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Total Synthesis of Incednam, the Aglycon of Incednine

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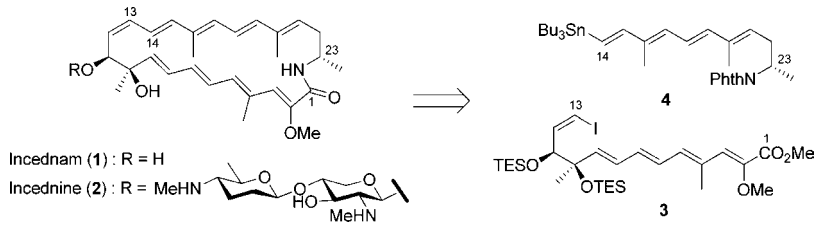
ABSTRACT



The first total synthesis of incednam (1), the aglycon of antibiotic incednine (2), is described. Incednine has been reported to exhibit significant inhibitory activity against the antiapoptotic oncoproteins Bcl-2 and Bcl-xL. The synthesis of 1 commenced with the preparation of the C1−C13 subunit 3 and the C14−C23 subunit 4. The construction of the novel 24-membered macrocycle was achieved by the application of a Stille coupling between 3 and 4, followed by macrolactamization.

Incednam (**1**) is the aglycon of the 24-membered macrolactam glycoside antibiotic incednine (**2**), which was isolated from *Streptomyses* sp. in 2008.[1] It was demonstrated that **2** exhibits significant inhibitory activity against the antiapoptotic oncoproteins Bcl-2 and Bcl-xL, with a mode of action distinctly different from those of other compounds that inhibit the binding capacity of Bcl-xL to the pro-apoptotic protein Bax. In addition, it is known that these proteins are overexpressed in many cancer cells, resulting in the expansion of a transformed population and the advancement of the multidrug-resistant stage.[2−4] Therefore, **2** is now expected to be a compound in the development of novel antitumor drugs. Furthermore, **2** is likely to be a useful tool for the further study of Bcl-2 and Bcl-xL functions. The identification of its target protein could provide insight into the antiapoptotic mechanism of the Bcl-2 family proteins. From a structural perspective, **1** and **2** contain unique salient features: an α-methoxy-α,β-unsaturated amide moiety and two independent conjugated polyene systems embedded in the 24-membered macrolactam ring. As a result of the nature of the highly conjugated polyene subunits, **1** and **2** are light- and acid-sensitive. Although **1** was also isolated from *Streptomyses* sp.,[1] its semisynthesis from **2** has not been realized, in part, because of the inherent chemical instabilities mentioned above. Furthermore, the stereochemical configuration at C23 was postulated on the basis of computational modeling studies, thus the configuration has not been conclusively defined. Because of its important biological

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(1) Futamura, Y.; Sawa, R.; Umezawa, Y.; Igarashi, M.; Nakamura, H.; Hasagawa, K.; Yamasaki, M.; Tashiro, E.; Takahashi, Y.; Akamatsu, Y.; Imoto, M. *J. Am. Chem. Soc.* **2008**, *130*, 1822.
(2) Tsujimoto, Y.; Finger, L. R.; Yunis, J.; Nowell, P. C.; Croce, C. M. *Science* **1984**, *226*, 1097.
(3) Reed, J. C.; Cuddy, M.; Slabiak, T.; Croce, C. M.; Nowell, P. C. *Nature* **1988**, *336*, 259.
(4) Gross, A.; McDonnell, J. M.; Korsmeyer, S. J. *Gene Dev.* **1999**, *13*, 1899.

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activity and novel molecular architecture, **1** and **2** were considered to be prime targets for chemical synthesis. Herein we report the first total synthesis of **1** leading to the unambiguous stereochemical assignment of the configuration at C23.

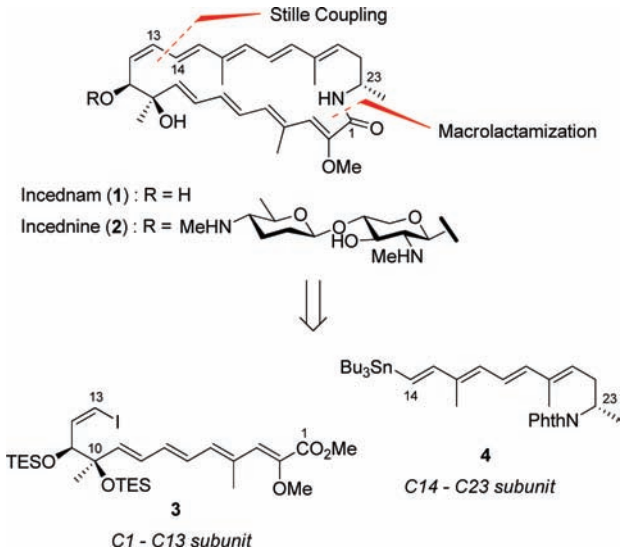
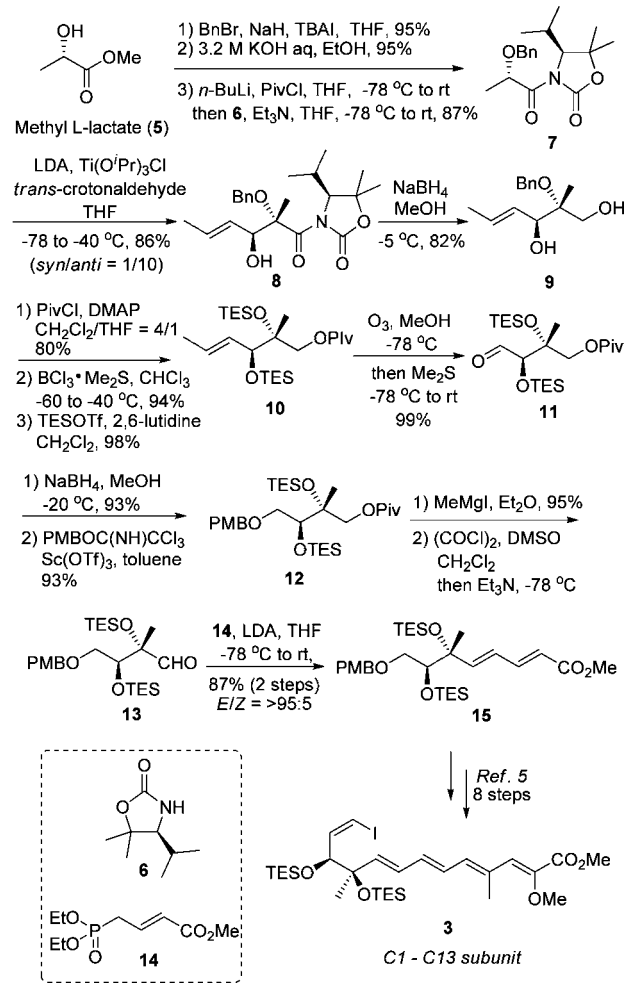


Figure 1. Retrosynthetic analysis of incednam (**1**).

The retrosynthetic analysis of **1** is depicted in Figure 1. The convergent strategy implemented toward the construction of the novel 24-membered macrocycle is based on the coupling of two domains: the C1−C13 subunit **3** containing the vinyl iodide moiety and the C14−C23 subunit **4** containing the vinyl stannane moiety. This union could be effected by the application of a Stille coupling and subsequent macrolactamization. Our group recently reported an asymmetric synthesis of **3**,[5] employing a Sharpless asymmetric epoxidation as the key step. However, in this sequence an optical resolution involving the stoichiometric use of an optical resolution agent was required to provide the enantiomerically pure subunit **3**. To circumvent this issue, we first developed a direct synthetic route toward the stereochemically pure subunit **3**, which was facilitated by an Evans aldol addition thereby establishing the C10 and C11 stereocenters.

The synthesis of the pentaenoate subunit **3**, corresponding to C1−C13 in **1**, is summarized in Scheme 1. The known 1,3-diol **9**[6] was prepared from methyl L-lactate (**5**). Benzylation of **5** and subsequent coupling with the chiral auxiliary **6**[7] provided the oxazolidinone derivative **7**. Following Kobayashi's procedure, the titanium-mediated Evans aldol addition of **7** with *trans*-crotonaldehyde using $Ti(O^iPr)_3Cl$

Scheme 1. Synthesis of the C1−C13 Subunit **3**



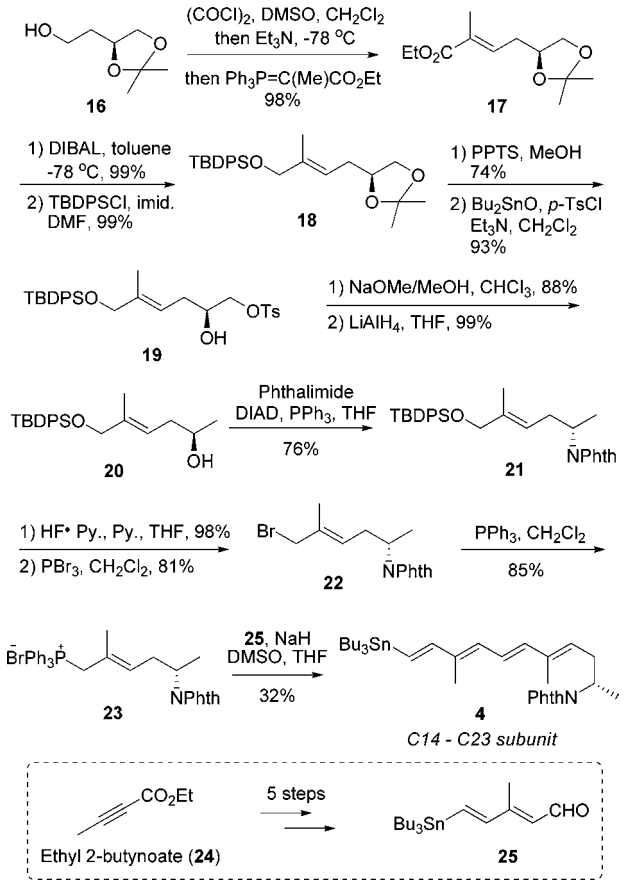
and LDA proceeded smoothly to give the desired Evans *anti* product **8** in 86% yield with high diastereoselectivity (dr =10:1). Subsequent cleavage of the chiral auxiliary in **8** with $NaBH_4$ provided the diol **9** in 82% yield. The primary alcohol was selectively protected as the pivaloyl ester, and the benzyl ether was cleaved using BCl_3•Me_2S[8] without affecting the pendant olefin. The resulting diol was subsequently protected using TESOTf and 2,6-lutidine to give the silyl ether **10** (74% overall yield). The disubstituted olefin was oxidatively cleaved with ozone to afford the aldehyde **11**, which was reduced with $NaBH_4$ to provide the primary alcohol. Protection of the resulting primary alcohol as the PMB ether using PMB trichloroacetimidate and $Sc(OTf)_3$,[9] provided **12** (86% overall yield from **10**). Cleavage of the pivaloyl ester in **12** using MeMgI,[10] without migration of the silyl groups, followed by Swern oxidation gave the aldehyde **13**. Horner−Wadsworth−Emmons olefination of **13** with the phosphonate ester **14**[11] provided the α,β,γ,δ-unsaturated ester

(5) Ohtani, T.; Kanda, H.; Misawa, K.; Urakawa, Y.; Toshima, K. *Tetrahedron Lett.* **2009**, *50*, 2270.
(6) Murata, Y.; Kamino, T.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2002**, *43*, 8121.
(7) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(8) Qureshi, S.; Shaw, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 875.
(9) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2008**, *130*, 16424.
(10) Heys, R. *J. Chem. Soc., Chem. Commun.* **1992**, 680.
(11) Barth, R.; Mulzer, J. *Tetrahedron* **2008**, *64*, 4718.

15 in high yield with high stereoselectivity (83% overall yield from **12** with *E*:*Z* = >95:5). The building block **15** was an intermediate in our previous studies and was converted into the C1−C13 subunit **3** in 8 steps in high overall yield.[5]

Next, the synthesis of the C14−C23 subunit **4** was established starting from the commercially available alcohol **16** as shown in Scheme 2. The one-pot Swern oxidation−Wittig olefination[12]

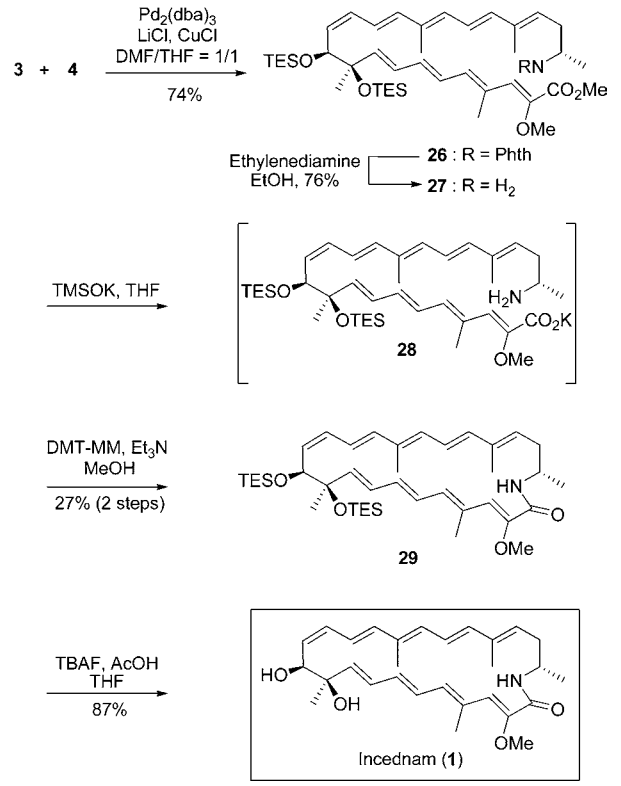
Scheme 2. Synthesis of the C14−C23 Subunit **4**



of **16** gave the α,β-unsaturated ester **17** in 98% yield with complete stereoselectivity. After the reduction of **17** with DIBAL, the resulting allylic alcohol was protected as the TBDPS ether in 98% overall yield. Deprotection of the acetonide in **17** under acidic conditions and subsequent selective tosylation of the resulting primary alcohol using Bu_2SnO, *p*-TsCl and Et_3N[13] afforded **19**. The intramolecular epoxide formation using NaOMe, followed by the selective ring opening of the resulting epoxide with $LiAlH_4$, led to **20** (60% overall yield from **18**). The secondary alcohol **20** was converted into the *N*-substituted phthalimide **21** with stereochemical inversion by the Mitsunobu reaction using phthalimide, DIAD, and PPh_3 in 76% yield. Deprotection of the TBDPS ether in **21** with HF•pyridine and subsequent bromination with PBr_3 provided the allylic bromide **22** without olefin isomerization; **22** was readily converted into the phosphonium salt **23** (67% overall yield from **21**). The Wittig olefination of **23** with the known aldehyde **25**[14] (prepared from ethyl 2-butynoate (**24**) in 5 steps) was examined under several conditions. As a result, it was found that the desired *E*-configured tetraene **4** could be obtained in 32% yield by using NaH and DMSO in THF[15] at 0 °C. Because **4** is extremely prone to oxidation and/or photochemical decomposition, it was used in the next step immediately after isolation. Considering the inherent convergency of the chemical union of **23** and **25**, the modest yield obtained in the olefination reaction is well justified. This strategy leads to the direct construction of the labile tetraene **4**, which contains the vinyl stannane moiety necessary for the subsequent Stille coupling.

Completion of the synthesis of **1** is summarized in Scheme 3. Conditions for the Stille coupling[16] of **3** with **4** was

Scheme 3. Total Synthesis of Incednam (**1**)



rigorously explored. After much experimentation, it was found that Corey's protocol[17] using Pd(0), LiCl, and CuCl gave the best result, providing the desired coupling product **26** in 74% yield. Removal of the phthaloyl group in **26** using ethylenediamine provided the amine **27** in 76%

(12) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533.

(13) Michael, J. M.; Naresh, K. N.; Eric, D. M.; Ulhas, P. D.; Joseph, M. P.; Rajappa, M. *Org. Lett.* **1999**, *1*, 447.

(14) (a) Betzer, J. F.; Delaloge, F.; Muller, B.; Panqrazi, A.; Pruner, J. *J. Org. Chem.* **1997**, *62*, 7768. (b) Michels, D. T.; Uhee, J. U.; Vanderwal, C. D. *Org. Lett.* **2008**, *10*, 4787.

(15) Tatsuta, K.; Nakagawa, A.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 1479.

(16) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.

(17) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

yield. Saponification of the methyl ester in **27** using TMSOK,[18] followed by treatment using reversed phase column chromatography, provided the potassium carboxylate **28**. Without further purification, macrolactamization of **28** utilizing DMT-MM[19] in MeOH was conducted. Gratifyingly, it was found that the macrolactamization proceeded smoothly to give the desired cyclic compound **29** in 27% overall yield from **27**. Deprotection of the TES groups in **29** was effected with TBAF and AcOH to furnish incednam (**1**). Data for an analytical sample of the synthetic incednam obtained by ^{1}H NMR, ^{13}C NMR, HRMS (ESI-TOF), and optical rotation matched those obtained for an authentic sample.[1] These results clearly confirm not only the complete synthesis of **1**, but also serve to conclusively establish the stereochemical configuration at C23 (*S* configuration), which was previously posited purely on the basis of molecular modeling.

(18) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.
(19) Kunishima, M.; Kawachi, C.; Hioki, K.; Terao, K.; Tani, S. *Tetrahedron* **2001**, *57*, 1551.

In conclusion, we have developed a convergent synthetic route to incednam (**1**), which is the aglycon of the 24-membered macrolactam glycoside antibiotic incednine (**2**). Furthermore, this synthesis serves to unambiguously define the stereochemical configuration at C23 in **1**. Additional studies with respect to the total synthesis of incednine (**2**) from **1** are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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