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Total Synthesis of (−)-Teucvidin

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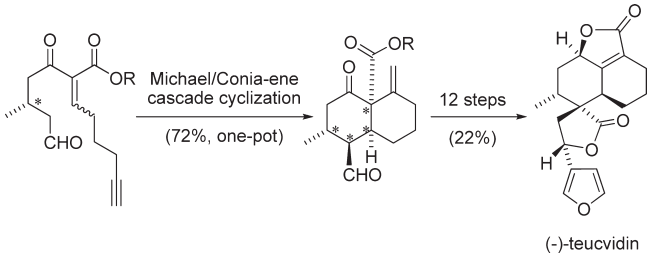
ABSTRACT



A concise enantioselective synthesis of (−)-teucvidin has been achieved. Our synthetic strategy involved the diastereoselective Michael/Conia−ene cascade cyclization reaction for rapid establishment of the *cis*-decalin skeleton with three new stereogenic centers in one pot (72%, single diastereomer), the epoxidation/dealkoxycarbonylation protocol for construction of the fused furanone moiety, and the *O*-allylation/Claisen rearrangement protocol for construction of the all-carbon quaternary center at C9 of the clerodane skeleton.

During the past years, over 1000 diterpenoids containing the clerodane skeleton (Figure 1) and their 19-*nor* variants have been reported, and they show a variety of interesting biological activities, including antifeedant, antifungal, antitumor, antimicrobial, and moluscicidal activities.[1]

Because of the structural diversity and the broad range of biology activities, extensive efforts have been directed toward the synthesis of clerodane diterpernoids.[2] Interestingly, synthetic efforts toward the 19-*nor*-clerodanes with a spiro γ-lactone at C9 are still very limited presumably due to their structural complexity. So far, only four racemic total syntheses of this subclass have been reported by Liu's group using a Diels−Alder (DA) approach for construction of the *cis*-decalin ring system.[3] Jung's group reported a DA approach for direct access of the spiro γ-lactone clerodane ring system in one-pot using allenic spiro-γ-lactones as the dienophiles.[4] Recently, Ley's group modified Jung's DA approach by switching the dienophiles to *cis*-furanospiro-γ-lactones.[5] However, these approaches are primarily racemic, and no enantioselective total synthesis on these spiro γ-lactone 19-*nor*-clerodanes has been reported.

In the course of developing an efficient and versatile asymmetric approach to the synthesis of the clerodane

(1) (a) Hanson, J. R. *Nat. Prod. Rep.* **1989**, *6*, 347–358. (b) Simmonds, M. S. J.; Blaney, W. M.; Ley, S. V.; Bruno, M.; Savona, G. *Phytochemistry* **1989**, *28*, 1069–1071. (c) Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, *9*, 243–287. (d) Tokoroyama, T. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 1164–1177. (e) Hanson, J. R. *Nat. Prod. Rep.* **2002**, *19*, 125–132. (f) Rijo, P.; Gaspar-Marques, C.; Simoes, M. S.; Duarte, A.; Apreda-Rojas, M. del-C.; Cano, F. H.; Rodriguez, B. *J. Nat. Prod.* **2002**, *65*, 1387–1390. (g) Salah, M. A.; Bedir, E.; Toyang, N. J.; Khan, I. A.; Harries, M. D.; Wedg, D. E. J. *Agric. Food Chem.* **2003**, *51*, 7607–7610. (h) Hanson, J. R. *Nat. Prod. Rep.* **2005**, *22*, 594–602. (i) Coll, J.; Tandron, Y. *Phytochemistry* **2005**, *66*, 2298–2303. (j) Tamokou, J. D.; Kuiate, J. R.; Tene, M.; Tane, P. *Indian J. Pharmacol.* **2009**, *41*, 60–63. (k) Stankovic, M. S.; Curcic, M. G.; Zizic, J. B.; Topuzovic, M. D.; Solujic, S. R.; Markovic, S. D. *Int. J. Mol. Sci.* **2011**, *12*, 4190–4205.

(2) For reviews, see: (a) Sarma, A. S. *J. Sci. Ind. Res.* **1987**, *46*, 492–504. (b) Tokoroyama, T. *Synthesis* **2000**, *5*, 611–633. For selected examples, see: (c) Grossman, R. B.; Rasne, R. M. *Org. Lett.* **2001**, *3*, 4027–4030. (d) Liu, H. J.; Ho, Y. L.; Wu, J. D. K.; Shia, S. *Synlett* **2001**, 1805–1807. (e) Kato, M.; Kosugi, H.; Ichiyanagi, T.; Hagiwara, H.; Kodaira, A.; Kusakari, T.; Suzuki, T.; Ando, M.; Lee, J.; Drechsel, P.; Vogler, B. *Tetrahedron* **2001**, *57*, 8243–8256. (f) Ling, T. T.; Rivas, F.; Theodorakls, E. A. *Tetrahedron Lett.* **2002**, *43*, 9019–9022. (g) Arns, S.; Barriault, L. *J. Org. Chem.* **2006**, *71*, 1809–1816. (h) Wasnaire, P.; Wiaux, M.; Touillaux, R.; Markó, I. E. *Tetrahedron Lett.* **2006**, *47*, 985–989. (i) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629–7632. (j) Kikuchi, T.; Mineta, M.; Ohtaka, J.; Matsumoto, N.; Katoh, T. *Eur. J. Org. Chem.* **2011**, 5020–5030. (k) Miyaoka, H.; Abe, Y.; Sekiya, N.; Mitome, H.; Kawashima, E. *Chem. Commun.* **2012**, *48*, 901–903.

(3) (a) Liu, H.-J.; Zhu, J.-L.; Chen, I.-C.; Jankowska, R.; Han, Y.; Shia, K.-S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1851–1853. Chen, I.-C.; Wu, Y.-K.; Liu, H.-J.; Zhu, J.-L. *Chem. Commun.* **2008**, 4720–4722.

(4) (a) Jung, M. E.; Zimmerman, C. N. *J. Am. Chem. Soc.* **1991**, *113*, 7813–7814. (b) Jung, M. E.; Zimmerman, C. N.; Lowen, G. T.; Khan, S. I. *Tetrahedron Lett.* **1993**, *34*, 4453–4456. (c) Jung, M. E.; Cordova, J.; Murakami, M. *Org. Lett.* **2009**, *11*, 3882–3885.

(5) Merritt, A. T.; Pouwer, R. H.; Williams, D. J.; Williams, C. M.; Ley, S. V. *Org. Biomol. Chem.* **2011**, *9*, 4745–4747.

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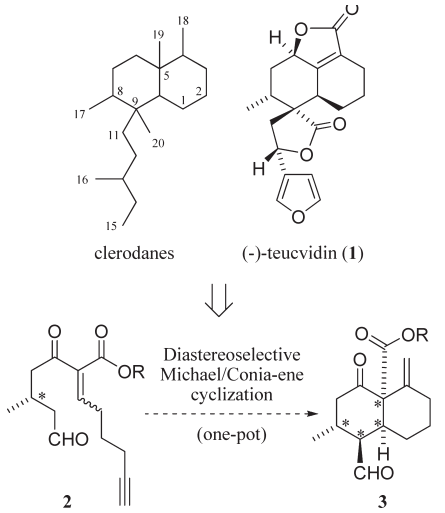
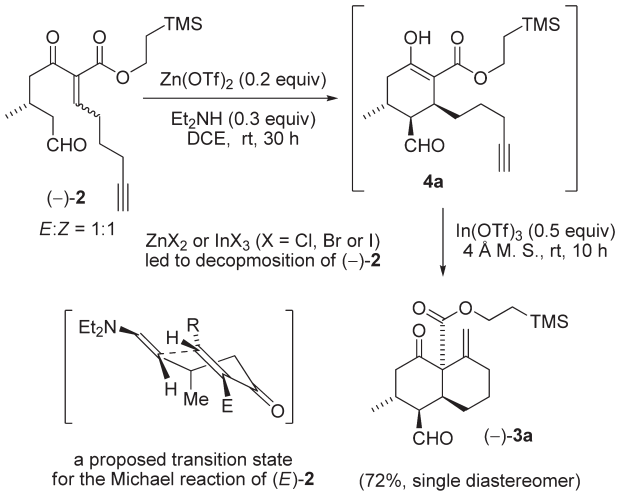


Figure 1. Synthetic strategy toward (−)-teucvidin and clerodane diterpenoids.

diterpenoids and their 19-*nor* variants, we have recently reported the amine-induced Michael/Conia−ene cascade cyclization, which can rapidly construct the *cis*-decalin ring system from an acyclic substrate in one-pot with good diastereoselectivity.[6] We envisioned that by introducing the stereogenic center at C8 of the clerodane skeleton, this cascade cyclization would provide the *cis*-decalin core with three new stereogenic centers stereoselectively in one-pot via the substrate control (Figure 1). The cyclized product (**3**) contains the required functionalities and stereogenic centers for synthesis of a variety of *cis*-clerodanes and the spiro γ-lactone 19-*nor*-clerodanes. We herein report the development of this diastereoselective Michael/Conia−ene cascade cyclization reaction and its application in the first total synthesis of (−)-teucvidin (**1**) in enantiomeric form. As isolated from *Teucrium viscidum* Blume var. *Miquelianum* by Fujita's group in 1975,[7] compound **1** is a 19-*nor*-clerdoane bearing an α,β-unsaturated γ-lactone moiety fused into the decalin core and a spiro γ-lactone moiety with a pendant furyl moiety at C9.

As shown in Scheme 1, the diastereoselectivity of the Michael/Conia−ene cascade cyclization reaction via substrate-control was studied using enantiomerically enriched (−)-**2** (a 1:1 *E*:*Z* isomers) as the cyclization precursor. Upon treatment with ZnI_2/Et_2NH in 1,2-dichloroethane,[6] hydrolysis of the 2-(trimethylsilyl)ethyl ester moiety of (−)-**2** resulted. Indeed, all Zn(II) or In(III) halides gave similar results. After a survey of different combinations of transition metal salts, amines and solvents, we found that the optimal conditions is to treat (−)-**2** with $Zn(OTf)_2$ (0.2 equiv) and diethylamine (0.3 equiv) in 1,2-dichloroethane at room temperature. Michael addition of the enamine derivative of **2** proceeded smoothly under this condition and gave the kinetic Michael adduct as the

Scheme 1. Development of Diastereoselective Michael/Conia−Ene Cascade Cyclization



intermediate (**4a**) (vide infra). After subsequent addition of $In(OTf)_3$ (0.5 equiv) and 4 Å molecular sieves, the Michael adduct (**4a**) generated in situ underwent Conia−ene reaction and afforded the *cis*-decalin ring system of (−)-**3a** in 72% yield as a single diastereomer. This one-pot cascade cyclization effectively established the *cis*-decalin skeleton containing three new stereogenic centers with desired stereochemistry from an acyclic cyclization precursor ((−)-**2**) (Scheme 1). The structure of cyclized product (−)-**3a** was fully characterized by NMR experiments.[8]

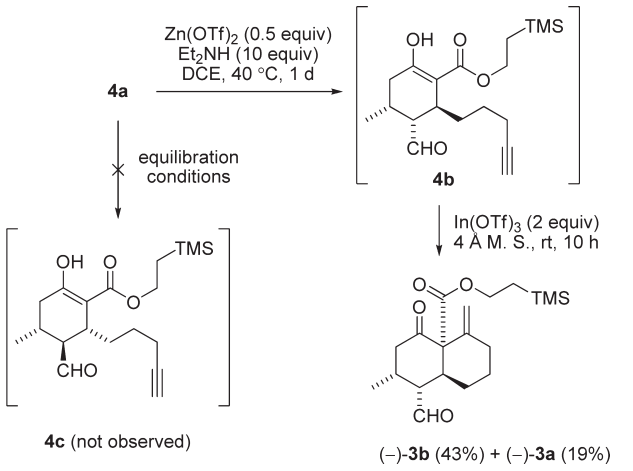
To study the effect of the alkene geometry on the stereochemistry of the Michael reaction, the (*E*)- and (*Z*)-isomers of **2** were separated. However, both (*E*)- and (*Z*)-isomers were found to be unstable, and they gradually equilibrated into *E*/*Z* mixtures in $CDCl_3$ or 1,2-dichloroethane. Based on the stereochemistry of (−)-**3a** and the result of the *E*/*Z* isomerization, we proposed that (*Z*)-**2** could be equilibrated to (*E*)-**2** under the reaction condition and the Michael reaction of (*E*)-**2** could lead to **4a** via the twisted-chair-like transition state in Scheme 1.

After the alkene isomerization study, the equilibration of the Michael reaction was investigated by using a variety of bases with $Zn(OTf)_2$. As shown in Scheme 2, all of the equilibration conditions led to either no equilibration or decomposition of **4a** upon heating. Equilibration occurred when the Michael adduct (**4a**) generated in situ was allowed to heat with $Zn(OTf)_2$ (0.5 equiv) and Et_2NH (10 equiv) at 40 °C for 1 day. However, the expected thermodynamic Michael adduct (**4c**) with all the substituents being equatorial was not obtained and the equilibration condition gave another diastereomer (**4b**), which could be resulted from the eqimerization of the aldehyde moiety in **4a**. The Michael adduct (**4b**) was converted to the bicyclic products by addition of $In(OTf)_3$ and 4 Å molecular sieves, which gave (−)-**3b**[8] as the major product

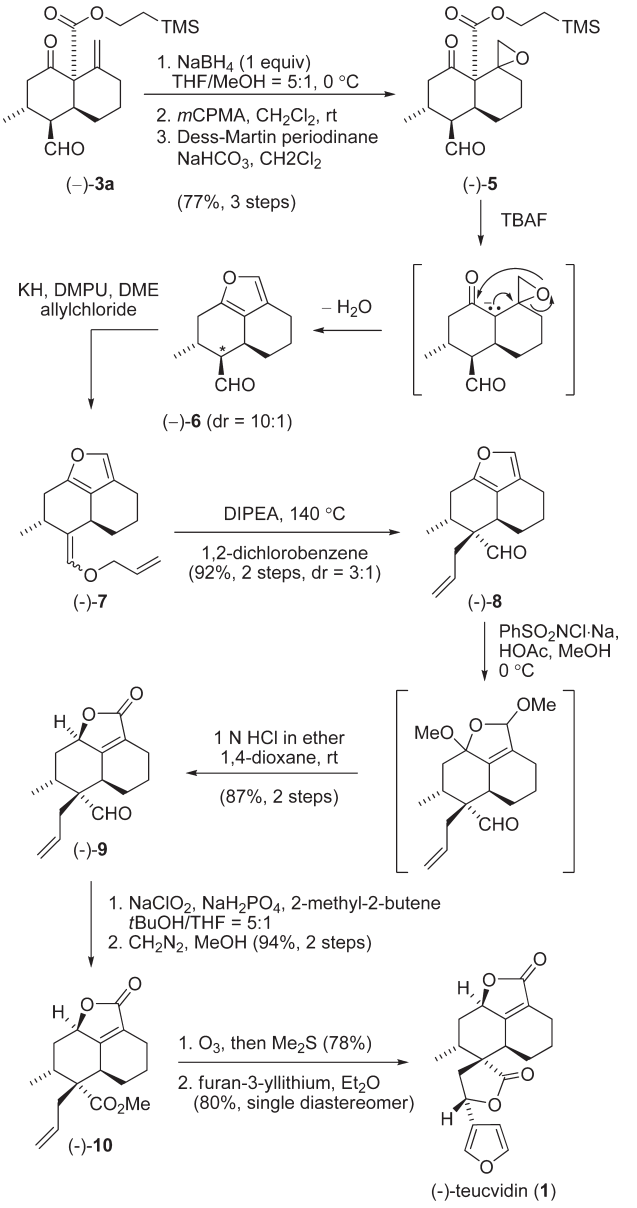
(6) Li, W.; Liu, X.; Zhou, X.; Lee, C.-S. *Org. Lett.* **2010**, *3*, 548–551.
(7) Uchida, I.; Fujita, T.; Fujita, E. *Tetrahedron* **1975**, *31*, 841–848.

(8) The characterization data and the NMR spectra of (−)-**3a**, **3b**, and **10** are available in the Supporting Information.

Scheme 2. Equilibration Study



Scheme 3. Total Synthesis of (−)-Teucvidin



(62%, a 1: 2.3 diastereomeric mixture of **3a** and **3b**). This result indicated that the initial Michael reaction could be irreversible and the equilibration condition can only lead to the epimerization of the aldehyde moiety via enamine formation.

With (−)-**3a** in hand, the β-keto β'-alkenyl ester moiety could be converted to a furan moiety via the epoxidation/dealkoxycarbonylation protocol[9] that was recently developed by our group. As shown in Scheme 3, the aldehyde moiety of (−)-**3a** was first reduced selectively with $NaBH_4$ to avoid Baeyer−Villager oxidation under the epoxidation condition. After epoxidation of the exocyclic alkene with *m*-CPBA and oxidation of the alcohol, compound (−)-**5** was converted to (−)-**6** in one-pot using TBAF. Under the reaction conditions, dealkoxycarbonylation of (−)-**5** generated an enolate, which underwent epoxide ring opening, acetal formation, and elimination of water to afford the fused furan moiety of (−)-**6** (81%, contains about 10% of the aldehyde epimer). However, attempts of *C*-allylation of the α-position of the aldehdye moiety in (−)-**6** failed probably due to the steric hindrance of the adjacent substituents. The allyl moiety was then installed via the *O*-allylation/Claisen rearrangement protocol,[10] which gave a 3:1 diastereomeric mixture (about 70% isolated yield for (−)-**8**). Oxidative methoxylation of the major diastereomer ((−)-**8**) using *N*-chlorobenzenesulfonamide sodium salt followed by treatment with acid[11] afforded the α,β-unsaturated γ-lactone moiety of (−)-**9** efficiently and diastereoselectively. Pinnick oxidation of the aldehyde moiety of (−)-**9** followed by treatment with diazomethane gave methyl ester (−)-**10**. The stereochemistry of (−)-**10** was assigned by detail analysis of the NOESY data.[8]

Moreover, a sample of racemic **10** was prepared from 3-methylglutaric anhydride using a similar synthetic route, and the crystals of (±)-**10** obtained by recrystallization from *n*-hexane/diethyl ether were found to be suitable for X-ray crystallography.[12] The X-ray structure of (±)-**10** (Figure 2) is fully consistent with the stereochemical assignment of (−)-**10** by NOESY. Finally, ozonolysis of the terminal alkene followed by addition of furan-3-yllithium installed the spiro γ-lactone moiety stereoselectively and finish the total synthesis of (−)-teucvidin. The high stereoselectivity of the spiro γ-lactone formation is probably due

(9) Huang, S.; Du, G.; Lee, C.-S. *J. Org. Chem.* **2011**, *76*, 6534–6541.

(10) (a) Miysoks, H.; Yokokura, T.; Okamura, T.; Nagaoka, H.; Yamada, Y. *Synlett* **2002**, 227–230. (b) Nicolaou, K. C.; Zhang, H.; Ortiz, A.; Dagneau, P. *Angew. Chem.* **2008**, *120*, 8733–8738.

(11) Shults, E. E.; Velder, J.; Schmalz, H.-G.; Chernov, S. V.; Rubalova, T. V.; Gatilov, Y. V.; Henze, G.; Tolstikov, G. A.; Prokop, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4228–4232.

(12) CCDC-868783 ((±)-**10**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

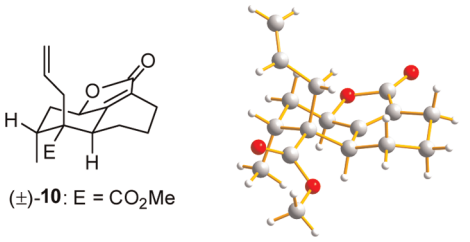


Figure 2. X-ray crystallography of (±)-**10**.

to the lithium chelation of the 1,4-dicarbonyl moiety.[13] The ^{1}H and ^{13}C NMR data of synthetic (−)-teucvidin are consistent with that reported for the natural product.[14]

In summary, we have developed a concise total synthesis of (−)-teucvidin in enantiomeric form. With the stereogenic center at C8 (clerodane skeleton), acyclic substrate (−)-**2a** underwent diastereoselective Michael/Conia−ene cascade cyclization and gave the *cis*-decalin skeleton containing three new stereogenic centers in one-pot. The cyclized product was concisely converted to (−)-teucvidin in 12 steps with 22% overall isolated yield, which is the first example of an enantioselective total synthesis of this subclass of clerodane diterpenoids. This cascade cyclization approach could provide an efficient and versatile strategy for asymmetric synthesis of a variety of *cis*-clerodane diterpenoids and their 19-*nor* variants.

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Supporting Information Available. Experimental procedures with characterization data for all new compounds and X-ray data for (±)-**10** (CIF) (CCDC-868783). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) Reissig, H. U.; Angert, H. *J. Org. Chem.* **1993**, *58*, 6280–6285.
(14) Rodríguez1, B.; Jimeno, M. L. *Magn. Reson. Chem.* **2004**, *42*, 605–616.