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Asymmetric Synthesis of a Hydroxylated Nine-membered Lactone from Tartaric Acid using the Claisen Rearrangement

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The synthesis of a hydroxylated vinyl-appended lactone, in five synthetic steps from tartaric acid, is reported. The *C2*-symmetrical *bis*-vinyl diol **12** was converted into the ketene acetal **14** via methylenation of the cyclic carbonate **13** or thermal elimination of benzeneselenenic acid from the selenoxide **17**. In both cases, the in situ generated ketene acetal **14** underwent spontaneous Claisen rearrangement to give the nine-membered lactone (+)-**15**. Lactones of this type are potentially advanced precursors to simplified eleutherobin analogues or other medium-ring lactone natural products.

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Eleutherobin (**1**) is an oxygenated diterpene glycoside first isolated from a rare alcyonacean soft coral, *Eleutherobia* sp., off the coast from Exmouth in Western Australia (Fig. 1).[1,2] Subsequent investigations by Andersen et al. suggested that the methylacetal **1** was an artefact of isolation due to the use of methanol as the extraction solvent,[3] and that the hemiacetal analogue of **1** is a more potent antimitotic agent than eleutherobin in cell-based assays.[4] Eleutherobin (**1**) displays microtubule-stabilizing properties by binding to the paclitaxel-binding site, with IC_{50} values of 10–15 nM.[1] The complex structure of **1**, together with its potent activity, has attracted much attention from the synthetic community.[5] The groups of Nicolaou[6] and Danishefsky[7] have completed total syntheses of **1**, and formal syntheses have been reported by the groups of Metz[8] and Gennari.[9] Many other groups have reported synthetic efforts towards the eleutherobin core,[10] as well as towards the synthesis and evaluation of simplified eleutherobin analogues.[11] Furthermore, the Nicolaou group has prepared, and evaluated for biological activity, analogues based on the closely related sarcodictyin family of natural products.[12]

In previous investigations we reported that the highly simplified eleutherobin B-C core analogue **2** possessed significant microtubule-stabilizing properties ($ED_{90} = 3\ \mu M$), which is only slightly less active than paclitaxel ($ED_{90} = 0.5\ \mu M$).[13–15] Incorporation of the urocanic acid side-chain to give **3** resulted in decreased activity in this series (Fig. 1). In order to elucidate the minimum structural requirements for biological activity[16] in analogues such as **2**, we required a shorter route towards the 11-oxabicyclo[6.2.1]undecane framework. This paper describes the efficient preparation of a novel nine-membered lactone, which could be applied towards simplified analogues of eleutherobin and other related bioactive natural products.

In designing a new route to simplified eleutherobin-core analogues we chose inexpensive starting materials readily available in a range of stereochemistry and substitution patterns. This would allow synthesis of a library of similar compounds to be evaluated for structure–activity relationships. A general retrosynthesis of these newly designed eleutherobin analogues **4** is outlined in Scheme 1.

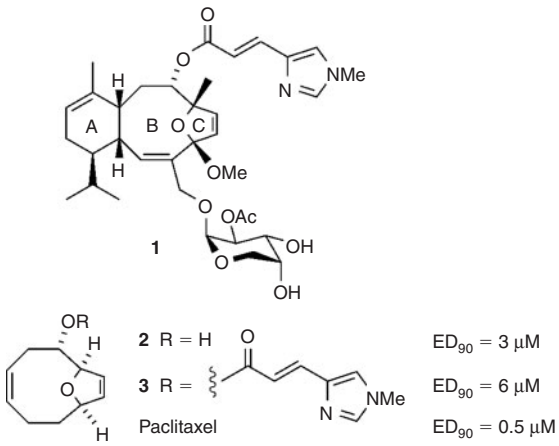

Fig. 1. Structure of eleutherobin (**1**) and promising simplified analogues **2** and **3**.[13]

Bicyclic ethers **4** could be prepared by Barbier-type ring-closure[17] of derivatives of the key intermediate lactone **5**. This method of ring closure would also allow access to the hemiacetal moiety (R = H), which is believed to be important for biological activity. Lactone **5** would in turn be produced from Claisen rearrangement[18] of a symmetrical divinyl-appended ketene acetal **6**. Incorporation of a group on the ketene acetal (R^6 in Scheme 1) would introduce an additional functional group at the position adjacent to the hemiacetal. Ketene acetal **6** could be derived from diol **7** by Tebbe[19] or Petasis[20] olefination of cyclic carbonate derivatives of **7**[21] or by elimination of

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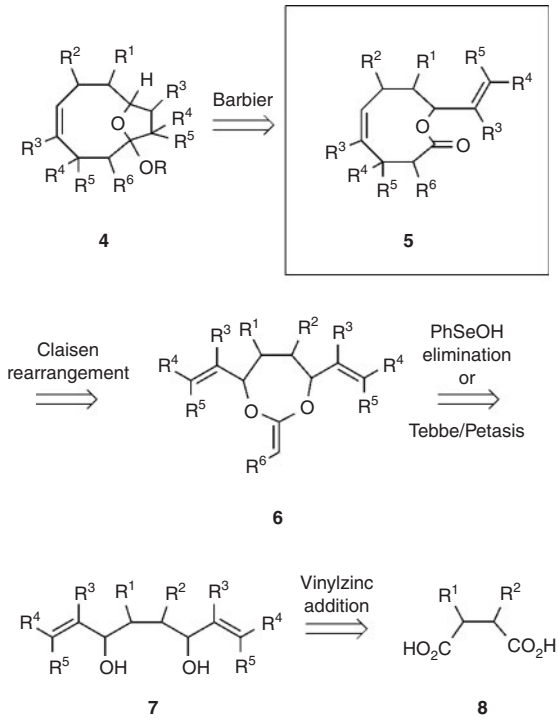
benzeneselenenic acid from selenoxide-substituted cyclic acetal derivatives of **7**.[22] *Bis*-vinyldiols **7** could be obtained by addition of vinylzinc reagent to dialdehydes, themselves derived from readily available 1,4-dicarboxylic acid derivatives **8**. A range of 1,4-dicarboxylic acids are commercially available (e.g. R^1, $R^2 = H$, alkyl, amino, hydroxy, etc.) or are readily synthesized. Differing substitution patterns on the bicyclic ether **4** could be introduced at various stages of the synthesis, as indicated by the positions of R^1–R^6 (Scheme 1).

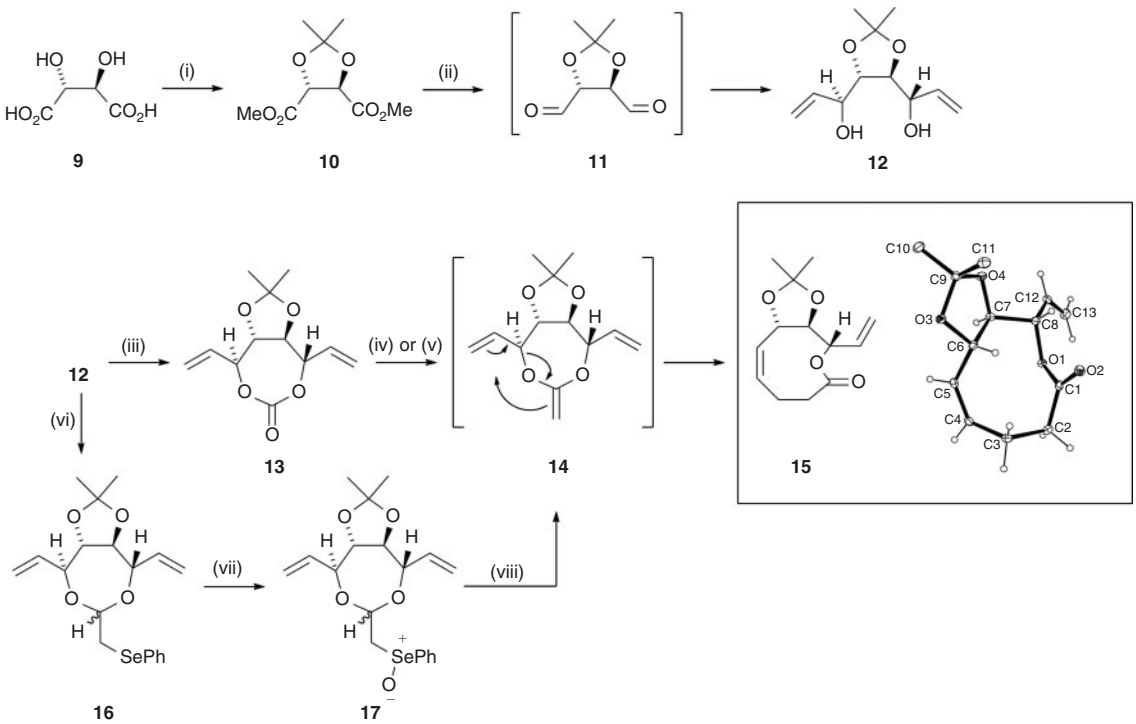


Scheme 1. A new approach to simplified eleutherobin analogues.

Our planned synthesis of medium-ring lactones,[23] such as **5** is analogous to our previously described methodology,[21,24–27] where we have used the Claisen rearrangement to synthesize marine-derived natural products such as ascidiatrienolide,[28] laurencin,[29] octalactins,[30] eunicellins,[15] and obtusenyne.[31] Such an approach to medium-ring lactone synthesis could prove useful for the preparation of complex marine natural products such as the brevetoxins.[27] Furthermore, lactone **5** forms the core carbon framework of structures like the halicholactones[32] and the topsentolides,[33] both of which are nine-membered lactone marine natural products with unsaturated side chains.

As proof-of-principle of this new approach, we chose L-tartaric acid as a starting material[34] that would translate into a dihydroxy-substituted nine-membered lactone **5** (R^1, $R^2 = OH$ in Scheme 1). L-Tartaric acid **9** underwent one-pot *bis*-esterification and diol protection by treatment with methanol and 2,2-dimethoxypropane, respectively, to give diester acetonide **10** (Scheme 2).[35] Reduction of the diester **10** with diisobutylaluminium hydride (DIBAL) at low temperature produced dialdehyde **11**, which was treated in situ with divinylzinc to afford a 10:1 diastereomeric mixture of diols. Flash chromatographic separation of the diols allowed for isolation of the major *C2*-symmetric diol **12** in reasonable yield and with high diastereomeric purity.[36]

Initially, we attempted to transform the diol **12** into the required ketene acetal **14** by carbonate formation (**12** → **13**)



Scheme 2. Synthesis of lactone **15**. Reagents and conditions: (i) dimethoxypropane, *p*-TsOH, MeOH, C_6H_{12}, reflux, 17 h, 67%; (ii) DIBAL, PhMe, −78°C; then divinyl zinc, THF, −78°C to 25°C, 10:1, 69%; (iii) triphosgene, pyridine, $NaHCO_3$, CH_2Cl_2, −78°C to 25°C, 72% (+ 18% recovered **12**); (iv) Cp_2TiMe_2, THF, 130°C microwave, 30 min, 15–28%; or (v) Tebbe reagent, DMAP, 4 Å molecular sieves, THF, 0°C to 25°C, 4 h, 35–57%; (vi) $PhSeCH_2CH(OEt)_2$, PPTS, PhMe, reflux; (vii) $NaIO_4$, $NaHCO_3$, CH_2Cl_2/MeOH/H_2O; (viii) 1,8-diazabicycloundecane, PhMe, reflux (53% from **12**). Inset: Thermal ellipsoid plot (20% probability) of lactone **15**; hydrogen atoms from the methyl groups have been omitted for clarity; absolute configuration was established by chemical means, using L-tartaric acid as starting material.

followed by methylenation with either the Tebbe[19] or Petasis[20] reagents, according to previously developed methodology.[21,25–27,30] Under both conditions, ketene acetal **14** was not observed; instead, a rapid Claisen rearrangement occurred to afford the desired lactone **15**. However, it was found that carbonate **13** was unstable towards chromatographic purification and the yields of **15** from one-pot methylenation-Claisen rearrangement could not be reproduced on larger scale (see Accessory Publication for details). For this sequence, and consistent with previous work where we have compared both routes,[26,27,30] we prefer the method involving selenoacetal **16**, which was more reliable. Thus, condensation of diol **12** with (2,2-diethoxyethylselanyl)benzene[37] afforded the phenylselenoacetaldehyde acetal **16** in 70% yield after chromatography. The selenide **16** was oxidized with sodium periodate to give the selenoxide **17**. The polar nature of this compound rendered it unsuitable to normal phase chromatography so the crude selenoxide **17** was subjected to elimination/rearrangement in dilute refluxing toluene, with 1,8-diazabicycloundecane as an additive to scavenge the by-product benzeneselenenic acid.[38] Cyclic ketene acetal **14** was not isolated under these conditions due to fast Claisen rearrangement, resulting in the chiral nine-membered lactone (+)-**15**. We found in optimizing the sequence towards lactone **15**, that the use of either pure or crude selenoacetal **16** gave similar results. Thus, lactone **15** was obtained in 53% yield over three chemical steps from diol **12** (an average of 85% yield for each transformation), without chromatographic purification of the intermediates. Medium-ring lactone **15** crystallized from a concentrated solution of chloroform, allowing examination by X-ray crystallography. This confirmed the *Z*-double bond geometry of the alkene, as well as the *s-cis*-conformation of the ester moiety. The relative stereochemistry of the vinyl group was also confirmed to be *anti* to the adjacent acetonide C–O bond (Scheme 2, inset).

In summary, we have developed an efficient, asymmetric route to vinyl-appended dihydroxy nine-membered lactones starting from L-tartaric acid. The key step in this route involves a stereoselective Claisen rearrangement of a *C2*-symmetrical ketene acetal into a *Z*-alkene containing lactone. We have converted **15** into an iodoethyl derivative; however, initial attempts at Barbier-type ring closure of the iodoethyl derivative, using samarium iodide, have resulted in a side-reaction involving reductive cleavage of the iodoethyl group. Further work will be towards: optimization of the ring closing reaction, exploration of the scope of the chemistry using other 1,4-dicarboxylic acid starting materials, and application of the chemistry to the preparation of bicyclic ether analogues of eleutherobin and related natural products systems.

Accessory Publication

The crystallographic information file has been deposited at the Cambridge Crystallographic Data Centre (CCDC-753692). This information, experimental procedures for **12** → **15** (both routes), characterization data for all new compounds, and ^{1}H and ^{13}C JMOD NMR data for **15** are available in the Accessory Publication on the Journal's website.

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