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Enantioselective total synthesis of cineromycin B

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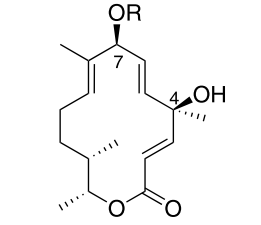
Abstract—The enantioselective total synthesis of cineromycin B, a 14-membered unsaturated macrolide with two doubly allylic alcohols, was completed using a Julia coupling, an oxidative [2,3]-sigmatropic rearrangement of selenide, and a Yamaguchi macrolactonization as key reactions.

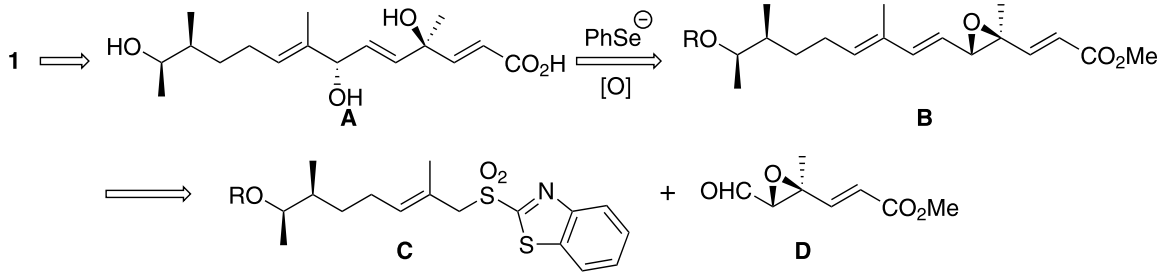
The fourteen-membered unsaturated macrolide, cineromycin B (**1**), was isolated from various strains of *Streptomyces* sp.,[1–3] and the close relation albocycline (**2**) was obtained from other strains of *Streptomyces* sp.[4,5] (Fig. 1). In addition to the antibiotic activity against *B. subtilis* and *S. aureus*,[1,4,6] these macrolides were reported to inhibit prolyl endopeptidases.[7] Although **2** exhibits notable antibacterial and inhibitory activities, those of **1** were moderate and no other remarkable activity was revealed. As a result of these biological properties, albocycline (**2**) has been synthesized previously by Tanner et al. in 1987,[8] but a synthesis of **1** has not yet been reported. Very recently, however, it was found that cineromycin (**1**) induces apoptosis of tumor cells[9] and this inspired us to embark upon a total synthesis. The structure contains two doubly allylic alcohols (C4, C7) in **1** and as a result is very acid sensitive. For this reason, in a synthesis of **1**, it is important to introduce chiral alcohols under mild and non-acidic conditions. Herein, we wish to describe a convergent and enantioselective synthesis of cineromycin B (**1**) making use of an oxidative [2,3]-sigmatropic rearrangement of selenide[10,11] for construction of ene-1,4-diol system.

Our plan for the synthesis of cineromycin B is shown in Scheme 1. Yamaguchi macrolactonization[12] of trihy-



Cineromycin B (**1**): R = H
Albocycline (**2**): R = Me

Figure 1.



Scheme 1.

Keywords: cineromycin B; doubly allylic alcohol; Julia coupling; oxidative [2,3]-sigmatropic rearrangement; Yamaguchi macrolactonization.
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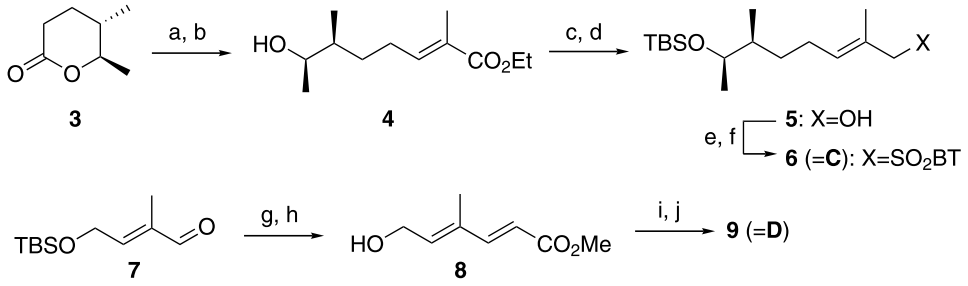


Scheme 2. *Reagents and conditions*: (a) DIBAL-H, CH_2Cl_2, −78°C; (b) $Ph_3P{=}C(CH_3)CO_2Et$, $CHCl_3$, 40°C (96%, two steps); (c) TBSCl, imidazole, DMF (96%); (d) DIBAL-H, CH_2Cl_2, −78°C (94%); (e) 2-mercaptobenzothiazole, PPh, DEAD, THF (98%); (f) H_2O_2, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, 0°C to rt (87%); (g) $Ph_3P{=}CHCO_2Me$, PhH, reflux (92%); (h) TBAF, THF, −78°C to 0°C (95%); (i) L-(+)-DET, TBHP, Ti(O-*i*-Pr)$_4$, MS 4Å, CH_2Cl_2, −25°C to 15°C (96%, 93% ee); (j) Dess–Martin oxidn., pyr., CH_2Cl_2, then recryst. (80%).

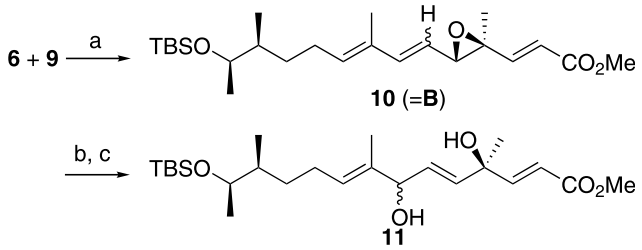
droxycarboxylic acid **A** was thought to form 14-membered macrolide predominantly due to the steric restriction of the *trans*-double bonds. Epoxide opening of **B** with selenide, followed by oxidative [2,3]-sigmatropic rearrangement[10,11] should provide a method for the stereoselective introduction of two doubly allylic alcohols. Epoxy triene **B** would be accessible by Julia coupling[13–15] of sulfone **C** with epoxy aldehyde **D**.

The synthesis commenced with the preparation of sulfone **6** for Julia coupling (Scheme 2). Reduction of known lactone **3**[16] with DIBAL-H to a corresponding lactol, followed by Wittig reaction with $Ph_3P{=}C(Me)CO_2Et$ afforded hydroxy ester **4**. Protection of the alcohol in **4** as a TBS ether and subsequent reduction of the ester moiety with DIBAL-H gave allylic alcohol **5** in satisfactory yield. Alcohol **5** was then transformed into corresponding sulfone **6** in two steps via Mitsunobu reaction with 2-mercaptobenzothiazole,[17,18] and ammonium heptamolybdate catalyzed oxidation.[18,19] The overall yield was 74% over six steps from **3**. We then moved to a synthesis of epoxy aldehyde **9**, a coupling partner in the Julia reaction. Known aldehyde **7**[20] was treated with $Ph_3P{=}CHCO_2Me$ to afford the corresponding conjugated ester, whose protected alcohol was then liberated by TBAF treatment to give allylic alcohol **8**. Katsuki–Sharpless asymmetric epoxidation[21,22] of **8** (0.5 equiv. of Ti(O*i*-Pr)$_4$, 0.6 equiv. of L-diethyl tartrate, 3.0 equiv. of TBHP) proceeded in excellent yield and acceptable enantioselectivity (96% yield, 93% ee). When a lesser amount of catalysts was used, a longer reaction time was required and enantioselectivity of the product has decreased. Dess–Martin oxidation and recrystallization afforded enantiomerically pure **9** (mp 76.5–76.8°C) in 67% overall yield (four steps) from **7**.

Thus, with both segments in hand, the Julia coupling[13–15] of **6** with **9** was investigated (Scheme 3). In this reaction, geometry of the newly introduced double bond is important since it is reflected in the stereochemistry of the secondary alcohol of **11**. Firstly, the coupling was performed under the standard condition (LHMDS, THF at −78°C) and the unstable product (**10**) was subjected immediately to the next reaction. As shown in Table 1 (entry 1), *E*/*Z* selectivity as well as the yield (after subsequent two steps) was disappointingly poor. On the other hand, when the reaction was carried out at −98°C, the yield was remarkably improved, while the undesired *Z* selectivity was observed (entry 2). We thought that this uncommon inverse selectivity was caused by some chelation effect of the epoxide oxygen and found that using HMPA and MS 4Å as additives restored the *E* selectivity to 70:30 (entry 3). Without separating the *E*/*Z* isomers, **10** was subjected to regio- and stereoselective epoxide opening with selenium reagent and the resulting selenide was oxidized to selenoxide with hydrogen peroxide, which caused [2,3]-sigmatropic rearrangement[10,11] at 0°C to afford **11**.

Cleavage of TBS ether in **11** with TBAF in HMPA followed by hydrolysis of the ester with NaOH gave trihydroxycarboxylic acid **12** (Scheme 4). However, Yamaguchi macrolactonization[12] of **12** did not afford cineromycin B (**1**), and γ-lactone **13** was obtained in 68% yield. Modified Keck's method (DCC, DMAP, DMAP·TFA),[23,24] which was used in the synthesis of **2**,[8] also gave the same result.

Since this isomerization of the double bond was thought to be caused by the presence of γ-tertiary alcohol, it was protected as the TES ether. Successive treatment with TESCl and TESOTf produced a compound whose all alcohols were protected. This sequence was necessary; using only TESCl led to the protection of the secondary alcohols, while using only TESOTf led to decomposition. Treatment of **15** with 2.0 equiv. of

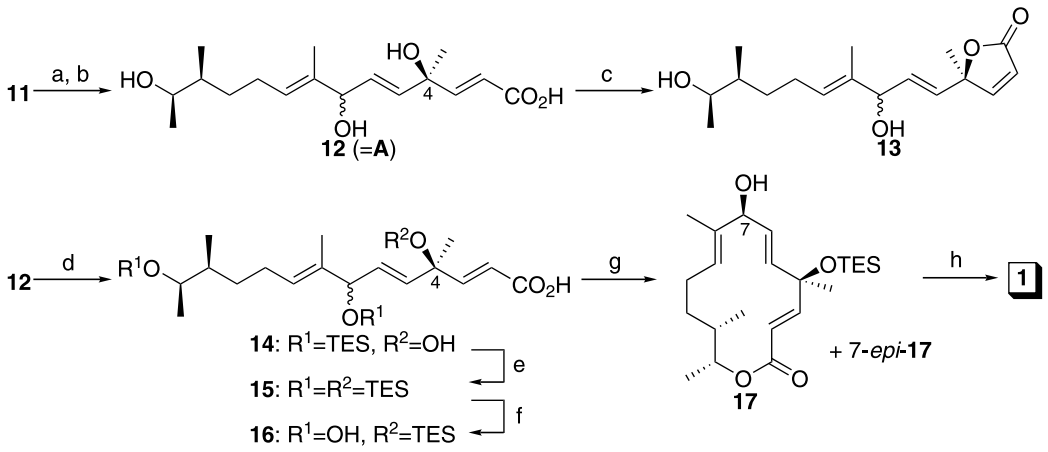


Scheme 3. *Reagents and conditions*: (a) LHMDS, THF, Table 1; (b) $(PhSe)_2$, $NaBH_4$, MeOH, 0°C to rt; (c) H_2O_2, THF, 0°C.

Table 1.

Entry	Additive (equiv.)	Temp. (°C)	E/Z*	Yield of **11** over three steps (%)
1	None	−78	50:50	14
2	None	−98	38:62	62
3	HMPA (2.0), MS 4Å	−98	70:30	52

* Determined by ^{1}H NMR of the crude product.



Scheme 4. *Reagents and conditions*: (a) TBAF·xH$_2$O, MS 4Å, HMPA (86%); (b) NaOH, H$_2$O/THF (1:1), 0°C (78%); (c) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, THF; DMAP, PhH, reflux (68%); (d) TESCl, pyr., 60°C; (e) TESOTf, pyr., 60°C (80%, two steps); (f) TBAF (2 equiv.), THF, rt (70%); (g) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, THF; DMAP, PhMe, reflux (**17**: 42%, 7-*epi*-**17**: 22%); (h) TBAF, THF (quant.).

TBAF at room temperature cleaved the secondary TES ethers to give **16**. Yamaguchi macrocyclization[12] afforded the desired lactone **17** (42%) along with its C-7 epimer (22%) which originated from Z isomer of **10**, and the ratio of diastereomers was in accord with E/Z ratio of **10**. Finally, cleavage of TES group with TBAF led **17** to cineromycin B (**1**) in quantitative yield. Our synthetic **1** was identical in all respects with the natural sample; mp 147.8–148.5°C (lit.[1] 149–150°C); $[\alpha]_D^{26} = -127°$ (c 0.48, methanol) [lit.[1] $[\alpha]_D^{24} = -110°$ (c 1, methanol)].

In conclusion, the first total synthesis of cineromycin B (**1**) has been accomplished by employing epoxide opening with selenide and subsequent oxidative rearrangement as key steps. The overall yield in the longest linear sequence (16 steps from lactone **3**) was 6.1%.

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