## Total Synthesis of Oidiodendrolides and Related Norditerpene Dilactones from a Common Precursor: Metabolites CJ-14,445, LL-Z1271 $\gamma$ , Oidiolactones A, B, C, and D, and Nagilactone F

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## ABSTRACT



An efficient, high-yielding strategy has been developed for the asymmetric total synthesis of seven norditerpenoid dilactones known for their diverse biological properties. The three key steps employed to obtain a tricyclic lactone intermediate involved a Morita–Baylis–Hillman reaction, the stereocontrolled construction of a  $\gamma$ -lactone through bromolactonization, and an efficient catalytic Reformatsky-type reaction. Access to CJ-14,445, LL-Z1271 $\gamma$ , oidiolactones A, B, C, and D, and nagilactone F was possible from a common intermediate. Structures and stereochemistry were determined by X-ray analysis.

The family of norditerpenoid dilactones known as podolactones consists of more than 70 members, exhibiting a wide range of biological activities.<sup>1</sup> The two natural sources of podolactones are of plant or fungal origin, representing different biosynthetic pathways, despite their seemingly similar structures (Figure 1).

The filamentous fungi represented by *Oidiodendron truncatum* and *Oidiodendron griseum* produce, among others, the tetranorditerpene dilactones oidiolactones A-D.<sup>2</sup> Podolactones such as nagilactone  $F^3$  are produced from different species of the *Podocarpus* plant. Unlike the oidiolactones, podolactones originating from plants possess a carbon branched appendage at C-14 of the bisnorditerpenoid dilactone framework, exemplified by nagilactone F. The biological activities of the podolactones in a host of physiologically and medicinally relevant areas, particularly as antifungal,<sup>2d</sup> antitumoral,<sup>4</sup> and antifeedant<sup>5</sup> agents, have attracted attention toward their synthesis and the study of their biogenetic

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Figure 1. Structures of naturally occurring norditerpene dilactones and strategic transformations toward a common precursor **8**.

interrelationships.<sup>6</sup> A collection of natural and synthetic podolactones have also been tested as allelochemicals for their potential herbicidal activities.<sup>7</sup> Recently, oidiolactone B was reported to inhibit production of human interleukin- $1\beta$  at a concentration equal to IC<sub>50</sub> 49 nM. Antagonism of such cytokines can have important effects in the treatment of inflammatory diseases.<sup>8</sup> Oidiolactone B also displays considerable antifungal activity against opportunistic pathogens such as *Candida albicans*.<sup>2d</sup>

The first semisynthesis of oidiolactone B by Adinolfi and co-workers was reported in 1972,<sup>9</sup> soon after the elucidation of its structure by Ellestad and co-workers.<sup>2c</sup> The starting material was marrubiin, a diterpene lactone isolated from *Marrubium vulgare*, that already harbors the C-9 branched decalin ring and the C-4–C-6 bridged  $\gamma$ -lactone. Barrero and co-workers<sup>10</sup> used *trans*-communic acid, obtained from the cones of *Juniperus communis*, as a naturally occurring chiron toward the semisynthesis of oidiolactone B and C, as well

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Scheme 1. Synthesis of the AB Ring System



as of nagilactone F. Imamura and co-workers<sup>11</sup> utilized abietic acid as a starting point for the synthesis of an oidiolactone analogue. Abietic acid was also used by Hayashi and co-workers<sup>12</sup> for the semisynthesis of nagilactone F. In spite of the importance of podolactones as biologically active natural products, very few reports of their *total* synthesis have been disclosed. An enantioselective synthesis of nagilactone F and a synthesis of racemic ( $\pm$ )-3 $\beta$ -hydroxy nagilactone F were reported by Burke<sup>13</sup> and de Groot,<sup>14</sup> respectively. Finally, a total synthesis of racemic oidiolactone B was reported by Welch in 1977.<sup>15</sup>

We wish to disclose the first enantioselective total syntheses of oidiolactones A-D and nagilactone F in an expedient, convergent, and highly stereocontrolled manner. A disconnective analysis illustrates key steps and the versatility of our approach that leads to a common intermediate **8**, from which the intended podolactones, as well as other natural and synthetic analogues, can be easily accessed (Figure 1).

The construction of the AB ring system as a single enantiomer was initiated from the readily available Wieland– Miescher ketone<sup>16</sup> **9** following literature reports by the Theodorakis<sup>17</sup> and Danishefsky<sup>18</sup> groups, which led to **10** and **11** in good overall yield (Scheme 1). Highly stereoselective conjugate reduction of **11** was mediated by Mg in MeOH<sup>19</sup> to give **12** (95:5 dr by <sup>1</sup>H NMR) in an excellent yield. Stereoselective methylation of the Li enolate at -78°C afforded the  $\alpha$ -methyl branched ester **13** as a single

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Scheme 2. Access to the Common Key Intermediate 19



isomer (>95:5 dr) in quantitative yield.<sup>20,21</sup> Previously published studies have shown that alkylation of the exocyclic Li enolate proceeds from the more accessible  $\alpha$ -face of the AB bicyclic system.<sup>22</sup> At this juncture, the ketal **13** was subjected to acid-catalyzed hydrolysis, and the resulting ketone was converted to the  $\Delta^{7,8}$ -enone via an efficient IBX-mediated dehydrogenation.<sup>23,24</sup> The recalcitrant C-19 methyl ester hydrolysis was achieved in the presence of concd sulfuric acid<sup>25</sup> in an excellent yield over three steps to give enone **14**.

With the fully functionalized AB ring of podolactone derivatives in hand, we focused our attention on building the D lactone ring across C-4 and C-6 (Scheme 2). To this end, the hydroxymethyl branch at C-8 was introduced in an efficient Morita-Baylis-Hillman<sup>26</sup> reaction, utilizing formaldehyde and dimethylphenylphosphine, to give 15 in excellent yield. Treatment of 15 with Br2 followed by addition of K<sub>2</sub>CO<sub>3</sub> in DMF in the presence of 18-crown-6 effected smooth bromolactonization and elimination to give the corresponding tricyclic  $\gamma$ -lactone core 17, which was isolated as the TES ether 18. This sequence is based on a modification of the bromolactonization reaction developed by Welch and co-workers.<sup>15</sup> In the event, bromination of the enone acid 15 proceeded to give the labile dibromoketo acid 16. Treatment with K<sub>2</sub>CO<sub>3</sub> induced dehydrohalogenation via a trans-diaxial elimination of the bromide substituent at C-7. The transient spiroepoxide 16' was converted in the presence of base via a facile intramolecular S<sub>N</sub>2' cyclization to lactone 17.<sup>27</sup> The Welch group approach for the construction of the

(20) Toyota, M.; Asano, T.; Ihara, M. *Org. Lett.* **2005**, *7*, 3929–3932. (21) We first sought to functionalize the AB ring system using the procedure described by Theodorakis and co-workers for the enantiomer (ref

17). However, in our hands, the yield never exceeded 30% (reported 58%) with unidentified byproducts.

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 $\gamma$ -lactone D ring relied on a seven-step sequence (36% overall yield) starting from the racemic acid **14**.<sup>15</sup> In our synthesis, we introduced the C-14 center prior to the  $\gamma$ -lactonization sequence (4 steps, 48% overall yield).

Having the fully functionalized intermediate **18** in hand, the next challenge was the introduction of the  $\delta$ -lactone moiety between C-8 and C-9 (ring C). Many attempts to introduce an acetic acid side-chain at C-9 in **18** were fraught with problems involving  $\gamma$ -lactone ring-opening, elimination, and poor recoveries of desired material.<sup>28</sup> However, an intermolecular *catalytic* Reformatsky-type reaction between enone **18** and ethyl iodoacetate in the presence of NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and Et<sub>2</sub>Zn, according to the Adrian–Snapper protocol,<sup>29</sup> led to the desired tertiary alcohol **19** as a single isomer in excellent yield (Scheme 2). To the best of our knowledge, this represents a seldom explored catalytic intermolecular Reformatsky reaction in natural product synthesis.

With the expedient total synthesis of this versatile lactone **19**, the stage was set for the introduction of appropriate functionality to access oidiolactones A–D, as well as nagilactone F, as shown in Scheme 3. Major difficulties arose in the seemingly simple dehydration of  $\beta$ -hydroxy ester **19**.<sup>30</sup> Eventually, treatment with the Burgess reagent<sup>31</sup> yielded unsaturated ester **20** in 79% yield. We were pleased to observe that *O*-silyl deprotection mediated by triethylamine trihydrofluoride complex (Et<sub>3</sub>N·3HF)<sup>32</sup> led to concomitant in situ cyclization to give biogenetic dilactone CJ-14,445 (1).<sup>33</sup> The structure and absolute stereochemistry of **1** were confirmed by X-ray analysis.

Intermediate **20** was subjected to epoxidation with dimethyldioxirane (DMDO) in the presence of 4 Å MS to afford epoxide **21** in excellent purity and yield. As expected, stereoselective epoxidation took place from the sterically less hindered face of the cyclohexene ring in **20**. Deprotection of the silyl group in **21** with Et<sub>3</sub>N•3HF followed by in situ lactonization provided oidiolactone C (**5**) in excellent yield.<sup>34</sup> The assigned absolute configuration was also firmly established by X-ray crystallography. Mild TES deprotection of

(30) Attempted dehydration of tertiary alcohol **19** via the mesylate, the triflate, or the methyl carbonate failed.

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(32) For a review, see: McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31–35.

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<sup>(27)</sup> The nonprotected allylic alcohol was necessary in this reaction, thus suggesting the formation of an allylic spiroepoxide as a key intermediate. An analogous vinylogous epoxide was reported by Barrero in the semi-synthesis of oidiolactone C (ref 10a).

<sup>(28)</sup> Among various attempts to introduce the acetic acid side chain, we tried inter- and intramolecular Horner–Wadsworth–Emmons olefinations, Reformatsky-type cyclizations, and Mukaiyama aldol additions.

<sup>(29)</sup> Adrian, J. C., Jr.; Snapper, M. L. J. Org. Chem. **2003**, 68, 2143–2150. Honda and co-workers also suggested the use of Wilkinson's catalyst [Rh(PPh<sub>3</sub>)<sub>3</sub>Cl], in the presence of Et<sub>2</sub>Zn (Org. Lett. **2000**, 2, 2549–2551). In our case, the best results were obtained with the combination of  $\alpha$ -bromoacetate and Wilkinson's catalyst in THF or  $\alpha$ -iodoacetate and NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> in DCM.

<sup>(34)</sup> Alternatively, the conversion of 1 to oidiolactone C can be done in the presence of DMDO according to Barrero (ref 10a). However, conversion to product necessitated repeated exposure to the reagent. **5** was eventually obtained as a single isomer in 72% yield. Other epoxidation reagents (*m*-CPBA, CF<sub>3</sub>CO<sub>3</sub>H) were not efficient.

Scheme 3. Syntheses of CJ-14,445, LL-Z1271y, Oidiolactones A-D, and Nagilactone F



**21** with CSA in MeCN–H<sub>2</sub>O (1:1) gave the corresponding primary alcohol, which was oxidized with the Dess–Martin periodinane reagent<sup>35</sup> (DMP) leading to the aldehyde **22**. Ensuing protic-promoted lactolization generated oidiolactone D (**6**), also known as CJ-14,515, in high yield as a mixture of epimers. The synthetic product exhibited spectral data identical to those reported<sup>2d</sup> for the natural material. Treatment of the lactol **6** with catalytic TsOH in MeOH provided oidiolactone A (PR 1388, **7**) and its epimer **7**' (1:1.2 ratio) in high yield.<sup>36</sup> After separation, the spectroscopic and chiroptical data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR,  $[\alpha]_D$ ) were identical to the reported data<sup>2b</sup> for natural **7**. Interestingly, the  $\beta$ -isomer **7**' can be hydrolyzed with K<sub>2</sub>CO<sub>3</sub> in MeOH<sup>2d</sup> or with AcOH in aqueous THF<sup>8a</sup> to oidiolactone D (**6**).

Having successfully synthesized four naturally occurring podolactones starting from the common intermediate **19**, we turned our attention to the efficient preparation of three other fungal podolactones, namely, LL-Z1271 $\gamma$  (**2**), oidiolactone B (**3**), and nagilactone F (**4**). Toward this objective, the versatile tricyclic ester **19** was hydrolyzed under acidic conditions, thus setting the stage for a selective DMPmediated oxidation to afford aldehyde **23** in quantitative yield. We believed that biogenic lactol **2** could be accessed from  $\beta$ -hydroxy ester **23** via dehydration of the tertiary alcohol. Indeed, treatment of **23** with the Burgess reagent followed by acid-catalyzed lactolization gave metabolite **2**,<sup>2c,9</sup> which was in equilibrium with its C-14 epimer. An X-ray structure of **2** confirmed the assignment of a  $\beta$ -anomer. Upon exposure to TsOH and MeOH, this was in turn converted to oidiolactone B (LL-Z1271 $\alpha$ , PR 1387, **3**), in excellent yield and good stereoselectivity (93%, 77:23 dr).<sup>37</sup> Finally, our interest turned to the synthesis of bioactive nagilactone F (**4**). Whereas Barrero reported its synthesis by treatment of hydroxylactone **2** with isopropylmagnesium bromide in 83% yield and high stereoselectivity (90:10 dr), in our hands, this led to low yield and moderate selectivity. To circumvent this problem, lactol **2** was treated with isopropenylmagnesium bromide to yield dilactone **24** in good yield and excellent diastereoselectivity. This was in turn submitted to homogeneous hydrogenation in the presence of Wilkinson's catalyst to give nagilactone F (**4**).

In conclusion, concise enantioselective total syntheses of metabolites CJ-14,445 (1) and LL-Z1271 $\gamma$  (2), oidiolactones A–D (7, 3, 5, 6), and nagilactone F (4) were achieved from a common, readily available precursor 19. Furthermore, the total syntheses of oidiolactones A (7) and D (6) were reported for the first time.

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Supporting Information Available: Experimental procedures, spectral data, and CIF files for 1-7, 7', and 24. This material is available free of charge via the Internet at http://pubs.acs.org.

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<sup>(36)</sup> Epoxidation of oidiolactone B (3) in the presence of *m*-CPBA (Na<sub>2</sub>HPO<sub>4</sub>, CHCl<sub>3</sub>,  $\Delta$ ) proved particularly difficult and required a prolonged reaction time (15% yield).

<sup>(37)</sup> The use of catalytic concentrated H<sub>2</sub>SO<sub>4</sub> in MeOH, as reported by Barrero (ref 10b), led to a mixture of LL-Z1227 $\alpha$  (3) (50%), its C-14 epimer 3' (35%), and the dimethylacetal methyl ester (15%), whereas the treatment with HCl/MeOH, as described by Adinolfi (ref 9), gave almost quantitatively a 1:3 mixture of LL-Z1227 $\alpha$  and its anomer.