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Synthetic studies of incednine: synthesis of C1–C13 pentaenoic acid segment

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ABSTRACT

Stereoselective synthesis of the C1–C13 pentaenoic acid segment (**4**) of the novel antibiotic incednine (**1**) is described.

In 2008, Imoto and co-workers reported the isolation of a novel antibiotic, incednine (**1**), from *Streptomyces* sp. Although determination of the configuration at the C-23 stereocenter was supported by computer modeling studies and the stereochemistry was not totally clear, they also disclosed the structural elucidation of **1**.[1] This novel natural product exhibited significant inhibitory activity against the anti-apoptotic oncoproteins Bcl-2 and Bcl-xL, with a mode of action distinct from those of other inhibitors which inhibit the binding capacity of Bcl-xL to pro-apoptotic protein Bax. These proteins are overexpressed in many cancers, resulting in the expansion of transformed populations and advancement of the multidrug-resistant stage.[2–4] Therefore, **1** is expected to be a leading compound in the development of novel anti-tumor drugs, and it is also expected to be a useful tool for further study of the Bcl-2 and Bcl-xL functions. The identification of its target protein could provide a new insight into the anti-apoptotic mechanism of Bcl-2 family proteins.

Structurally, **1** has been shown to contain several unique features. It contains α-methoxy-α,β-unsaturated amide structure and independent conjugated pentaene and tetraene systems in the 24-membered macrolactam core. Furthermore, the macrolactam core is coupled with two amino sugars by β-glycosidic bonds. Because of its important biological activity and novel molecular architecture, **1** has been deemed as a prime target for total synthesis. Herein we report the stereoselective synthesis of the C1–C13 pentaenoic acid segment **4**.

In our strategy for the total synthesis of **1**, as shown in Figure 1, the C-11 glycosidic bond is constructed in the last stage of the synthesis. The aglycon **2** is prepared from the pentaenoic acid segment **4**, which is prepared from ethylene glycol (**6**), and the tetraene segment **3**. The pentaene structure in **4** is constructed by various olefination reactions, and the creation of the C-10 and C-11 stereocenters is achieved by Sharpless asymmetric epoxidation[5] of the allylic alcohol **5** (Fig. 1).

The synthesis of pentaenoic acid segment **4**, corresponding to the C1–C13 of **1**, is summarized in Schemes 1 and 3. We first synthesized the known epoxide **9**, referring to the procedure of Shimizu and Nakata.[6] Ethylene glycol (**6**) was protected as a mono-PMB ether using PMBCl and KOH at 130 °C in 92% yield.[7] The resulting primary alcohol **7** was then converted into the α,β-unsaturated ester **8** by a one-pot Swern oxidation-Wittig reaction,[8] using $Ph_3PC(Me)CO_2Et$, in 99% yield with *E* selectivity. After reduction of **8** to the allylic alcohol **5** in 99% yield using DIBAL-H, **5** was treated with Ti(O-*i*Pr)$_4$, (−)-DIPT, and TBHP at −78 °C (Sharpless asymmetric epoxidation) to furnish epoxide **9** in 78% yield with 90% ee. At this stage, we examined the regioselective introduction of a hydroxyl group function to epoxide **9**. After many attempts, we finally found that applying Honda's conditions[9] using $Me_4NBH(OAc)_3$ gave the desired diol **10** in high yield (92%). The terminal hydroxyl group of **10** was protected as a TBS ether in 94% yield, and the acetyl group was then removed using NaOMe to give diol **11** in 78% yield. It was found under these conditions that migration of the silyl group produced **11** and **12** in a ratio of 78:21. Fortunately, however, the undesired silyl ether **12** could easily be converted into the desired **11** by treatment with NaOMe in MeOH. Protection of the 1,2-diol in **11** as a cyclic acetal isopropylidene group, using $Me_2C(OMe)_2$ and CSA, followed by deprotection of the TBS group with TBAF and Swern oxidation of the resulting primary alcohol produced aldehyde **13** in 88% overall yield. Subsequent Wittig

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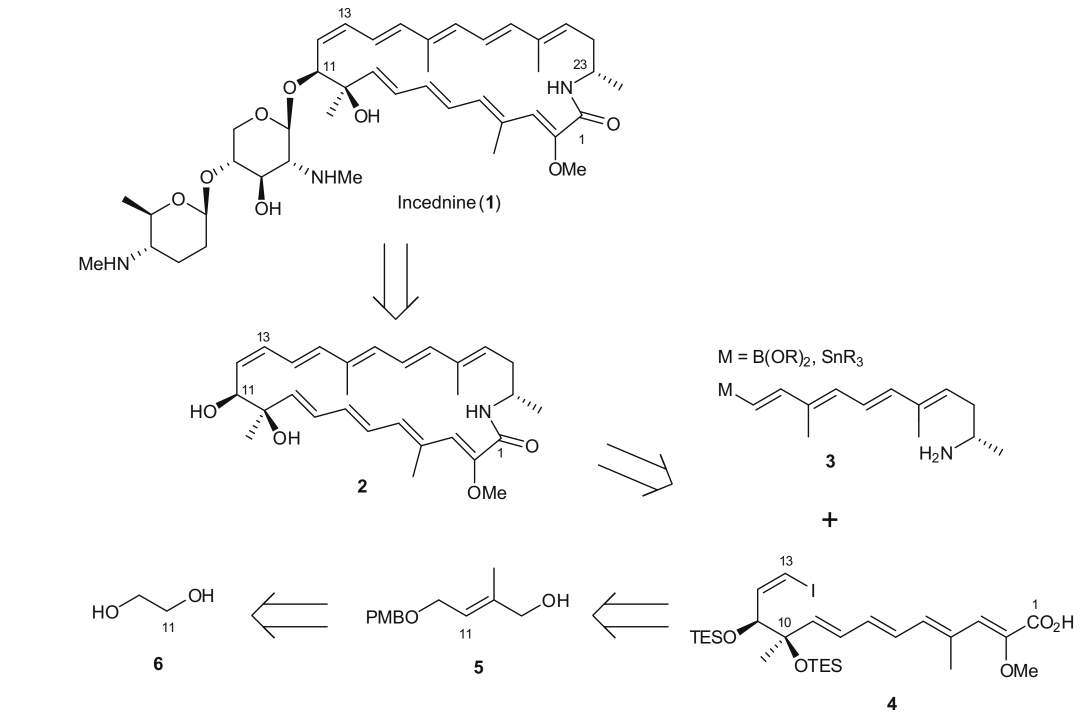
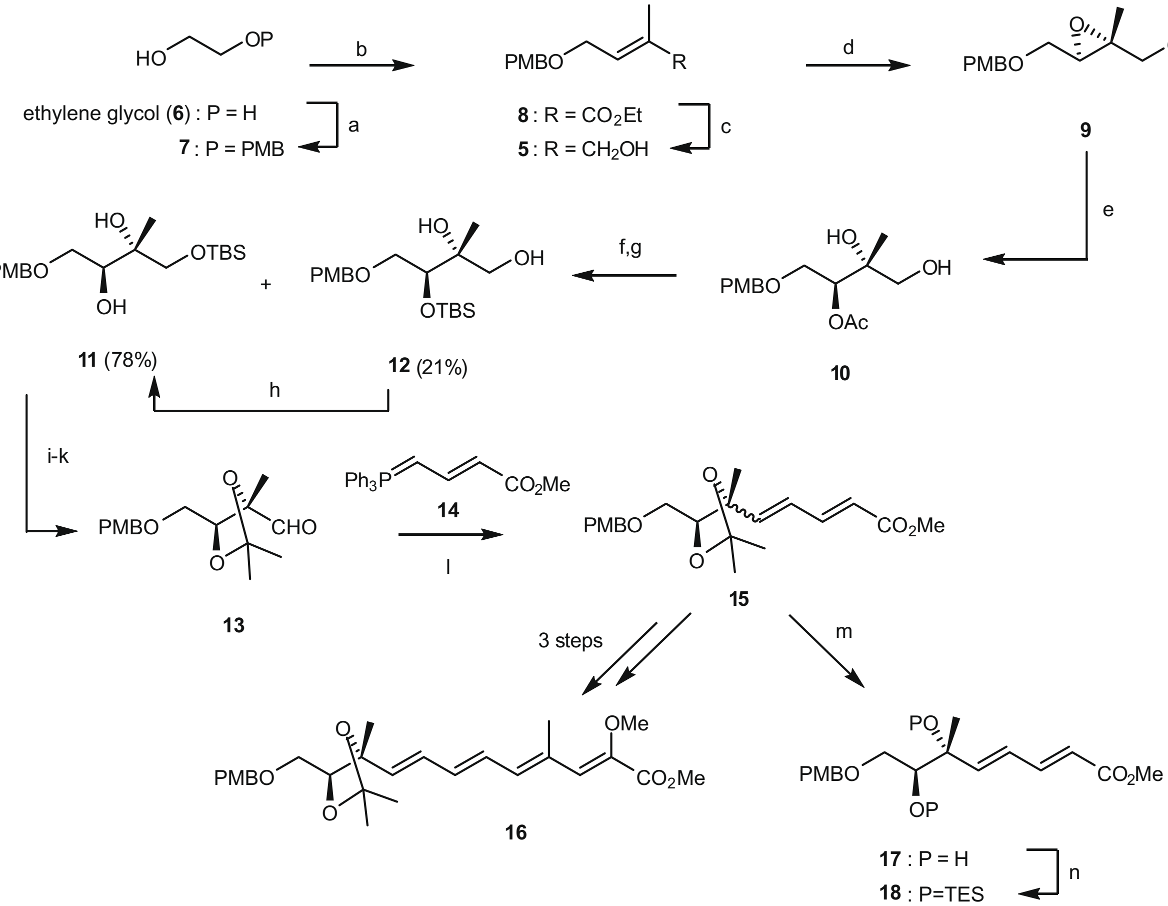


Figure 1. Retrosynthetic analysis of incednine (**1**).

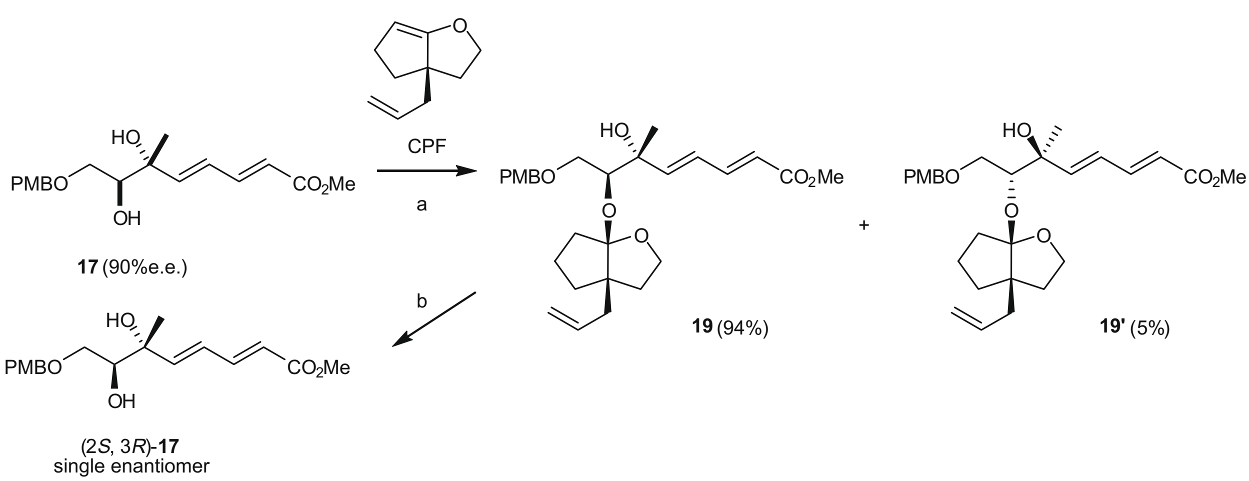


Scheme 1. Reagents and conditions: (a) PMBCl, KOH, 130 °C, 3 h (Dean–Stark), then 35 °C, 14 h, 92%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 1 h, then $Ph_3PC(Me)CO_2Et$, rt, 30 min, 99%; (c) DIBAL-H, PhMe, −78 °C, 20 min, 99%; (d) $Ti(Oi\text{-}Pr)_4$, (−)-DIPT, TBHP/decane, MS4A, CH_2Cl_2, −20 °C, 65 h, 78% (90% ee); (e) $Me_4NBH(OAc)_3$, PhMe, 60 °C, 13 h, 92%; (f) TBSCl, imid., DMF, 0 °C to rt, 3 h, 94%; (g) NaOMe, MeOH, −20 °C, 24 h, 78%; (h) NaOMe, MeOH, 0 °C to rt, 75%; (i) $Me_2C(OMe)_2$, CSA, acetone, 0 °C, 2 h, 98%; (j) TBAF, THF, rt, 5 h, 97%; (k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −20 °C, 1.5 h, 93%; (l) **14**, PhMe, 60 °C, 21 h, 97% (*E*/*Z* = 79/21); (m) PPTS, MeOH, rt to 40 °C, 4 d, 64%; (n) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 20 min, 98%.

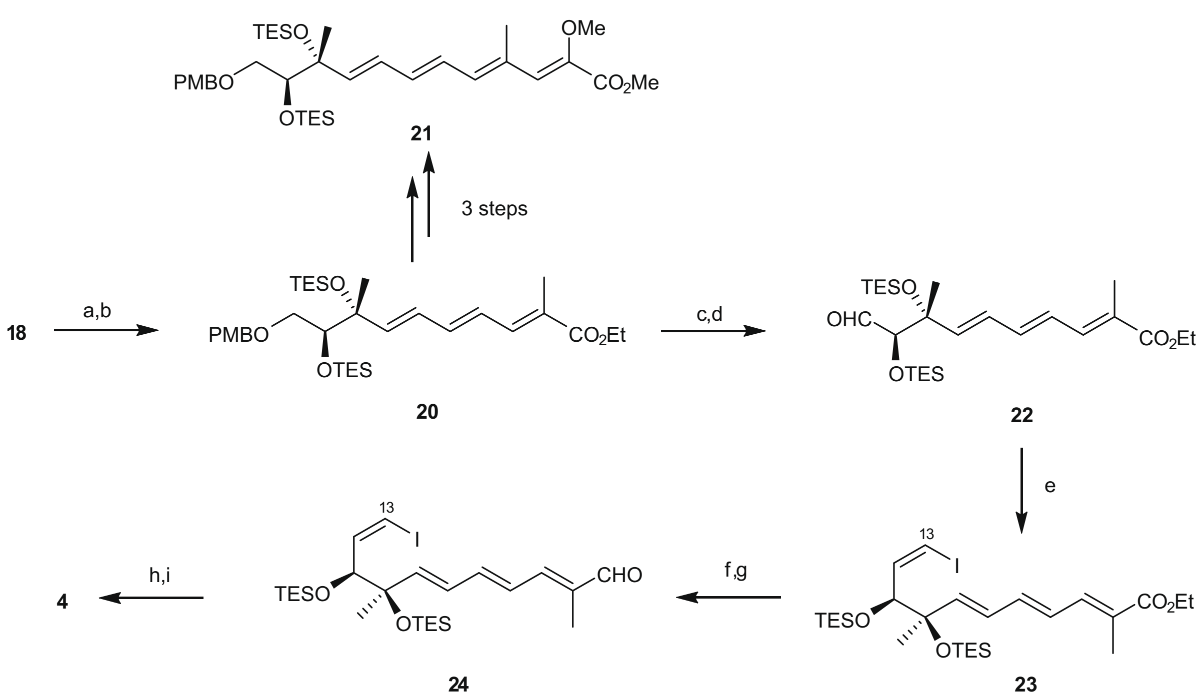
reaction of **13** with **14**[10] introduced the diene structure, producing **15** in 97% yield with *E*/*Z* = 79/21. Although the *E*/*Z* isomers were inseparable at this stage, we were able to separate them at the following stage. Compound **15** was converted to the tetraene segment **16** in three steps (1: DIBAL-H reduction (93%); 2: One-pot MnO_2 oxidation-Wittig reaction using $Ph_3PC(Me)CHO$ (74%); and 3: Horner–Wadsworth–Emmons reaction using $(i\text{-PrO})_2P(O)CH(OMe)CO_2Me$ (49%)). Unfortunately, all attempts to selectively remove the PMB group in **16** failed due to instability under acidic and oxidative conditions. It was also predicted that deprotection of the isopropylidene group at the C10 and C11 positions in the latter step would prove to be a difficult problem in the synthesis of **1**. Therefore, at this stage, the cyclic acetal of **15** was removed using PPTS in MeOH, and the resulting diol **17** was protected with TES groups using TESOTf and 2,6-lutidine to give **18** in 63% overall yield.

Fortunately, we found that optical resolution of diol **17** using the chiral resolving reagent (*R*)-3a-allyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan (CPF)[11] developed by Nemoto et al. was effective (Scheme 2). Subjecting **17** to CPF in the presence of catalytic amounts of PPTS in PhMe led to the corresponding acetals in 99% yield as a mixture of diastereomers, **19** (94%) and **19'** (5%), which could easily be separated by flash column chromatography (CH_2Cl_2/EtOAc = 10/1 (ΔR_f = 0.089)). Removal of CPF from **19** using PTSA in MeOH gave (2*S*,3*R*)-**17** as a single enantiomer in 99% yield.

Enantiomerically pure **18**, obtained as described above, was treated with DIBAL-H to reduce the ester function, and the resulting allylic alcohol was oxidized with MnO_2 and then treated with



Scheme 2. Reagents and conditions: (a) CPF, PPTS, PhMe, rt, 1.5 h, 99%; (b) *p*-TsOH, MeOH, rt, 2 h, 99%.



Scheme 3. Reagents and conditions: (a) DIBAL-H, PhMe, −78 °C, 30 min, 95%; (b) MnO_2, PhMe, 40 °C, 5 h, then $Ph_3PC(Me)CO_2Et$, 40 °C, 16 h, 95%; (c) DDQ, CH_2Cl_2/pH 7.2 phosphate buffer (1/1), 0 °C to rt, 19 h, 72%; d) Dess–Martin periodinane, pyr., CH_2Cl_2, 0 °C to rt, 17 h, 92%; (e) $(Ph_3P^+CH_2I)I^-$, NaHMDS, HMPA, THF, −98 °C, 1 h, 67%; (f) DIBAL-H, PhMe, −78 °C, 10 min, 98%; (g) MnO_2, CH_2Cl_2, 40 °C, 2 h, 77%; (h) $(MeO)_2P(O)CH(OMe)CO_2Me$, KHMDS, 18-crown-6 ether, THF, 0 °C to rt, 1 h, 82%; (i) 1.0 M KOH aq, 1,4-dioxane, 0 °C to 30 °C, 2 h, 66%.

$Ph_3P{=}C(Me)CO_2Et$ to furnish the α,β-unsaturated ester **20** in 90% overall yield. At this stage we again constructed an enol ether structure **21** in three steps (1:DIBAL-H reduction (78%); 2:MnO_2 oxidation (89%):3. Horner–Wadsworth–Emmons reaction using $(MeO)_2P(O)CH(OMe)CO_2Me$) (54%)). Unfortunately, deprotection of PMB group of **21** was again unsuccessful. Therefore, we next attempted to introduce a vinyl iodide structure to the α,β-unsaturated ester **20** in advance. It was found, fortunately, that removal of the PMB group in **20** with DDQ proceeded very smoothly, and Dess–Martin oxidation of the resulting alcohol gave aldehyde **22** in 66% overall yield. Wittig reaction of **22** with $(Ph_3P^+CH_2I)I^-$ in the presence of NaHMDS and HMPA in THF at −98 °C led to vinyl iodide **23** in 67% yield with *Z* selectivity. The α,β-unsaturated ester in **23** was reduced by DIBAL-H, and the resulting allylic alcohol was oxidized by MnO_2 to furnish aldehyde **24** in 75% overall yield. Finally, Horner–Wadsworth–Emmons olefination of **24** using $(MeO)_2P(O)CH(OMe)CO_2Me$ in the presence of KHMDS and 18-crown-6 ether[12] in THF, followed by hydrolysis using KOH, gave the C1–C13 pentaenoic acid segment **4**[13] in 54% overall yield.

In conclusion, we achieved a stereoselective synthesis of pentaenoic acid segment **4**, which is a key segment in the synthesis of incednine (**1**).

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