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Enantioselective Total Synthesis of (−)-Candelalide A, a Novel Blocker of the Voltage-Gated Potassium Channel Kv1.3 for an Immunosuppressive Agent

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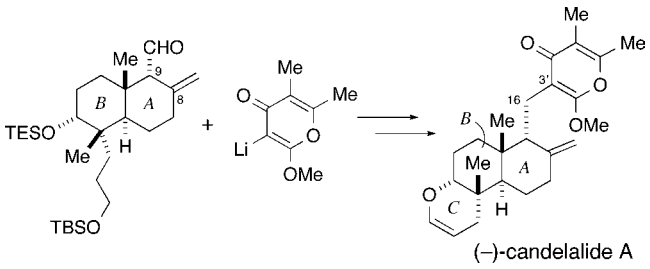
ABSTRACT



A convergent route to (−)-candelalide A involved the union of a *trans*-decalin portion (AB ring) and a γ-pyrone moiety through the C16−C3′ bond to assemble the whole carbon framework and subsequent formation of the dihydropyran ring (C ring) as the crucial steps. A strategic [2,3]-Wittig rearrangement was employed for establishing the stereogenic center at C9 and an *exo*-methylene function at C8 present in the decalin portion.

Candelalide A (**1**, Scheme 1), isolated from the culture broth of *Sesquicillium candelabrum* by the Merck research group in 2001,[1] has been shown to be a novel blocker of voltage-gated potassium channel Kv1.3. This channel plays pivotal roles in the control of membrane potential in human T cells where it sets the resting potential.[2] Blockade of Kv1.3 causes membrane depolarization of human T cells, and this prevents the Ca^{2+} entry required for T cell activation.[2] These processes lead to diminution of lymphokine release and synthesis from the calcium-dependent pathway, thus suppressing activation and proliferation of human T cells.[2] Consequently, **1** is expected to be a promising new agent for the treatment of T cell-mediated autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and insulin-dependent diabetes.[2] The gross structure of **1** was determined by extensive spectroscopic studies. It consists of a novel tricyclic decahydro-1*H*-benzo[*f*]chromene skeleton (ABC ring system) appended to a fully substituted γ-pyrone ring via a methylene linkage, in which five contiguous asymmetric carbons are involved.[1] The attractive biological properties and unique structural features prompted us to undertake a project directed toward the total synthesis of candelalide A (**1**) in an enantiomerically pure form. The elegant total synthesis of (±)-sesquicillin, a structurally related diterpenoid α-pyrone isolated from *Acremonium* sp., was recently achieved by Danishefsky and Zhang;[3] however, no total synthesis of

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(1) Singh, S. B.; Zink, D. L.; Dombrowski, A. W.; Dezeny, G.; Bills, G. F.; Felix, J. P.; Slaughter, R. S.; Goetz, M. A. *Org. Lett.* **2001**, *3*, 247.

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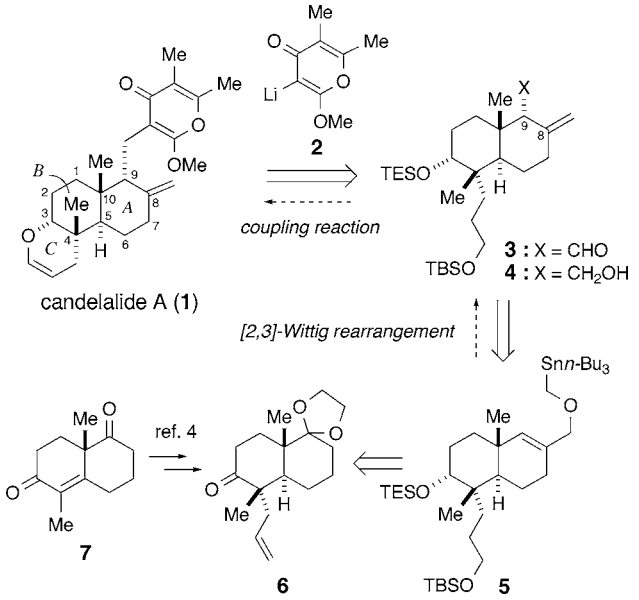
Scheme 1. Retrosynthetic Plan for Candelalide A (**1**)



candelalide A (**1**) has been reported so far. In this communication, we describe the first total synthesis of naturally occurring (−)-candelalide A (**1**) using a convergent approach.

The retrosynthetic plan for candelalide A (**1**) is outlined in Scheme 1. We envisioned that the target molecule **1** would be available through a coupling of the highly and appropriately functionalized *trans*-decalin aldehyde **3** (accessible from the intermediate **4**) with the fully substituted 3-lithio-γ-pyrone **2**, if followed by construction of the characteristic dihydropyran ring (C ring). This coupling reaction is synthetically challenging at the synthetic chemistry level because the C9 formyl group in the decalin **3** lies in a sterically congested axial orientation. The advanced key intermediate **4**, possessing both a hydroxymethyl group at C9 and an *exo*-methylene moiety at C8, would be delivered through the [2,3]-Wittig rearrangement of stannylmethyl ether **5**, which we expected to establish the requisite asymmetric carbon center C9. The key intermediate **5** would be derived from the known *trans*-decalone **6**,[4] which is readily prepared from the enantiomerically pure (+)-5-methyl-Wieland−Miescher ketone (**7**) (>99% ee),[5] by sequential functional group manipulation and deprotection, or vice versa.

The synthesis began with the preparation of intermediate **5**, the substrate for the key [2,3]-Wittig rearrangement, starting from the known enantiomerically pure *trans*-decalone **6**[5] (Scheme 2). Our route to the allyl alcohol **17** was based on Danishefsky's synthesis of (±)-sesquicillin.[3] Stereoselective reduction of the C3 carbonyl group in **6** by the use of L-Selectride provided the desired alcohol **8** in 91% yield as the sole isolable product. Due to its instability, compound **8** was immediately subjected to hydroboration followed by hydrogen peroxide oxidation to give the requisite diol **9** in 69% yield. After deprotection of the ethylene acetal moiety in **9** by acid hydrolysis (91%), the two hydroxy groups in the resulting ketone **10** were differentially protected as the *tert*-butyldimethylsilyl (TBS) and triethylsilyl (TES) ethers, which provided the corresponding disilyl ether **12** in 76% yield for the two steps. For the introduction of a formyl group to the C8 position, compound **12** was treated with ethyl formate in the presence of potassium hydride to afford the enol **13** (97%), whose hydroxy group was then protected as its ethoxyethyl (EE) ether to produce the enol ether **14** in 96% yield. Subsequent sodium borohydride reduction of **14** furnished the alcohol **15** in 98% yield as a single stereoisomer with respect to C9. Simultaneous dehydration of the C9 hydroxy function and deprotection of the EE group within **15** was effected by treatment with methanesulfonyl chloride in the presence of triethylamine at 0 °C for 30 min, which led to formation of the desired α,β-unsaturated aldehyde **16** in 88% yield. Finally, compound **16** was converted to the requisite stannylmethyl ether **5** in 85% overall yield through a two-step sequence involving sodium borohydride reduction of the formyl group in **16** followed by stannylmethylation[6] of the resulting alcohol **17** with iodomethyltributyltin in the presence of potassium hydride and 18-crown-6.

With the key intermediate **5** in hand, the stage was set for the critical stereocontrolled [2,3]-Wittig rearrangement[7,8] of **5** to construct the requisite decalin system **4** possessing both

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(3) Zhang, F.; Danishefsky, S. J. *Angew. Chem.* **2002**, *114*, 1492; *Angew. Chem., Int. Ed.* **2002**, *41*, 1434.

(4) Hagiwara, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1803.

(5) For our recent synthetic studies of biologically important natural products using (+)- or (−)-5-methyl-Wieland−Miesher ketone (**7** or *ent*-**7**) as the starting material, see: (a) Iwasaki, K.; Nakatani, M.; Inoue, M.; Katoh, T. *Tetrahedron* **2003**, *59*, 8763. (b) Suzuki, A.; Nakatani, M.; Nakamura, M.; Kawaguchi, K.; Inoue, M.; Katoh, T. *Synlett* **2003**, 329. (c) Nakatani, M.; Nakamura, M.; Suzuki, A.; Inoue, M.; Katoh, T. *Org. Lett.* **2002**, *4*, 4483. (d) Iwasaki, K.; Nakatani, M.; Inoue, M.; Katoh, T. *Tetrahedron Lett.* **2002**, *43*, 7937. (e) Nakamura, M.; Suzuki, A.; Nakatani, M.; Fuchikami, T.; Inoue, M.; Katoh, T. *Tetrahedron Lett.* **2002**, *43*, 6929. (f) Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terashima, S. *Org. Lett.* **2001**, *3*, 2701.

(6) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.

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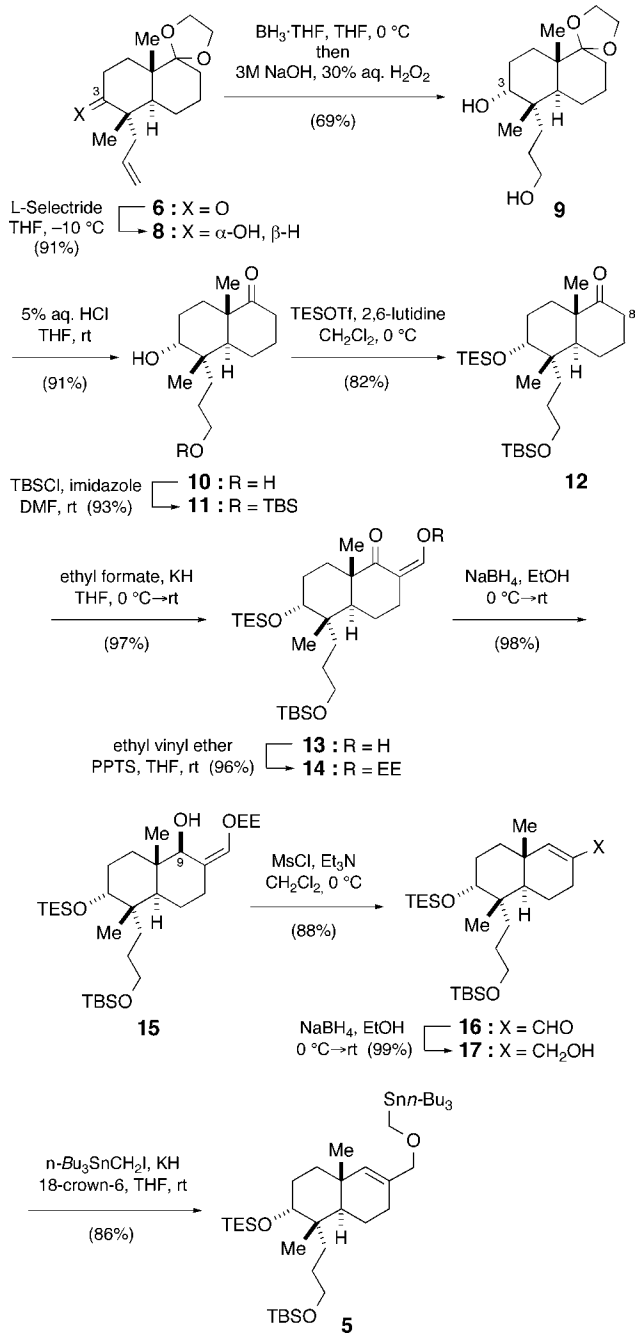
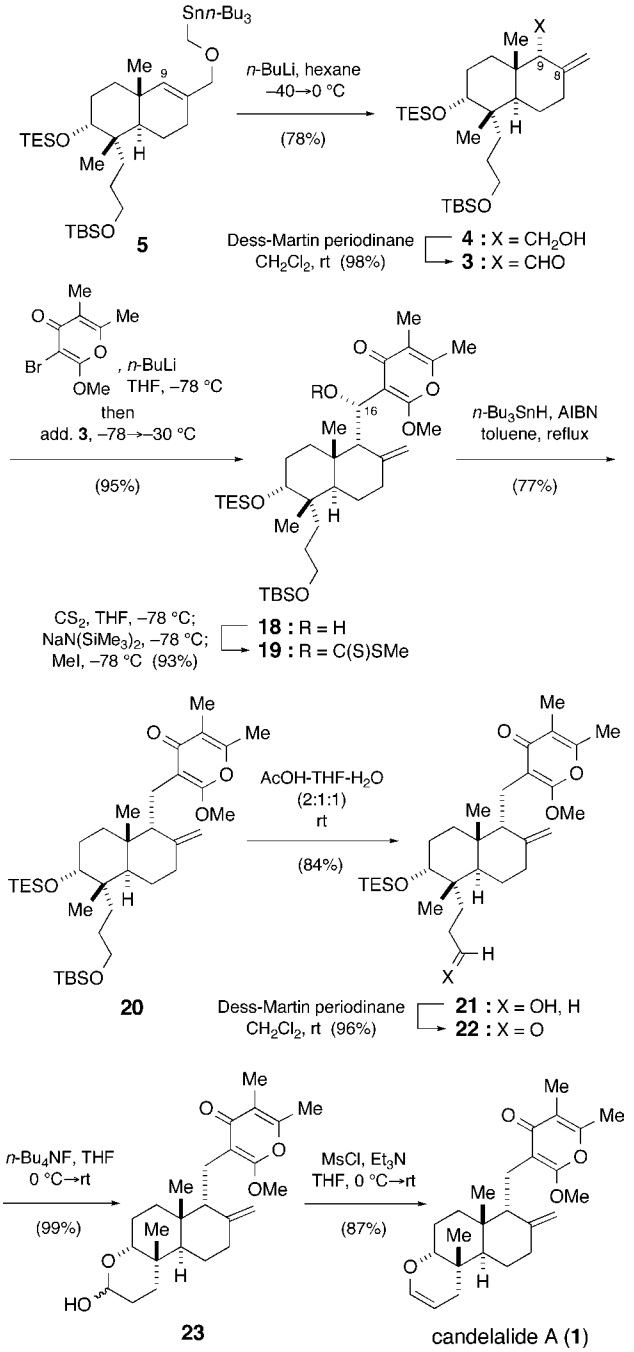
(8) A related Eschenmoser−Claisen rearrangement has been reported for the total synthesis of (±)-sesquicillin (see ref 3), while, to the best of our knowledge, this type of [2,3]-Wittig rearrangement (cf. **5** → **4**) is unprecedented.

Scheme 2. Synthesis of the Key Intermediate **5**[a]



Scheme 3. Synthesis of Candelalide A (**1**)[a]



a hydroxymethyl group at C9 with the correct stereochemistry and an *exo*-methylene moiety at C8 (Scheme 3). After screening several reaction conditions, we were very pleased to find that the designed [2,3]-Wittig rearrangement of **5** proceeded smoothly and cleanly by treatment with *n*-butyllithium in hexane[9] at −40→0 °C for 16 h, leading to the desired **4** (78%) with a small amount of its C9 epimer (not depicted) (9%) and the hydroxy compound **17** (cf. Scheme 2) (3%); these products were readily separated by column chromatography on silica gel. The configuration of the newly formed C9 stereocenter in **4** was confirmed by NOESY experiments in the 500 MHz ^{1}H NMR spectrum.[10] The stereochemical outcome observed for this [2,3]-Wittig rearrangement can be rationalized by considering that the attack of the carbanion, generated in situ by tin/lithium exchange of the stannane **5**, on the C9 olefinic carbon occurs preferentially from the less hindered α-face of the molecule under the influence of the *β*-oriented axial methyl group at the decalin junction, leading to **4** as the major product. To

(9) In this reaction, the use of hexane as the solvent was crucial. When THF or Et_2O was used instead of hexane, the yields of the desired rearrangement product **4** were reduced to ∼30%. Detailed results and discussion will be reported in a full account.

(10) See Supporting Information for NOESY experiments of the [2,3]-Wittig rearrangement product **4** and its C-9 epimer.

continue the synthesis, the rearrangement product **4** was then subjected to Dess−Martin oxidation to afford the desired decalin aldehyde **3** in 98% yield.

The challenging coupling reaction of **3** with the 3-lithio-γ-pyrone **2** was successfully achieved by an initial bromine/lithium exchange on 3-bromo-2-methoxy-5,6-dimethyl-4*H*-pyran-4-one[11] and subsequent reaction with **3** at −78 → −30 °C for 2 h. The desired coupling product **18**[12] was obtained as a single diastereomer in 95% yield. It is noteworthy that the regiochemical integrity of the sensitive *exo*-methylene moiety was maintained during the coupling reaction. Removal of the sterically hindered hydroxy group in **18** was carried out smoothly by applying the Barton−McCombie procedure[13] with some improvements of the reaction conditions. Thus, treatment of a mixture of **18** and carbon disulfide with sodium bis(trimethylsilyl)amide [$NaN(SiMe_3)_2$] at −78 °C, followed by addition of iodomethane at the same temperature, afforded the corresponding methyl xanthate **19** in 93% yield, which was further treated with tri-*n*-butyltin hydride and 2,2′-azobis(isobutyronitrile) (AIBN) in refluxing toluene to furnish the desired deoxygenated product **20** in 77% yield.

Having successfully obtained the advanced key intermediate **20** possessing the whole carbon framework with the requisite substituents and asymmetric carbons, we next investigated the final route that led to completion of the projected synthesis; the sequence involved the crucial construction of the characteristic dihydropyran ring (C ring). Toward this end, selective deprotection of the TBS group in **20** through exposure to aqueous acetic acid in THF and Dess−Martin oxidation of the resulting alcohol **21** provided the corresponding aldehyde **22** in 81% yield for the two steps. Subsequent deprotection of the TES group in **22** with tetrabutylammonium fluoride resulted in the production of the expected cyclized hemiacetal **23** in 99% yield. Finally, the dehydration of **23** was efficiently achieved by treatment with methanesulfonyl chloride (MsCl) in THF containing triethylamine at 0 °C → room temperature for 1 h, leading to the formation of the target (−)-candelalide A (**1**) in 87% yield. The spectroscopic properties (IR, ^1H and ^{13}C NMR, HRMS) of the synthetic sample **1** were fully identical with those of the natural product **1**. The optical rotation of the synthetic **1** ($[\alpha]^{22}_D$ −25.1° (*c* 0.35, CH_3OH)) showed good accordance with that of natural **1** (lit.[1] $[\alpha]^{22}_D$ −23.1° (*c* 0.26, CH_3OH)).

In conclusion, we have accomplished the first total synthesis of (−)-candelalide A (**1**) starting from the known *trans*-decalone **6** in a convergent fashion. The key steps of the synthesis were (i) the stereocontrolled [2,3]-Wittig rearrangement of the stannylmethyl ether **5** (**5** → **4**), (ii) the coupling reaction of the *trans*-decalin aldehyde **3** with the 3-lithio-γ-pyrone **2** (**3** + **2** → **18**), and (iii) the efficient construction of the dihydropyran ring (C ring) (**22** → **23** → **1**). The explored synthetic route should hold promise for preparing various candelalide A analogues in enantiomerically pure forms due to its generality and flexibility.

Acknowledgment. We are especially grateful to Dr. Sheo B. Singh (Merck Research Laboratories) for providing us with copies of the ^1H and ^{13}C NMR spectra of natural (−)-candelalide A (**1**). We also thank Dr. N. Sugimoto (National Institute of Health Sciences) and Dr. N. Kawahara (National Institute of Health Sciences) for measurements of HRMS and assistance with NMR experiments. This work was supported in part by a Grant-in-Aid for High Technology Research Program from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, which we gratefully acknowledge.

Supporting Information Available: Detailed experimental procedures and full characterization data, including copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) 3-Bromo-2-methoxy-5,6-dimethyl-4*H*-pyran-4-one was prepared starting from the known 4-hydroxy-5,6-dimethyl-2*H*-pyran-2-one [Hagiwara, H.; Fujimoto, N.; Suzuki, T.; Ando, M. *Heterocycles* **2000**, *53*, 549] via a two-step sequence of reactions [(a) *N*-bromosuccinimide, Et_3N, THF, 0 °C; (b) CH_2N_2, MeOH, 0 °C, 43% (two steps)] (see Supporting Information for experimental details).

(12) Stereochemistry at C16 (candelalide A numbering) in the coupling product **18** was tentatively assigned on the basis of the usual Felkin−Anh model.

(13) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.