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Total Synthesis of (+)- and (−)-Sundiversifolide via Intramolecular Acylation and Determination of the Absolute Configuration

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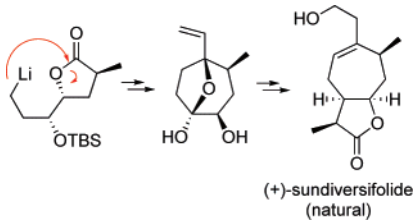
ABSTRACT



Intramolecular acylation of an organolithium leads to an efficient stereocontrolled total synthesis of both enantiomers of sundiversifolide. The absolute configuration was determined by HPLC analysis and allelopathy assay. The γ-lactone moiety resulted from a butenolide was obtained by the condensation of a bicyclic α-hydroxyhemiacetal with $Ph_3P{=}CMe(CO_2R)$.

Sundiversifolide (**1**) was isolated from the exudate of germinating sunflowers (*Helianthus annuus* L.) as an allelopathic compound,[1] that is, a plant release chemical compound that environmentally affects the germination or growth of different plant species growing in their vicinity. At a concentration of around 30 ppm, sundiversifolide inhibits the root development of cat's-eye seedlings by 50%. Sundiversifolide also reduced the conidial germination rate of the fungus, *Neurospora crassa*, at approximate concentrations of 30 μM when its conidia were incubated with the liquid medium for 3 h.[2] These promising results potentially could lead to a naturally occurring herbicide or anti-microbial agent that could become an important tool for chemical ecology and/or the food industry as a food additive. Although the structure elucidation of this novel dinorxanthane sesquiterpene bearing four stereocenters was established by analysis of its IR, MS, and NMR spectra, the absolute configuration has not been determined. Since this compound is available in only tiny quantities from seeds and seems to partially decompose or isomerize during purification by HPLC, it is difficult to obtain enough of the pure form from nature, and the optical rotation of the natural product has not been reported. Owing to the few reports on the synthetic studies

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(1) Ohno, S.; Tomita-Yokotani, K.; Kosemura, S.; Node, M.; Suzuki, T.; Amano, M.; Yasui, K.; Goto, T.; Yamamura, S.; Hasegawa, K. *Phytochemistry* **2001**, *56*, 577.

(2) (a) Kato, T.; Tomita-Yokotani, K.; Suzuki, T.; Hasegawa, K. *Weed Biol. Manag.* in press. (b) Tomita-Yokotani, K.; Suzuki, T.; Kato, T. In *Current Concepts in Botany*; Mukerji, K. G., Manoharachary, C., Eds.; I. K. International: India, 2006; pp 371−376.

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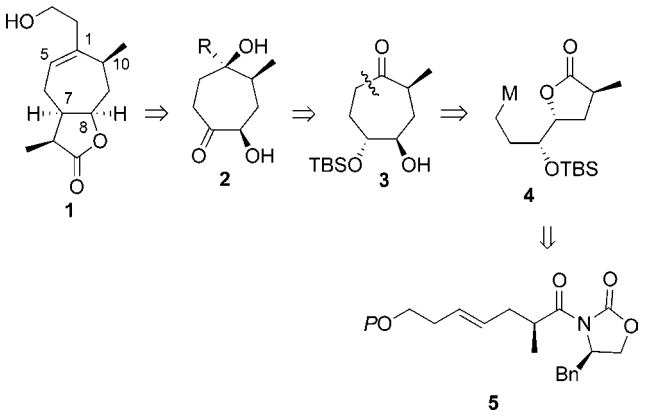
of xanthanolides, the development of an efficient synthetic strategy is needed to supply the natural product.[3,4] Herein, we report the efficient total synthesis of both enantiomers of sundiversifolide via a route of acylation of an organolithium by a γ-lactone, and the absolute configuration determination by HPLC analysis and allelopathy assay of the synthetic molecules.

Our synthetic strategy for sundiversifolide is illustrated in Scheme 1. The γ-lactone moiety would be formed by an

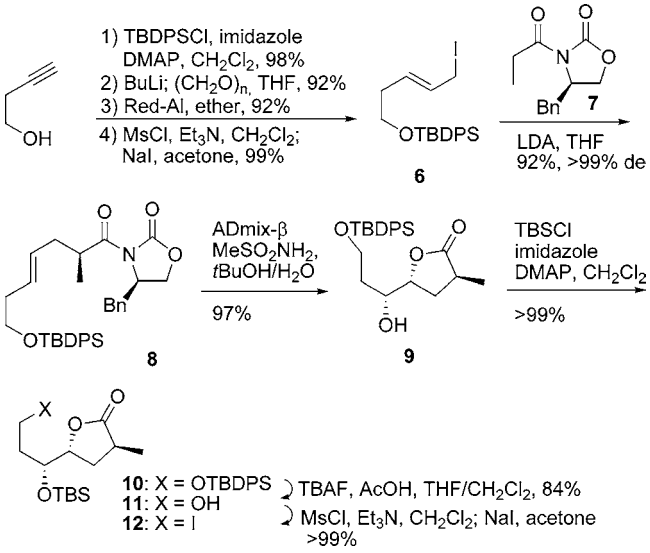
Scheme 1. Retrosynthesis of Sundiversifolide (**1**)



olefination-lactonization of the hydroxyketone **2**, followed by hydrogenation. The 2-hydroxyethyl side chain then would be introduced by alkylation of the ketone **3**. The seven-membered ring construction, which is much more challenging than the six-membered ring, would be achieved by an intramolecular acylation of an organometallic species on the $\gamma-$lactone **4**.[5] The asymmetric centers on **4** would be obtained by stereocontrolled alkylation using a chiral oxazolidinone, followed by stereocontrolled dihydroxylation of the resulting **5**.

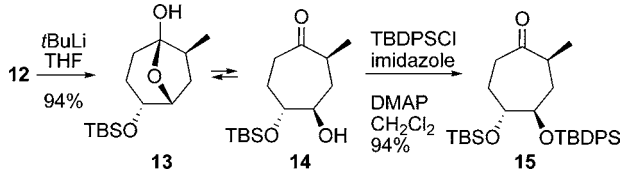
The stereocontrolled alkylation of Evans' oxazolidinone **7** with **6**, prepared from 3-butyn-1-ol in 72% yield for the five steps, provided **8** in good yield with excellent stereoselectivity.[6] The stereocontrolled dihydroxylation of **8** with AD-mixβ[7] was accompanied by spontaneous lactonization of the intermediate diol to afford the lactone **9** as a single isomer. The protection of the secondary alcohol with TBSCl and selective deprotection of the primary TBDPS ether with TBAF/acetic acid in THF/CH_2Cl_2,[8] followed by iodination, furnished the iodolactone **12** in good yield (Scheme 2).

Scheme 2. Asymmetric Synthesis of γ-Lactone**12**



The pivotal intramolecular acylation forming the seven-membered ring was first attempted with SmI_2 under various conditions and resulted in no reaction. Instead, lithiation of the iodide **12** using *t*-BuLi successfully provided the seven-membered ring in excellent yield.[9] The NMR spectra showed that the product is in equilibrium between the hemiacetal **13** and the cycloheptanone **14** in $CDCl_3$. Although MOMCl reacted with both of the hydroxyl groups on **13** and **14**, TBDPSCl protected only the secondary alcohol of **14** to afford **15** quantitatively (Scheme 3).

Scheme 3. Intramolecular Acylation of the Alkyllithium Giving Cycloheptanone



With the seven-membered skeleton in hand, we next attempted the introduction of the C2−C3 unit along with the formation of the C1−C5 endo-olefin. The enol triflation of the ketone **15** gave only recovered starting material, and the Shapiro reaction of the corresponding *p*-toluenesulfonyl

(3) (a) Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3371. (b) Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 4621. (c) Kummer, D. A.; Brenneman, J. B.; Martin, S. F. *Tetrahedron* **2006**, *62*, 11437. (d) Rudler, H.; Alvarez, C.; Parlier, A.; Perez, E.; Denise, B.; Xu, Y.; Vaissermann, J. *Tetrahedron Lett.* **2004**, *45*, 2409.

(4) For total synthesis of sundiversifolide, see; (a) (+)-form: H. Yokoe, H.; Sasaki, H.; Yoshimura, T.; Shindo, M.; Yoshida, M.; Shishido *Org. Lett.* **2007**, *9*, 969. (b) (±)-form: Hashimoto, T.; Tashiro, T.; Sasaki, M.; Takikawa, H. *Biosci. Biotecnol. Biochem.* **2007**, *71*, 2046.

(5) The relevant protocol has been reported by Molander using SmI_2. For a review, see: (a) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603. See, also: (b) Kawamura, K.; Hinou, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **2003**, *44*, 5259.

(6) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(7) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

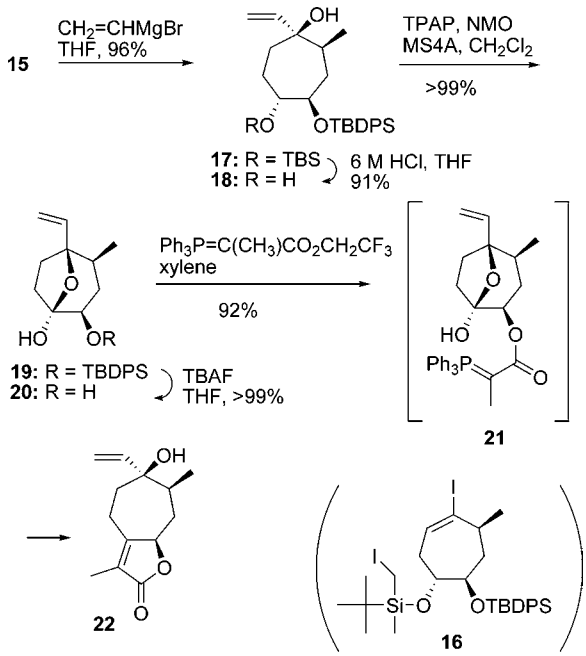
(8) Without use of CH_2Cl_2 as a co-solvent, the diol was mainly generated. See: Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. *Synlett* **2000**, 1306.

(9) For cyclization of iodo esters with organolithiums, see: (a) Cooke, M. P., Jr.; Houpis, I. N. *Tetrahedron Lett.* **1985**, *26*, 4987. (b) Saito, T.; Takeuchi, T.; Matsuhashi, M.; Nakata, T. *Heterocycles* **2007**, *72*, 151.

hydrazone resulted in the alkenyl iodide **16**[10] in moderate yield after trapping of the alkenyl lithium with iodine. While the keto group on **15** was inert to olefinations, such as the Wittig or the Peterson reactions, vinyl magnesium bromide effectively added to the ketone to afford the adduct **17** in excellent yield as a single isomer. Since dehydration of the tertiary alcohol giving the endo-olefin was unsuccessful at this stage, we decided to assemble the lactone first. The selective deprotection of the TBS group, TPAP oxidation, and removal of the TBDPS group provided the hydroxy hemiacetal **20** nearly quantitatively.

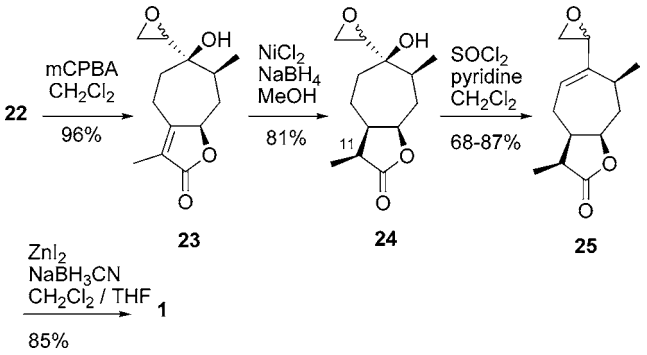
We next tried to construct the lactone moiety from **20**, which is equivalent to an α-hydroxyketone. Olefination of **20** with the Wittig reagent ($Ph_3P{=}C(CH_3)CO_2C_2H_5$) under reflux in xylene for 9 h directly provided the butenolide **22** in 91% yield, the structure of which was unambiguously assigned by X-ray diffraction study. In contrast to Garner's report on the Wittig reaction of α-hydroxy ketones giving (*E*)-olefins,[11] this reaction was exclusively (*Z*)-selective. The mechanism of this direct lactonization could be postulated as transesterification giving the intermediate **21**, followed by intramolecular olefination, because the ketone on **20** was masked by hemiacetalization. The reaction using the Wittig reagent with the trifluoroethyl ester ($Ph_3P{=}C(CH_3)CO_2CH_2CF_3$) was completed in only 4 h (92% yield), also suggesting that the intramolecular olefination had occurred (Scheme 4).

Scheme 4. Synthesis of Lactone **22**



With the carbon skeleton in hand, we then investigated the less substituted endo-alkene formation. Dehydration using MsCl/Et_3N gave S_N2' products and not the desired compound. Since the double bond on the allylic alcohol had to be protected prior to dehydration, **22** was treated with mCPBA to give the epoxide **23**, which was subjected to hydrogenation with the nickel boride derived from $NiCl_2$ and $NaBH_4$[12] to afford a separable mixture of **24** (81%) and its C11-epimer (14%). After numerous attempts, the best results for a kinetically controlled dehydration of **24** were obtained using a protocol involving slow addition of a solution of freshly distilled $SOCl_2$ (2 equiv) and pyridine (4 equiv) in CH_2Cl_2 at −20 °C. Under these conditions, the desired endo-alkene **25** was successfully obtained in yields ranging from ∼68−87%. Finally, the epoxide in **25** was regioselectively reduced with $NaBH_3CN$ in the presence of ZnI_2[13] to provide sundiversifolide (**1**) in 85% yield. The synthetic **1** {$[\alpha]^{22}_D$ = +33.0 (c 0.44, $CHCl_3$)} was found to be identical to the natural **1** according to spectroscopic properties (^1H and ^{13}C NMR, IR, and MS) (Scheme 5).

Scheme 5. Completion of the Total Synthesis of (+)-Sundiversifolide **1**



The enantiomer *ent*-**1** {$[\alpha]^{22}_D$ = −33.7 (c 0.46, $CHCl_3$)} was also synthesized in a similar manner, using the chiral oxazolidinone derived from L-Phe in the asymmetric alkylation and ADmix-α in the asymmetric dihydroxylation, which also gave a single isomer. The HPLC analysis using chiral column (Daicel Chiralpak IA, hexane/isopropanol 93:7) indicated that the natural **1** is identical with the synthetic (+)-**1**. This study therefore determined that the absolute configuration of the naturally occurring sundiversifolide isolated from the sunflower is that shown in **1**.

The effect of sundiversifolide on the growth of cat's-eye seedlings and the germination rate in a model microbe, *Neurospora crassa*, were tested. (+)-Sundiversifolide (**1**) inhibited the elongation of root growth of cat's-eye seedlings at a concentration of 100 μM. The compound also reduced the conidial germination rate of *Neurospora crass* by 50% of the control at concentrations greater than 20 μM when its conidia were incubated with liquid medium for 2.5 h. On the other hand, (−)-sundiversifolide (*ent*-**1**) did not show significant inhibition.

(10) The methyl group on the TBS ether was also lithiated by the Shapiro reaction.

(11) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1987**, *52*, 2629.

(12) Kido, F.; Tsutsumi, K.; Maruta, R.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1979**, *101*, 6420.

(13) Finkielsztein, L. M.; Aguirre, J. M.; Lantano, B.; Alesso, E. N.; Moltrasio Iglesias, G. Y. *Synth. Commun.* **2004**, *34*, 895.

In conclusion, we have achieved an efficient asymmetric total synthesis of (+)- and (−)-sundiversifolide in 25% overall yield, using a strategy involving a seven-membered ring construction via intramolecular acylation of an organolithium and a one-pot lactonization with a Wittig reagent. We also determined the absolute configuration of the natural product by HPLC analysis using a chiral column. Biological tests also show its potential as an allelochemical. Work is underway to synthesize xanthanolide families and their analogues in order to find novel allelochemicals and other medicinal resources.

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Supporting Information Available: Synthetic procedures, spectroscopic data for new compounds, and crystallographic data for **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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