Pergamon

Tetrahedron Letters 42 (2001) 8873–8876

TETRAHEDRON LETTERS

Synthetic studies on apoptolidin: synthesis of the C1–C21 macrolide fragment

Kazunobu Toshima,* Tsuyoshi Arita, Koji Kato, Daisuke Tanaka and Shuichi Matsumura

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Received 13 September 2001; revised 9 October 2001; accepted 12 October 2001

Abstract—The stereoselective and convergent synthesis of the C1–C21 macrocyclic segment (**2**) of the apoptosis inducing macrolide antibiotic, apoptolidin (**1**), is described.

Novel drugs that can selectively sensitize cancer cells to apoptosis induction are very useful for treating certain cancers. Apoptolidin (**1**), isolated in 1997 by Seto and Hayakawa,[1] possesses impressive biological properties. Thus, **1** induces apoptotic cell death in rat glia cells transformed with the adenovirus E1A oncogene but not in normal glia cells. Recently, Khosla and co-workers identified the mitochondrial F_0F_1-ATPase as one possible target to explain this biological action.[2] The relative and absolute configuration of **1** has been established by extensive NMR analysis and degradation studies.[3] Apoptolidin (**1**) possesses a novel molecular structure

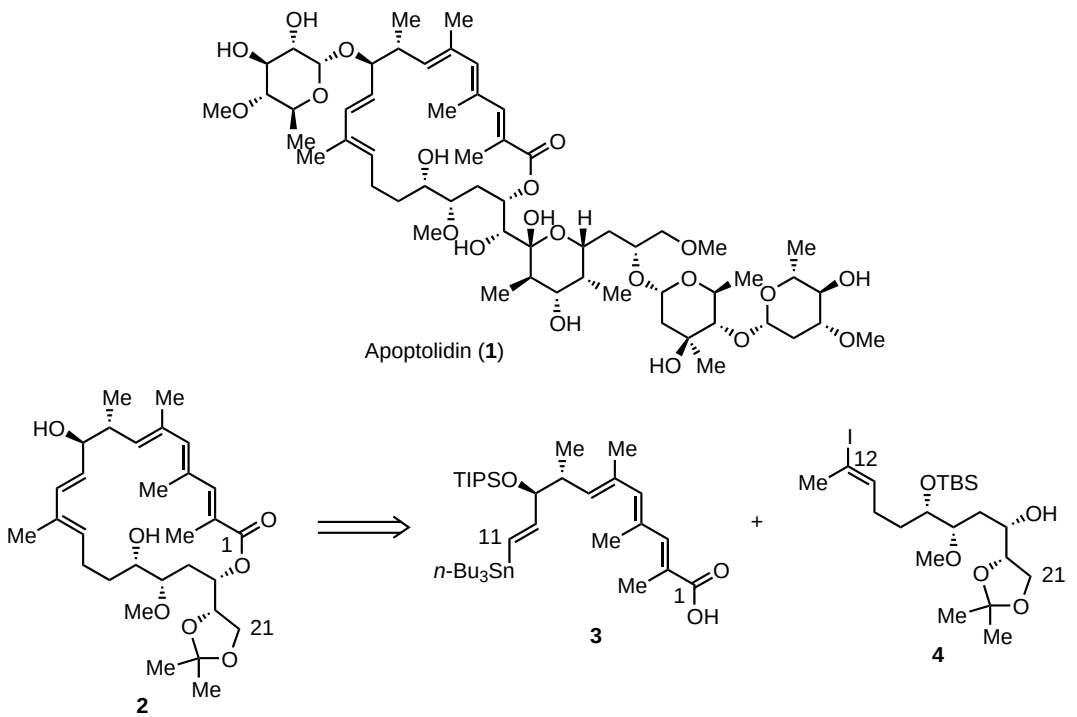


Figure 1.

Keywords: apoptolidin; apoptosis; macrolide; macrocyclization.

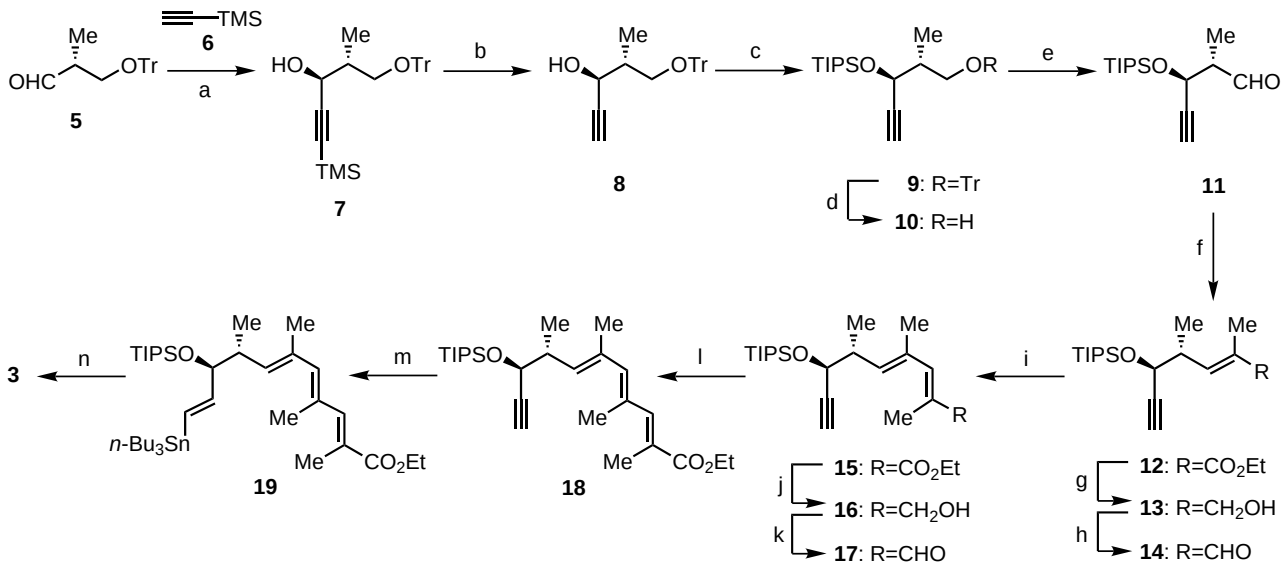
* Corresponding author. Tel./fax: +81 45 566 1576; e-mail: toshima@applc.keio.ac.jp

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01948-7

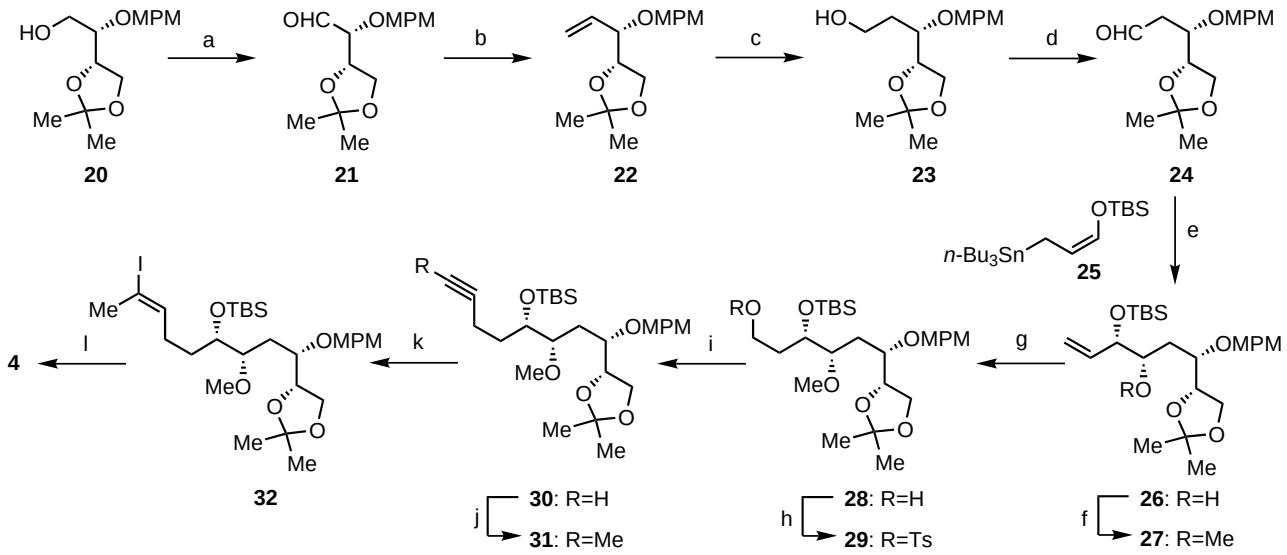
which consists of a complex aglycon and two sugar units. The aglycon is constructed of a 20-membered macrocyclic lactone containing independent conjugated triene and diene systems and a side chain at C19 containing a six-membered cyclic hemiacetal. A β-D-oleandrosyl-α-L-olivomycose disaccharide is located at C27, while a novel sugar, 6-deoxy-4-*O*-methyl-α-L-glucose is attached at C9. Because of its important biological activity and novel molecular architecture, apoptolidin (**1**) has been deemed a prime target for total synthesis. In this context, elegant synthetic studies on **1** have independently been announced by Koert's,[4a] Nicolaou's[5] and Sulikowski's[6] groups, and the synthesis of apoptolidinone,[4b] the aglycon of apoptolidin, has very recently been reported by Koert and co-workers. Herein we now disclose the stereoselective and convergent synthesis of the C1–C21 macrocyclic core (**2**) of **1**, which makes use of the key synthetic intermediates, the C1–C11 (**3**) and the C12–C21 (**4**) segments (Fig. 1).

The synthesis of the vinyl tributyltinated carboxylic acid **3** corresponding to the C1–C11 segment of **1** is summarized in Scheme 1. Reaction of the aldehyde **5**, which was readily prepared from methyl (*R*)-3-hydroxy-2-methylpropionate by Terashima's method,[7] and the trimethylsilylacetylene **6** activated by *n*-BuLi in THF at −78°C proceeded stereoselectively to afford the desired Cram-adduct **7** in 60% yield in a Cram:anti-Cram ratio of 2:1. The deprotection of the trimethylsilyl group in **7** under basic conditions using K_2CO_3 in MeOH gave **8** in 99% yield. The secondary alcohol **8** was protected with the triisopropylsilyl (TIPS) group and then the trityl group was selectively deprotected under mild acidic conditions using CSA to give the primary alcohol **10** via **9** in 78% overall yield. The primary alcohol **10** was subjected to Swern oxidation and then Wittig reaction employing $Ph_3P{=}C(Me)CO_2Et$ in toluene to furnish only the desired *trans*-olefin **12** via **11** in 96% overall yield. Subsequent reduction of the ethyl ester in **12** utilizing DIBAL-H followed by oxidation of the resulting allyl alcohol **13** employing MnO_2 gave the α,β-unsaturated aldehyde **14** in 93% overall yield. Repeating the elongation of **14** by Wittig reaction ($Ph_3P{=}C(Me)CO_2Et$), reduction (DIBAL-H) and oxidation (MnO_2) afforded the all-*trans* diene aldehyde **17** in 94% overall yield. Subsequent Horner–Wadsworth–Emmons olefination employing $(Et_2O)_2(O)PCH(Me)CO_2Et$ and *n*-BuLi in THF provided only the desired all-*trans* triene **18** in 99% yield. It was found that Wittig reaction employing $Ph_3P{=}C(Me)CO_2Et$ gave a small amount of the *cis*-isomer. Pd^0-catalyzed hydrostannylation (*n*-Bu_3SnH, cat. $PdCl_2(PPh_3)_2$)[8] proceeded regio- and stereoselectively to furnish the desired *trans*-vinyl tributyltin **19** in 92% yield. In the final transformation, hydrolysis of the ethyl ester in **19** under basic conditions (LiOH, 1,4-dioxane) yielded the carboxylic acid **3** in 79% yield.

The construction of the vinyl iodidenated secondary alcohol **4** corresponding to the C12–C21 segment of **1** from diethyl L-tartrate is depicted in Scheme 2. The primary alcohol **20**, which was easily obtained from diethyl L-tartrate by Somfai's procedure in four steps,[9] was subjected to Dess–Martin oxidation[10] and then Wittig reaction employing $Ph_3P{=}CH_2$ to furnish the olefin **22** via **21** in 60% overall yield. Hydroboration of **22** utilizing dicyclohexylborane proceeded effectively to give the alcohol **23** in 88% yield after the subsequent oxidative work-up. Dess–Martin oxidation[10] of the resulting alcohol **23** yielded the aldehyde **24** in quantita-



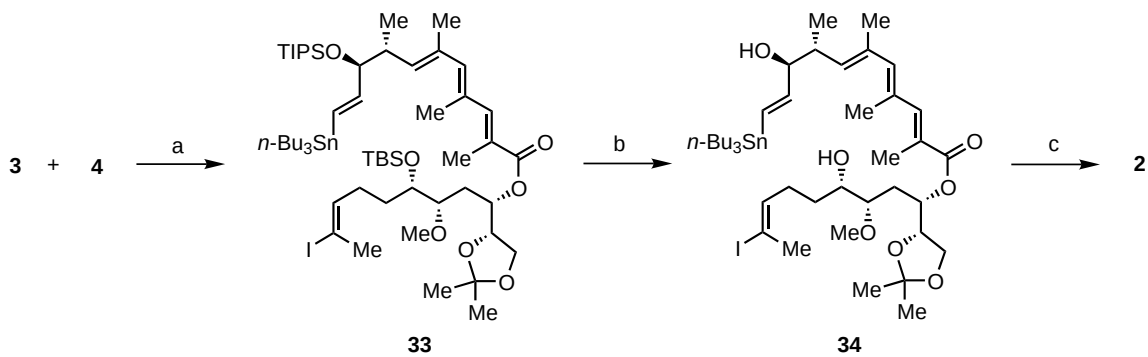
Scheme 1. *Reagents and conditions*: (a) *n*-BuLi, THF, −78°C, 13 h, 60%; (b) K_2CO_3, MeOH, 25°C, 2 h, 99%; (c) TIPSOTf, Py, 0°C, 1 h, 90%; (d) CSA, MeOH–CH_2Cl_2, 30°C, 40 min, 87%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 20 min; (f) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 110°C, 13 h, 96% ($E/Z=100/0$) from **10**; (g) DIBAL-H, PhMe, −78°C, 30 min, 98%; (h) MnO_2, CH_2Cl_2, 25°C, 1 h, 95%; (i) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 110°C, 14 h, 99% ($E/Z=97/3$); (j) DIBAL-H, PhMe, −78°C, 1 h, 97%; (k) MnO_2, CH_2Cl_2, 25°C, 30 min, 98%; (l) $(EtO)_2(O)PCH(Me)CO_2Et$, *n*-BuLi, THF, 0°C, 13 h, 99% ($E/Z=100/0$); (m) *n*-Bu_3SnH, cat. $PdCl_2(PPh_3)_2$, PhMe, 0°C, 45 min, 92%; (n) LiOH (aq.), 1,4-dioxane, 80°C, 10 h, 79%.



Scheme 2. *Reagents and conditions*: (a) Dess–Martin periodinane, Py, 25°C, 1 h, 73%; (b) $Ph_3P{=}CH_2$, PhH, 25°C, 2.5 h, 81%; (c) $(c\text{-Hex})_2BH$, THF, 25°C, 1 h, 88%; (d) Dess–Martin periodinane, 25°C, 1 h, 99%; (e) $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, –20°C, 14 h, 83%; (f) MeOTf, 2,6-di-*tert*-butylpyridine, 25°C, 10 h, 90%; (g) $(c\text{-Hex})_2BH$, THF, 25°C, 1 h, 89%; (h) TsCl, Et_3N, TMEDA, MeCN, 0°C, 1 h, 95%; (i) LiC≡CH, DMSO, 25°C, 30 min, 86%; (j) MeI, *n*-BuLi, THF, 25°C, 1 h, 96%; (k) Cp_2ZrHCl, NIS, THF, 0°C, 15 min, 80%; (l) DDQ, CH_2Cl_2–H_2O, 25°C, 18 h, 99%.

tive yield. At this stage, it was found that the addition of the allylstannane **25**[11] to **24** in the presence of $MgBr_2{\cdot}OEt_2$ in CH_2Cl_2 at –20°C proceeded with high stereoselectivity consistent with β-chelation control to give a 92:8 mixture of the desired alcohol **26** and the diastereomer in 91% combined yield. Methylation of the hydroxy group in **26** using MeOTf and 2,6-di-*tert*-butylpyridine furnished **27** whose terminal olefin underwent hydroboration employing dicyclohexylborane to provide the alcohol **28** in 80% overall yield. It was found that methylation using MeI and NaH in DMF caused the migration of the silyl group in **26**. Tosylation of the alcohol **28** yielded the tosylate **29** which was subjected to the reaction with lithium acetylide in DMSO to give the acetylene **30** via **29** in 82% overall yield. After methylation of the terminal alkyne in **30** using MeI and *n*-BuLi, the resulting **31** was treated with Cp_2ZrHCl and NIS in THF[12] to afford only the trisubstituted *trans*-vinyl iodide **32** in 77% overall yield as the sole isolated product. Finally, selective deprotection of the MPM group in **32** using DDQ[13] afforded the secondary alcohol **4** in quantitative yield.

With both key intermediates **3** and **4** in hand, the synthesis of the C1–C21 macrocyclic lactone (**2**) was addressed (Scheme 3). The esterification of the carboxylic acid **3** and the secondary alcohol **4** was best effected by the Yamaguchi method[14] to give the ester **33** in 89% yield. Unfortunately, the macrocyclizations of the fully protected **33** by intramolecular Stille coupling under several conditions failed. After many attempts, we finally found that the macrocyclization of **34**, which was obtained by TBAF-mediated deprotection of two silyl groups in **33** in 67% yield, was realized by intramolecular Stille coupling[15] using a catalytic amount of $PdCl_2(MeCN)_2$ in the presence of $Ph_2PO_2NBu_4$[16] and LiCl in DMF at 25°C for 3 h to furnish the desired 20-membered lactone **2** in 30% yield as the only isolated product.[17]



Scheme 3. *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 4-DMAP, PhMe, 25°C, 16 h, 89%; (b) TBAF, THF, 25°C, 12 h, 67%; (c) cat. $PdCl_2(MeCN)_2$, $Ph_2PO_2NBu_4$, LiCl, DMF, 25°C, 3 h, 30%.

In conclusion, we have demonstrated, for the first time, the stereoselective and convergent synthesis of the apoptolidin macrocyclic core by the macrocyclization using the intramolecular Stille coupling reaction.

Acknowledgements

We thank Dr. T. Jyojima and Mr. M. Fujii for their early contribution to this study.

References

1. Kim, J. W.; Adachi, H.; Shin-ya, K.; Hayakawa, Y.; Seto, H. *J. Antibiot*. **1997**, *50*, 628.
2. (a) Salomon, A. R.; Voehringer, D. W.; Herzenberg, L. A.; Khosla, C. *Chem. Biol*. **2001**, *8*, 71; (b) Salomon, A. R.; Zhang, H.; Seto, H.; Khosla, C. *Org. Lett*. **2001**, *3*, 57.
3. Hayakawa, Y.; Kim, J. W.; Adachi, H.; Shin-ya, K.; Fujita, K.; Seto, H. *J. Am. Chem. Soc*. **1998**, *120*, 3524.
4. (a) Schuppan, J.; Ziemer, B.; Koert, U. *Tetrahedron Lett*. **2000**, *41*, 621; (b) Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Angew. Chem., Int. Ed*. **2001**, *40*, 2063.
5. Nicolaou, K. C.; Li, Y.; Weyershausen, B.; Wei, H. *Chem. Commun*. **2000**, 307.
6. Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu, B. *Org. Lett*. **2000**, *2*, 1439.
7. Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S. *Tetrahedron Lett*. **1986**, *27*, 6241.
8. Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem*. **1990**, *55*, 1857.
9. Somfai, P.; Olsson, R. *Tetrahedron Lett*. **1993**, *34*, 6645.
10. Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *24*, 4155.
11. Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett*. **1987**, *28*, 139.
12. (a) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem*. **1971**, *27*, 373; (b) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc*. **1975**, *97*, 679.
13. Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 885.
14. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989.
15. Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508.
16. Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc*. **1997**, *119*, 12376.
17. In contrast to Nicolaou's[5] and Koert's[4b] observations, an alternative route towards this macrocycle, including a macrolactonization using several methods, was less effective than the present macrocyclization.