

## Synthesis and Cytotoxicity of a Salicylihalamide A Analogue

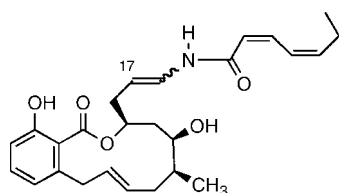
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The synthesis of a simple analogue of salicylihalamide A with a truncated lactone ring ( $\pm 2$ ) was achieved in 10 steps. Its cytotoxicity profile in the NCI 60-cell-line human tumor assay differed significantly from that of salicylihalamide A in both level and specificity.

In 1997, the secondary metabolites salicylihalamides A (**1a**) and B (**1b**) were first isolated from a marine sponge of the genus *Haliclona*.<sup>1</sup> These macrolides possess a novel combination of structural moieties that include a 12-membered salicylate lactone and a highly unsaturated enamide side chain, a feature that had not been found previously in natural products.



Salicylihalamide A: 17E (**1a**)

Salicylihalamide B: 17Z (**1b**)

Salicylihalamide A displayed a unique differential cytotoxicity profile in the NCI 60-cell-line human tumor assay, with the melanoma cell lines showing the highest average sensitivity. COMPARE pattern-recognition analyses of the NCI 60-cell mean graph screening profile<sup>2</sup> of **1a** did not reveal any significant correlations to the profiles of known antitumor compounds in NCI's standard agent database. Further investigation showed that salicylihalamide A is a potent selective inhibitor of mammalian vacuolar ( $H^+$ )-ATPase, the first substance to demonstrate such selectivity.<sup>3</sup>

Discovery of the salicylihalamides was followed by the isolation of a host of other natural products with the common traits of this new benzolactone enamide class but isolated from such diverse sources as bacteria, fungi, myxobacteria, and two different marine animal phyla. Examples include the lobatamides, apicularen A, oximidines I and II, CJ-12950, and CJ-1335,<sup>4</sup> each with the highly unsaturated enamide side chain, the salicylate moiety, and the macrolactone ring, as illustrated in Figure 1 (Z represents a linker of variable length, composition, and stereochemistry).<sup>3</sup>

The first total synthesis of salicylihalamide A was achieved by De Brabander's group<sup>5</sup> and was soon followed by many other total syntheses,<sup>4,6</sup> as well as formal total syntheses<sup>4,7</sup> and analogue syntheses,<sup>4,8</sup> paving the way for structure–activity studies. Necessary elements for biological activity include the enamide side chain with a free NH as well as a free phenolic OH group. Less clear is the role of the macrolactone ring. To explore this question, we undertook the synthesis of a simplified salicylihalamide analogue with a truncated lactone ring, specifically a six-membered ring in place of the 12-membered lactone of the parent compounds.

A convergent process linking the enamide side chain to the salicylate lactone can be envisioned in several ways, as illustrated in Figure 2. In pathway *a* the bond between the amide carbonyl of **2** and its  $\alpha$ -carbon is broken to obtain an isocyanate and a

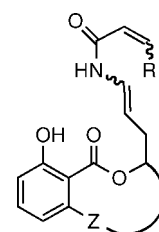


Figure 1. Generic structure of the benzolactone enamides.

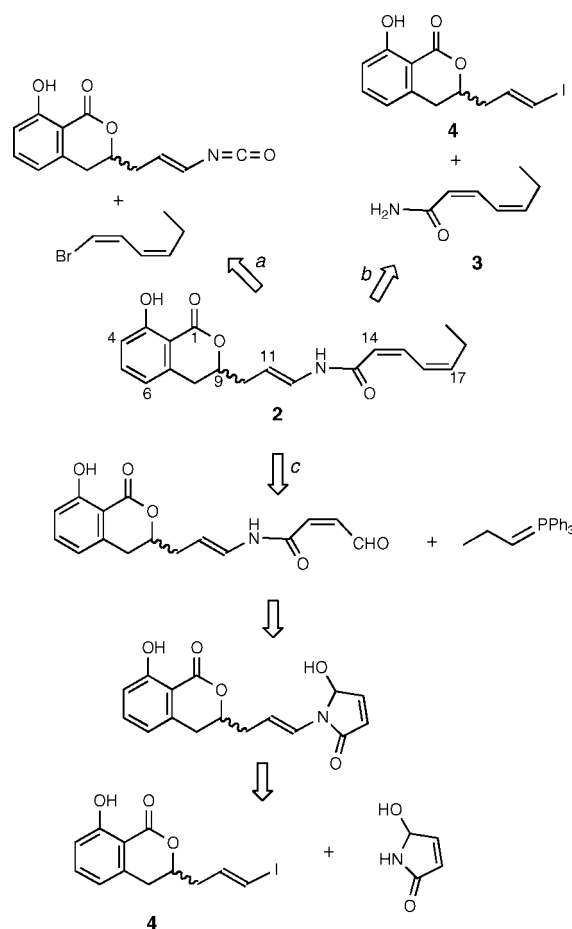
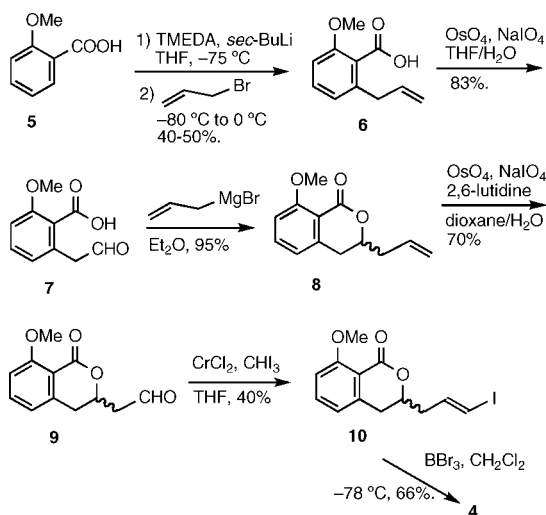


Figure 2. Retrosynthetic analysis for **2**.

hexadienyl halide, an approach similar to that reported in the first total synthesis of salicylihalamide A.<sup>5</sup> In pathway *b* the vinyl C–N bond is disconnected to heptadienoic amide **3** and vinyl iodide **4**. This same bond is also ultimately disconnected in pathway *c*, giving the same vinyl iodide (**4**) as pathway *b*. Here the nitrogen is introduced via the hydroxylactam derived from the reduction of

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## Scheme 1. Synthesis of Salicylate Vinyl Iodide 4



maleimide, a method introduced by Coleman<sup>9</sup> for constructing enamide groups.

In our work, all three pathways were investigated with *a* as the initial choice. However, difficulties were encountered in the synthesis of 1,3-(*Z,Z*)-hexadienyl bromide. Hydrogenation of its precursor, 1-bromo-(*3Z*)-hexen-1-yne, consistently gave very low yields of product. This, together with the inability to successfully couple the hexadienyl bromide to the lactone isocyanate, terminated work on this pathway.

In pathway *c* the coupling reaction of vinyl iodide lactone 4 with the *tert*-butyl dimethylsilyl ether of the hydroxylactam was problematic. Despite the fact that model compounds gave acceptable yields of coupled product, 4 did not under a variety of reaction conditions. More importantly, the subsequent Wittig reaction to attach the terminal propenyl group was completely unsuccessful. Thus, this pathway was also abandoned in favor of pathway *b*.

Scheme 1 illustrates the synthesis of salicylate vinyl iodide 4. Allylation of lithium *o*-anisate represents the most direct route to 6-allyl-2-methoxybenzoic acid (6).<sup>10</sup> Although the yields in this reaction are typically poor, in dilute solution yields of 40–50% were consistently obtained, and with rapid introduction of the lithium reagent, one run actually proceeded in >90% yield.

Oxidative cleavage of the double bond of 6 with osmium tetraoxide/sodium periodate afforded aldehyde 7. Although originally extracted into the ether layer during the reaction workup, once concentrated, aldehyde 7 did not redissolve in common organic solvents. This observation may be explained by a dimerization/polymerization equilibrium depicted in Figure 3.<sup>11</sup> The existence of the cyclic pseudoacid form was evident from the proton NMR, where the methine H was found as a multiplet at  $\delta$  5.8, and the methylene protons at  $\delta$  3.00 (dd,  $J = 16.2, 5.7$  Hz) and 3.22 (dd,  $J = 16.2, 6.6$  Hz).

Aldehyde 7 was converted to allyl lactone 8 in one step upon treatment with allylmagnesium bromide, followed by acidification, which triggered the lactonization. Cleavage of the double bond of

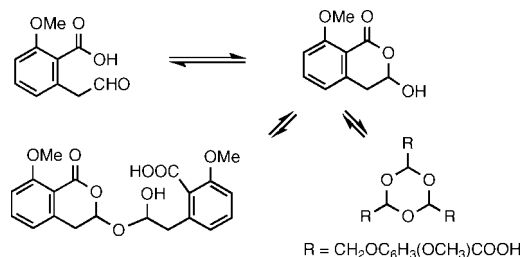
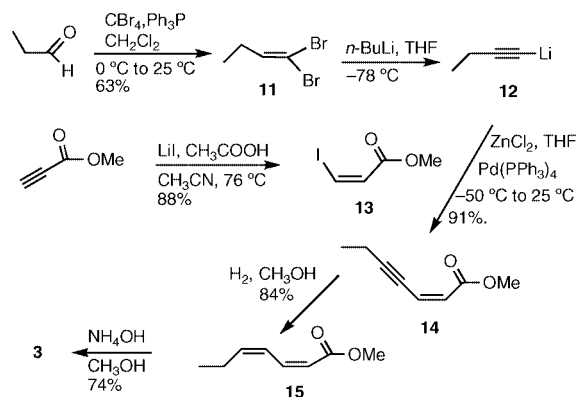


Figure 3. Pseudoacid forms of 7.

## Scheme 2. Synthesis of Dienamide 3



8 was achieved with OsO<sub>4</sub>/NaIO<sub>4</sub> in 2,6-lutidine.<sup>12</sup> The resulting lactone aldehyde (9) was then subjected to Takai's stereoselective one carbon chain elongation reaction<sup>13</sup> followed by demethylation of the phenolic group, affording 4.

The synthesis of (2*Z*,4*Z*)-hepta-2,4-dienamide (3) is depicted in Scheme 2 and parallels the protocol developed by Fürstner et al.<sup>14</sup> and Maier et al.<sup>15</sup> Propionaldehyde was first brominated to give *gem*-dibromide 11.<sup>16</sup> Elimination with *n*-butyllithium generated the terminal acetylide anion (12), which then underwent a Negishi coupling reaction<sup>17</sup> with methyl 3-iodo-(*Z*)-2-propenoate (13)<sup>18</sup> to give enyne ester 14. Classical Lindlar reduction afforded the desired *Z,Z*-diene ester 15. Finally, aminolysis of 15 converted it to amide 3, the synthon needed for coupling with salicylate vinyl iodide 4.

The copper(I)-mediated cross-coupling reaction of vinyl halides and amides to generate enamides<sup>19</sup> was first reported by Ogawa.<sup>20</sup> Porco's group rejuvenated this reaction in their synthetic work on the salicylate macrolides.<sup>21</sup> Liebeskind's copper(I) thiophenecarboxylate (CuTc)<sup>22</sup> was found to be effective in promoting coupling between vinyl iodides and amides to afford enamides with good stereoselectivity. The reaction had to be performed in polar aprotic solvents in the presence of a base, either Cs<sub>2</sub>CO<sub>3</sub> or Rb<sub>2</sub>CO<sub>3</sub>.

Following Porco's work, this methodology found its way into many natural product syntheses including the benzolactone enamides,<sup>14,23</sup> although there have been problems and failures.<sup>24</sup> Other studies have been done in attempts to improve the reaction.<sup>25</sup> In our case, the coupling of 3 and 4, or the *tert*-butyldimethylsilyl derivative of 4, employing Liebeskind's CuTc and Cs<sub>2</sub>CO<sub>3</sub>, was totally unsuccessful. The bases Rb<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, and K<sub>2</sub>CO<sub>3</sub> were effective, but none were superior to the others and yields were consistently very low (around 10%), although model compounds gave modest yields (45–56%). Various reaction conditions were investigated with no significant improvement, leaving the final step in the synthesis of analogue 2 one of very poor conversion.

In the National Cancer Institute's 60-cell-line assay, 2 displayed a cytotoxicity pattern distinctly different from salicylilhalamide A. Analogue 2 showed only modest activity, with the highest level displayed in the leukemia SR cell line (GI<sub>50</sub> = 2  $\mu$ M). Melanoma line SK-Mel-5 displayed a GI<sub>50</sub> of 27  $\mu$ M, and breast cell lines MCF7 and MDA-MB-435 had GI<sub>50</sub> values of 49 and 11  $\mu$ M, respectively. In comparison, salicylilhalamide A showed high selectivity for the melanoma cell lines (range of differential sensitivity  $\geq 10^3$ ) with an average GI<sub>50</sub> in these lines of 7  $\pm$  2 nM.<sup>1</sup> Obviously, features apparently important for cytotoxicity in salicylilhalamide A are missing in 2. In addition to smaller lactone ring size, analogue 2 lacks the ring hydroxyl and methyl substituents as well as its multiple bond. Moreover, 2 is not a single enantiomer. Any one or combination of these differences could alter the level and pattern of cytotoxicity that is displayed by the parent molecule. On their own, the salicylilhalamide A structural features intact in 2 are insufficient for comparable activity.

## Experimental Section

For general experimental procedures see the Supporting Information.

**2-Methoxy-6-(1-oxoethyl) Benzoic Acid (7).** To a solution of **6** (2.13 g, 11 mmol) in THF (66 mL) and H<sub>2</sub>O (22 mL) was added OsO<sub>4</sub> (56 mg, 2 mol%), followed by NaIO<sub>4</sub> (7.31 g, 33 mmol) in 4 portions over 30 min. The mixture was stirred at rt for 1.5 h and then filtered to remove the precipitate, which was washed with EtOAc. The aqueous layer was separated and extracted with EtOAc (3×). The organic extracts were combined, washed with brine, and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed *in vacuo*, and the residue was mixed with CH<sub>2</sub>Cl<sub>2</sub>. The product, an insoluble white solid, was removed by filtration and washed with more CH<sub>2</sub>Cl<sub>2</sub>. The CH<sub>2</sub>Cl<sub>2</sub> filtrate was concentrated and subjected to vacuum liquid chromatography (VLC) on silica gel eluting with EtOAc to obtain additional product (1.79 g total, 83%): IR  $\nu_{\max}$  3363, 3088, 3015, 2969, 2949, 2848, 1699, 1654, 1599, 1585, 1477, 1278, 1241, 1081, 1038, 1003, 929, 792, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (acetone-*d*<sub>6</sub>, 600 MHz)  $\delta$  3.00 (dd, 1H, *J* = 16.2, 5.7 Hz, H-8<sub>b</sub>), 3.22 (1H, dd, *J* = 16.2, 6.6 Hz, H-8<sub>a</sub>), 3.87 (3H, s, OCH<sub>3</sub>), 5.75 (1H, m, H-9), 6.50 (1H, d, *J* = 5.6 Hz, OH), 6.92 (1H, d, *J* = 7.4 Hz, H-6), 7.05 (1H, d, *J* = 8.6 Hz, H-4), 7.51 (1H, dd, *J* = 7.4, 8.6 Hz, H-5); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>)  $\delta$  161.7 (C-1), 160.7 (C-3), 140.4 (C-7), 135.2 (C-5), 121.1 (C-6), 115.2 (C-2), 112.0 (C-4), 95.6 (C-9), 56.3 (OCH<sub>3</sub>), 36.4 (C-8); HREIMS *m/z* 194.0568 (calcd for C<sub>10</sub>H<sub>10</sub>O<sub>4</sub>, 194.0574).

**Allyl Lactone 8.** To a solution of 1.70 g (8.8 mmol) of aldehyde **7** in 40 mL of dry THF cooled in an ice bath was added allyl magnesium bromide (22 mL, 1.0 M in ether). The addition was finished in 20 min, and the reaction mixture was stirred at rt for 24 h. HCl (10%, 17 mL) was added dropwise to the reaction mixture cooled in an ice bath. Stirring was continued for another 24 h. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3×). The organic extracts were combined, washed with brine, and dried over MgSO<sub>4</sub>. After the solvent was removed, the crude product was purified by silica gel VLC eluting with 50% EtOAc/petroleum ether to afford lactone **8** (1.82 g, 95%) as a yellow oil: IR  $\nu_{\max}$  3076, 3009, 2941, 2841, 1728, 1643, 1599, 1585, 1477, 1456, 1439, 1277, 1233, 1086, 1061, 802, 774, 699 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.43 (1H, m, H-8<sub>b</sub>), 2.56 (1H, m, H-8<sub>a</sub>), 2.86 (2H, m, H-10), 3.93 (3H, s, OCH<sub>3</sub>), 4.44 (1H, m, H-9), 5.18 (2H, m, H-12), 5.90 (1H, m, H-11), 6.80 (1H, d, *J* = 7.4 Hz, H-6), 6.92 (1H, d, *J* = 8.6 Hz, H-4), 7.45 (1H, dd, *J* = 8.2, 7.8 Hz, H-5); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  162.6 (C-1), 161.1 (C-3), 141.8 (C-7), 134.5 (C-5), 132.5 (C-11), 119.3 (C-6), 118.6 (C-12), 113.6 (C-2), 110.9 (C-4), 76.9 (C-9), 56.1 (OCH<sub>3</sub>), 38.9 (C-10), 33.7 (C-8); HREIMS *m/z* 218.0938 (calcd for C<sub>13</sub>H<sub>14</sub>O<sub>3</sub>, 218.0937).

**Aldehyde 9.** To a solution of allyl lactone **8** (749 mg, 3.43 mmol) in 32 mL of dioxane/H<sub>2</sub>O (3:1) was added 2,6-lutidine (802  $\mu$ L, 6.84 mmol), OsO<sub>4</sub> (17 mg, 2 mol%), and NaIO<sub>4</sub> (2.93 g, 13.72 mmol, in portions). The suspension was stirred at rt for 1 h, then mixed with 60 mL of H<sub>2</sub>O and filtered. The filtrate was washed with CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was separated and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×). The combined organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was subjected to silica gel VLC eluting with EtOAc to give product **9** (531 mg, 70%) as a yellow oil: IR  $\nu_{\max}$  3100, 3088, 2925, 2847, 2741, 1761, 1723, 1598, 1585, 1478, 1459, 1439, 1278, 1235, 1082, 1061, 804, 777, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  2.73 (1H, dd, *J* = 17.6, 5.9 Hz, H-8<sub>b</sub>), 2.88 (2H, d, *J* = 7.0 Hz, H-10), 2.96 (1H, dd, *J* = 17.6, 6.6 Hz, H-8<sub>a</sub>), 3.83 (3H, s, OCH<sub>3</sub>), 4.84 (1H, quintet, *J* = 7.0 Hz, H-9), 6.72 (1H, d, *J* = 7.4 Hz, H-6), 6.84 (1H, d, *J* = 8.6 Hz, H-4), 7.37 (1H, dd, *J* = 7.4, 8.6 Hz, H-5), 9.73 (1H, s, H-11); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  198.6 (C-11), 161.6 (C-1), 160.9 (C-3), 141.0 (C-7), 134.7 (C-5), 119.2 (C-6), 113.0 (C-2), 111.0 (C-4), 72.2 (C-9), 56.0 (OCH<sub>3</sub>), 47.8 (C-10), 33.9 (C-8); HREIMS *m/z* 220.0732 (calcd for C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>, 220.0730).

**Methyl Ether 10.** Anhydrous CrCl<sub>2</sub> (680 mg, 5.53 mmol) was transferred under an argon atmosphere into a rb flask containing 5 mL of THF. To the slurry was added a solution of aldehyde **9** (203 mg, 0.92 mmol) and iodoform (726 mg, 1.84 mmol) in 9 mL of THF via syringe. The reaction mixture was stirred at rt for 1.5 h. The solution was then mixed with 50 mL of ether and washed with 70 mL of H<sub>2</sub>O. The organic layer was separated, and the aqueous layer was saturated with NaCl and extracted with 30 mL of ether once. All the organic layers were combined, then were washed with brine and dried over MgSO<sub>4</sub>. After solvent removal, the crude product was subjected to VLC on silica gel eluting with 50% EtOAc/petroleum ether to afford **10** (122

mg, 39%) as a colorless syrup: IR  $\nu_{\max}$  3059, 3008, 2939, 2905, 2839, 1763, 1726, 1598, 1584, 1476, 1438, 1278, 1233, 1107, 1085, 1058, 948, 911, 801, 774, 729, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.41 (1H, m, H-8<sub>b</sub>), 2.49 (1H, m, H-8<sub>a</sub>), 2.80 (2H, m, H-10), 3.85 (3H, s, OCH<sub>3</sub>), 4.36 (1H, m, H-9), 6.16 (1H, d, *J* = 14.6 Hz, H-12), 6.53 (1H, dt, *J* = 14.4, 7.3 Hz, H-11), 6.73 (1H, d, *J* = 7.3 Hz, H-6), 6.85 (1H, d, *J* = 8.2 Hz, H-4), 7.38 (1H, dd, *J* = 7.3, 8.2 Hz, H-5); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  162.0 (C-1), 161.0 (C-3), 141.2 (C-7), 140.0 (C-11), 134.6 (C-5), 119.2 (C-6), 113.3 (C-2), 110.9, (C-4), 78.8 (C-12), 75.7 (C-9), 56.1 (OCH<sub>3</sub>), 40.6 (C-10), 33.5 (C-8); HREIMS *m/z* 343.9896 (calcd for C<sub>13</sub>H<sub>13</sub>O<sub>3</sub>I, 343.9904).

**Salicylate Vinyl Iodide 4.** To a solution of methyl ether **10** (76 mg, 0.22 mmol) in 15 mL of CH<sub>2</sub>Cl<sub>2</sub> at -70 °C (2-propanol/dry ice bath) was added BBr<sub>3</sub> (680  $\mu$ L, 1.0 M in CH<sub>2</sub>Cl<sub>2</sub>), and the reaction mixture was stirred for 2 h then brought to rt, added to 50 mL of H<sub>2</sub>O, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×). The combined organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The product, a colorless solid, was obtained in 66% yield as a mixture of stereoisomers, which were separated by preparative TLC (35% EtOAc/petroleum ether) to afford vinyl iodide **4**: *E*-isomer: IR  $\nu_{\max}$  3021, 3055, 2916, 1674, 1617, 1462, 1229, 1207, 1163, 1115, 1039, 949, 807, 657 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz)  $\delta$  2.58 (2H, m, H-8), 2.93 (2H, m, H-10), 4.63 (1H, m, H-9), 6.29 (1H, d, *J* = 14.5 Hz, H-12), 6.64 (1H, dt, *J* = 14.5, 7.4 Hz, H-11), 6.70 (1H, d, *J* = 7.4 Hz, H-6), 6.89 (1H, d, *J* = 8.6 Hz, H-4), 7.42 (1H, dd, *J* = 8.2, 7.6 Hz, H-5), 10.92 (1H, s, OH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  169.5 (C-1), 162.3 (C-3), 139.5 (C-11), 138.9 (C-7), 136.4 (C-5), 118.1 (C-6), 116.5 (C-4), 108.3 (C-2), 79.5 (C-12), 77.7 (C-9), 41.0 (C-10), 32.3 (C-8); *Z*-isomer: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$  2.71 (2H, t, *J* = 6.3 Hz, H-8), 2.98 (2H, m, H-10), 4.72 (1H, td, *J* = 10.6, 6.3 Hz, H-9), 6.46 (2H, m, H-11, H-12), 6.71 (1H, d, *J* = 6.6 Hz, H-6), 6.90 (1H, d, *J* = 8.6 Hz, H-4), 7.42 (1H, dd, *J* = 8.2, 7.8 Hz, H-5), 10.93 (1H, s, OH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  169.6 (C-1), 162.3 (C-3), 139.1 (C-7), 136.4 (C-5), 135.2 (C-11), 118.2 (C-6), 116.5 (C-4), 109.9 (C-2), 86.9 (C-12), 77.9 (C-9), 40.0 (C-10), 32.5 (C-8); HREIMS *m/z* 329.9753 (calcd for C<sub>12</sub>H<sub>11</sub>O<sub>3</sub>I, 329.9747).

**Salicylaldehyde Analogue 2.** A solution of **4** (39 mg, 0.12 mmol) in 2 mL of dioxane was carefully purged with argon for 30 min. The flask was covered with aluminum foil, and CuTc (14 mg, 0.07 mmol), DMEDA (15 mL, 0.14 mmol), diene amide **3** (23 mg, 0.18 mmol), and K<sub>3</sub>PO<sub>4</sub> (51 mg, 0.24 mmol) were introduced. The solution was degassed for another 15 min before the temperature was raised to 90 °C, and stirring was continued for 28 h. The slurry was cooled to rt, diluted with EtOAc, and washed with pH 7 buffer (3×). The aqueous layer was extracted with EtOAc (3×). The organic layers were combined, dried with Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The crude sample was subjected to preparative TLC (50% EtOAc/petroleum ether) to give **2** (2 mg, 5%): <sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>, 600 MHz)  $\delta$  1.03 (3H t, *J* = 7.6 Hz, H-19), 2.30 (2H, quintet, *J* = 7.6 Hz, H-18), 2.56 (2H, m, H-8), 2.99 (2H, m, H-10), 4.63 (1H, m, H-9), 5.37 (1H, dt, *J* = 14.7, 7.0 Hz, H-11), 5.70 (1H, d, *J* = 11.7 Hz, H-14), 5.84 (1H, m, H-17), 6.79 (1H, d, *J* = 7.6 Hz, H-6), 6.84 (1H, d, *J* = 8.2 Hz, H-4), 6.88 (1H, d, *J* = 14.1 Hz, H-12), 6.90 (1H, t, *J* = 11.7 Hz, H-15), 7.31 (1H, t, *J* = 11.4 Hz, H-16), 7.45 (1H, dd, *J* = 8.2, 7.6 Hz, H-5); <sup>13</sup>C NMR (MeOH-*d*<sub>4</sub>)  $\delta$  171.4 (C-1), 165.9 (C-13), 163.2 (C-3), 142.8 (C-17), 141.5 (C-7), 138.0 (C-15), 137.5 (C-5), 127.1 (C-12), 125.3 (C-16), 120.2 (C-14), 119.4 (C-6), 116.8 (C-4), 109.5 (C-2), 108.4 (C-11), 81.1 (C-9), 36.4 (C-10), 33.0 (C-8), 21.5 (C-18), 14.4 (C-19); HRMS *m/z* 328.1541 (M + H) (calcd for C<sub>19</sub>H<sub>21</sub>O<sub>4</sub>N 328.1543).

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**Supporting Information Available:** General experimental procedures, preparation of compounds **3**, **6**, and **11–15**, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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