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Convergent and enantioselective total synthesis of (−)-nalanthalide, a potential Kv1.3 blocking immunosuppressant

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Abstract—The first total synthesis of (−)-nalanthalide (**1**), a novel blocker of the voltage-gated potassium channel Kv1.3 from a microorganism, was accomplished in a convergent manner by utilizing coupling reaction of the *trans*-decalin **5** with 3-lithio-γ-pyrone **4**. The key intermediate **5** was efficiently prepared from the known *trans*-decalone **7** through a [2,3]-Wittig rearrangement of the stannylmethyl ether **6** to install the stereogenic center at C9 and the *exo*-methylene function at C8.

In 2001, the Merck research group reported the isolation and structure elucidation of nalanthalide (**1**, Fig. 1), from the culture broth of *Nalanthamala* sp.[1] This natural product was found to be a novel blocker of the voltage-gated potassium channel Kv1.3.[2] In human T cells, Kv1.3 channels exist as tetramers of four identical subunits and control the resting membrane potential of the cells.[3] Blockade of Kv1.3 channels causes membrane depolarization, which attenuates intracellular Ca^{2+} levels required for T cell activation and proliferation.[4] Nalanthalide (**1**), therefore, is expected to be a promising new lead for the treatment of T cell-mediated autoimmune diseases such as rheumatoid arthritis and insulin-dependent diabetes.[1,3,4]

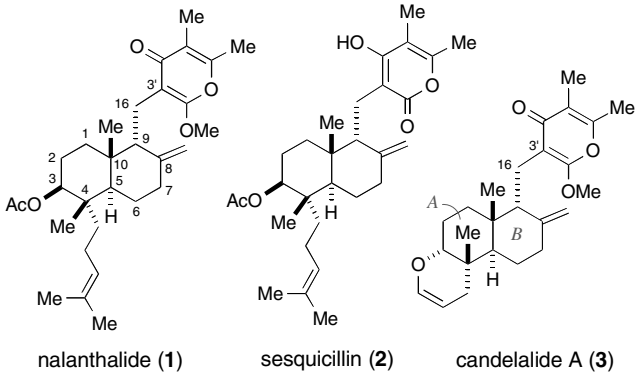

Figure 1. Structure of nalanthalide (**1**), sesquicillin (**2**), and candelalide A (**3**).

The gross structure and stereochemistry of nalanthalide (**1**) was revealed by analysis of 2D NMR spectra including COSY, NOESY, and HETCOR experiments.[1,5] It consists of a *trans*-decalin skeleton connected with a fully substituted γ-pyrone ring via a methylene linkage.

The attractive biological properties and unique structural features prompted us to undertake a project directed toward the total synthesis of **1** in an enantiomerically pure form. A closely related diterpenoid α-pyrone sesquicillin (**2**),[6] wherein the γ-pyrone ring of **1** is replaced by an α-pyrone ring, was previously isolated from *Acremonium* sp. as a glucocorticoid antagonist. Recently, the elegant total synthesis of (±)-**2** has been achieved by Danishefsky and Zhang,[7] however, to the best of our knowledge, total synthesis of **1** has not been reported to date. More recently, we have disclosed a successful

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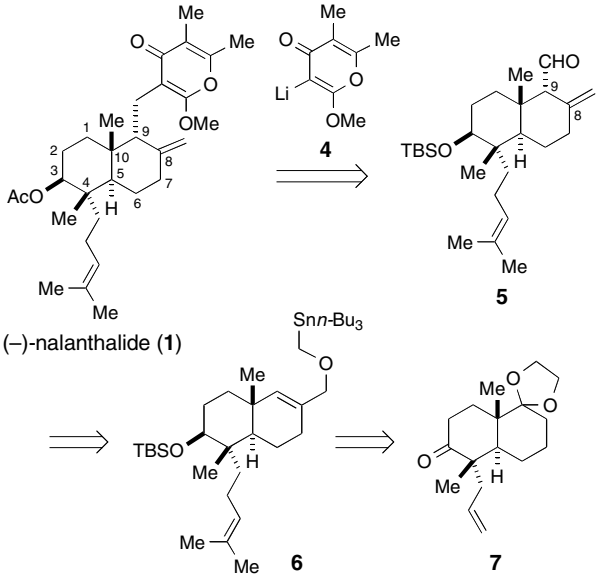
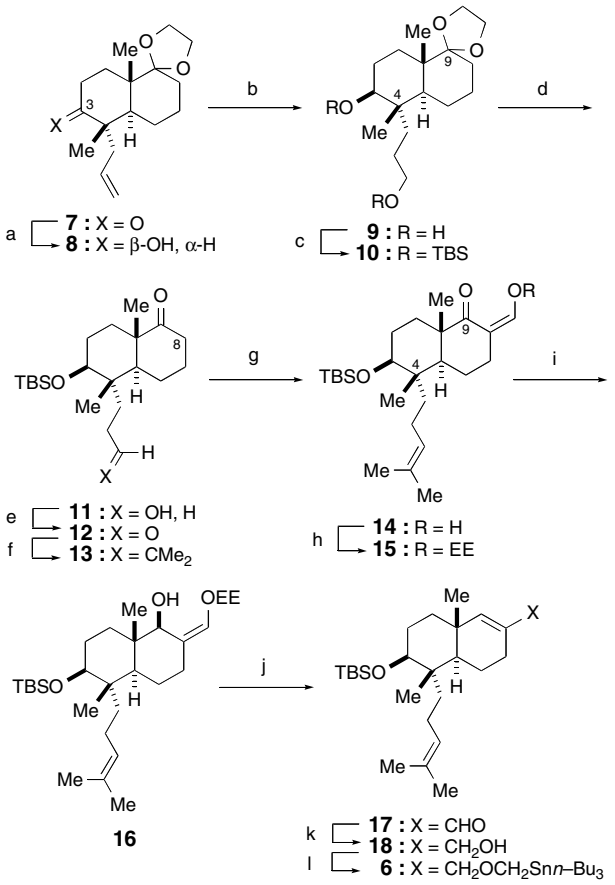
convergent strategy for the total synthesis of (−)-candelalide A (**3**),[8] a Kv1.3 blocker from *Sesquicillium candelabrum*, which involved the union of a *trans*-decalin portion (AB ring) and a γ-pyrone moiety through the C16–C3′ bond to assemble the whole carbon framework as the pivotal step. We herein describe the first total synthesis of naturally occurring (−)-nalanthalide (**1**) applying this convergent strategy.

The synthetic plan for (−)-nalanthalide (**1**) is outlined in Scheme 1, which was devised on the basis of our preliminary work.[8] We envisioned that the target molecule **1** would be elaborated through a coupling reaction between the appropriately substituted *trans*-decalin **5** and the fully substituted 3-lithio-γ-pyrone **4**.[8] The intermediate **5** would be available through the strategic [2,3]-Wittig rearrangement of stannylmethyl ether **6**, where we believed that the stereocenter at C9 and the *exo*-methylene function at C8 would be simultaneously established. The intermediate **6** should in turn be accessed from the known *trans*-decalone **7**,[8] which has previously been prepared in an enantiomerically pure form in our laboratories.

At first, as shown in Scheme 2, we pursued the synthesis of the intermediate **6**, a substrate for the key [2,3]-Wittig rearrangement, starting from the *trans*-decalone **7**[8] (>99% ee). The route to the allyl alcohol **18** from **7** has been established (30% overall yield in 11 steps) in Danishefsky's elegant total synthesis of (±)-sesquicillin (**2**).[7] Therefore, we decided to follow the Danishefsky's route with some improvements of the reaction steps and conditions (cf. **8**→**9**→**10**→**11**→**12**→**13**, **16**→**17**), which ultimately allowed increase of the total yield of **18** (39% overall yield in 11 steps). Thus, reduction of the C3 carbonyl group in **7** with lithium aluminum hydride afforded the desired β-alcohol **8** in 98% yield as the single stereoisomer. Subsequent hydroboration of **8** followed by oxidative treatment with 30% aqueous hydrogen peroxide produced the requisite diol **9** in 67% yield. The two hydroxy groups in **9** were simultaneously protected as the bis(*tert*-butyldimethylsilyl) (TBS) ethers to provide the corresponding disilyl ether **10** in quantitative yield. Compound **10** was then converted to the aldehyde **12** (86% overall yield) by selective deprotection of the TBS group in the C4 side chain and the ethylene acetal moiety at C9, followed by Dess–Martin oxidation[9] of the resulting primary alcohol **11**. Wittig reaction of **12** with isopropyridene(triphenyl)phosphorane completed the elaboration of the side chain at C4, and afforded the decalone **13** in 86% yield. In order to introduce a formyl group to the C8 position, the decalone **13** was treated with ethyl formate in the presence of sodium hydride to give the desired enol **14** (quantitative yield), whose hydroxy group was then protected as the ethoxyethyl (EE) ether to furnish the enol ether **15** in 92% yield. After reduction of the C9 carbonyl group in **15** with sodium borohydride (92%), the resulting alcohol **16** was subjected to dehydration employing methanesulfonyl chloride and triethylamine, which provided



Scheme 1. Retrosynthetic plan for (−)-nalanthalide (**1**).



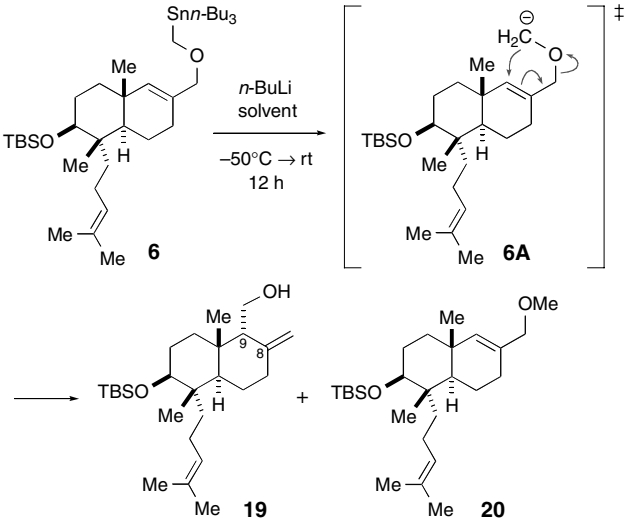
Scheme 2. Synthesis of the intermediates **6**. Reagents and conditions: (a) $LiAlH_4$, Et_2O, −45 °C→rt, 1.5 h, 98%; (b) BH_3·THF, THF, 0 °C→rt, 1 h; 3 M NaOH, 30% aq H_2O_2, 0 °C→rt, 1.5 h, 67%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, quant.; (d) AcOH–THF–H_2O (3:1:1), 50 °C, 4 h, 90%; (e) Dess–Martin periodinane, CH_2Cl_2, rt, 96%; (f) Me_2CHPPh_3I, *n*-BuLi, THF, 0 °C, 1 h, 86%; (g) ethyl formate, NaH, THF, 0 °C→rt, 1 h, quant.; (h) ethyl vinyl ether, H_3PO_4, rt, 4 h, 92%; (i) $NaBH_4$, EtOH, 0 °C→rt, 2 h, 92%; (j) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 94%; (k) $NaBH_4$, EtOH, 0 °C→rt, 30 min, quant.; (l) *n*-Bu_3SnCH_2I, KH, 18-crown-6, THF, 0 °C→rt, 1 h, 98%.

the desired α,β-unsaturated aldehyde **17** in 94% yield. The aldehyde **17** was effectively converted to the requisite stannylmethyl ether **6** in 98% overall yield via a two-step sequence involving sodium borohydride reduction of **17** followed by stannylmethylation[10] of the resulting alcohol **18**.

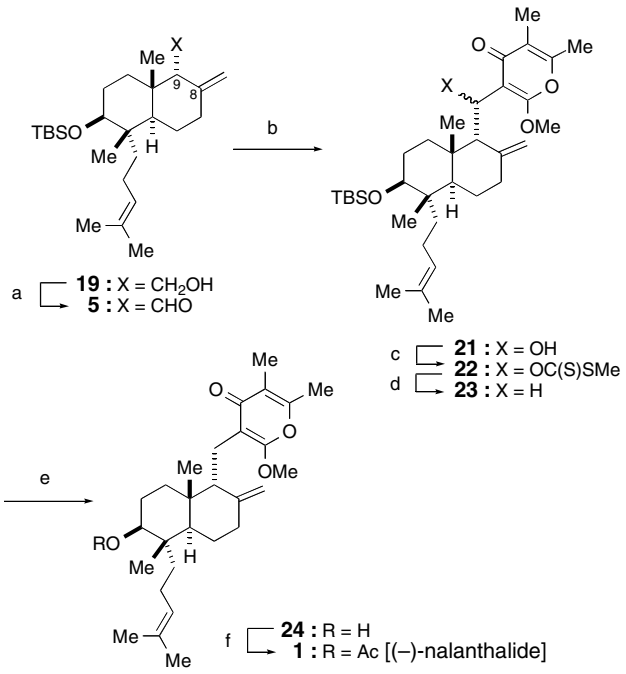
Having obtained the key intermediate **6**, we next focused our attention on the critical stereocontrolled [2,3]-Wittig rearrangement[11] of **6** to construct the requisite decalin system **19** possessing both a hydroxymethyl group at C9 and a methylene function at C8. As shown in Table 1, after several experiments, we were pleased to find that the [2,3]-Wittig rearrangement proceeded efficiently in a highly stereoselective manner by treating **6** with *n*-butyllithium in hexane at −50 °C→room temperature for 12 h. The desired rearrangement product **19** was obtained in 91% yield as the single stereoisomer (entry 1). The stereostructure of **19** was confirmed by extensive spectroscopic analysis including NOE experiments in the 500 MHz ^{1}H NMR spectrum.[12] In this reaction, the use of hexane as the solvent was critical. When THF or Et_2O was used instead of hexane, the yields of the desired rearrangement product **4** were reduced to 41–69% yields, and the undesired methyl ether **20** was obtained in 20–40% yields as the by-product (entries 2 and 3). The by-product **20** was probably formed by protonation of the intermediate carbanion **6A**, generated in situ by tin/lithium exchange; **6A** might have brought about a proton abstraction from the ethereal solvents such as THF and Et_2O because the methylene position adjacent to oxygen atom in those solvents is activated.

Dess–Martin oxidation of **19** provided the key intermediate **5**[13] in quantitative yield (Scheme 3). The crucial coupling of **5** with 3-lithio-γ-pyrone **4**[8] was achieved

Table 1. [2,3]-Wittig rearrangement of the stannylmethyl ether **6**



Entry	Solvent	Yield of **19** (%)	Yield of **20** (%)
1	Hexane	91	0
2	THF	41	40
3	Et_2O	69	20



Scheme 3. Synthesis of (−)-nalanthalide (**1**). Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, quant.; (b) 3-bromo-2-methoxy-5,6-dimethyl-4*H*-pyran-4-one, *n*-BuLi, THF, −78 °C, 5 min; at −78 °C, add **5**, −78→−55 °C, 1 h, 87%; (c) $NaN(SiMe_3)_2$, CS_2, MeI, THF, −78 °C, 2 h, 89%; (d) *n*-Bu_3SnH, AIBN, toluene, reflux, 6 h, 92%; (e) $BF_3{\cdot}Et_2O$, MeCN, 0 °C→rt, 4 h, 95%; (f) Ac_2O, DMAP, pyridine, rt, 1 h, 82%.

by an initial bromine/lithium exchange of 3-bromo-2-methoxy-5,6-dimethyl-4*H*-pyran-4-one followed by reaction with **5** at −78→−55 °C for 1 h, which provided the expected coupling product **21** in 87% yield as a mixture of epimeric alcohols (ca. 1:1 by 500 MHz ^{1}H NMR) that were very difficult to separate. Removal of the sterically hindered hydroxy group in **21** was attained by applying the modified Barton–McCombie procedure,[14] giving rise to the deoxygenated product **23** in 82% overall yield via the methyl xanthate **22**. Deprotection of the TBS group in **23** was achieved by exposure to $BF_3{\cdot}Et_2O$[15] in acetonitrile at ambient temperature, affording alcohol **24** in 95% yield. Finally, acetylation of **24** under conventional conditions (Ac_2O/pyridine/DMAP/rt) produced the target (−)-nalanthalide (**1**)[16] in 82% yield, whose spectroscopic properties (IR, ^{1}H and ^{13}C NMR, and MS) were identical with those of natural **1**. The optical rotation of a pure synthetic sample of **1** [$[\alpha]_D^{25}$ −48.3 (*c* 1.02, $CHCl_3$)] was essentially identical to that of natural **1** [lit.[1] $[\alpha]_D^{25}$ −58.2 (*c* 0.275, $CHCl_3$)], verifying its absolute configuration to be as depicted in the formulation **1**.

In summary, we have completed the first total synthesis of (−)-nalanthalide (**1**) starting from the known *trans*-decalone **7** in a convergent manner (19% overall yield in 19 steps). The key transformation of this synthesis is a highly stereocontrolled [2,3]-Wittig rearrangement of the stannylmethyl ether (**6**→**19**) and a straightforward coupling of the *trans*-decalin **5** and the 3-lithio-γ-pyrone **4** (**5**+**4**→**21**). Importantly, the synthesis has the

potential for producing nalanthalide analogues in enantiomerically pure forms due to its generality and flexibility. These efforts are currently underway.

Acknowledgments

We are especially grateful to Dr. Sheo B. Singh (Merck Research Laboratories) for providing us with copies of the ^{1}H and ^{13}C NMR spectra of natural (−)-nalanthalide (**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 Grants-in-Aid for High Technology Research Program and for Scientific Research on Priority Areas (17035073) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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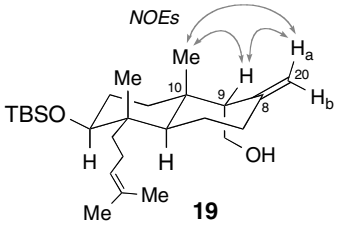
12. The configuration of the newly formed C9 stereocenter in **19** was confirmed by NOESY experiments as depicted in the following figure, where clear NOE interactions between the angular methyl group (C10–Me) and C9–H, C20–Ha and between C9–H and C20–Ha were observed, respectively.



This remarkable stereoselectivity can be rationalized by the consideration that the attack of the in situ generated carbanion on the C9 olefinic carbon occurred exclusively from the less hindered α-face of the molecule under an influence of the β-oriented axial methyl group at C10.
13. Data for **5**: Colorless viscous oil, $[\alpha]_D^{20}$ +42.4 (*c* 0.81, $CHCl_3$). IR (neat) 2930, 2857, 1719, 1460, 1385, 1254, 1101, 1065, 937, 891, 837, 774, 619, 523, 415 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.04 (3H, s), 0.77 (3H, s), 0.87 (9H, s), 0.97 (3H, s), 1.15–1.30 (3H, m), 1.35–1.40 (1H, m), 1.44–1.50 (1H, m), 1.50–1.58 (4H, m), 1.61 (3H, s), 1.68 (3H, s), 1.80–1.88 (2H, m), 2.20–2.30 (1H, m), 2.40–2.47 (1H, m), 2.61 (1H, d, $J = 3.8$ Hz), 3.52 (1H, dd, $J = 4.3$, 11.1 Hz), 4.77 (1H, br s), 4.94 (1H, t, $J = 1.8$ Hz), 5.04 (1H, br t, $J = 7.0$ Hz), 9.88 (1H, d, $J = 3.9$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.0, −3.6, 17.8, 17.9, 18.0, 20.8, 21.6, 22.0, 25.9 (three carbons), 27.8, 33.0, 35.1, 36.1, 36.9, 38.9, 41.3, 41.8, 71.1, 73.5, 113.9, 124.6, 131.0, 142.2, 202.6. HREIMS (*m*/*z*) calcd for $C_{26}H_{46}O_2Si$ (M^+): 418.3267; found 418.3253.
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15. Deprotection of the TBS group of **23** under the usual conditions (tetrabutylammonium fluoride, THF, rt→ reflux) was unsuccessful. The γ-pyrone moiety of **23** was labile under these basic conditions.
16. Data for **1**: amorphous white solid, mp 144–146 °C [lit.[1] 96.5–98 °C], $[\alpha]_D^{25}$ −48.3 (*c* 1.02, $CHCl_3$) [lit.[1] $[\alpha]_D^{25}$ −58.2 (*c* 0.275, $CHCl_3$)]. IR (neat) 702, 735, 881, 982, 1026, 1240, 1252, 1317, 1375, 1417, 1458, 1599, 1670, 1732, 2854, 2925 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, s), 0.96 (3H, s), 1.14–1.22 (1H, m), 1.22–1.33 (1H, m), 1.35–1.40 (2H, m), 1.50–1.54 (1H, m), 1.61 (3H, s), 1.68 (3H, s), 1.70–1.78 (3H, m), 1.85–1.93 (1H, m), 1.89 (3H, s), 1.92–2.00 (2H, m), 1.97 (1H, dd, $J = 3.2$, 11.9 Hz), 2.04 (3H, s),

2.10 (1H, dd, $J = 3.2$, 13.7 Hz), 2.24 (3H, s), 2.35–2.42 (1H, m), 2.43 (1H, t, $J = 12.4$ Hz), 2.67 (1H, dd, $J = 3.6$, 12.8 Hz), 3.84 (3H, s), 4.20 (1H, t, $J = 1.3$ Hz), 4.51 (1H, t, $J = 2.2$ Hz), 4.82 (1H, dd, $J = 7.3$, 9.1 Hz), 5.06 (1H, t, $J = 7.3$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.0, 17.0, 17.5, 18.1, 20.0, 21.3, 21.8, 22.7, 23.0, 24.1, 25.7, 30.7, 33.8, 37.4, 37.9, 39.2, 40.0, 55.3, 55.6, 76.3, 103.3, 109.5, 118.6, 124.7, 131.3, 148.7, 154.8, 162.8, 170.7, 180.3. HRFABMS (m/z) calcd for $C_{30}H_{45}O_5$ [$(M+H)^+$]: 485.3267, found 485.3251.