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Total Synthesis of Oidiodendrolides and Related Norditerpene Dilactones from a Common Precursor: Metabolites CJ-14,445, LL-Z1271γ, Oidiolactones A, B, C, and D, and Nagilactone F

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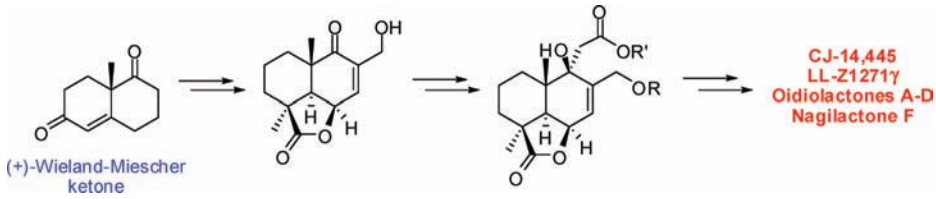
ABSTRACT



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 γ-lactone through bromolactonization, and an efficient catalytic Reformatsky-type reaction. Access to CJ-14,445, LL-Z1271γ, 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.[1] 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.[2] 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,[2d] antitumoral,[4] and antifeedant[5] agents, have attracted attention toward their synthesis and the study of their biogenetic

(1) (a) Barrero, A. F.; Quílez Del Moral, J. F.; Herrador, M. M. *Stud. Nat. Prod. Chem.* **2003**, *28*, 453–516. (b) Banerjee, A. K.; Laya, M. S.; Mora, H. R.; Cabrera, E. V. *Curr. Org. Chem.* **2008**, *12*, 1050–1070.

(2) (a) John, M.; Krohn, K.; Flörke, U.; Aust, H.-J.; Draeger, S.; Schulz, B. *J. Nat. Prod.* **1999**, *62*, 1218–1221. (b) For isolation of oidiolactone A, see: Andersen, N. R.; Rasmussen, P. R.; Falshaw, C. P.; King, T. J. *Tetrahedron Lett.* **1984**, *25*, 469–472. (c) For isolation of oidiolactone B, see: Ellestad, G. A.; Evans, R. H., Jr.; Kunstmann, M. P. *J. Am. Chem. Soc.* **1969**, *91*, 2134–2136. (d) For isolation of oidiolactones C and D, see: Hosoe, T.; Nozawa, K.; Lumley, T. C.; Currah, R. S.; Fukushima, K.; Takizawa, K.; Miyaji, M.; Kawai, K.-I. *Chem. Pharm. Bull.* **1999**, *47*, 1591–1597.

(3) For isolation of nagilactone F, see: Hayashi, Y.; Yokoi, J.; Watanabe, Y.; Sakan, T. *Chem. Lett.* **1972**, 759–762.

(4) Hembree, J. A.; Chang, C.-J.; McLaughlin, J. L.; Cassady, J. M.; Watts, D. J.; Wenkert, E.; Fonseca, S. F.; De Paiva Campello, J. *Phytochemistry* **1979**, *18*, 1691–1694.

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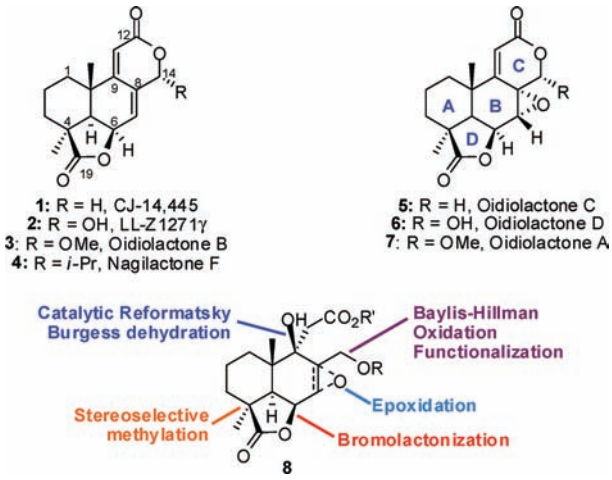
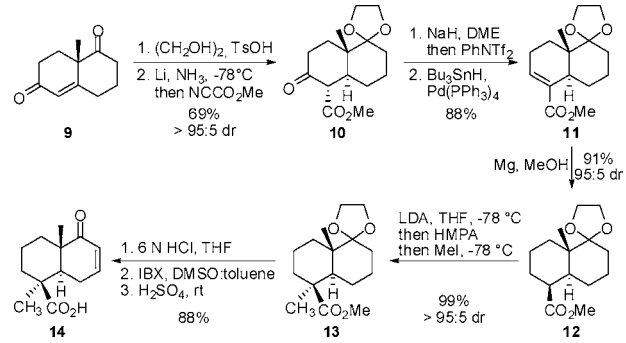


Figure 1. Structures of naturally occurring norditerpene dilactones and strategic transformations toward a common precursor **8**.

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

The first semisynthesis of oidiolactone B by Adinolfi and co-workers was reported in 1972,[9] soon after the elucidation of its structure by Ellestad and co-workers.[2c] 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 γ-lactone. Barrero and co-workers[10] 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 as of nagilactone F. Imamura and co-workers[11] utilized abietic acid as a starting point for the synthesis of an oidiolactone analogue. Abietic acid was also used by Hayashi and co-workers[12] 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 (±)-3β-hydroxy nagilactone F were reported by Burke[13] and de Groot,[14] respectively. Finally, a total synthesis of racemic oidiolactone B was reported by Welch in 1977.[15]

Scheme 1. Synthesis of the AB Ring System



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[16] **9** following literature reports by the Theodorakis[17] and Danishefsky[18] 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[19] to give **12** (95:5 dr by ^{1}H NMR) in an excellent yield. Stereoselective methylation of the Li enolate at −78 °C afforded the α-methyl branched ester **13** as a single

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(6) (a) Hayashi, Y.; Takahashi, S.; Ona, H.; Sakan, T. *Tetrahedron Lett.* **1968**, *17*, 2071–2076. (b) Kakisawa, H.; Sato, M.; Ruo, T.-i.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **1973**, 802–803. (c) Sato, M.; Kakisawa, H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2407–2413.

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(8) (a) Ichikawa, K.; Hirai, H.; Ishiguro, M.; Kambara, T.; Kato, Y.; Kim, Y. J.; Kojima, Y.; Matsunaga, Y.; Nishida, H.; Shiomi, Y.; Yoshikawa, N.; Huang, L. H.; Kojima, N. *J. Antibiot.* **2001**, *54*, 697–702. (b) Ichikawa, K.; Ikunaka, M.; Kojima, N.; Nishida, H.; Yoshikawa, N. *European Patent 0 933 273 A1*, 1999. (c) Ichikawa, K.; Inagaki, T.; Kojima, Y.; Nakamura, T.; Nishida, H.; Ueno, Y.; Kojima, N. *J. Antibiot.* **2001**, *54*, 977–979.

(9) Adinolfi, M.; Mangoni, L.; Barone, G.; Laonigro, G. *Gazz. Chim. Ital.* **1973**, *103*, 1271–1279.

(10) (a) For the synthesis of oidiolactone C, see: Barrero, A. F.; Arseniyadis, S.; Quílez del Moral, J. F.; Herrador, M. M.; Valdivia, M.; Jiménez, D. *J. Org. Chem.* **2002**, *67*, 2501–2508. (b) For the syntheses of oidiolactone B and nagilactone F, see: Barrero, A. F.; Sánchez, J. F.; Elmarabet, J.; Jiménez-González, D.; Macías, F.; Simonet, A. M. *Tetrahedron* **1999**, *55*, 7289–7304.

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(14) Reuvers, J. T. A.; de Groot, A. *J. Org. Chem.* **1986**, *51*, 4594–4599.

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(16) Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth.* **1990**, *7*, 368–372.

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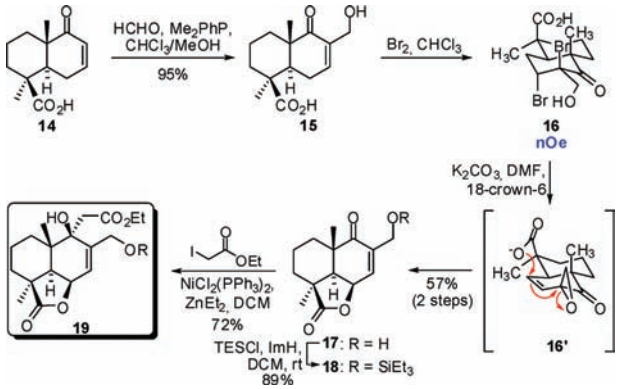
(19) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409–2410.

Scheme 2. Access to the Common Key Intermediate **19**



isomer (>95:5 dr) in quantitative yield.[20,21] Previously published studies have shown that alkylation of the exocyclic Li enolate proceeds from the more accessible α-face of the AB bicyclic system.[22] 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.[23,24] The recalcitrant C-19 methyl ester hydrolysis was achieved in the presence of concd sulfuric acid[25] 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[26] reaction, utilizing formaldehyde and dimethylphenylphosphine, to give **15** in excellent yield. Treatment of **15** with Br_2 followed by addition of K_2CO_3 in DMF in the presence of 18-crown-6 effected smooth bromolactonization and elimination to give the corresponding tricyclic γ-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.[15] In the event, bromination of the enone acid **15** proceeded to give the labile dibromoketo acid **16**. Treatment with K_2CO_3 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_N2' cyclization to lactone **17**.[27] The Welch group approach for the construction of the γ-lactone D ring relied on a seven-step sequence (36% overall yield) starting from the racemic acid **14**.[15] In our synthesis, we introduced the C-14 center prior to the γ-lactonization sequence (4 steps, 48% overall yield).

Having the fully functionalized intermediate **18** in hand, the next challenge was the introduction of the δ-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 γ-lactone ring-opening, elimination, and poor recoveries of desired material.[28] However, an intermolecular *catalytic* Reformatsky-type reaction between enone **18** and ethyl iodoacetate in the presence of $NiCl_2(PPh_3)_2$ and Et_2Zn, according to the Adrian−Snapper protocol,[29] 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 β-hydroxy ester **19**.[30] Eventually, treatment with the Burgess reagent[31] yielded unsaturated ester **20** in 79% yield. We were pleased to observe that *O*-silyl deprotection mediated by triethylamine trihydrofluoride complex ($Et_3N{\cdot}3HF$)[32] led to concomitant in situ cyclization to give biogenetic dilactone CJ-14,445 (**1**).[33] 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 $Et_3N{\cdot}3HF$ followed by in situ lactonization provided oidiolactone C (**5**) in excellent yield.[34] The assigned absolute configuration was also firmly established by X-ray crystallography. Mild TES deprotection of

(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.

(22) (a) Welch, S. C.; Hagan, C. P.; Kim, J. H.; Chu, P. S. *J. Org. Chem.* **1977**, *42*, 2879–2887. (b) Welch, S. C.; Hagan, C. P. *Synth. Commun.* **1973**, *3*, 29–32.

(23) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.

(24) Previous syntheses consisted of bromination−dehydrohalogenation (ref 15) or selenoxide elimination (ref 12).

(25) Reuvers, J. T. A.; Wijnberg, J. B. P. A.; de Groot, Ae. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 16–18.

(26) Ito, H.; Takenaka, Y.; Fukunishi, S.; Iguchi, K. *Synthesis* **2005**, 3035–3038.

(27) 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 semisynthesis of oidiolactone C (ref 10a).

(28) 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.

(29) 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 $[Rh(PPh_3)_3Cl]$, in the presence of Et_2Zn (*Org. Lett.* **2000**, *2*, 2549−2551). In our case, the best results were obtained with the combination of α-bromoacetate and Wilkinson's catalyst in THF or α-iodoacetate and $NiCl_2(PPh_3)_2$ in DCM.

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

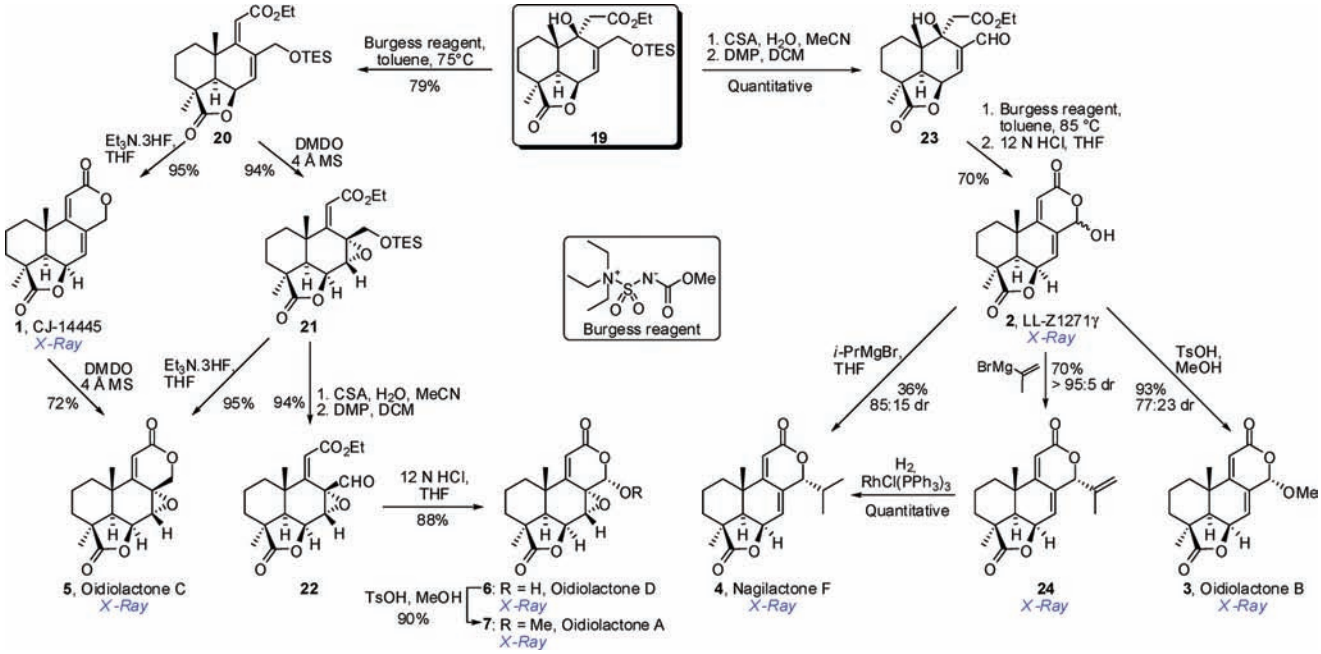
(31) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26–31.

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

(33) Sato, M.; Ruo, T.-i.; Hayashi, T.; Kakisawa, H.; Miyaki, T.; Yamamoto, H.; Fujisawa, K. *Tetrahedron Lett.* **1974**, *25*, 2134–2136.

(34) 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_3CO_3H) were not efficient.

Scheme 3. Syntheses of CJ-14,445, LL-Z1271γ, Oidiolactones A−D, and Nagilactone F



21 with CSA in MeCN−H_2O (1:1) gave the corresponding primary alcohol, which was oxidized with the Dess−Martin periodinane reagent[35] (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[2d] 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.[36] After separation, the spectroscopic and chiroptical data (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$) were identical to the reported data[2b] for natural **7**. Interestingly, the β-isomer **7′** can be hydrolyzed with K_2CO_3 in MeOH[2d] or with AcOH in aqueous THF[8a] 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-Z1271γ (**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 DMP-mediated oxidation to afford aldehyde **23** in quantitative yield. We believed that biogenic lactol **2** could be accessed from β-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**,[2c,9] which was in equilibrium with its C-14 epimer. An X-ray structure of **2** confirmed the assignment of a β-anomer. Upon exposure to TsOH and MeOH, this was in turn converted to oidiolactone B (LL-Z1271α, PR 1387, **3**), in excellent yield and good stereoselectivity (93%, 77:23 dr).[37] 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-Z1271γ (**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.

Acknowledgment. We thank NSERC, FQRNT, and Syngenta (Basel, Switzerland) for financial assistance.

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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(35) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

(36) Epoxidation of oidiolactone B (**3**) in the presence of *m*-CPBA (Na_2HPO_4, $CHCl_3$, Δ) proved particularly difficult and required a prolonged reaction time (15% yield).

(37) The use of catalytic concentrated H_2SO_4 in MeOH, as reported by Barrero (ref 10b), led to a mixture of LL-Z1227α (**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-Z1227α and its anomer.