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Divergent Synthesis of the Co-isolated Mycotoxins Longianone, Isopatulin, and (*Z*)-Ascladiol via Furan Oxidation

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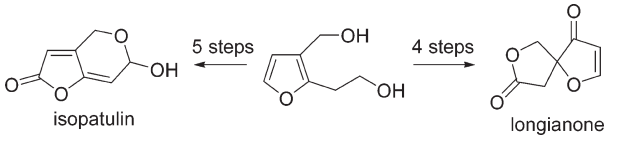
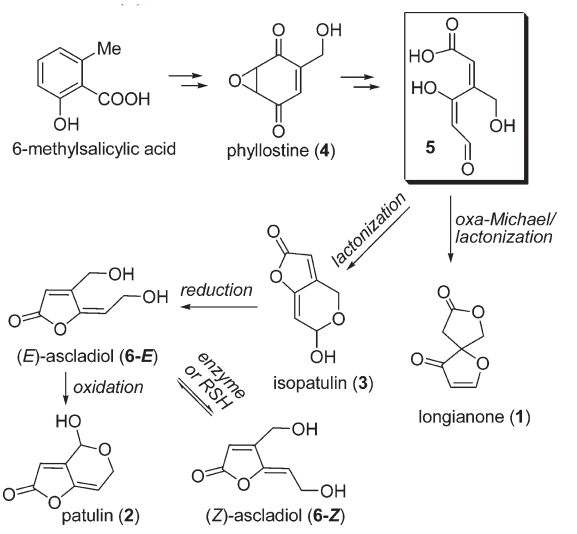


Longianone and the biosynthetically related mycotoxins isopatulin and (*Z*)-ascladiol were prepared following a divergent route from a readily available furan diol. The route toward longianone features an unprecedented TBAF-promoted intramolecular oxa-Michael reaction to a conjugated keto enoate, and the oxidation of dihydrolongianone to longianone with stabilized IBX. The route to isopatulin features a chemoenzymatic synthesis of (*Z*)-ascladiol, and the regioselective oxidation of (*Z*)-ascladiol to isopatulin with MnO_2.

Longianone[1] (**1**), patulin[2] (**2**), and isopatulin[3] or neopatulin (**3**) are isomeric metabolites that are produced by the fungus *Xylaria longiana*. Isopatulin and primarily patulin have an unusual complex chemistry for compounds of such a low molecular weight. They have been extensively studied because of their antibiotic properties and potent toxicity if present on fruits and grains. It has been established[4] that longianone, patulin, and isopatulin arise from 6-methylsalicylic acid. Following several biosynthetic steps, 6-methylsalicylic acid transforms to phyllostine (**4**), which hydrolyzes to **5** (Scheme 1). The postulated highly functionalized acyclic intermediate **5** leads to longianone via an oxa-Michael/lactonization sequence. Longianone has been postulated[4] as an intermediate during the biosynthesis of secosyrins and syringolides. An alternative intramolecular lactonization

SCHEME 1. Proposed Biosynthesis of Longianone (1), Patulin (2), Isopatulin (3), and (*E*)/(*Z*)-Ascladiol (6)



pathway of **5** affords isopatulin (**3**). An enzyme-catalyzed reduction/oxidation sequence on isopatulin yields patulin (**2**)[4] via the intermediate formation of (*E*)-ascladiol[5] (**6-*E***). (*E*)-Ascladiol isomerizes partially to (*Z*)-ascladiol (**6-*Z***)[6] during the bacterial degradation of patulin, as well as through a nonenzymatic pathway catalyzed by sulfhydryl compounds.[5] Ascladiols are also potent toxins; however, their activity has not been fully investigated[6] due to the lack of adequate quantities.

The synthesis of **1**−**3** has attracted in the past the interest of organic chemists. Woodward was the first to report the structure elucidation and the synthesis of patulin (**2**),[7] a synthetic landmark at that time,[8] yet, in a very low yield. Patulin also has been synthesized by the groups of Pattenden,[9] Tada,[10] Riguera,[11] and Boukouvalas.[12] Isopatulin (**3**) has been synthesized twice,[13] while 10 years ago Steel[14] reported the only known synthesis of longianone (**1**), using tetronic acid as starting material and featuring a free radical cyclization (Bu_3SnH, AIBN) of an enyne, as a key step, to construct the spirocyclic carbon skeleton of **1**.

It is indicative that there is no connectivity among the existing synthetic approaches to longianone, patulin, and isopatulin, despite their common biosynthetic origin. We

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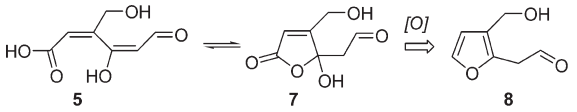
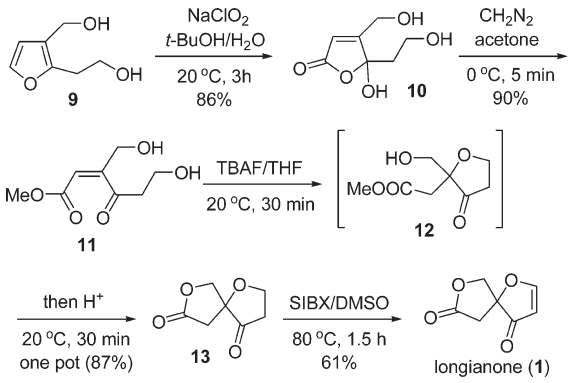
SCHEME 2. Retrosynthetic Analysis for the Acyclic Intermediate 5



SCHEME 3. Synthesis of Longianone (1) from Furan Diol 9



envisioned a common divergent synthetic route to **1**−**3** and **6** on the basis of the biosynthetic scenario presented in Scheme 1. Thus, the synthesis of the postulated acyclic intermediate **5** was targeted. Compound **5** is essentially the acyclic form of the γ-hydroxybutenolide **7**, which could derive from the suitable oxidation[15] of furan **8** (Scheme 2). While furan **8** with its hydroxyl protected as TBS silyl ether is a known compound,[16] all attempts to reproduce its synthesis in an acceptable yield failed. The major obstacle was the ortho-metalation of the precursor TBS-protected 3-furylmethanol, which proceeds in extremely low yield despite several modifications which were attempted. A similar observation has been noted by Katsumura and co-workers.[17]

The failure to prepare **8** led us to attempt the synthetic approach to **1**−**3** and **6**, slightly modifying the retrosynthetic analysis presented in Scheme 2. Thus, we decided to use the readily available furan **9**[10] as the starting material, and perform an additional oxidation at a latter stage[18] (Scheme 3). Furan **9** can be easily prepared in multigram scale and in ~80% yield by condensation of dimethyl 3-oxoglutarate with chloroacetaldehyde followed by reduction of the resulting diester with $LiAlH_4$. The $NaClO_2$-mediated[19] oxidation of **9** cleanly afforded the γ-hydroxybutenolide **10** in 86% isolated yield. Compound **10**, which is insoluble in nonpolar solvents, is essentially the reduced aldehyde form of **7**. To undertake the cyclization of **10** to the [5,5]-spirocyclic skeleton of longianone, we treated **10** with 1.0 equiv of CH_2N_2 to form **11** in high yield (90%). The oxa-Michael cyclization of keto enoate **11** to the dihydrofuran-3(2*H*)-one **12** was surprisingly achieved in 93% isolated yield after column chromatography by reacting with 1.0 equiv of TBAF in THF (25 °C, 30 min). While compound **12** can be isolated, direct acidification of the crude reaction mixture (one-pot) with *p*-TsOH (for 30 min) provides the desired spirobicyclic **13** (dihydrolongianone)[1,14] in 87% yield over the two steps. All attempts to achieve the transformation of **11** to **13** by using acidic[20] (*p*-TsOH, HCl, BF_3) or basic catalysts[21] in various solvents provided after prolonged reaction times complex mixtures of products with **13** seen as a minor product in some cases. While TBAF has been used as a promoter in intramolecular oxa-Michael reactions of enoates,[22] to the best of our knowledge this is the first example of an oxa-Michael reaction to a conjugated keto enoate. It is notable that the TBAF-promoted spirocyclization is free of byproduct, and proceeds relatively fast despite the steric hindrance imposed by the hydroxymethylene substituent.

Our next challenge was the oxidation (dehydrogenation) of **13** to longianone (**1**). In his synthetic approach to longianone, Steel[14] prepared **13** and succeeded in the introduction of the double bond within two steps (PhSeCl, O_3), yet in a very low overall yield (< 17%). Trying to develop an alternative more efficient methodology, we attempted the two-step procedure described by Rovis and Orellana[23] during the introduction of a double bond in a structurally similar spirocyclic system (TESOTf, $Ph_3C^+BF_4^-$). Our efforts were unsuccessful, despite several attempts and modifications. Indeed, Steel[14] had already indicated difficulties in generating the enolate of **13** in agreement with our failures. Subsequently, we turned our attention to the direct oxidation of **13** to **1** using IBX.[24] Notably, there are no examples in the literature regarding the IBX oxidation of the 5-membered dihydrofuran-3(2*H*)-ones. Testing the oxidation of **13**, we found that by using 3 equiv of IBX in DMSO the reaction proceeds relatively fast (~70% conversion after 1 h), yet with a < 60% mass balance (GC analysis with an internal standard). After 12 h no starting material could be detected, yet the reaction mass balance, and accordingly the product yield, drops dramatically to < 10%, indicative that IBX causes decomposition of the product. After extensive experimentation we found that stabilized IBX[25] (SIBX) is significantly more effective. Thus, in the reaction **13** with 2.0 equiv of SIBX (DMSO, 80 °C) a 70% conversion was achieved after 1.5 h while the reaction mass balance was maintained high (> 90%). Then the reaction mixture was carefully chromatographed to separate longianone (slightly more polar, TLC) from unreacted **13**. Under those reaction conditions, a 47%

(15) Recent selected examples of natural product syntheses featuring furan oxidation: (a) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5465–5468. (b) Margaros, I.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2007**, *9*, 5585–5588. (c) Margaros, I.; Vassilikogiannakis, G. *J. Org. Chem.* **2008**, *73*, 2021–2023. (d) Boukouvalas, J.; Wang, J. X.; Marion, O.; Ndzi, B. *J. Org. Chem.* **2006**, *71*, 6670–6673. (e) Helliwell, M.; Karim, S.; Parmee, E. R.; Thomas, E. J. *Org. Biomol. Chem.* **2005**, *3*, 3636–3653. (f) Sofikiti, N.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G.; Stratakis, M. *Org. Lett.* **2005**, *7*, 2357–2359. (g) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001–1011.

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(17) Katsumura, S.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1987**, *28*, 1191–1194.

(18) Although furan **9** could be considered as a precursor to **8**, it is known[10] that its oxidation with MnO_2 occurs exclusively on the side chain of C-3.

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(20) Intramolecular oxa-Michael reactions of enediones have been recently shown to proceed efficiently under *p*-TsOH catalysis: Tofi, M.; Koltsida, K.; Vassilikogiannakis, G. *Org. Lett.* **2009**, *11*, 313–316.

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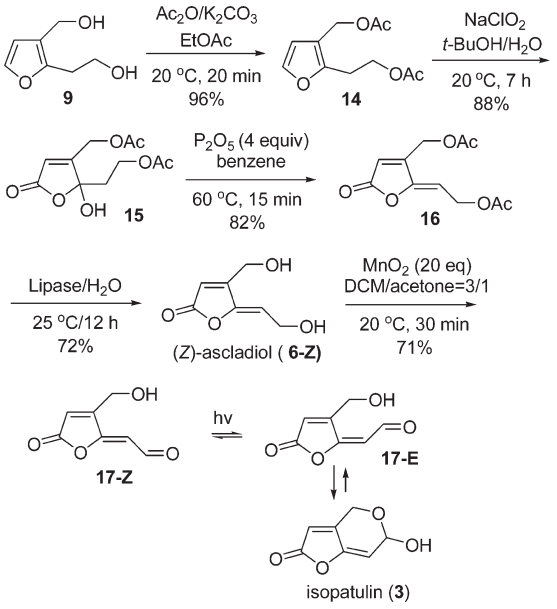
SCHEME 4. Synthesis of (*Z*)-Ascladiol (6-*Z*) and Isopatulin (3)



yield of longianone (61% based on the recovered starting material) was obtained.

Having synthesized longianone, we envisioned the dehydration of butenolide **10** to form (*E*)- and (*Z*)-ascladiol. All attempts to perform an acid-catalyzed dehydration of **10** failed as the expected ascladiol is extremely sensitive under basic or acidic conditions (see the discussion below). Thus, we decided to use as starting material the diacetate of **9**. Furan diol **9** was acetylated to form diacetate **14** in 96% yield, and subsequently **14** was oxidized with $NaClO_2$ to form the γ-hydroxybutenolide **15** in 88% yield (Scheme 4). The crude **15** underwent facile dehydration with P_2O_5 in benzene[26] (60 °C, 15 min) to (*Z*)-ascladiol diacetate **16** in 82% yield after column chromatography. The (*E*)-isomer was formed only in traces. The selective formation of the **16** could be rationalized in terms of its higher thermodynamic stability compared to the more hindered (*E*)-isomer. The hydrolysis of **16** to (*Z*)-ascladiol (**6-*Z***) seemed quite straightforward; however, all attempts by chemical means, either under basic (K_2CO_3/MeOH, LiOH/THF, etc.) or acidic conditions, proved unsuccessful with formation of mixtures of unidentified products in very poor yield. We then decided to perform an enzymatic hydrolysis. Treatment of **16** with a commercially available lipase from *Candida cylindracea* in a buffered aqueous solution (pH 7.2) led after 12 h to its clean hydrolysis to (*Z*)-ascladiol (**6-*Z***) in 71% isolated yield. (*Z*)-Ascladiol is relatively unstable and partially transforms on standing (> 50% after a week) into a mixture of nonidentified compounds. Subsequently, **6-*Z*** was oxidized with 20 equiv of activated MnO_2 (DCM/acetone = 3/1, 20 °C, 30 min) to form exclusively **17-*Z***. This regioselective oxidation can be rationalized due to the higher acidity of the allylic hydrogen atoms next to the hydroxyl at the 2′-position of the side chain, as the exocyclic double bond is the most electron-deficient. On standing in $CDCl_3$ or acetone-d_6 **17-*Z*** slowly isomerizes to isopatulin (~20−25% conversion after 24 h). Irradiation of the solution with a 300 W xenon lamp for 2−3 min accelerates substantially the transformation of **17-*Z*** to **3**. Isopatulin was purified by recrystallization (white solid) from ethyl acetate in 78% isolated yield. We observed that **3** is in equilibrium with its open forms **17-*Z*** and **17-*E***, with the lactol form (isopatulin) being predominant (ca. 90%). A similar observation was noted by Pattenden and co-workers[13a] in their isopatulin synthesis.

In conclusion, we have presented a simple, efficient, and bioinspired route to longianone, (*Z*)-ascladiol, and isopatulin using a divergent route from an easily accessible furan. The current syntheses complement the work of Tada,[10] who used furan **9** as the starting material to synthesize patulin.

Experimental Section

5-Hydroxy-5-(2-hydroxyethyl)-4-(hydroxymethyl)furan-2(5*H*)-one (10). To a solution of furan **9** (400 mg, 2.8 mmol) in *t*-BuOH/H_2O (5/1) (12 mL) were added in one portion at 20 °C $NaClO_2$ (760 mg, 8.4 mmol) and NaH_2PO_4 (650 mg, 4.2 mmol). The reaction was monitored by TLC and after 3 h it was complete. Ethyl acetate (30 mL) was added and the solvents were evaporated under vacuum. The residue was washed with acetone (3 × 10 mL), and after evaporation of the solvents, the γ-hydroxybutenolide **10** was isolated in 86% yield as colorless syrup. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.91 (t, J = 2.0 Hz, 1H), 4.54 (dd, J_1 = 16.0 Hz, J_2 = 2.0 Hz, 1H), 4.45 (dd, J_1 = 16.0 Hz, J_2 = 2.0 Hz, 1H), 3.81 (m, 2H), 3.68 (m, 2H), 2.27 (m, 1H), 1.99 (m, 1H). ^{13}C NMR (75 MHz, acetone-d_6) δ 172.2, 169.7, 115.3, 106.4, 57.4, 57.2, 38.9. MS (EI) 174 (1%), 156 (5%), 144 (4%), 138 (10%), 129 (9%), 110 (26%), 98 (9%), 83 (13%), 66 (12%), 55 (100%). HRMS (CI) calcd for $C_7H_{10}O_5$ + H 175.06080, found 175.06065.

(*Z*)-Methyl 6-Hydroxy-3-(hydroxymethyl)-4-oxohex-2-enoate (11). To a solution of **10** (210 mg, 1.2 mmol) in acetone (3 mL) was added dropwise at 0 °C a solution of CH_2N_2 in ether until a slightly yellow color persisted. The solvents were evaporated, and the residue was purified by column chromatography (hexane:EtOAc:acetone 5:1:1) to afford 199 mg of **11** (90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (t, J = 2.0 Hz, 1H), 4.35 (d, J = 2.0 Hz, 2H), 3.96 (t, J = 5.0 Hz, 2H), 3.72 (s, 3H), 2.89 (t, J = 5.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 165.8, 159.7, 116.1, 62.9, 57.8, 52.1, 45.1. MS (EI) 170 (2%), 157 (17%), 143 (42%), 127 (11%), 115 (15%), 98 (5%), 83 (44%), 73 (19%), 55 (100%). HRMS (CI) calcd for $C_8H_{12}O_5$ + H 189.07635, found 189.07630.

1,7-Dioxaspiro[4.4]nonane-4,8-dione (13). To a solution of ester **11** (176 mg, 1.0 mmol) in THF (2 mL) was added dropwise at 20 °C a solution of TBAF (1 M in THF, 1.1 mL, 1.1 mmol). After 30 min, the solvent was evaporated under vacuum, and the residue was purified by column chromatography (hexane:EtOAc 1:1) to afford 164 mg of **12** (93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (m, 2H), 3.66 (s, 3H), 3.63 (dd, J_1 = 11.5 Hz, J_2 = 8.0 Hz, 1H), 3.53 (dd, J_1 = 11.5 Hz, J_2 = 5.0 Hz, 1H), 2.84 (m, 1H), 2.83 (d, J = 16.5 Hz, 1H), 2.69 (d, J = 16.5 Hz, 1H), 2.59 (m, 1H), 2.13 (t, J = 8.0 Hz, 1H, −OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 170.5, 81.8, 65.7, 64.8, 52.0, 38.8, 36.6. MS (EI) 157 (7%), 143 (72%), 127 (27%), 115 (23%), 97 (10%), 83 (61%), 67 (26%), 55 (100%). Acidification of the above crude reaction mixture to pH ~4 with *p*-TsOH afforded after 30 min the spirobicyclic **13** (dihydrolongianone), which was purified after evaporation of the solvents without extracting by column chromatography (hexane:EtOAc 2:1) to afford 136 mg of **13** (94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (d, J = 11.0 Hz, 1H), 4.29 (d, J = 11.0 Hz, 1H), 4.23 (m, 2H), 2.79 (d, J = 17.5 Hz, 1H), 2.63 (d, J = 8.0 Hz, 1H), 2.62 (d, J = 17.5 Hz, 1H), 2.61 (d, J = 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 173.1, 84.3, 74.2, 63.2, 37.7, 35.9. MS (EI) 156

(26) Cane, D.; Ukachukwu, V. C. *J. Org. Chem.* **1985**, *50*, 2195–2198.

(M^+, 27%), 126 (89%), 116 (13%), 106 (11%), 98 (100%), 94 (5%), 85 (8%), 78 (15%), 72 (29%), 56 (18%). The above two-step process can be performed in one pot (87% yield) without isolating **12**.

Longianone (1). To a 0.5 M solution of dihydrolongianone **13** (30 mg, 0.21 mmol) in dry DMSO (0.2 mL) was added 2 equiv of stabilized IBX (0.43 mmol) and the mixture was heated to 80 °C. The reaction progress was monitored by GC, and after 90 min longianone had been formed in ~70% relative yield. Ethyl acetate was added, and the reaction mixture was extracted with a saturated solution of $NaHCO_3$. The organic residue was carefully purified by column chromatography (hexane:EtOAc gradually from 10:1 to 5:1), affording 14 mg of longianone (**1**) and 7 mg of **13** (61% yield of **1** based on recovered **13**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 2.5 Hz, 1H), 5.82 (d, J = 2.5 Hz, 1H), 4.43 (d, J = 11.0 Hz, 1H), 4.39 (d, J = 11.0 Hz, 1H), 3.04 (d, J = 18.0 Hz, 1H), 2.71 (d, J = 18.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 177.6, 172.3, 106.8, 89.4, 73.9, 37.6. MS (EI) 154 (M^+, 20%), 136 (8%), 124 (27%), 110 (11%), 96 (52%), 71 (39%), 54 (100%).

(2-(2-Acetoxyethyl)furan-3-yl)methyl Acetate (14). 14 was prepared in 96% yield by acetylating furan **9** with acetic anhydride (K_2CO_3, DMAP in ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 2.0 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 4.92 (s, 2H), 4.27 (t, J = 7.0 Hz, 2H), 3.02 (t, J = 7.0 Hz, 2H), 2.05 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.8, 150.2, 141.4, 116.2, 111.5, 62.3, 57.5, 25.9, 20.9, 20.8. MS (EI) 226 (M^+ < 1%), 184 (2%), 166 (79%), 153 (6%), 137 (8%), 124 (100%), 107 (50%), 95 (51%), 78 (62%), 65 (22%), 55 (13%). HRMS (ESI) calcd for $C_{11}H_{14}O_5$ + Na 249.07304, found 249.07334.

(2-(2-Acetoxyethyl)-2-hydroxy-5-oxo-2,5-dihydrofuran-3-yl) methyl Acetate (15). To a solution of **14** (225 mg, 1.0 mmol) in *t*-BuOH/H_2O (5/1) (5 mL) were added in one portion and at 20 °C $NaClO_2$ (0.3 g, 3.35 mmol) and NaH_2PO_4 (260 mg, 1.7 mmol). The reaction was monitored by TLC, and after 7 h the starting material had disappeared. Ethyl acetate (10 mL) was added, the solvents were evaporated under vacuum, and the residue was washed with acetone (2 × 5 mL). The γ-hydroxybutenolide **15** (227 mg) was isolated after evaporation of the solvents in 88% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (m, 1H), 4.92 (m, 2H), 4.21 (t, J = 6.0 Hz, 2H), 2.39 (m, 1H), 2.13 (s, 3H), 2.10 (m, 1H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.4, 169.0, 164.6, 117.8, 105.5, 59.2, 58.7, 35.7, 20.7, 20.5. MS (EI) 156 (6%), 144 (12%), 138 (14%), 101 (42%), 94 (27%), 84 (70%), 55 (100%). HRMS (ESI) calcd for $C_{11}H_{14}O_7$ + Na 281.06314, found 281.06318.

(*Z*)-Ascladiol Diacetate (16). To a solution of γ-hydroxybutenolide **15** (130 mg, 0.5 mmol) in benzene (5 mL) was added in one portion at 60 °C 4 equiv of P_2O_5 (0.37 g, 2 mmol). After 15 min the reaction mixture was filtered and the solids were washed with ethyl acetate (3 × 3 mL). The residue after the evaporation of the combined solvent extracts was purified by column chromatography (hexane:EtOAc 4:1), affording **16** (99 mg) in 82% yield as a single diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (s, 1H), 5.39 (t, J = 7.0 Hz, 1H), 4.97 (d, J = 1.5 Hz, 2H), 4.85 (d, J = 7.0 Hz, 2H), 2.11 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 169.9, 167.1, 152.5, 148.8, 118.0, 106.3, 58.2, 57.3, 20.6, 20.4. MS (EI) 240 (M^+, 1%), 198 (1%), 180 (21%), 169 (4%), 156 (6%), 138 (100%), 127 (3%), 110 (67%), 93 (10%), 67 (21%), 55 (37%). HRMS (ESI) calcd for $C_{11}H_{12}O_6$ + Na 263.05238, found 263.05261.

(*Z*)-Ascladiol (6-*Z*). Diacetate **16** (60 mg, 0.25 mmol) was added into a suspension of lipase from *Candida cylindracea* (150 mg) in 2 mL of H_2O buffered with NaH_2PO_4. The reaction mixture was stirred at 25 °C and monitored by TLC. After 12 h, the reaction mixture was extracted with ethyl acetate (5 × 5 mL). The combined organic extracts were dried over $MgSO_4$, the organic solvents were removed under vacuum, and the residue was purified by column chromatography (hexane:EtOAc 1:2), to afford 28 mg of (*Z*)-ascladiol (**6-*Z***) in 72% yield. ^{1}H NMR (300 MHz, acetone-d_6) δ 6.18 (s, 1H), 5.54 (t, J = 6.5 Hz, 1H), 4.76 (br s, 1H, −OH), 4.63 (s, 2H), 4.37 (d, J = 6.5 Hz, 2H), 4.30 (br s, 1H, −OH). ^{13}C NMR (75 MHz, acetone-d_6) δ 168.1, 160.4, 147.0, 114.9, 112.0, 56.3, 56.1. MS (EI) 138 ($M^+ - H_2O$, 41%), 124 (2%), 110 (61%), 84 (39%), 68 (63%), 55 (100%).

Isopatulin (3). To solution of (*Z*)-ascladiol **6-*Z*** (25 mg, 0.15 mmol) in a 2 mL mixture of dichloromethane/acetone (3/1) was added activated MnO_2 (265 mg). The resulting slurry was stirred at 20 °C and monitored by TLC. After 30 min the reaction mixture was filtered through a short pad of Celite and the solids were washed with ethyl acetate. The combined organic extracts were concentrated under vacuum and the residue was purified by column chromatography (hexane:EtOAc 1:2), affording 17 mg of aldehyde **17-*Z*** (71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (d, J = 8.0 Hz, 1H), 6.47 (t, J = 1.0 Hz, 1H), 5.60 (d, J = 8.0 Hz, 1H), 4.69 (d, J = 1.0 Hz, 2H). ^{1}H NMR (300 MHz, acetone-d_6) δ 10.21 (d, J = 8.0 Hz, 1H), 6.63 (m, 1H), 5.85 (d, J = 8.0 Hz, 1H), 4.79 (d, J = 1.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 166.1, 159.1, 158.6, 119.2, 106.9, 57.1. MS (EI) 154 (M^+, 1%), 136 ($M^+ - H_2O$, 49%), 123 (19%), 118 (13%), 97 (9%), 69 (100%), 55 (65%). On standing in $CDCl_3$ or acetone-d_6, aldehyde **17-*Z*** slowly isomerizes to isopatulin (**3**) (~25% conversion after 24 h). Irradiation with a 300 W xenon lamp for 2−3 min accelerates substantially the transformation of **17-*Z*** to **3**. Isopatulin is in equilibrium with its open forms **17-*Z*** and **17-*E***, with the lactol form being predominant (> 90%). ^{1}H NMR of isopatulin (300 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.86 (m, 1H), 5.80 (m, 1H), 5.06 (dd, J_1 = 16.5 Hz, J_2 = 2.0 Hz, 1H), 4.74 (dd, J_1 = 16.5 Hz, J_2 = 2.0 Hz, 1H). ^{13}C NMR of isopatulin (75 MHz, $CDCl_3$) δ 168.2, 150.7, 149.4, 110.2, 106.3, 89.4, 57.4. MS (EI) 154 (M^+, 12%), 136 ($M^+ - H_2O$, 29%), 126 (24%), 110 (87%), 97 (23%), 82 (38%), 69 (95%), 55 (100%).

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Supporting Information Available: Copies of ^{1}H, ^{13}C NMR, MS, and HRMS of key compounds and reactions. This material is available free of charge via the Internet at http://pubs.acs.org.