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Total Synthesis and Structural Revision of the Cytotoxin Aruncin B

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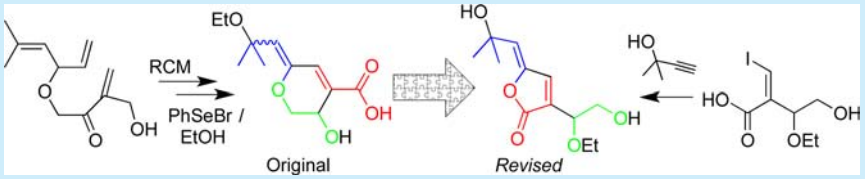
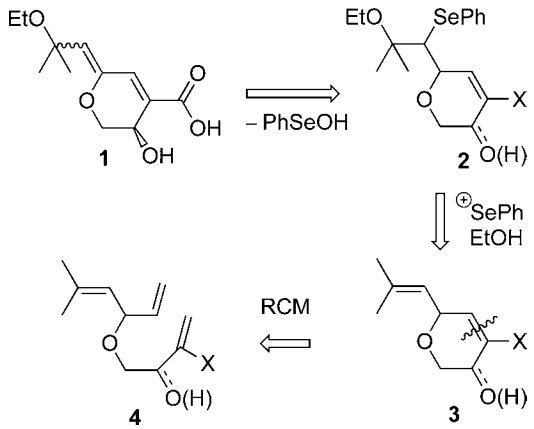
Supporting Information



ABSTRACT: The sodium salts *E*-**15** and *Z*-**15** of the originally proposed dihydropyran acid structure of aruncin B (**1**) were prepared through ring-closing alkene metathesis (RCM) and ethoxyselenation−selenoxide elimination, but acid sensitivity of these salts, together with inconsistencies in the spectral data, suggested a significant structural misassignment. A β-iodo Morita−Baylis−Hillman reaction to give *Z*-iodo ester **24**, followed by Sonogashira cross-coupling−5-*exo*-*dig* lactonization, provided concise access to a *Z*-γ-alkylidenebutenolide **18**, which possessed data corresponding to those originally reported for aruncin B.

In 2011, Woo and co-workers reported cytotoxicity-directed isolation of extracts from the plant *Aruncus dioicus* var. *kamtschaticus*, obtained from the Korean island Ulleungdo, which enabled discovery of the monoterpenoid (+)-aruncin B (**1**) (Scheme 1, 29 mg from 6.9 kg of aerial parts).[1] Studies indicated

Scheme 1. Structure of Aruncin B (1) Assigned by Woo and Co-workers,[1] and Retrosynthetic Analysis



inhibition of Bcl-2 antiapoptotic proteins, with selective cytotoxicity for malignant tumor cells over normal human T cells suggesting potential as an antitumor agent.[1b]

The structure of aruncin B was assigned using spectroscopic methods (NMR, MS, UV, and IR) and shows interesting features: an enol ether with a unique cross-conjugated pattern, along with a potentially acid-labile tertiary allylic ethyl ether coexisting with carboxylic acid functionality. The exocyclic double bond geometry and absolute configuration were not established. The intriguing structure and biological activity make aruncin B (**1**) an attractive target for synthesis. Late-stage installation of the potentially sensitive enol ether motif was envisaged using an ethoxyselenation−selenoxide elimination sequence[2] (Scheme 1, **3** → **2** → **1**). The precursor dihydropyran-containing core **3** would be formed by ring-closing alkene metathesis (RCM) of a triene **4**. Appropriate ring and side-chain (X) oxidation levels for this strategy would be established through experimentation.

The synthesis of the postulated structure began with 1,2-addition of vinylmagnesium bromide to prenal (**5**) (Scheme 2), followed by *O*-alkylation of the resulting crude dienol[3] with *tert*-butyl bromoacetate, under phase transfer conditions,[4] to give ester **6**. Following phosphonation,[5] phosphonate **7** underwent the Villieras variant of the Horner−Wadsworth−Emmons reaction[6] to give, after purification by column chromatography (the first required in this sequence), α-hydroxymethyl enone **8**. RCM[7] of the latter using Grubbs' II catalyst gave hydroxymethyldihydropyranone **9**. Due to metathetical involvement of the *gem*-dimethyl substituted alkene, ∼10% of undesired dihydropyranone **10** was originally obtained as an inseparable RCM byproduct; this issue was overcome by subsequent addition of excess 2-methyl-2-butene.[8]

Hydroxymethyldihydropyranone **9** contains all the core carbon atoms of aruncin B. Reduction using DIBALH[9] gave a diol **11** (Scheme 3, 3:1 dr) from which the primary alcohol was selectively oxidized to the hydroxyaldehyde **12** through TEMPO catalysis;[10] no ketone was observed. For analytical convenience the hydroxyaldehyde **12** diastereoisomers were separated at this stage, and subsequent chemistry was carried out on the major (*trans*[11]) diastereoisomer.

Ethoxyselenation[2] occurred selectively at the electron-rich olefin of the hydroxyaldehyde **12mj**, to give the ethoxyselenide **13** as a single diastereoisomer (Scheme 4).[12] Periodate oxidation[13] of the crude ethoxyselenide **13** followed by

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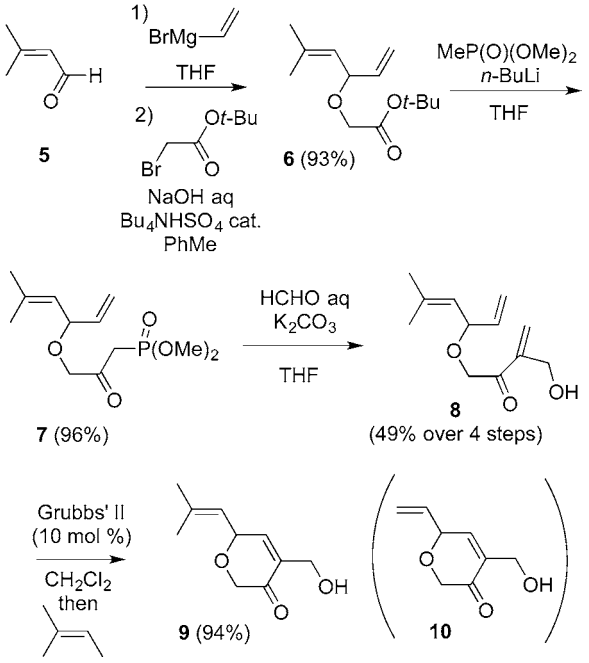
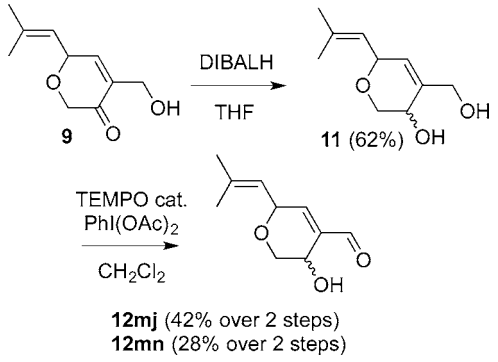
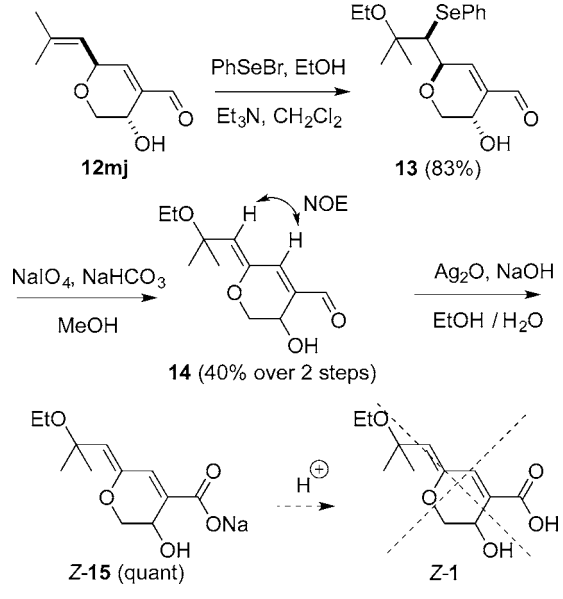
Scheme 2. Synthesis of Hydroxymethyldihydropyranone 9



Scheme 3. Redox Adjustment



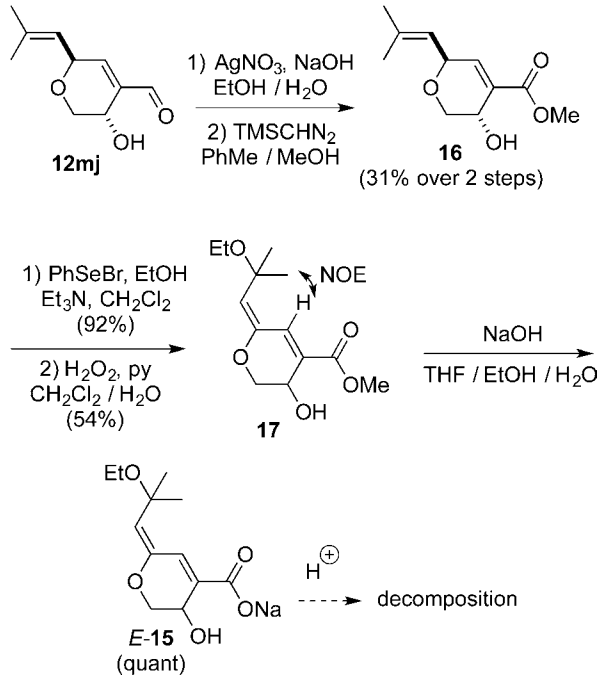
Scheme 4. Ethoxyselenation−Selenoxide Elimination Sequence, Final Oxidation and Attempted Acidification



selenoxide elimination gave the desired enol ether **14** as the *Z*-isomer. The *E*-isomer was observed in the crude mixture[14] but not isolated; it is suspected to be the initial product from *syn* elimination, but isomerization of the double bond occurs rapidly (possibly by reversible conjugate addition at the δ-position of the dienal) to deliver the *Z*-isomer, likely favored due to minimization of allylic strain. Final chemoselective oxidation of the aldehyde to the carboxylic acid was anticipated to be achievable using freshly prepared silver oxide under alkaline conditions.[15] While this proceeded smoothly to deliver the Na-salt *Z*-**15** of the originally assigned structure, all attempts to obtain the free acid from *Z*-**15** led only to complete and rapid decomposition. For example, mild acidification conditions, such as pH 6 buffer solution, addition of accurately measured 1 equiv of HCl (at −78 °C), or carboxylic acid-supported ion-exchange resins all proved unsuccessful.

Since enol ether geometry of aruncin B had not been established in the isolation paper,[1a] we were interested in seeing whether the *E*-isomer would possess different acid stability character and correspond to the natural product. It was considered that switching from an aldehyde to a slightly less electron-withdrawing group, such as an ester, might retard isomerization and thereby enable the access to the *E*-configured exocyclic unsaturation. Oxidation[16] of hydroxyaldehyde **12mj**, then esterification using $TMSCHN_2$, delivered hydroxy ester **16** (Scheme 5). Ethoxyselenation as before, followed by hydrogen

Scheme 5. Synthesis of the Na-Salt *E*-15



peroxide-induced oxidation[17] of the resulting selenide, gave the *E*-enol ether **17**, which exhibited greater configurational stability than enol ether **14**. Saponification of *E*-enol ether **17** delivered the *E*-Na-salt *E*-**15** which, however, possessed the same sensitivity to acid as previously found with *Z*-Na-salt *Z*-**15**.

Our above studies suggested that acid **1** is intrinsically unstable, due to the coexistence of tertiary allylic ether and carboxylic acid functionality: acid-induced loss of EtOH, assisted by the enol ether, leads to decomposition. While UV data supported the presence of a γ-alkoxy-$\alpha,\beta,\gamma,\delta$-unsaturated

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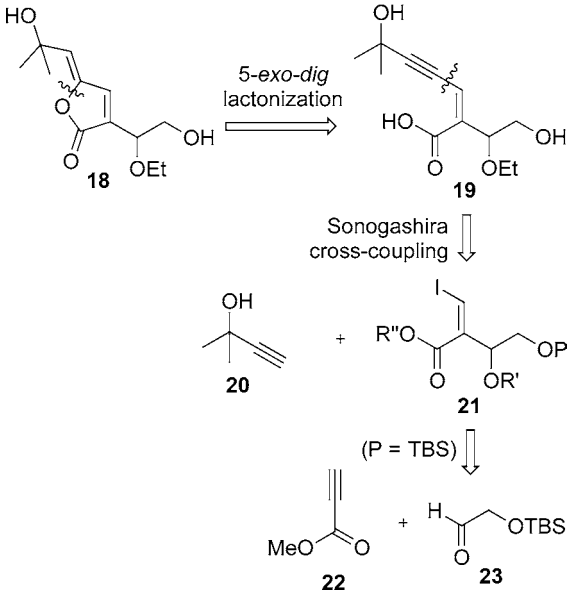
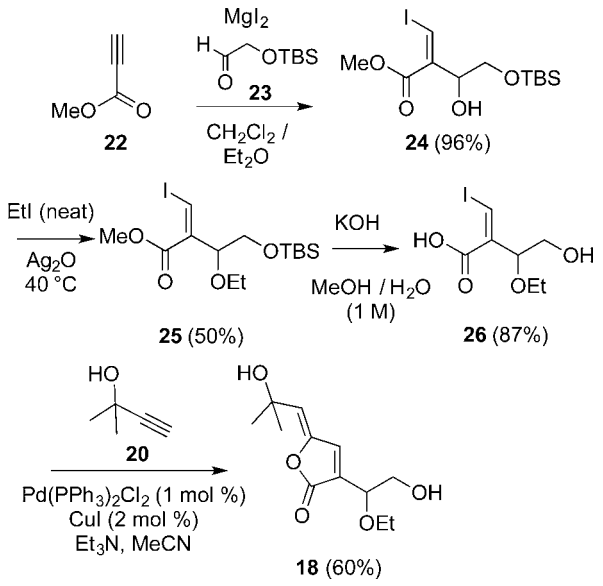
carboxyl motif,[18,19] acid sensitivity, together with inconsistencies in the ^{1}H and ^{13}C NMR data between **1** and the two Na-salts (*Z*-**15** and *E*-**15**),[20] indicated that a structural revision was necessary. Detailed analysis of the data suggested that, in particular, a better match for the originally assigned ring CH_2 would be as a primary alcohol,[21] rather than an (enol) ether. Further inspection of the original structure assignment of aruncin B (**1**)[1a] indicated that the site of etherification was not determined unambiguously and, based on the ^{13}C NMR data, a structure featuring tertiary allylic alcohol and the ethyl ether of a secondary alcohol would be a more reasonable alternative.[22] These considerations led us to consider a *Z*[23]-γ-alkylidenebutenolide **18** (Scheme 6) as being more consistent with available data.[24] The γ-alkylidenebutenolide motif is present in several natural products,[25] including novaxenicin D[26] and an oxidized tirucallane triterpenoid[27] which possess *E*-γ-(hydroxy)isobutylidene and *Z*-γ-(methoxy)isobutylidene substitution, respectively. However, the α-dioxygenated side chain has not previously been observed. While many routes to γ-alkylidenebutenolides are known,[25] we were attracted to a Sonogashira cross-coupling−5-*exo*-*dig* lactonization sequence[28] (**20** + **21** → **19** → **18**, Scheme 6) due to its functional group tolerance, stereocontrol, and brevity. The *Z*-vinyl iodide substrate **21** bearing the requisite α-dioxygenated side chain could be prepared via a β-iodo-Morita−Baylis−Hillman (MBH) reaction.[29]

Scheme 6. New Postulated Structure of Aruncin B (Butenolide 18) and Retrosynthetic Plan



The synthesis starts with methyl propiolate (**22**) and the aldehyde **23**.[30] The β-iodo-MBH reaction was carried out using *in situ* generated MgI_2 as an iodide source,[31] giving *Z*-iodoester **24** (Scheme 7). This powerful one-step transformation installs the dioxygenated side chain and sets the *Z*-vinyl iodide functionality necessary for the subsequent cross-coupling. *O*-Ethylation of the secondary alcohol was achieved using Ag_2O in neat EtI, to give the ether **25**. Subsequent saponification of the methyl ester was accompanied by desilylation to give the desired cross-coupling substrate *Z*-iodoacid **26**. The Sonogashira cross-coupling−5-*exo*-*dig* lactonization sequence could be achieved in the presence of free alcohol functionality in both partners, and with as little as 1 mol % $Pd(PPh_3)_2Cl_2$ and 2 mol % CuI (~1 mmol scale, leading to 200 mg of *Z*-butenolide **18**). To our delight, the spectroscopic data for synthetic γ-alkylidenebutenolide **18** corresponded to those reported for the originally isolated aruncin B.[20,32]

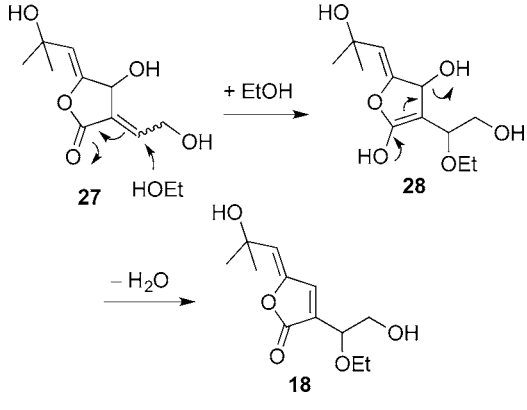
Scheme 7. Synthesis of the Correct Structure of Aruncin B: Butenolide 18



Enantiopure samples of (+)- and (−)-aruncin B were obtained from *Z*-butenolide **18** by semiprep HPLC. The specific rotation values found for the synthetic materials ($[\alpha]_D^{25}$ + /− 90 (*c* 1.0 in MeOH)) were significantly higher than that reported for the natural isolate ($[\alpha]_D^{20}$ + 27 (*c* 0.1 in MeOH)).[1b] This discrepancy suggests that the original isolate may not be enantiopure, but rather partially enantioenriched. An intriguing structural feature of the correct structure of aruncin B is the ethoxy group at the β'-position. Interestingly, aruncin B was isolated by EtOH extraction of the aerial plant parts. The possibility of low enantiomeric enrichment and unusual presence of the ethoxy group could indicate that butenolide **18** is an artifact of the isolation process, resulting from a modestly diastereoselective conjugate addition of EtOH to an α-(2-hydroxyethylidene)-γ-lactone **27**,[33] followed by loss of water (Scheme 8).

In summary, RCM followed by ethoxyselenation−selenoxide elimination proved to be a viable strategy to (ethoxy)-isobutylidene-substituted dihydropyranols, which was applied in stereocontrolled syntheses of the Na-salts of the *Z*- and *E*-

Scheme 8. Potential Origin of Butenolide 18



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isomers of the originally postulated structure of aruncin B (**1**). However, the free acids could not be obtained from these Na-salts. This instability, together with inconsistencies in the collected analytical data, led to the conclusion that aruncin B has been misidentified.[34] An alternative butenolide **18** structure has been proposed and synthesized in four steps, through β-iodo-MBH reaction and Sonogashira cross-coupling−lactonization. The data for butenolide **18** match with those originally reported for aruncin B. With the structure of aruncin B now reassigned and a concise and flexible synthetic approach to it established, studies can now be undertaken to probe in more detail the biological activity of aruncin B and analogues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02120.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all reported compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(11) Assigned according to ring $^{3}J_{\text{H-H}}$ values; see the Supporting Information.

(12) Acidic workup was used to deprotect small amounts of the corresponding diethyl acetal of **13** formed during the course of the reaction.

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