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Note

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Total Synthesis of the Antitumor Antibiotic Basidalin

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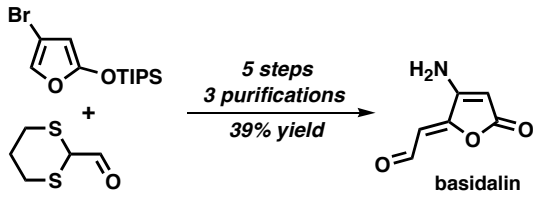
ABSTRACT:



The first synthesis of the tetronamide antibiotic basidalin was accomplished in five steps and 39% overall yield from readily available 4-bromo-2-triisopropylsilyloxyfuran and 2-formyl-1,3-dithiane. Highlights include: (i) regio and stereocontrolled assemblage of a pivotal (*Z*)−γ−ylidene−β−bromobutenolide intermediate by stereodirected vinylogous aldol condensation (SVAC), (ii) installation of the amino group via aza-Michael addition/elimination, and crucially (iii) facile access to basidalin by late-stage dithiane removal.

Basidalin (**1**, Figure 1) is a small but richly functionalized antibiotic first isolated in 1983 from the fungus *Leucoagaricus naucina*,[1] and again in 1994 from a related fungus, *Leucoagaricus cameifolia*.[2] Its unique tetronamide structure, including the *Z*-geometry of the formylmethylidene moiety, was firmly established by X-ray analysis.[1] Notwithstanding the frequent use of tetronamides in chemical, pharmaceutical and agrochemical research,[3-5] basidalin holds the prominent position of being the first, and to date only, tetronamide known to occur in Nature. In addition, **1** possesses antibacterial properties and significant antitumor activity against leukemia,[1,2] both in vitro (IC_{50} = 0.11 μg/mL) and in vivo, dose-dependently prolonging the survival of mice inoculated with L1210 cells.[1]

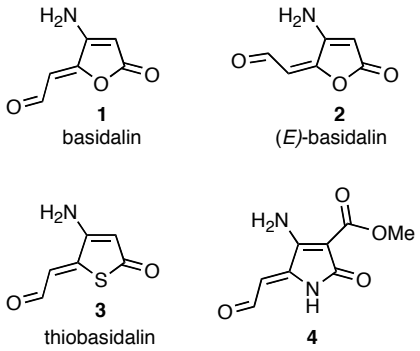


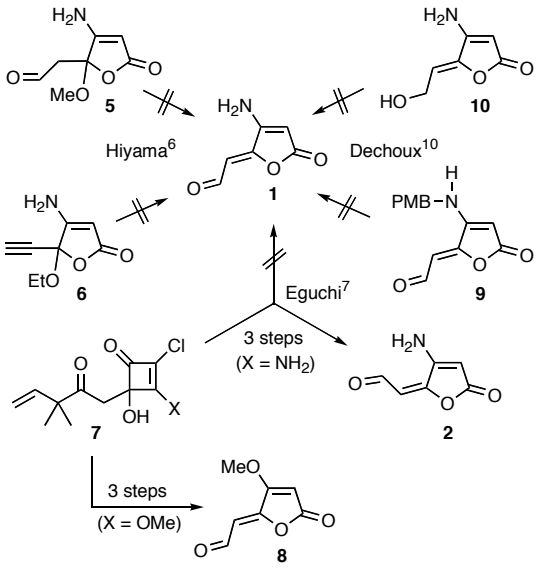
Figure 1. Basidalin and Relatives

These attributes have stimulated considerable interest not only in the synthesis of **1** but also in a variety of its analogues.[6-10] However, while certain analogues have succumbed to synthesis (e.g. **2**-**4**, Figure 1),[7-9] basidalin itself has so far proven remarkably elusive.[6,7,10]

Thus, Hiyama's advanced intermediates **5** and **6** (Scheme 1), each synthesized in five steps, failed to undergo conversion to **1** under an extensive array of conditions.[6] Using an elegant ring transformation of cyclobutenones **7**, Eguchi and co-workers were able to

synthesize (*Z*)−γ−formylmethylenetetronate **8**, but when this chemistry was applied to basidalin, the *E*-isomer **2** was obtained instead.[7] Recently, Dechoux's group employed a decarboxylative Knoevenagel-type reaction to assemble *Z*-configured intermediates **9** and **10**. However, neither of them could be transformed into **1**.[10]

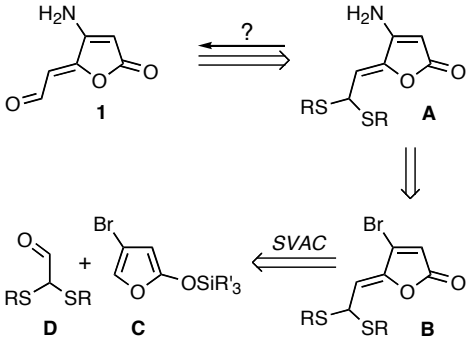
Scheme 1. Attempted Syntheses of 1



Herein we describe the first successful synthetic approach to basidalin (**1**), which illustrates a new and potentially general strategy for constructing (*Z*)−γ−alkylidene-tetronamides. Considering the difficulties experienced in generating **1** from seemingly ideal precursors[10] (cf. **9**-**10**, Scheme 1), it was not a priori possible to predict with confidence which endgame tactics would succeed. After reviewing several options, we came to favor *S,S*-acetal **A** as the ultimate precursor (Scheme 2). The availability of highly specific and mild conditions for cleavage of the thioacetal group[11] was expected to greatly simplify the task of acquiring basibalin. Access to **A** was to be gained from bromobutenolide **B**, which would in turn derive from **C** with **D** by utilizing our stereodirected vinylogous aldol condensation (SVAC) method.[12] Previously, we had used bromine as a removable stereocontrol element for making (*Z*)−β−unsubstituted−γ−alkyl-idenebutenolides.[12] In the present instance, bromine would serve the dual purpose of

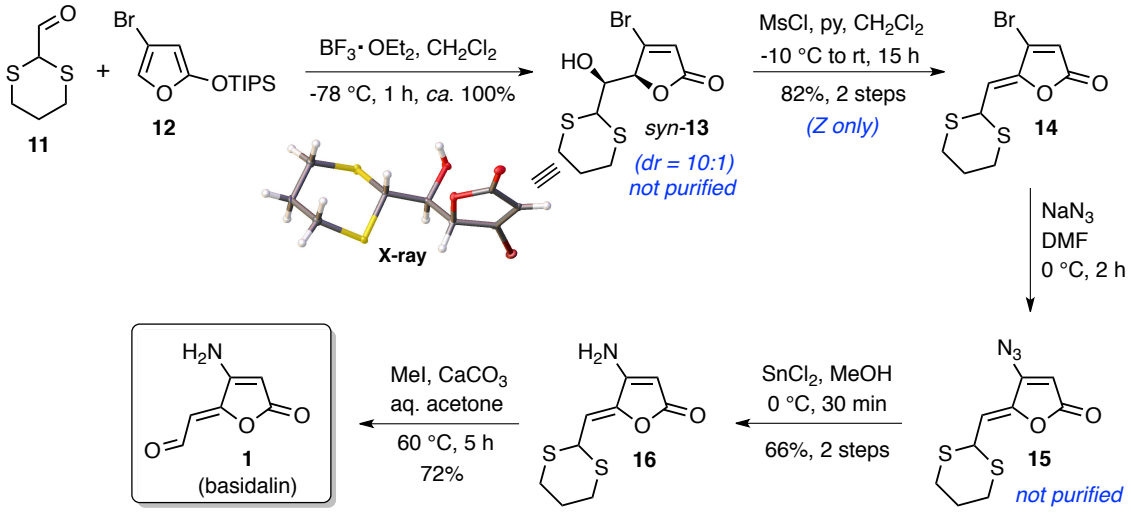
stereodirecting and activating group, thereby enabling its replacement by an amino substituent (**B** → **A**, Scheme 2).

Scheme 2. Our Retrosynthetic Analysis



The synthesis began with 2-formyl-1,3-dithiane **11** and 2-silyloxyfuran **12** (Scheme 3), each prepared in one step from commercial chemicals.[13,14] In keeping with previous experience,[15] BF_3-mediated vinylogous Mukaiyama aldol reaction (VMAR)[16] of **11** with **12** swiftly provided **13** in essentially quantitative yield as a 10:1 mixture of the *syn* and *anti* diastereoisomers. To ascertain their respective identities, the major isomer (*syn*-**13**) was isolated and subjected to X-ray analysis. However, since both stereoisomers were deemed capable of undergoing *Z*-selective elimination,[12,17] the *syn*/*anti* mixture was carried forward without purification. Initial attempts to bring about elimination under standard conditions (cf. $MsCl/Et_3N$)[12,18] led to complex mixtures containing only ca. 10-25% of the desired (*Z)*-ylidenebutenolide **14** and traces of (*E)*-**14** (1-2%). On the positive side, the ketene thioacetal isomer of **14** could not be observed among the products.[19] Conceivably, complications may stem from the high acidity of the allylic C-H in **14** and enhanced reactivity of the corresponding carbanion. Pleasingly, recourse to a weaker base than triethylamine solved the problem. Thus, treatment of the crude *syn*/*anti*-**13** mixture with mesyl chloride and pyridine in CH_2Cl_2 at -10 °C afforded **14** as the only detectable isomer, isolated in 82% yield after flash chromatography.

Scheme 3. Total Synthesis of Basidalin



Next, the plan called for aza-Michael addition/elimination to introduce the amino group (cf. **14** → **16**, Scheme 3). Given the propensity of γ–alkylidenebutenolides to undergo facile ring opening with ammonia, leading to 5-hydroxypyrrol-2(5*H*)-ones,[20] the desired transformation was not apt to be realized directly.[21] Ultimately, a two-step process via azide **15** was explored and found highly effective. In the event, exposure of **14** to sodium azide in DMF at 0 °C led smoothly to the conjugate addition/elimination product **15**. The azide proved to be somewhat unstable at room temperature and was therefore immediately reduced with $SnCl_2$/MeOH[22] at 0 °C to furnish tetronamide **16** in an overall yield of 66% after purification. To the best of our knowledge, only β–halobutenolides lacking the γ–ylidene functionality have been previously converted to azides (NaN_3, MeOH, rt).[23] Interestingly, the use of MeOH instead of DMF as solvent, led to substantially slower, incomplete conversion of **14** to **15** at 0 °C. Even after running the reaction for 24 h at rt, some unreacted **14** could be observed by TLC, resulting in a lower yield of **16** after reduction (57%). Finally, alkylative hydrolysis of the dithiane group under the mild Fetizon conditions (MeI/$CaCO_3$)[24] uneventfully delivered basidalin (**1**,

72%) whose ^{1}H and ^{13}C NMR spectra were in full agreement with those reported in the literature.[1]

In summary, the first synthesis of the tetronamide antibiotic basidalin has been achieved in 5 steps and 39% overall yield from readily available compounds. In addition to providing unfettered access to the natural product for further biological evaluation, the synthesis demonstrates the utility of SVAC technology for rapid, regio and stereocontrolled assemblage of densely functionalized (*Z*)–γ–ylidenebutenolides and tetronamides.

EXPERIMENTAL SECTION

General Protocols. The following procedures were used unless otherwise noted. Moisture-sensitive reactions and dry solvent distillation were carried out in flame-dried glassware sealed under a positive pressure of dry argon. Moisture-sensitive liquids, solutions and anhydrous solvents were transferred by syringe or cannula through rubber septa.

Unless noted otherwise, all commercial reagents were used as received. Anhydrous DMF was used as received. Dry dichloromethane and methanol were distilled from calcium hydride. Dry pyridine was distilled from potassium hydroxide.

Flash chromatography was performed on an automated system (UV- vis detector) using silica gel as stationary phase. NMR spectra were recorded at room temperature in $CDCl_3$, $(CD_3)_2CO$ and $(CD_3)_2SO$. Chemical shifts are reported relative to chloroform (δ_H 7.26; δ_C 77.16), acetone (δ_H 2.05; δ_C 29.84, 206.26) and dimethyl sulfoxide (δ_H 2.50; δ_C 39.52). ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet;

q = quartet; m = multiplet or combinations of the above. High-resolution mass spectra were obtained on a time-of-flight instrument using electrospray ionization (ESI).

5-((1,3-Dithian-2-yl)(hydroxy)methyl)-4-bromofuran-2(5*H*)-one (13). To a solution of silyloxyfuran **12** (300 mg, 0.94 mmol) in dry CH_2Cl_2 (6 mL) that had been cooled to -78 °C, were sequentially added in a dropwise fashion 1,3-dithiane-2-carbaldehyde **11** (120 μL, 1.03 mmol, 1.1 equiv) and BF_3•OEt_2 complex (140 μL, 1.13 mmol, 1.2 equiv). After 1 h, the mixture was poured to saturated aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford **13** (292 mg, 100%) as a 10:1 mixture of the *syn* and *anti* isomers. Their stereostructures were assigned by integration of diagnostic NMR signals (^{1}H NMR: δ_{syn} 5.56, 4.31, 3.97 ppm; δ_{anti} 4.87, 4.41, 4.18 ppm; and ^{13}C NMR: δ_{syn} 148.2, 122.9, 83.6, 67.7, 26.0, 25.2, 24.9 ppm; δ_{anti} 146.5, 123.8, 84.5, 71.2, 27.0, 25.9, 25.0 ppm). The 10:1 mixture (*syn*/*anti*-**13**) was used as obtained in the synthesis of compound **14**.

For the purpose of characterization, the experiment was repeated and the major (*syn*) isomer was purified by preparative TLC (100% CH_2Cl_2): *syn*-**13** (86%); white solid: mp 106-112 °C dec; IR (NaCl, film) ν 3436, 3100, 2895, 1755, 1603, 1422, 1281, 1159, 1102, 1023, 994, 907, 823, 775, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 5.56 (s, 1H), 4.31 (d, J = 10.0 Hz, 1H), 3.97 (d, J = 10.0 Hz, 1H), 2.93–3.05 (m, 2H), 2.86 (d, J = 1.6 Hz, 1H), 2.58–2.73 (m, 2H), 2.05–2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 148.2, 122.9, 83.6, 67.6, 45.2, 26.0, 25.1, 24.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{12}BrO_3S_2$ 310.9406, found 310.9405.

Suitable crystals for X-ray crystallography were obtained by recrystallization from hot absolute ethanol.

(*Z*)-5-((1,3-Dithian-2-yl)methylene)-4-bromofuran-2(5*H*)-one (14). Crude **13** (dr = 10:1, 170 mg, 0.55 mmol) was dissolved in dry CH_2Cl_2 (4 mL) and the solution was cooled to -10 °C. To this solution was added pyridine (90 μL, 1.09 mmol, 2 equiv) before dropwise addition of methanesulfonyl chloride (80 μL, 0.98 mmol, 1.8 equiv). The mixture was allowed to stir at the same temperature for 1 h, another 90 μL of pyridine was added and the solution was slowly allowed to warm to room temperature while stirred overnight. After 15 h, the mixture was poured to aq 1 N HCl (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by flash column chromatography (5% EtOAc in hexanes) to provide **14** (132 mg, 82%) as a pale brown solid: mp 97-100 °C dec; IR (NaCl, film) ν 3133, 2901, 1781, 1670, 1559, 1422, 1293, 1000, 967, 905, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.45 (s, 1H), 5.68 (d, J = 11.0 Hz, 1H), 5.19 (d, J = 11.0 Hz, 1H), 2.90–2.96 (m, 4H), 2.04–2.20 (m, 1H), 1.85–2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.8, 147.9, 137.3, 121.8, 110.7, 40.2, 29.2, 24.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{10}BrO_2S_2$ 292.9300, found 292.9286. Anal. Calcd for $C_9H_9BrO_2S_2$: C, 36.87; H, 3.09: Found: C, 36.47; H, 2.77.

(*Z*)-5-((1,3-Dithian-2-yl)methylene)-4-azidofuran-2(5*H*)-one (15). A mixture of **14** (120.4 mg, 0.41 mmol) and sodium azide (29.3 mg, 0.45 mmol, 1.1 equiv) in DMF (0.4 mL) were stirred at 0 °C for 2 h. The mixture was diluted with ethyl acetate (30 mL) and washed successively with cold water (20 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give crude azide **15** (102.5 mg), which was unstable at rt and was used in the next step without purification: IR (NaCl, film) ν 2927, 2126, 1765, 1468, 1243, 1171, 930, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.52 (d, J = 11.1 Hz, 1H), 5.13 (d, J = 11.1 Hz, 1H), 2.89–2.92 (m,

2H), 2.07–2.18 (m, 2H), 1.87–2.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 165.9, 155.6, 143.8, 107.3, 102.3, 40.0, 29.2, 24.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{10}N_3O_2S_2$ 256.0209, found 256.0197.

(*Z*)-5-((1,3-Dithian-2-yl)methylene)-4-aminofuran-2(5*H*)-one (16). To a stirred suspension of stannous chloride (113.6 mg, 0.61 mmol, 1.5 equiv) in MeOH (0.5 mL) cooled at 0 °C was added dropwise a solution of the crude azide **15** (102.5 mg) in MeOH (5 mL). The reaction was exothermic and N_2 gas was evolved. After the addition, the reaction mixture was stirred at 0 °C for 30 min. Methanol was removed under reduced pressure, the residue was diluted with cold water (10 mL) and freshly prepared alkaline with 2 N NaOH. Ethyl acetate (20 mL) was added and the layers separated. The aqueous layer was saturated with solid sodium chloride (~ 5 g) and re-extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure and the residue was purified by flash column chromatography (50% EtOAc in hexanes) to furnish tetronamide **16** (62.2 mg, 66% for 2 steps) as a yellow solid: mp 150-153 °C dec; IR (NaCl, film) ν 3197, 1716, 1642, 1584, 1568, 1355, 937, 771, 664 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 6.67 (broad s, 2H), 5.67 (d, J = 10.7 Hz, 1H), 5.19 (d, J = 10.7 Hz, 1H), 4.88 (s, 1H), 2.01–3.10 (m, 2H), 2.85–2.94 (m, 2H), 2.07–2.15 (m, 1H), 1.78–1.92 (m, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 169.4, 159.6, 146.3, 103.5, 85.0, 41.0, 29.6, 25.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{12}NO_2S_2$ 230.0304, found 230.0292.

Basidalin (1). To tetronamide **16** (50.3 mg, 0.22 mmol) and $CaCO_3$ (327.3 mg, 3.27 mmol, 15 equiv), suspended in 5 mL of acetone/H_2O (4:1), MeI (0.27 mL, 4.36 mmol, 20 equiv) was added dropwise. The reaction mixture was heated at 60 °C for 5 h. After cooling to rt, the volatiles were evaporated under reduced pressure, and the residue was

diluted with ethyl acetate (10 mL) and washed with water (10 mL). The mixture was dried (Na_2SO_4), and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc in hexanes) provided **1** (22.1 mg, 72%) as a yellowish solid: mp 138-142 °C dec; lit.[1] 142-149 °C dec; IR (NaCl, film) ν 3300, 2200, 1754, 1671, 1584, 1416, 1400, 1320, 1184, 1028, 926, 835, 786 cm^{-1}; ^1H NMR **(**500 MHz, $(CD_3)_2SO$**)** δ 10.01 (d, J = 7.8 Hz, 1H), 7.73 (br s, 2H), 6.11 (d, J = 7.8 Hz, 1H), 4.96 (s, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 189.3, 168.2, 159.5, 158.5, 102.9, 81.8; ^1H NMR **(**400 MHz, $(CD_3)_2CO$**)** δ 10.11 (d, J = 7.7 Hz, 1H), 7.01 (br s, 2H), 5.96 (d, J = 7.7 Hz, 1H), 5.05 (s, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ 189.2, 168.6, 160.0, 159.6, 103.4, 84.7; HRMS (ESI-TOF) m/z $[M + H]^+$calcd for $C_6H_6NO_3$ 140.0342, found 140.0346.

Supporting Information: Copies of ^1H and ^{13}C NMR spectra of all products and crystallographic data for *syn*-**13** (PDF and CIF). This material is available free of charge at http://pubs.acs.org.

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