# A Convergent Route for the Total Synthesis of the Eleuthesides**

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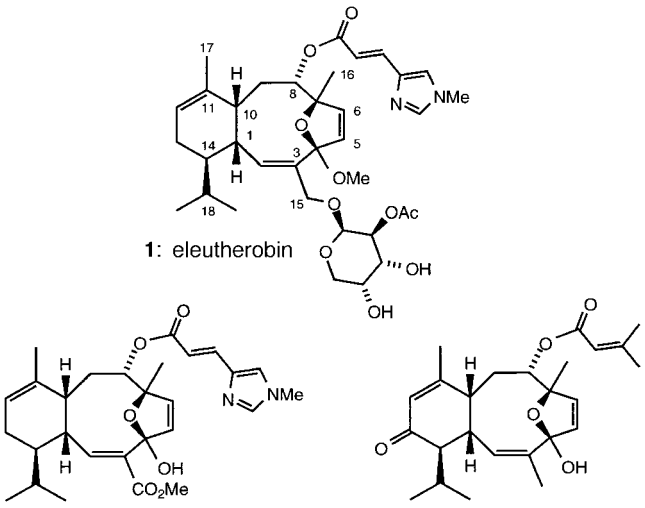
The marine environment is taking its place beside plant sources and fermentation in providing access to biologically active substances.[1] From the standpoint of organic chemistry, the aquatic biomass warrants particularly close attention, due to the richly varied structures provided therein. Moreover, the reliability of marine feedstocks as a bulk source of natural products is often less than the case with their plant and microbially derived counterparts. Hence, marine-derived natural products may well furnish excellent opportunities for the subspecialty of synthesis.

Such an opportunity is presented by a group of structurally related natural products, which we loosely group under the term "eleuthesides" (e.g. eleutherobin (**1**),[2] sarcodictyin (**2**),[3] and valdivone (**3**)[4]). These are each isolated from different marine sources. Interest in the family was considerably heightened by the recent report by Fenical et al.[2] that eleutherobin displays excellent potency in a variety of tumor cell lines and that the mechanism of its cytotoxicity involves inhibition of microtubule disassembly. Thus, at least eleutherobin (**1**), manifests a taxol—epothilone—discodermolide mode of action.[5] In light of the very interesting structures of these closely related compounds, the high potency of **1,** and the difficult availability of all of the eleuthesides from their natural habitats, this family presents a challenging opportunity for creative chemistry.




Given the discussion above, we defined the criteria for success in our synthetic venture as going beyond the completion of a ceremonial level route to the natural products. Rather, the substantive goal is that of providing significant quantities of end products for thorough biological scrutiny in the context of a detailed SAR (structure – activity relationship) investigation. An account of the attainment of a flexible and convergent synthesis of the eleuthesides is provided herein.

The underlying logic of our scheme, in qualitative terms, is implicit in Scheme 1. Reference to this scheme will identify the stages of the synthesis subsequently documented in Scheme 2 (vide infra). The chiral matrix material selected for elaboration is the readily available *R*-(−)-$\alpha$-phellandrene (**4**).[6] This compound undergoes cycloaddition with a ketene derivative (dichloroketene). A C1 fragment is then appended to the modified cyclobutanone cycloadduct, and the ring is fragmented to produce a system of the type **5** with differentiated arms for subsequent elaboration.

A furanoid building block (2,5-dibromofuran (**6**)[7]) provides system **7** as a nucleophile. The remaining furyl – bromine bond constitutes a latent form of carbon nucleophilicity, to be exploited later (vide infra). In the first coupling event, system **7** is delivered to the aldehyde function of **5**. Next, the "arm" extending from the C1 ester linkage is expanded by one carbon through a cyanation reaction. An eventual acetaldehyde appendage is coupled to the "bromofuryl" carbon (C4), producing a compound of type **8**, a highly strained 2,5-furano[6]phane. In this construction, the two benzylic oxygen functions at C8 and C3 in **8,** are presented in differentiated forms. The free hydroxyl group at C8 (R = H) accelerates oxidation of the proximal furan. Following bond reorganization (**9** → **10**), ring formation between the hydroxyl and appropriate keto group leads to a pyranose of the type **11**. In this system, the C7 keto group, destined for nucleophilic methylation, has been uniquely identified. Moreover, in **11**, the setting for entry of the methyl group in the desired stereochemical sense has been established, since reaction would be directed *anti* to the more sterically demanding five-membered carbon bridge. Following suitable manipulations, the pyranose ring in **11** is rearranged to a furanose, thereby exposing the two oxygen atoms projecting from C3 and C8 of the skeleton in differentiated form (see compound **12**).

The actual steps employed for building the eleutheside are summarized in Scheme 2. To be noted here is the regiospecificity of the cycloaddition of dichloroketene to **4** (the stereoselectivity is 9:1 in favor of the shown isomer **13**).[8] The product (**14**) resulting from the dechlorination of the initial cycloadduct (**13**) is subjected to a Bredereck-type trans-

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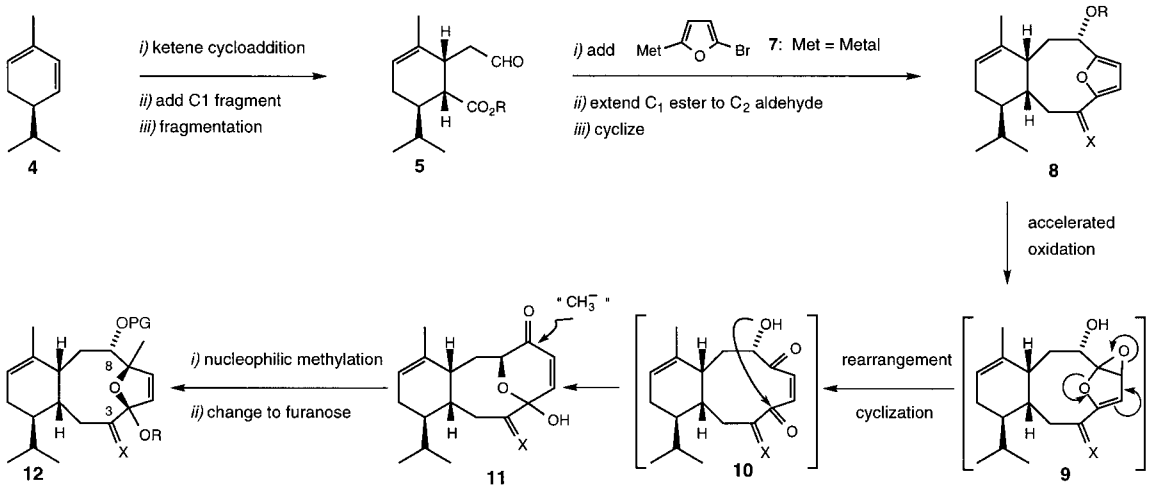
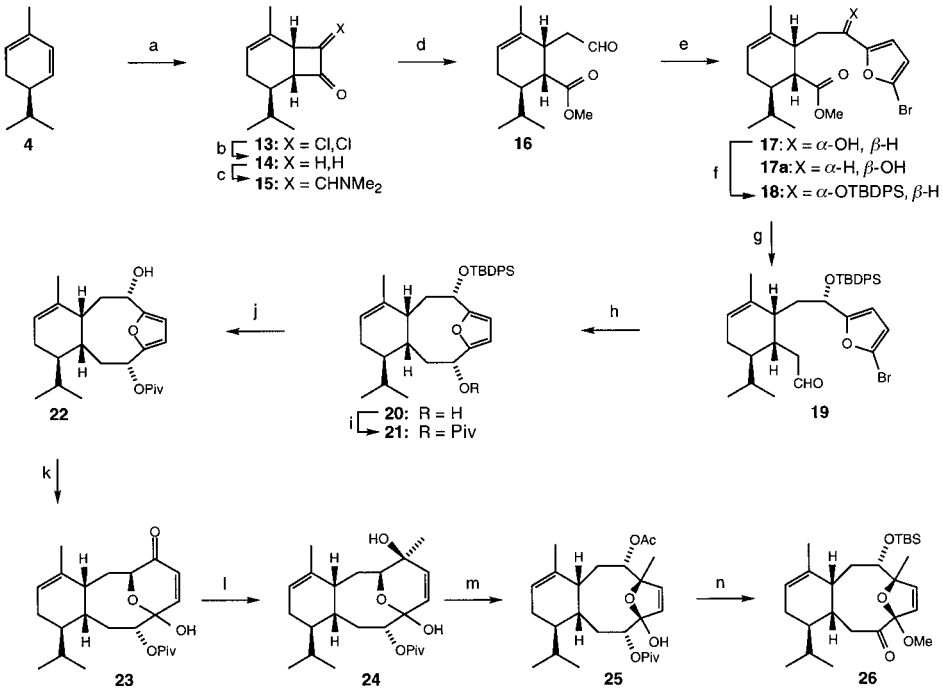



Scheme 1. Underlying logic of the synthetic plan. PG = protecting group.




Scheme 2. Construction of the eleutheside skeleton. a) trichloroacetyl chloride, Zn, $Et_2O$, sonication, 0 °C, 65 %; b) Zn, MeOH, $NH_4Cl$, 87 %; c) *t*BuOCH($NMe_2$)$_2$, 60 °C, 75 %; d) 1. *p*TsOH · $H_2O$, MeOH, 60 °C, 2. *p*TsOH · $H_2O$, $Me_2CO$, 60 % for the two steps; e) 2,5-dibromofuran (**6**) + *n*BuLi, THF, −78 °C, →**7** (Met = Li), **7**+**16** in THF →**17**, 57 %; f) TBDPSCl, imidazole, DMAP, 0 °C, 97 %; g) 1. DIBAL – toluene, toluene, −78 °C, >95 %; 2. MsCl, pyridine, DMAP, 0 °C, >95 %; 3. KCN, [18]crown-6, $CH_3CN$, 80 °C, 96 %; 4. DIBAL-hexanes, toluene, −78 °C to 0 °C, 84 %; h) $CrCl_2$/$NiCl_2$, DMF, 70 %; i) PivCl, $CH_2Cl_2$, $Et_3N$, DMAP, 0 °C, >95 %; j) TBAF, THF, 92 %; k) DMDO, $(CH_3)_2CO$, $CH_2Cl_2$, −78 °C; l) MeLi-$Et_2O$, THF, −78 °C, 42 % for k) and l); m) $Ac_2O$, DMAP, $CH_2Cl_2$, 0 °C, 73 %; n) 1. $Ag_2O$, MeI-MeCN, 94 %; 2. KCN, EtOH, 60 °C, >95 %; 3. TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 91 %; 4. DIBAL-hexanes, $CH_2Cl_2$, −78 °C, 95 %; 5. cat. TPAP, NMO, $CH_2Cl_2$, >95 %. TBDPS = *tert*-butyldiphenylsilyl, DMAP = 4-dimethylaminopyridine, DIBAL = diisobutylaluminum hydride, Ms = mesyl, DMDO = dimethyldioxirane, Piv = pivaloyl (CO*t*Bu), TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide.

formation, leading to **15**.[9] An elegant and little appreciated acid-catalyzed fragmentation of the cyclobutanone[8, 9] exposes a formyl group and a methyl ester; the carbonyl carbon atoms of the product **16** correspond to C2 and C8 of the eleutheside. We have found that 2,5-dibromofuran (**6**) can be monolithiated; the resulting, interesting organolithium compound **7** (Met = Li) can be appended to **16** to give compound **17** and its redeemable C8 epimer, **17a**. Following suitable protection of the hydroxyl group, **18** was obtained.[10] At this point, the one-carbon ester in **18** was expanded to a two-carbon aldehyde (see compound **19**), in which the formyl carbon corresponds to the eventual C3 of the eleuthesides. The critical step leading to the metacyclophane **20** was a remarkable and stereoselective Nozaki – Kishi[11] reaction. The hydroxyl group at the future C3 was protected as its pivaloate ester (cf. **21**).

The groundwork was now secure to move on to construction of the eleutheside skeleton. After removal of the silyl

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