

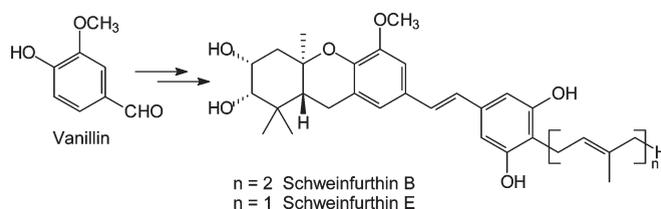
## Total Synthesis of (+)-Schweinfurthins B and E

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The first total synthesis of (+)-schweinfurthin B, a potent and differentially active cytotoxic agent, has been accomplished. Completion of the synthesis required just 16 steps in the longest linear sequence from commercially available vanillin. Key synthetic transformations included a Shi epoxidation and an efficient cascade cyclization initiated by treatment of the resulting epoxide with  $\text{BF}_3 \cdot \text{OEt}_2$ . Furthermore, use of a methyl ether as a stable protecting group for benzylic alcohols dramatically increased the efficiency of the overall sequence. The benzylic ether can be removed from this electron-rich aromatic system through oxidation with DDQ that provided the desired aldehyde intermediate in quantitative yield and shortened the synthetic sequence. Introduction of the A-ring diol in the required cis stereochemistry then became viable through a short sequence highlighted by an aldol condensation with benzaldehyde to introduce an olefin as a latent carbonyl group at the C-3 position. This synthesis established for the first time the absolute stereochemistry of the natural product, and provides access to material on a scale that will advance biological studies. The total synthesis of the closely related compound (+)-schweinfurthin E also is reported.

### Introduction

For some years, our research group has been interested in the schweinfurthins and the closely related compound vedelianin, a small family of isoprene substituted stilbenes (1–9, Figure 1).<sup>1–4</sup> These natural products have been isolated from various *Macaranga* species in small and in some cases not easily reproducible quantities. We became interested in the schweinfurthins because they display significant and differential cytotoxicity based on the National Cancer

Institutes's (NCI) 60-cell line assay.<sup>1</sup> Although compounds are known with greater potency, only the stelletins,<sup>5–7</sup> cephalostatins,<sup>8–11</sup> and OSW-1<sup>12</sup> display a similar pattern of activity in the 60-cell line assay. Furthermore the schweinfurthins do not correlate through the COMPARE statistical analysis<sup>13</sup> to any clinical agent in NCI's standard agent database, which suggests that they attack a new target or have a novel mode of action. At present no mechanism has been determined to account for their biological activity. The

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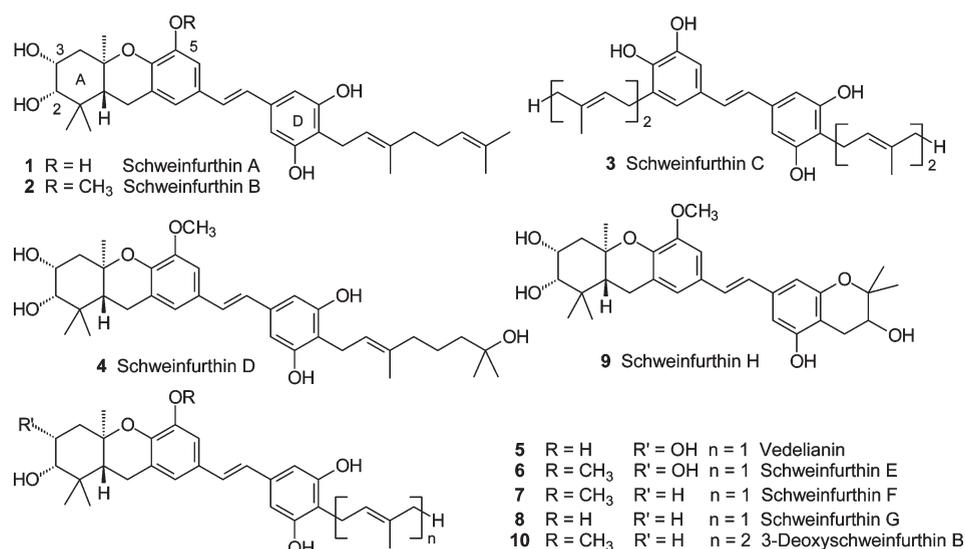
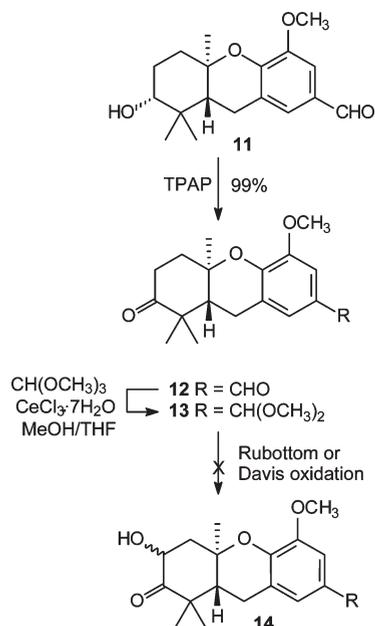


FIGURE 1. The schweinfurthins.

schweinfurthins, which may be the most synthetically accessible of these families, show special potency toward central nervous system-derived cell lines including those from glioblastoma multiforme (e.g., SF-295, < 10 nM GI<sub>50</sub>) for which there is no effective clinical treatment. It is this pattern of selective activity, together with the scarcity of the natural materials, that drove us to initiate studies aimed at the synthesis of the schweinfurthins.

Our group's initial efforts resulted in the synthesis of schweinfurthin C (**3**), the simplest member of the family.<sup>14</sup> This effort demonstrated the utility of a Horner–Wadsworth–Emmons (HWE) condensation for assembly of the central stilbene olefin, and provided intermediates representing the D-ring that have been useful in the preparation of subsequent targets. Expanding on this work, we were able to synthesize the hexahydroxanthene skeleton of the tetracyclic schweinfurthins, initially via an acid-mediated cascade cyclization of a phenylselenide.<sup>15</sup> Unfortunately, while the resulting tricyclic intermediate was obtained as a single diastereomer, it was not easily elaborated to the A-ring diol of a natural product.<sup>15</sup> Further investigation led to use of a similar cascade on an epoxide, mediated first by a Bronsted acid<sup>16</sup> and then by Lewis acid catalysts.<sup>17</sup> These advances provided reasonable quantities of the A-ring alcohol found in 3-deoxyschweinfurthin B (3dSB, **10**) prior to the isolation of schweinfurthins F (**7**) and G (**8**),<sup>16</sup> and thus 3dSB became the lead compound for our biological investigations.<sup>18</sup> Improvements to the original sequence have allowed the preparation of numerous schweinfurthin analogues<sup>19</sup> as well as

### SCHEME 1. Oxidations of Hexahydroxanthenes



schweinfurthin G (**8**) and both enantiomers of schweinfurthin F (**7**).<sup>17,20</sup> Although this work has allowed meaningful SAR studies, the natural schweinfurthins that contain an A-ring diol have as yet eluded total synthesis. Presented here is a detailed description of the first total synthesis of schweinfurthins B (**2**) and E (**6**), which both contain the key A-ring diol. Apart from providing access to material on a scale that the natural source of schweinfurthin B has not been able to deliver, the present studies establish the absolute stereochemistry of these intriguing natural products.

### Results and Discussion

Once the hexahydroxanthene core of the schweinfurthins was obtained via cascade cyclization,<sup>17</sup> access to the natural

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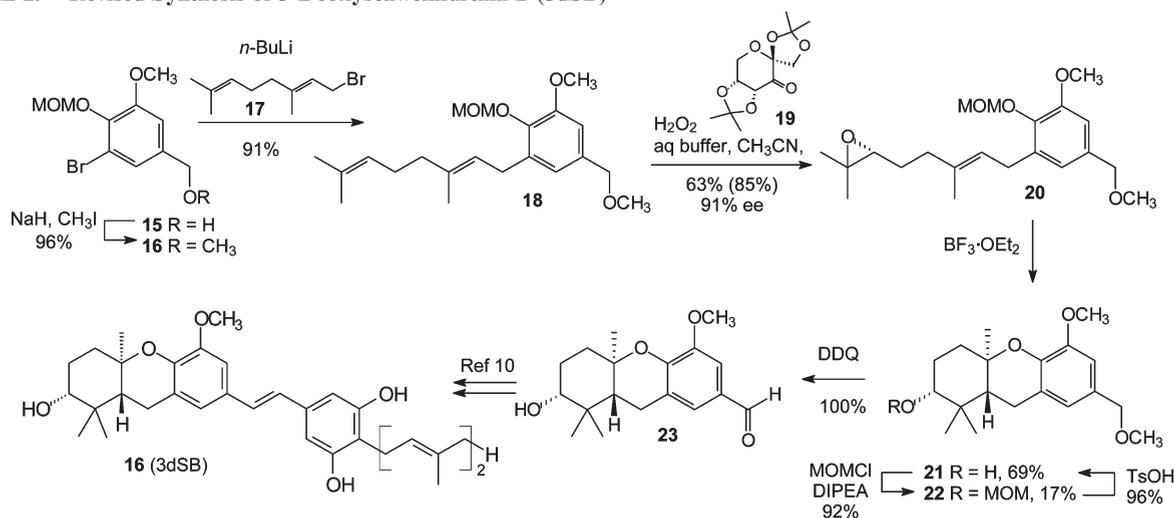
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## SCHEME 2. Revised Synthesis of 3-Deoxyschweinfurthin B (3dSB)

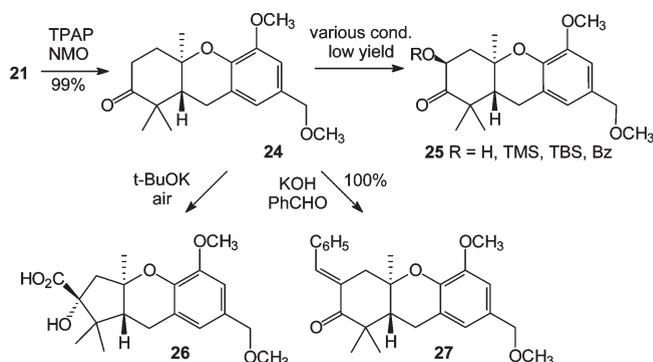


A-ring diols could have been pursued either through oxidation of a tricyclic intermediate or via a parallel cascade process that employed a more oxidized substrate. Because the trans ring fusion and absolute stereochemistry of the hexahydroxanthenes had been verified by our earlier syntheses, we chose to pursue oxidation of the tricyclic compounds and began with studies of the key intermediate **11** (Scheme 1). At the outset of these studies, this compound was available via our previous work in 12 total steps from vanillin.<sup>16,17,21</sup>

Treatment of aldehyde **11** with TPAP<sup>22</sup> gave the crystalline ketone **12** in excellent yield, and once suitable crystals were obtained a diffraction analysis was secured. Oxidation of the C-3 position of keto aldehyde **12** was attempted under conditions developed by Davis,<sup>23,24</sup> but in all cases (with LDA, LiHMDS, or NaHMDS as the base) there was no evidence for formation of an acyloin product and significant quantities of starting material were recovered. To avoid the possibility of competitive aldol processes, the aldehyde group of compound **12** was protected under Luche conditions<sup>25</sup> as its dimethyl acetal **13**, and this product then was subjected to Rubottom<sup>26–28</sup> and Davis conditions. Again, no evidence for acyloin **14** was observed. At this stage it became evident that a more efficient synthesis of the hexahydroxanthene core would be desirable to support further attempts at oxidation of the C-3 position, and this became the immediate goal.

An apparently trivial change in the protecting group strategy had a dramatic impact on the efficiency of the central reaction sequence. The elegant work of Danishefsky<sup>29,30</sup>

## SCHEME 3. Oxidations of Ketone 24



suggested use of a benzyl methyl ether as a masked benzaldehyde in place of the TBS ether employed as a protecting group in our previous work.<sup>17</sup> This modification dramatically improved material throughput, cost effectiveness, and atom economy. The new sequence (Scheme 2) began with benzyl alcohol **15**, which itself was available in 3 steps and 94% overall yield from vanillin.<sup>15,16</sup> Methylation via a Williamson ether synthesis provided compound **16**, which was then exposed to *n*-BuLi to induce halogen–metal exchange. Reaction of the resulting aryl anion with geranyl bromide (**17**) furnished intermediate **18** in excellent overall yield. The methyl ether **18** was much more easily purified by column chromatography than the corresponding TBS analogues, which allowed preparation of this intermediate on a 5- to 10-g scale.

Compound **18** was epoxidized under Shi's conditions with the sugar derivative **19**.<sup>21,31</sup> This protocol consistently produced epoxide **20** in greater than 90% ee as determined by HPLC. Although the yield for this step was modest, significant quantities of starting material were recovered and could be recycled, which makes the yield based on recovered starting material more attractive (85%). As anticipated,<sup>17</sup> cyclization of epoxide **20** occurred upon brief exposure to  $\text{BF}_3 \cdot \text{OEt}_2$  and produced a mixture of compounds **21** and **22** in excellent overall yield. The formation of this mixture was

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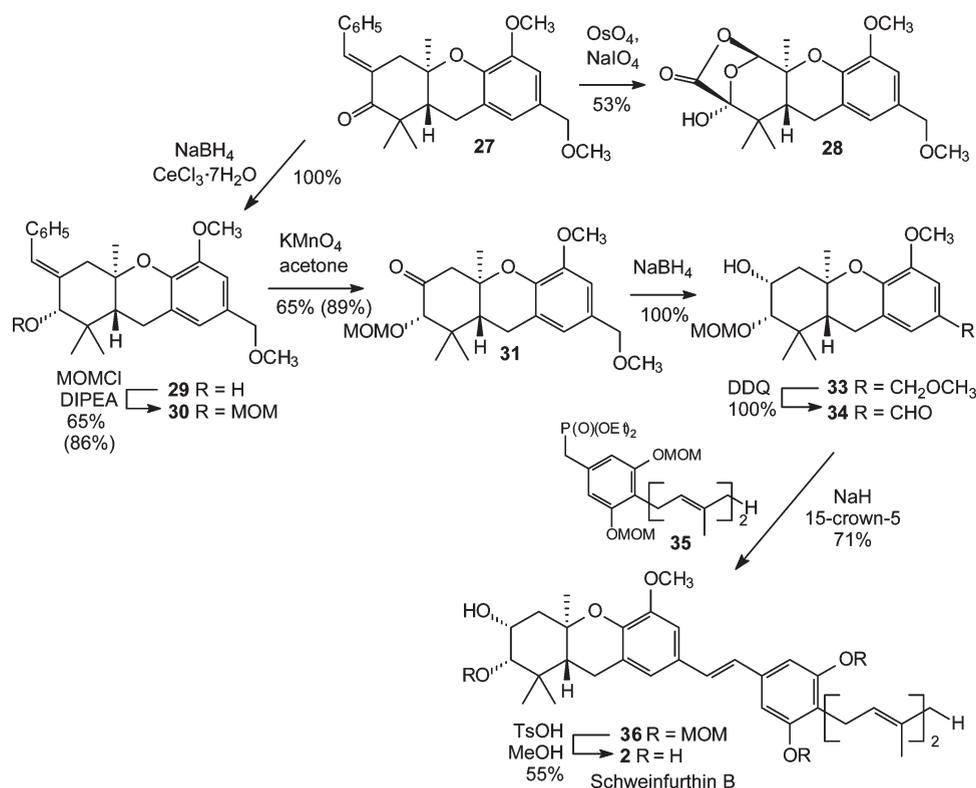
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## SCHEME 4. Formation of an A-Ring Diol and Synthesis of Schweinfurthin B



of little consequence because compounds **21** and **22** could be interconverted in excellent yield and both are useful intermediates.<sup>17</sup> A final DDQ oxidation of compound **21** proceeded in quantitative yield to produce aldehyde **23**, simplifying the previously established desilylation/oxidation sequence into a single step. Preparation of intermediate **23**, now available in much improved yield and in just 8 total steps from commercial vanillin,<sup>19,20</sup> intersected our previous efforts and thus constituted a formal synthesis of both 3-deoxyschweinfurthin B (**10**)<sup>16</sup> and schweinfurthin F (**7**).<sup>17</sup>

To continue efforts aimed at schweinfurthin B, hexahydroxanthene **21** was oxidized under Ley's conditions<sup>22</sup> to afford ketone **24** in excellent yield (Scheme 3). Ketone **24** then served as a platform for numerous oxidations. The Rubottom approach was explored by using the more reactive silyl triflates to encourage enol ether formation.<sup>32,33</sup> Even so, conversion to the silyl enol ether was incomplete (~60%), as observed by <sup>1</sup>H NMR analysis of a reaction conducted in CD<sub>2</sub>Cl<sub>2</sub> or by analysis of the initial product mixture. When this mixture was treated with mCPBA, the best result obtained was a 9% isolated yield of acyloin **25**. Attempted MoOPH oxidation<sup>34</sup> of ketone **24** afforded only recovered starting material. Attempted use of the recent procedure of Tomkinson,<sup>35</sup> based on treatment of a ketone with *N*-methyl-*O*-benzoylhydroxylamine and rearrangement to the  $\alpha$ -benzyloxy compound, also failed even though it worked superbly on

our model systems. When more forcing conditions were attempted with this oxidation, only decomposition was observed. In hindsight, the intransigence of this ketone to oxidation is consistent with the difficulty observed upon attempted oxidation of an A-ring olefin.<sup>15</sup> Ketone **24** proved to be more reactive to oxidation by O<sub>2</sub> under basic conditions,<sup>35</sup> but in this case the only isolated product had undergone rearrangement to an acid tentatively assigned structure **26**, a product similar to one observed by Danishefsky.<sup>36</sup>

The limited success of direct methods for oxidation of ketone **24** drove us to consider less straightforward strategies for preparation of the cis A-ring diol. Furthermore, even if the yield to compound **25** could be improved, obtaining the desired diol stereoisomer from this compound might require a lengthy reaction sequence. Reduction of a C-2 ketone favored the equatorial alcohol in the 3dSB series, and the diffraction analysis of compound **12** suggested that reduction also would occur cleanly from the less hindered face. Therefore, a stepwise approach where reduction of a C-2 ketone was followed by reduction of a C-3 ketone to introduce that axial alcohol appeared to be promising. Indeed, a literature precedent involving reduction of a triterpene with an A-ring  $\alpha$ -diketone was very encouraging.<sup>37</sup> However, given that attempted oxidation of ketone **24** to an A-ring diketone was not straightforward, an approach based on use of an aldol condensation to generate a latent carbonyl group in the form of an exocyclic olefin at C-3 was examined.<sup>38,39</sup> After some experimentation, it was discovered that brief

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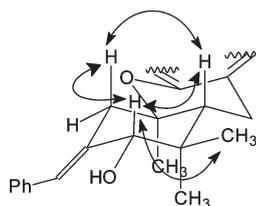


FIGURE 2. Key NOE correlations for alcohol **29**.

exposure of ketone **24** to benzaldehyde and base in ethanol produced enone **27** in quantitative yield. The availability of this enone allowed exploration of a variety of strategies for formation of a 3-keto compound.

One might reasonably assume that the limited functionality of enone **27** would enable straightforward oxidation of the exocyclic olefin (Scheme 4). However, direct treatment of compound **27** with  $\text{OsO}_4/\text{NaIO}_4$ <sup>40</sup> gave the complex acetal **28** as the sole product. Compound **28** may result from formation of the desired  $\alpha$ -diketone followed by overoxidation of the corresponding enol form, similar to observations by Sejbal<sup>41</sup> and Hanson.<sup>42</sup> To circumvent this problem, a more stepwise approach was pursued. Reduction of the  $\alpha,\beta$ -unsaturated ketone **27** under Luche conditions<sup>43,44</sup> afforded alcohol **29** with the desired configuration at the C-2 position as evidenced by key NOESY correlations (Figure 2). To stay any potential side reactions, the hindered alcohol **29** was protected as a MOM acetal, under forcing conditions to afford compound **30** in moderate yield, albeit a significant amount of starting material also could be recovered. Initial attempts at oxidative cleavage of the olefin via reaction with  $\text{OsO}_4/\text{NaIO}_4$ <sup>40</sup> did provide a modest yield of ketone **31** (32%) along with a significant amount of diol **32** (26%, Figure 3). Addition of excess  $\text{NaIO}_4$ , use of longer reaction time, and application of a higher reaction temperature all failed to effect a complete conversion. However, the use of a more active oxidant in excess ( $\text{KMnO}_4$ , 10 equiv)<sup>45</sup> did provide a satisfactory yield of the desired ketone **31** along with significant quantities of recovered starting material even after prolonged exposure. It is worth noting that attempted ozonolysis of intermediates **27**, **29**, and **30** under both standard and modified<sup>46</sup> conditions produced only complex mixtures.

With ketone **31** in hand, the remainder of the synthesis proceeded smoothly. Ketone **31** was reduced upon treatment with  $\text{NaBH}_4$  in quantitative yield to afford alcohol **33** as the only observed diastereomer.<sup>37</sup> The relative stereochemistry of the C-3 center was assigned based on coupling constants: H-3 appears as an apparent quartet with  $J = 3.2$  Hz. Exposure of compound **33** to DDQ afforded aldehyde **34** directly from the methyl ether. Aldehyde **34** then was coupled to known phosphonate **35**<sup>14</sup> under standard HWE conditions to yield stilbene **36**. Finally, acidic hydrolysis of the three MOM acetals under standard conditions<sup>20</sup>

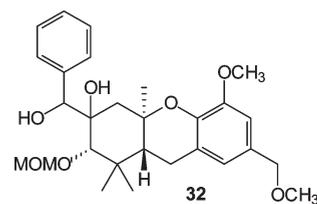
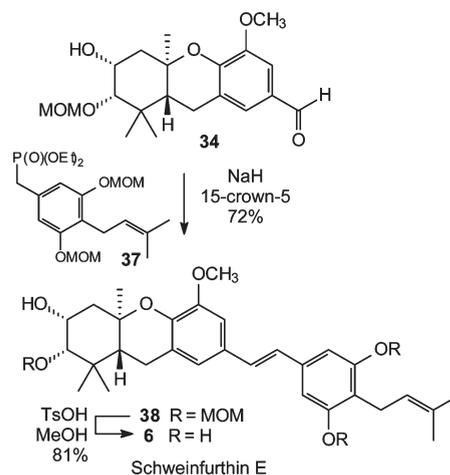


FIGURE 3. Intermediate diol **32**.

### SCHEME 5. Synthesis of Schweinfurthin E



provided schweinfurthin B (**2**) in moderate yield. Synthetic schweinfurthin B proved to be identical with an authentic sample of the natural material in all respects,<sup>1</sup> including specific rotation after correction for the known ee of the synthetic material.

One key advantage of the convergent approach to the schweinfurthins we have developed is that both the left and right half subunits can be employed in a divergent fashion to afford multiple products efficiently. In this vein, aldehyde **34** also was coupled with phosphonate **37**<sup>20</sup> (Scheme 5) to produce stilbene **38**. Deprotection of compound **38** afforded schweinfurthin E (**6**) in excellent yield. Synthetic schweinfurthin E prepared in this fashion displayed identical <sup>1</sup>H NMR and <sup>13</sup>C NMR data, and a specific rotation very similar to that reported for the natural material.<sup>2</sup>

In conclusion, we have successfully synthesized the natural antipode of schweinfurthins B and E via a Shi epoxidation/cascade cyclization sequence. Although attempts at direct  $\alpha$ -oxidation of some hexahydroxanthene intermediates were not productive, it was possible to develop a reaction sequence based on a classic aldol condensation. A subsequent oxidation/reduction sequence furnished the desired cis 2,3-dihydroxyhexahydroxanthene. This synthesis has determined the absolute stereochemistry of both schweinfurthin B and E for the first time. Now that this route to the natural A-ring diols has been established, future efforts can focus on the synthesis of schweinfurthin A (**1**) and should be straightforward given our past synthesis of schweinfurthin G (**8**).<sup>10</sup> In addition, aldehyde **34** can be used as a point of divergence to continue exploration of the schweinfurthins' essential pharmacophore as well as the mechanism(s) responsible for their biological activity. Our efforts along these lines will be reported in due course.

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## Experimental Section

**Methyl Ether 16.** To a solution of the known benzyl alcohol **15**<sup>21</sup> (4.42 g, 15.9 mmol) in THF at 0 °C was added NaH (1.2 g, 60% in oil, 30 mmol) followed by CH<sub>3</sub>I (1.5 mL, 24 mmol). After 3 h the reaction was quenched by addition of water. The resulting solution was extracted with ethyl acetate, and the organic extract was washed with brine. After the organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo, final purification by column chromatography (3:1 hexanes/ethyl acetate) afforded methyl ether **16** (4.84 g, 96%) as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.06 (s, 1H), 6.82 (s, 1H), 5.12 (s, 2H), 4.31 (s, 2H), 3.80 (s, 3H), 3.60 (s, 3H), 3.33 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 153.6, 142.8, 135.8, 124.1, 117.7, 111.0, 98.8, 73.9, 58.4, 58.1, 56.2; HRMS (ESI) *m/z* calcd for C<sub>11</sub>H<sub>15</sub>O<sub>4</sub>Br (M<sup>+</sup>) 290.0154, found 290.0157.

**Geranyl Arene 18.** To a solution of methyl ether **16** (2.0 g, 6.9 mmol) in THF at -78 °C was added *n*-BuLi (3.0 mL, 2.5 M in hexanes) over 5 min. After ~30 min geranyl bromide (**17**, 1.5 mL, 7.9 mmol) was added dropwise. The solution was kept cold for 50 min and quenched by addition of water. The resulting solution was extracted with ethyl acetate, and the combined organic phases were washed with brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. Final purification by column chromatography (9:1 hexanes/ethyl acetate) afforded arene **18** (2.2 g, 91%) as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.78 (s, 1H), 6.73 (s, 1H), 5.32 (t, *J* = 7.2 Hz, 1H), 5.13–5.10 (m, 1H), 5.07 (s, 2H), 4.37 (s, 2H), 3.84 (s, 3H), 3.59 (s, 3H), 3.43 (d, *J* = 7.2 Hz, 2H), 3.38 (s, 3H), 2.12–2.02 (m, 4H), 1.71 (s, 3H), 1.69 (s, 3H), 1.60 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 152.1, 143.3, 136.0, 135.5, 134.0, 131.2, 124.2, 122.6, 121.0, 109.3, 98.8, 74.6, 58.0, 57.3, 55.6, 39.6, 28.2, 26.5, 25.6, 17.6, 16.0; HRMS (ESI) *m/z* calcd for C<sub>21</sub>H<sub>32</sub>O<sub>4</sub> (M<sup>+</sup>) 348.2301, found 348.2309.

**Epoxide 20.** To a solution of arene **18** (2.8 g, 8.0 mmol) and Shi's catalyst (**19**, 590 mg, 2.1 mmol) in aq buffer (30 mL, 2 M K<sub>2</sub>CO<sub>3</sub> and 4 mM EDTA) and organic phase (50 mL, 1:1:1 CH<sub>2</sub>Cl<sub>2</sub>/MeCN/EtOH) at 0 °C was added hydrogen peroxide (7 mL, 30%) over 7 h. After an additional 2 h the reaction was quenched by addition of aq Na<sub>2</sub>SO<sub>3</sub>. The resulting solution was extracted with ethyl acetate, and the combined organic phases were washed with brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. Final purification by column chromatography (4:1 hexanes/ethyl acetate) afforded recovered starting material (0.62 g, 22%) and epoxide **20** (1.84 g, 63%) as a colorless oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.75 (s, 1H), 6.69 (s, 1H), 5.34 (t, *J* = 7.1 Hz, 1H), 5.04 (s, 2H), 4.34 (s, 2H), 3.81 (s, 3H), 3.55 (s, 3H), 3.40 (d, *J* = 7.1 Hz, 2H), 3.35 (s, 3H), 2.68 (t, *J* = 6.3 Hz, 1H), 2.31–2.08 (m, 2H), 1.71 (s, 3H), 1.68–1.63 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 152.0, 143.2, 135.2, 135.0, 134.0, 123.1, 120.8, 109.3, 98.7, 74.5, 64.0, 58.2, 58.0, 57.3, 55.5, 36.2, 28.2, 27.2, 24.7, 18.6, 16.0; HRMS (ESI) *m/z* calcd for C<sub>21</sub>H<sub>32</sub>O<sub>5</sub> (M<sup>+</sup>) 364.2250, found 364.2262.

**Tricyclic Ether 21.** To a solution of epoxide **20** (958 mg, 2.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (350 mL) at -78 °C was added BF<sub>3</sub>·OEt<sub>2</sub> (2.0 mL, 16 mmol). After 7 min the reaction was quenched by addition of TEA (4.1 mL, 29 mmol). The resulting solution was concentrated in vacuo, dissolved in CH<sub>2</sub>Cl<sub>2</sub>, and washed with water then brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. Final purification by column chromatography (1:1 hexanes/ethyl acetate) afforded desired tricyclic ether **21** (583 mg, 69%) as a yellow oil: [α]<sub>D</sub><sup>26.4</sup> +122 (*c* 1.3, CH<sub>3</sub>OH, 92% ee by HPLC); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.69 (s, 1H), 6.67 (s, 1H), 4.33 (s, 2H), 3.83 (s, 3H), 3.38 (s, 3H), 3.38–3.33 (m, 1H), 2.70–2.67 (m, 2H), 2.13–2.04 (m, 1H), 1.87–1.76 (m, 3H), 1.68–1.57 (m, 2H), 1.24 (s, 3H), 1.06 (s, 3H), 0.85 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 148.7, 142.1, 129.0, 122.3, 121.3, 109.0, 77.8, 76.7, 74.9, 58.0, 55.9, 46.6, 38.3, 37.6, 28.2, 27.3, 23.0, 19.7, 14.2; HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>28</sub>O<sub>4</sub> (M<sup>+</sup>) 320.1988, found

320.1991. The MOM acetal **22** (140 mg, 17%) also was isolated from this reaction mixture: [α]<sub>D</sub><sup>26.4</sup> +34.8 (*c* 1.56, CH<sub>3</sub>OH, 92% ee by HPLC); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.67 (s, 1H), 6.66 (s, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.31 (s, 2H), 3.82 (s, 3H), 3.40 (s, 3H), 3.36 (s, 3H), 3.24 (dd, *J* = 11.5, 4.2 Hz, 1H), 2.68–2.65 (m, 2H), 2.12–2.07 (m, 1H), 1.98–1.93 (m, 1H), 1.78–1.53 (m, 3H), 1.21 (s, 3H), 1.05 (s, 3H), 0.87 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 148.6, 142.0, 128.9, 122.2, 121.1, 108.9, 96.0, 83.9, 76.6, 74.8, 57.8, 55.8, 55.5, 46.8, 38.1, 37.4, 27.2, 25.1, 22.9, 19.6, 15.0; HRMS (ESI) *m/z* calcd for C<sub>21</sub>H<sub>32</sub>O<sub>5</sub> (M<sup>+</sup>) 364.2250, found 364.2256.

**Aldehyde 23.**<sup>16</sup> To a solution of tricyclic ether **21** (36 mg, 0.11 mmol) in CH<sub>2</sub>Cl<sub>2</sub>/water (10:1) at rt was added DDQ (67 mg, 0.30 mmol), and after 75 min the reaction was quenched by addition of NaHCO<sub>3</sub>. The resulting solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic phases were washed with brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo. Final purification by column chromatography (1:1 hexanes/ethyl acetate) afforded tricyclic aldehyde **23** (34 mg, 100%) as a yellow wax. The spectroscopic data and reactivity of this material were identical with those of aldehyde **23** prepared via different methods.<sup>16</sup>

**Ketone 24.** To a solution of tricyclic ether **21** (119 mg, 0.28 mmol) in CH<sub>2</sub>Cl<sub>2</sub> at rt was added TPAP (9 mg, 0.03 mmol) and NMO (49 mg, 0.41 mmol). After 18.5 h the reaction mixture was diluted with ethyl acetate, filtered through Celite, and concentrated in vacuo. Final purification by column chromatography (2:3 hexanes/ethyl acetate) afforded ketone **24** (117 mg, 99%) as a colorless oil: [α]<sub>D</sub><sup>26.4</sup> 91.8 (*c* 1.1, CH<sub>3</sub>OH, 92% ee by HPLC); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.72 (s, 1H), 6.70 (s, 1H), 4.34 (s, 2H), 3.85 (s, 3H), 3.39 (s, 3H), 2.81 (dd, *J* = 16.0, 13.6 Hz, 1H), 2.73–2.63 (m, 2H), 2.48 (ddd, *J* = 18.5, 4.7, 3.2 Hz, 1H), 2.37 (ddd, *J* = 13.1, 5.7, 3.2 Hz, 1H), 2.16 (dd, *J* = 14.4, 4.7 Hz, 1H), 2.07 (dd, *J* = 13.0, 4.9 Hz, 1H), 1.43 (s, 3H), 1.20 (s, 3H), 1.11 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 213.6, 148.8, 141.8, 129.6, 121.5, 121.0, 109.2, 75.6, 74.8, 58.0, 55.9, 47.4, 46.4, 38.0, 35.2, 24.5, 23.7, 20.8, 19.0; HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>26</sub>O<sub>4</sub> (M<sup>+</sup>) 318.1831, found 318.1812.

**Enone 27.** To a solution of ketone **24** (152 mg, 0.48 mmol) in ethanol at rt was added benzaldehyde (0.2 mL, 1.7 mmol) followed by KOH (209 mg, 3.7 mmol). After 2 h the reaction was quenched by addition of NH<sub>4</sub>Cl, the resulting solution was extracted with ethyl acetate, and the combined organic extract was washed with brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated in vacuo. Final purification of the residue by column chromatography (3:1 hexanes/ethyl acetate) afforded enone **27** (194 mg, 100%) as a colorless oil: [α]<sub>D</sub><sup>26.4</sup> 201 (*c* 1.0, CHCl<sub>3</sub>, 92% ee by HPLC); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.63 (d, *J* = 3.2 Hz, 1H), 7.45–7.33 (m, 5H), 6.74 (d, *J* = 1.2 Hz, 1H), 6.71 (m, 1H), 4.35 (s, 2H), 3.86 (s, 3H), 3.55 (d, *J* = 15.6 Hz, 1H), 3.39 (s, 3H), 3.00 (dd, *J* = 15.6, 2.8 Hz, 1H), 2.81–2.71 (m, 2H), 2.35 (dd, *J* = 12.4, 5.2 Hz, 1H), 1.32 (s, 3H), 1.21 (s, 3H), 1.17 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 205.0, 148.5, 141.5, 138.6, 135.0, 132.3, 130.0 (2C), 129.5, 128.6, 128.3 (2C), 121.2, 120.8, 109.3, 75.4, 74.6, 57.8, 55.9, 45.9, 45.3, 41.7, 28.7, 24.2, 22.3, 19.0; HRMS (ESI) *m/z* calcd for C<sub>26</sub>H<sub>30</sub>O<sub>4</sub> (M<sup>+</sup>) 406.2144, found 406.2135.

**Alcohol 29.** To a solution of ketone **27** (1.75 g, 4.3 mmol) in CH<sub>3</sub>OH at rt was added CeCl<sub>3</sub>·7H<sub>2</sub>O (1.81 g, 4.9 mmol) followed by NaBH<sub>4</sub> (300 mg, 7.9 mmol). After 20 min, the reaction was quenched by addition of water and concentrated in vacuo. The resulting solution was extracted with ethyl acetate, and the combined extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated in vacuo, to afford alcohol **29** (1.75 g, 100%) as white crystals. This material was used in the next step without further purification: [α]<sub>D</sub><sup>26.4</sup> 45.3 (*c* 1.0, CHCl<sub>3</sub>, 92% ee by HPLC); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.33–7.21 (m, 5H), 6.77 (s, 1H), 6.68–6.67 (m, 2H), 4.32 (s, 2H), 3.91 (s, 1H), 3.81 (s, 3H), 3.39 (s, 3H), 3.36 (d, *J* = 7.2 Hz, 1H), 2.72–2.60

(m, 2H), 2.29 (d,  $J = 12.8$  Hz, 1H), 1.90 (dd,  $J = 11.6, 5.6$  Hz, 1H), 1.19 (s, 3H), 1.04 (s, 3H), 0.83 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  148.7, 142.2, 138.2, 137.4, 129.2, 128.8 (2C), 128.2 (2C), 126.4, 124.0, 122.2, 121.3, 109.1, 80.0, 78.1, 74.9, 58.0, 55.9, 47.2, 41.2, 39.7, 27.3, 23.2, 19.8, 14.2; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{26}\text{H}_{32}\text{O}_4$  ( $\text{M}^+$ ) 408.2301, found 408.2295. Images of the NOSEY and COSEY spectra are included in the SI.

**Arene 30.** To a solution of alcohol **29** (236 mg, 0.58 mmol) in  $\text{CH}_2\text{Cl}_2$  at rt was added DIPEA (0.4 mL, 2.3 mmol) followed by MOMCl (0.1 mL, 1.3 mmol). After 15 h, the reaction was quenched by addition of water. The resulting solution was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic phases were washed with 1 N HCl followed by brine. The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. Final purification by column chromatography (4:1 hexanes/ethyl acetate) afforded recovered starting material (42 mg, 18%) and the MOM acetal **30** (262 mg, 68%) as a colorless oil:  $[\alpha]^{26.4}_{\text{D}}$  21.7 ( $c$  1.1,  $\text{CHCl}_3$ , 92% ee by HPLC);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.34–7.19 (m, 5H), 6.68–6.67 (m, 3H), 4.78 (d,  $J = 6.8$  Hz, 1H), 4.70 (d,  $J = 7.2$  Hz, 1H), 4.33 (s, 2H), 3.99 (d,  $J = 1.2$  Hz, 1H), 3.82 (s, 3H), 3.45 (s, 3H), 3.40 (d,  $J = 10.8$  Hz, 1H), 3.38 (s, 3H), 2.73–2.67 (m, 2H), 2.29 (d,  $J = 12.4$  Hz, 1H), 1.95 (dd,  $J = 12.4, 5.6$  Hz, 1H), 1.21 (s, 3H), 1.01 (s, 3H), 0.88 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  148.7, 142.2, 137.3, 135.1, 129.3, 128.8 (2C), 128.2 (2C), 126.4, 124.9, 122.3, 121.2, 109.0; 96.2, 85.6, 78.2, 74.8, 58.0, 56.4, 55.9, 47.4, 41.4, 39.6, 27.3, 23.2, 19.6, 15.0; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{36}\text{O}_5$  ( $\text{M}^+$ ) 452.2563, found 452.2561.

**Ketone 31.** To a solution of compound **30** (35 mg, 0.08 mmol) in acetone was added  $\text{NaHCO}_3$  (14 mg, 0.17 mmol) followed by  $\text{KMnO}_4$  (23 mg, 0.15 mmol). After 20 h at rt, additional  $\text{NaHCO}_3$  (70 mg, 0.83 mmol) and  $\text{KMnO}_4$  (20 mg, 0.13 mmol) were added. After an additional 24 h at rt, the reaction mixture was filtered through Celite, washed with acetone, and concentrated in vacuo. Final purification by column chromatography (3:1 hexanes/ethyl acetate) afforded recovered starting material (8 mg, 23%) and ketone **31** (19 mg, 65%) as a colorless oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.73 (s, 1H), 6.71 (s, 1H), 4.73 (d,  $J = 7.2$  Hz, 1H), 4.70 (d,  $J = 7.2$  Hz, 1H), 4.36 (s, 2H), 4.14 (s, 1H), 3.86 (s, 3H), 3.44 (s, 3H), 3.40 (s, 3H), 3.00–2.78 (m, 4H), 2.34 (dd,  $J = 12.4, 5.6$  Hz, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 0.88 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  206.4, 150.0, 142.8, 131.2, 122.9, 122.2, 110.5, 97.4, 87.4, 79.6, 75.9, 59.2, 57.8, 57.4, 55.0, 48.4, 42.0, 28.3, 24.4, 21.8, 16.8; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{30}\text{O}_6$  ( $\text{M}^+$ ) 378.2049, found 378.2042.

**Alcohol 33.** To a solution of ketone **31** (18 mg, 0.05 mmol) in  $\text{CH}_3\text{OH}$  at rt was added  $\text{NaBH}_4$  (24 mg, 0.66 mmol). After 10 min, the reaction was quenched by addition of water and concentrated in vacuo. The resulting solution was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated in vacuo. This afforded alcohol **33** (18 mg, 100%) as a white solid, which was used in the subsequent step without further purification:  $[\alpha]^{26.4}_{\text{D}}$  22.2 ( $c$  1.1,  $\text{CH}_3\text{OH}$ , 92% ee by HPLC);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.70 (s, 1H), 6.68 (s, 1H), 4.82 (d,  $J = 6.4$  Hz, 1H), 4.70 (d,  $J = 7.2$  Hz, 1H), 4.34 (s, 2H), 4.31 (ddd,  $J = 3.2, 3.2, 3.2$  Hz, 1H), 3.85 (s, 3H), 3.45 (s, 3H), 3.38 (s, 3H), 3.26 (d,  $J = 3.2$  Hz, 1H), 2.77–2.60 (m, 2H), 2.54 (dd,  $J = 14.0, 3.6$  Hz, 1H), 2.36 (br d, 1H), 1.96 (dd,  $J = 14.4, 3.6$  Hz, 1H), 1.77 (dd,  $J = 12.8, 5.2$  Hz, 1H), 1.45 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  148.9, 141.8, 129.1, 122.6, 121.2, 109.2, 96.9, 84.9, 76.2, 74.9, 68.7, 57.9, 56.1, 56.0, 47.1, 42.3, 37.8, 28.7, 22.9, 21.4, 16.6; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{32}\text{O}_6$  ( $\text{M}^+$ ) 380.2199, found 380.2183.

**Aldehyde 34.** To a solution of methyl ether **33** (50 mg, 0.13 mmol) in  $\text{CH}_2\text{Cl}_2$ /water (4:1) at rt was added DDQ (34 mg, 0.15 mmol). After 80 min the reaction was quenched by addition of brine and  $\text{NaHCO}_3$ . The resulting solution was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic phases were washed with a

small amount of water followed by brine. The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. Aldehyde **34** (48 mg, 100%) was obtained as a faintly yellow wax that was used without further purification:  $[\alpha]^{26.4}_{\text{D}}$  41.6 ( $c$  1.0,  $\text{CH}_3\text{OH}$ , 92% ee by HPLC);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.80 (s, 1H), 7.25 (s, 1H), 7.24 (s, 1H), 4.83 (d,  $J = 6.6$  Hz, 1H), 4.73 (d,  $J = 6.6$  Hz, 1H), 4.32 (ddd,  $J = 3.6, 3.6, 3.6$  Hz, 1H), 3.90 (s, 3H), 3.47 (s, 3H), 3.27 (d,  $J = 3.6$  Hz, 1H), 2.86–2.79 (m, 2H), 2.59 (dd,  $J = 14.4, 3.6$  Hz, 1H), 2.39 (br d, 1H), 1.98 (dd,  $J = 14.4, 3.6$  Hz, 1H), 1.79 (dd,  $J = 13.2, 5.4$  Hz, 1H), 1.49 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  191.0, 149.7, 148.5, 128.8, 127.2, 122.7, 107.5, 97.0, 84.7, 78.0, 68.6, 56.2, 56.1, 46.9, 42.1, 38.0, 28.8, 22.9, 21.8, 16.7; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{28}\text{O}_6$  ( $\text{M}^+$ ) 364.1886, found 364.1896.

**Stilbene 36.** To a solution of aldehyde **34** (23 mg, 0.063 mmol) and phosphonate **35**<sup>14</sup> (50 mg, 0.1 mmol) in THF at rt was added 15-crown-5 (0.01 mL) followed by NaH (44 mg, 60% in oil, 1.1 mmol). After 3.5 h the reaction was quenched by addition of water, the resulting solution was extracted with ethyl acetate, and the combined organic phases were washed with brine. The organic phase was dried ( $\text{MgSO}_4$ ) and concentrated in vacuo. Final purification by preparative thin layer chromatography (2:8 hexanes/ethyl acetate) afforded stilbene **36** (31 mg, 71%) as a yellow wax:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.97–6.86 (m, 6H), 5.22 (s, 4H), 5.23–5.22 (m, 1H), 5.07–5.06 (m, 1H), 4.83 (d,  $J = 6.4$  Hz, 1H), 4.72 (d,  $J = 6.8$  Hz, 1H), 4.32 (ddd,  $J = 3.2, 3.2, 3.2$  Hz, 1H), 3.90 (s, 3H), 3.50 (s, 6H), 2.46 (s, 3H), 3.40 (d,  $J = 7.2$  Hz, 2H), 3.27 (d,  $J = 2.8$  Hz, 1H), 2.79–2.74 (m, 2H), 2.56 (dd,  $J = 14.4, 3.2$  Hz, 1H), 2.36 (br d, 1H), 2.06–1.94 (m, 5H), 1.79 (s, 3H), 1.81–1.77 (m, 1H), 1.65 (s, 3H), 1.57 (s, 3H), 1.47 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  155.9 (2C), 149.0, 142.3, 136.7, 134.6, 131.2, 128.9, 128.3, 126.4, 124.4, 122.8, 122.6, 120.5, 119.5, 107.0 (2C), 106.0, 96.9, 94.5 (2C), 84.9, 76.5, 68.7, 56.1 (2C), 56.0, 55.9, 47.2, 42.3, 39.8, 37.9, 28.8, 26.7, 25.6, 23.0, 22.7, 21.5, 17.6, 16.7, 16.1; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{41}\text{H}_{58}\text{O}_9$  ( $\text{M}^+$ ) 694.4081, found 694.4077.

**Schweinfurthin B (2).** To a solution of compound **36** (12 mg, 0.017 mmol) in  $\text{CH}_3\text{OH}$  was added TsOH (24 mg, 0.13 mmol) and the resulting solution was stirred at rt. After 46 h, the reaction was quenched by addition of  $\text{NaHCO}_3$  and concentrated in vacuo. The resulting solution was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated in vacuo. After final purification by preparative thin layer chromatography (1:9 hexanes/ethyl acetate), schweinfurthin **B (2)**, 5.3 mg, 55%) was obtained as colorless wax:  $[\alpha]^{26.4}_{\text{D}}$  +40.2 ( $c$  0.41, EtOH, 92% ee by HPLC); lit.<sup>1</sup>  $[\alpha]^{26.4}_{\text{D}}$  +44.7 ( $c$  1.0, EtOH); the  $^1\text{H}$  and  $^{13}\text{C}$  NMRs were found to be identical with the literature spectra.<sup>1</sup> HRMS (ESI)  $m/z$  calcd for  $\text{C}_{35}\text{H}_{46}\text{O}_6$  ( $\text{M}^+$ ) 562.3294, found 562.3287.

**Stilbene 38.** To a solution of aldehyde **34** (21 mg, 0.058 mmol) and phosphonate **39**<sup>14</sup> (38 mg, 0.09 mmol) in THF (5 mL) at rt was added 15-crown-5 (0.01 mL) followed by NaH (60 mg, 60% in oil, 1.5 mmol), and after 4 h the reaction was quenched by addition of water. The resulting solution was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated in vacuo. Final purification by column chromatography (3:7 hexanes/ethyl acetate) afforded stilbene **38** (26 mg, 72%) as a white wax:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.97–6.87 (m, 6H), 5.21 (s, 4H), 5.24–5.19 (m, 1H), 4.83 (d,  $J = 6.8$  Hz, 1H), 4.72 (d,  $J = 6.8$  Hz, 1H), 4.31 (ddd,  $J = 3.2, 3.2, 3.2$  Hz, 1H), 3.90 (s, 3H), 3.50 (s, 6H), 3.46 (s, 3H), 3.39 (d,  $J = 7.2$  Hz, 2H), 3.27 (d,  $J = 3.2$  Hz, 1H), 2.80–2.74 (m, 2H), 2.56 (dd,  $J = 14.4, 3.2$  Hz, 1H), 2.36 (br d, 1H), 1.98 (dd,  $J = 14.4, 3.2$  Hz, 1H), 1.81–1.77 (m, 1H), 1.79 (s, 3H), 1.66 (s, 3H), 1.48 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  158.5, 155.8 (2C), 149.0, 142.3, 136.7, 131.0, 128.9, 128.3, 126.4, 122.8, 120.4, 119.4, 107.0, 105.9 (2C), 96.9, 94.5 (2C), 84.9, 76.5, 68.7, 56.1, 56.0, 56.0 (2C), 47.2, 42.3, 37.9, 28.8,

25.8, 22.9, 22.8, 21.5, 17.7, 16.6; HRMS (ESI)  $m/z$  calcd for  $C_{36}H_{50}O_9$  ( $M^+$ ) 626.3455, found 626.3466.

**Schweinfurthin E (6).** Stilbene **38** (12 mg, 0.02 mmol) was treated with TsOH (24 mg, 0.13 mmol) in  $CH_3OH$  as described for compound **36**. After standard workup and final purification by preparative thin layer chromatography (1:9 hexanes/ethyl acetate), schweinfurthin E (**6**, 7.6 mg, 81%) was obtained as a colorless oil:  $[\alpha]_D^{26.4} +40.5$  ( $c$  0.67,  $CH_3OH$ ; 92% ee by HPLC); lit.<sup>2</sup>  $[\alpha]_D^{26.4} +49.2$  ( $c$  0.13,  $CH_3OH$ ); the  $^1H$  and  $^{13}C$  NMR spectra were identical with literature data.<sup>2</sup> HRMS (ESI)  $m/z$  calcd for  $C_{30}H_{38}O_6$  ( $M^+$ ) 494.2668, found 494.2670.

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**Supporting Information Available:** General experimental procedures, experimental paragraphs for compounds **12**, **21**, **22**, **25**, **26**, **28**, and **32**,  $^1H$  and  $^{13}C$  NMR spectra for compounds **2**, **6**, **12**, **16**, **18**, and **20–34**, details of the diffraction analysis of compound **12**, along with NOESY and COSEY spectra of compound **29**. This material is available free of charge via the Internet at <http://pubs.acs.org>.