J = 11.6 hz, 1 H, C-5″), 3.69 (s, 3 H, C-9), 3.47 (dd, J = 11.6, 4.4 Hz, 1 H, C-5″), 3.19 (s, 3 H, C-21), 2.58 (bd, J = 11.2 Hz, 1 H, C-10), 2.26 (bd, J = 17.0 Hz, 1 H, C-13), 2.05−1.94 (m, 2 H), 2.02 (s, 3 H, C-2″), 1.97 (bd, J = 17.8 Hz, 1 H, C-13), 1.61−1.51 (m, 2 H, C-9), 1.51 (s, 3 H, C-17), 1.43−1.40 (m, 1 H, C-18), 1.42 (s, 3 H, C-16), 1.25−1.22 (m, 1 H, C-14), 0.95 (d, J = 6.6 Hz, 3 H, C-19 or C-20), 0.90 (d, J = 6.6 Hz, 3 H, C-19 or C-20), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.2, 166.7, 139.2, 138.4, 136.3, 134.2, 133.9, 133.3, 130.8, 122.7, 121.2, 115.9, 95.0, 89.8, 81.5, 71.5, 69.5, 69.3, 64.0, 60.4, 49.6, 42.5, 38.6, 34.0, 33.6, 29.6, 29.0, 25.8, 24.4, 24.3, 22.2, 22.0, 21.1, 21.0, 20.6, 18.2, 18.1, 14.2, −4.2, −4.5, −4.7, −4.9; HRMS (FAB) calcd for $C_{47}H_{76}N_2O_{10}Si_2$ (M + Cs^+) 1017.4093, found 1017.4139.

Eleutherobin (1). To a solution of disilyl ether **23** (15.5 mg, 0.017 mmol, 1.0 equiv) in THF (4.0 mL) at 0 °C were added AcOH (1.0 M in THF, 0.070 mL, 0.070 mmol, 4.1 equiv) and TBAF (1.0 M in THF, 0.30 mL, 0.30 mmol, 17.6 equiv). The reaction mixture was warmed to 25 °C and stirred for 2.5 h, after which water (1.0 mL) and saturated $NaHCO_3$ solution (1.0 mL) were added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated to provide a crude residue which was purified by flash chromatography (silica gel, 2% MeOH in CH_2Cl_2 with 1% Et_3N) to afford eleutherobin **1** (11.0 mg, 96%): R_f = 0.22 (silica gel, MeOH−CH_2Cl_2, 1:20); [α] −67 (*c* 0.15, MeOH); FT-IR (neat) ν_{max} 3388, 2933, 2851, 1735, 1708, 1637, 1367, 1247, 1162, 1039, 998 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 15.6 Hz, 1 H), 7.44 (s, 1 H), 7.08 (s, 1 H), 6.54 (d, J = 15.6 Hz, 1 H), 6.10 (d, J = 5.9 Hz, 1 H), 6.06 (d, J = 5.9 Hz, 1 H), 5.54 (d, J = 9.4 Hz, 1 H), 5.26 (bs, 1 H), 4.96 (dd, J = 9.9, 3.6 Hz, 1 H), 4.89 (d, J = 3.5 Hz, 1 H), 4.80 (d, J = 7.4 Hz, 1 H), 4.29 (d, J = 12.3 Hz, 1 H), 4.05−3.92 (m, 3 H), 3.86 (d, J = 12.3 Hz, 1 H), 3.82 (d, J = 12.3 Hz, 1 H), 3.70 (s, 3 H), 3.70−3.68 (m, 1 H), 3.20 (s, 3 H), 2.66−2.57 (m, 2 H, OH), 2.42−2.39 (m, 1 H), 2.33−2.24 (m, 1 H), 2.10 (s, 3 H), 2.00−1.94 (m, 1 H), 1.62−1.56 (m, 2 H), 1.50 (s, 3 H), 1.43 (s, 3 H), 1.38 (ddd, J = 15.0, 12.5, 7.5 Hz, 1 H), 1.26−1.17 (m, 1 H), 0.96 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.4, 166.7, 139.2, 138.4, 137.4, 136.4, 134.1, 133.6, 132.8, 131.0, 122.8, 121.3, 115.9, 115.8, 93.4, 89.9, 81.5, 77.2, 71.8, 69.4, 69.1, 68.1, 62.1, 49.7, 42.3, 38.7, 34.2, 33.6, 31.4, 29.0, 24.5, 24.2, 22.2, 22.0, 21.1, 20.5, 19.8, 14.1, 13.7; HRMS (FAB) calcd for $C_{35}H_{48}N_2O_{10}$ (M + Cs^+) 789.2334, found 789.2363.

***β*-Glycoside 25.** A solution of alcohol **7** (20.0 mg, 0.0355 mmol, 1.0 equiv) and imidate **9** (62.1 mg, 0.0966 mmol, 2.7 equiv) in 2:1 dioxane−toluene (6.0 mL) was chilled to 0 °C, TMSOTf (0.05 M in ether, 40 μL, 0.002 mmol, 0.05 equiv) was added, and the reaction was stirred at 0 °C for 10 min after which Et_3N (20 μL) was added followed by $NaHCO_3$ (3 mL). The reaction mixture was then extracted with ether (3 × 20 mL), and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give a crude residue which was purified by flash chromatography (silica gel, 3% EtOAc in hexanes) to afford **25** (27.9 mg, 75%): R_f = 0.56 (silica gel, EtOAc−hexane,1:5); [α] −27.7 (*c* 1.0, $CHCl_3$); FT-IR (neat) ν_{max} 2954, 1676, 1612, 1512, 1461, 1364, 1250, 1114, 1038, 835, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1 H, C-4), 7.21 (d, J = 8.5 Hz, 2 H), 6.94 (d, J = 11.5 Hz, 1 H, C-2), 6.82 (d, J = 8.5 Hz, 2 H), 5.38 (bs, 1 H, C-12), 4.74 (d, J = 2.0 Hz, 1 H), 4.62 (d, J = 11.9 Hz, 1 H), 4.42 (d, J = 11.9 Hz, 1 H), 4.21 (m, 2 H), 3.92 (bs, 1 H), 3.78 (s, 3 H), 3.72 (m, 1 H), 3.50 (m, 4 H), 2.25 (m, 1 H), 2.01 (m, 3 H), 1.89 (m, 2 H), 1.75 (m, 1 H), 1.66 (s, 3 H), 1.57 (m, 2 H), 1.42 (m, 2 H), 1.31 (s, 3 H), 1.23 (m, 2 H), 0.89 (m, 35 H), 0.66 (m, 16 H), −0.03 (m, 12 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 189.6, 159.1, 155.5, 136.3, 136.2, 130.8, 129.5, 121.0, 113.6, 99.3, 86.8, 78.8, 76.4, 75.5, 73.0, 72.7, 71.4, 67.1, 64.0, 55.2, 39.0, 37.2, 34.2, 29.7, 28.4, 26.0, 25.9, 24.4, 23.6, 21.9, 21.2, 18.2, 18.1, 17.0, 7.1, 7.0, 6.0, 5.6, −4.5, −4.6, −4.7, −4.9; HRMS (FAB) calcd for $C_{57}H_{102}O_9Si_4$ (M + Na^+) 1065.6499, found 1065.6543.

α-Anomer of Eleutherobin (27). The α-anomer of eleutherobin was constructed by following the same reaction sequence depicted in Scheme 2 from compound **26**: R_f = 0.1 (silica gel, MeOH−CH_2Cl_2, 1:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 15.6 Hz, 1 H, C-3′), 7.47 (s, 1 H, C-7), 7.11 (s, 1 H, C-5′), 6.57 (d, J = 15.6 Hz, 1 H, C-2′), 6.21 (d, J = 5.9 Hz, 1 H, C-5), 6.00 (d, J = 5.9 Hz, 1 H, C-6), 5.62 (d, J = 9.5 Hz, 1 H, C-2), 5.30−5.26 (m, 1 H), 4.97 (dd, J = 3.8, 2.0 Hz, 1 H, C-2″), 4.82 (d, J = 7.5 Hz, 1 H, C-8), 4.70 (d, J = 2.0 Hz, 1 H, C-1″), 4.17 (d, J = 10.8 Hz, 1 H, C-15), 3.99−3.96 (m, 1 H), 3.96 (d, J = 10.8 Hz, 1 H, C-15), 3.92−3.88 (m, 1 H), 3.88−3.84 (m, 1 H), 3.72 (s, 3 H, C-9), 3.65−3.62 (m, 2 H), 3.55−3.43 (m, 2 H), 3.23 (s, 3 H, C-21), 3.02−2.94 (m, 1 H), 2.71−2.63 (m, 1 H), 2.40−2.25 (m, 2 H), 2.11 (s, 3 H, C-2‴), 2.01−1.96 (m, 2 H), 1.56−1.21 (m, 1 H), 1.53 (s, 3 H, C-17), 1.46 (s, 3 H, C-16), 1.28−1.20 (m, 1 H), 1.00 (d, J = 6.6 Hz, 3 H, C-18 or C-19), 0.94 (d, J = 6.6 Hz, 3 H, C-18 or C-19); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.2, 166.3, 139.7, 138.1, 137.4, 136.3, 135.8, 134.9, 133.8, 130.2, 123.2, 121.7, 116.7, 91.2, 86.7, 81.7, 72.7, 72.0, 71.9, 70.2, 62.1, 49.9, 38.9, 34.4, 33.9, 33.8, 29.9, 29.6, 29.3, 24.7, 24.3, 22.5, 22.3, 21.3, 20.7.

Bis-acetoxy Eleutherobin (28) and Methyl Ketal Precursors of Eleuthosides A and B (29 and 30). To a solution of natural eleutherobin (**1**) (10.0 mg, 0.015 mmol, 1.0 equiv), Et_3N (6.0 μL, 0.043 mmol, 3.0 equiv), and DMAP (0.40 mg, 0.0033 mmol, 0.2 equiv) in CH_2Cl_2 (0.60 mL) at 0 °C was added Ac_2O (1.0 M in CH_2Cl_2, 0.017 mL, 0.017 mmol, 1.1 equiv), and the reaction was stirred at the same temperature for 1 h. The reaction was then quenched by addition of saturated $NaHCO_3$ solution (0.50 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to provide a crude residue which was was purified by flash chromatography (silica gel, 2% MeOH in CH_2Cl_2) to afford triacetate **28** (1.8 mg, 16%) along with an inseparable mixture of eleuthosides **29** and **30** (7.8 mg, 73%) and recovered **1** (0.5 mg, 5%). For **28**: R_f = 0.44 (silica gel, MeOH− CH_2Cl_2, 1:20); [α] −67.3 (*c* 1.2, $CHCl_3$); FT-IR (neat) ν_{max} 2962, 1746, 1740, 1644, 1634, 1372, 1226, 1156, 1068, 759, 668, 617 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 15.5 Hz, 1 H, C-3′), 7.45 (s, 1 H, C-7′), 7.09 (s, 1 H, C-5′), 6.55 (d, J = 15.5 Hz, 1 H, C-2′), 6.11 (d, J = 5.5 Hz, 1 H, C-5), 6.07 (d, J = 5.5 Hz, 1 H, C-6), 5.52 (d, J = 9.5 Hz, 1 H, C-2), 5.36 (dd, J = 11.0, 3.5 Hz, 1 H, C-3″), 5.34−5.30 (m, 1 H, C-4″), 5.30−5.27 (m, 1 H, C-12), 5.18 (dd, J = 11.0, 3.5 Hz, 1 H, C-2), 4.96 (d, J = 3.5 Hz, 1 H, C-1″), 4.81 (d, J = 7.5 Hz, 1 H, C-8), 4.33 (d, J = 11.5 Hz, 1 H, C-15), 3.97−3.93 (m, 1 H, C-1), 3.90 (dd, J = 13.0, 1.0 Hz, 1 H, C-5″), 3.88 (d, J = 11.5 Hz, 1 H, C-15), 3.70 (s, 3 H, C-9′), 3.63 (dd, J = 13.0, 2.0 Hz, 1 H, C-5″), 3.66−3.62 (m, 1 H), 3.21 (s, 3 H, C-21), 2.60 (bd, J = 10.6 Hz, 1 H, C-10), 2.30 (bd, J = 16.0 Hz, 1 H, C-13), 2.12 (s, 3 H), 2.03 (s, 3 H), 1.99 (s, 3 H), 1.99−1.92 (m, 1 H, C-13), 1.68−1.55 (m, 2 H, C-9, C-18), 1.53 (s, 3 H, C-17), 1.44 (s, 3 H, C-16), 1.36 (ddd, J = 15.0, 12.0, 7.5 Hz, 1 H, C-9), 1.25−1.20 (m, 1 H, C-14), 0.96 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 170.4, 170.1, 170.0, 166.7, 139.2, 138.4, 137.6, 136.4, 134.1, 133.6, 132.8, 131.0, 122.8, 121.3, 115.8, 115.7, 93.15, 89.8, 81.5, 69.2, 69.0, 68.0, 67.3, 60.5, 49.7, 42.2, 38.0, 34.2, 33.0, 31.4, 29.0, 24.4, 24.1, 22.2, 21.9, 21.0, 20.9, 20.7, 20.5; HRMS (FAB) calcd for $C_{39}H_{52}N_2O_{12}$ (M + Cs^+) 873.2575, found 873.2546.

Eleuthosides A and B (2 and 3). To a solution of **27** and **28** mixture (7.8 mg, 0.011 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) and H_2O (0.20 mL) at 25 °C was added CSA (5.2 mg, 0.022 mmol, 2.0 equiv), and the reaction was stirred at the same temperature for 48 h. Once complete (TLC monitoring), the reaction was quenched by addition of saturated $NaHCO_3$ solution (0.50 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to provide a crude residue which was purified by flash chromatography (silica gel, 3% MeOH in CH_2Cl_2) to afford an inseparable mixture of eleuthoside A (**2**) and B (**3**) (5.3 mg, 80%). Data for mixture of **2** and **3**: R_f = 0.32 (silica, MeOH−CH_2Cl_2, 1:20); FT-IR (neat) ν_{max} 3734, 3628, 2962, 2928, 2866, 1734, 1700, 1684, 1652, 1646, 1636, 1558, 1456, 1374, 1252, 1160, 1065, 1037, 986, 884, 874 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 15.5 Hz, 1 H), 7.45 (s, 1 H), 7.09 (s, 1 H), 6.55 (d, J = 15.5 Hz, 1 H), 6.13 (d, J = 5.5 Hz, 1 H), 6.12 (d, J = 5.0 Hz, 1 H), 6.08 (d, J = 5.5 Hz, 1 H), 6.07 (d, J = 5.0, 1 H), 5.51 (d, J = 9.5 Hz, 1 H), 5.50 (d, J = 9.5 Hz, 1 H), 5.31−5.23 (m) 5.15−5.13 (m, 1 H), 5.04 (dd, J = 10.0, 3.5 Hz, 1 H), 4.99 (d, J = 3.5 Hz, 1 H), 4.81 (d, J = 7.0 Hz, 1 H), 4.23 (d, J

= 11.0 Hz, 1 H), 4.16 (dd, *J* = 10.5, 4.0 Hz, 1 H), 4.12 (m, 1 H), 4.02 (m, 1 H), 3.93 (d, *J* = 11.0 Hz, 1 H), 3.89−3.72 (m, 3 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.33 (m, 1 H), 2.68−2.62 (m, 1 H), 2.36−2.26 (m, 1 H), 2.16 (s, 3 H), 2.12 (s, 3 H), 2.09 (s, 1 H), 2.08−2.00 (m, 1 H), 2.05 (s, 3 H), 2.00 (s, 3 H), 1.69−1.53 (m, 3 H), 1.48 (s, 3 H), 1.47 (s, 3 H), 1.37−1.28 (m, 1 H), 0.99 (d, *J* = 6.5 Hz, 3 H), 0.97 (d, *J* = 6.0 Hz, 3 H), 0.94 (d, *J* = 6.0 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 171.2, 170.8, 170.3, 169.9, 166.7, 139.2, 138.4, 138.2, 138.0, 137.8, 136.4, 136.4, 134.2, 134.1, 133.2, 133.1, 132.1, 133.0, 126.3, 122.7, 121.3, 121.2, 115.8, 115.8, 112.2, 95.4, 95.3, 90.3, 81.1, 71.9, 71.2, 69.9, 67.9, 66.4, 62.2, 60.5, 58.9, 53.4, 42.2, 41.9, 38.6, 38.6, 34.3, 33.6, 31.6, 29.0, 25.6, 24.4, 24.1, 22.2, 22.0, 21.1, 21.0, 20.5, 19.7, 13.7; HRMS (FAB) calcd for $C_{36}H_{48}N_2O_{11}$ ($M + Cs^+$) 817.2312, found 817.2283.

Regioisomeric Eleutherobin (31) and Deacetoeleutherobin (32). To a solution of disilyl ether **23** (5.4 mg, 6.1 μmol) in THF (350 μL) was added TBAF (1.0 M in THF, 20 μL, 20 μmol, 3.3 equiv), and the reaction mixture was stirred for 6 h at ambient temperature. After completion (TLC analysis), the crude residue was immediately purified by column chromatography (gradually increasing the eluting solvent from 2 to 10% MeOH in CH_2Cl_2) to afford eleutherobin **1** (22%), migration product **31** (60%), and triol **32** (8%). For **31**: R_f = 0.28 (silica, ×2, MeOH−CH_2Cl_2,1:20); FT-IR (neat) ν_{max} 3355, 2964, 2925, 1704, 1638, 1260, 1070, 800 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 15.5 Hz, 1 H, C-3′), 7.44 (s, 1 H, C-7′), 7.08 (s, 1 H, C-5′), 6.55 (d, *J* = 15.5 Hz, 1 H, C-2′), 6.18 (d, *J* = 5.8 Hz, 1 H, C-5), 5.96 (d *J* = 5.8 Hz, 1 H, C-6), 5.92 (d, *J* = 9.2 Hz, 1 H, C-2), 5.27 (m, 1 H, C-12), 4.89 (s, 1 H), 4.81 (d, *J* = 7.0 Hz, 1 H), 4.27 (d, *J* = 12.1 Hz, 1 H, C-15), 3.98−3.94 (m, 1 H), 3.91 (d, *J* = 12.1 Hz, 1 H, C-15), 3.89 (dt, *J* = 9.9, 3.7 Hz, 1 H), 3.83 (d, *J* = 12.8 Hz, 1 H), 3.76 (d, *J* = 9.9 Hz, 1 H), 3.74−3.68 (m, 2 H), 3.69 (s, 3 H, C-9′), 3.21 (s, 3 H, C-21), 2.65−2.59 (m, 1 H), 2.32−2.24 (m, 1 H), 2.27 (d, *J* = 4.0 Hz, 1 H), 2.24 (d, *J* = 10.3 Hz, 1 H), 2.12 (s, 3 H), 2.03−1.97 (m, 1 H), 1.65−1.60 (m, 1 H), 1.56 (s, 3 H), 1.51 (bs, 2 H), 1.44 (s, 3 H), 1.39 (ddd, *J* = 15.0, 12.0, 7.0 Hz, 1 H), 1.29−1.22 (m, 2 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.2 Hz, 3 H); HRMS (FAB) calcd for $C_{35}H_{48}N_2O_{10}$ ($M + Cs^+$) 789.2363, found 789.2384; [α] −22.5 (*c* 0.2, $CHCl_3$). For **32**: R_f = 0.16 (silica, ×2, MeOH−CH_2Cl_2,1:20); FT-IR (neat) ν_{max} 3355, 2964, 2925, 2872, 1704, 1634, 1260, 1070, 800 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 15.5 Hz, 1 H, C-3′), 7.45 (s, 1 H, C-7′), 7.09 (s, 1 H, C-5′), 6.56 (d, *J* = 15.5 Hz, 1 H, C-2′), 6.18 (d, *J* = 6.0 Hz, 1 H, C-5′), 5.99 (d, *J* = 6.0 Hz, 1 H, C-6′), 5.59 (d, *J* = 10.0 Hz, 1 H, C-2′), 5.27 (bs, 1 H, C-12), 4.92−4.85 (m, 1 H, C-1″), 4.81 (d, *J* = 7.0 Hz, 1 H, C-8), 4.28 (d, *J* = 12.0 Hz, 1 H, C-15), 3.98−3.95 (m, 1 H), 3.91 (d, *J* = 12.0 Hz, 1 H, C-15), 3.82−3.73 (m, 4 H), 3.71 (s, 3 H), 3.38 (−3.32 (m, 4 H), 3.22 (s, 3 H, C-21), 2.69−2.59 (m, 1 H, C-10), 2.37−2.25 (m, 1 H, C-13), 2.08−1.96 (m, 1 H, C-13), 1.61−1.40 (m, 3 H), 1.51 (s, 3 H, C-17), 1.45 (s, 3 H, C-16), 1.28−1.22 (m, 1 H, C-14), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 181.2, 165.6, 139.2, 136.4, 135.0, 134.1, 133.4, 130.9, 129.8, 122.7, 121.3, 115.9, 97.7, 90.2, 81.2, 70.9, 68.1, 59.0, 49.7, 42.2, 38.6, 34.1, 33.6, 31.5, 29.0, 28.9, 24.2, 24.1, 22.2, 22.0, 20.5, 19.8, 13.7; HRMS (FAB) calcd for $C_{33}H_{46}N_2O_9$ ($M + Cs^+$) 747.2258, found 747.2282.

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Supporting Information Available: Selected physical data for intermediates leading to the α-anomer of eleutherobin (**27**) from α-glycoside **26** (11 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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