Tetrahedron Letters 53 (2012) 2813–2816

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Toward the total synthesis of Luminamicin: construction of 14-membered lactone framework possessing versatile enol ether moiety

Aoi Kimishima, Tomoyasu Hirose, Akihiro Sugawara, Takanori Matsumaru, Kaoru Nakamura, Ken Katsuyama, Masaki Toda, Hirokazu Takada, Rokuro Masuma, Satoshi Ōmura *, Toshiaki Sunazuka *

Kitasato Institute for Life Sciences and Graduate School of Infection Control Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

ARTICLE INFO

Article history:
Received 20 February 2012
Revised 21 March 2012
Accepted 26 March 2012
Available online 29 March 2012

Keywords:
Luminamicin
Coloradocin
Antianaerobic activity
14-Membered macrolactone
Conjugated enol ether

ABSTRACT

Luminamicin (**1**) was found to exhibit selective antibacterial activity against anaerobic bacteria by our group in 1985. The concise structure of 14-membered lactone of **1** was synthesized. Construction of a versatile enol ether moiety was achieved by Stille cross coupling via hydrostanylation of the ethynyl ether, and a maleic anhydride moiety was derived from the furan constitution by the oxidation after the macrolactonization at a late-stage.

In 1985, Luminamicin (**1**, Fig. 1) was isolated from the fermentation broth of *Streptomyces* sp. OMR-59 by our group. It was found to exhibit selective antibacterial activity against anaerobic bacteria, particularly *Clostridium* sp., with a minimum inhibitory concentration (MIC) value of 3–12 μ/mL.[1] Two years after its discovery, McAlpine and co-workers reported the isolation of Coloradocin, an antianaerobic bactericide from the fermentation broth of *Actinoplanes coloradoensis*,[2] and showed it to be identical to **1**.[3]

Luminamicin contains a highly functionalized oxa-bridged *cis*-decalin ring system, namely 11-oxatricyclo[5.3.1.^{1,7}0^{3,8}]undecane, associated with a 10-membered macrolactone moiety possessing trisubstituted *E*-olefin and a 14-membered macrolactone with an enol ether conjugated with a maleic anhydride functionality. In 2005, the absolute configuration of **1** was determined, as shown in Figure 1, by our group using conformational analysis via high temperature molecular dynamics, NMR spectroscopy, and the modified Mosher method.[4]

Due to its intriguing architectural structure and interesting biological activity, synthetic studies of the oxa-bridged *cis*-decaline core of **1**, 11-oxatricyclo[5.3.1.^{1,7}0^{3,8}]undecane, have been reported by Kallmerten,[5] Gössinger,[6] and our group.[7] However, no synthetic study of the 14-membered macrolactone, the C(16–21–29) framework with an enol ether, and maleic anhydride functionality has, as yet, been reported.

Importantly, **1** and the related macrolide, Lustromycin (**2**),[8] exhibit antibacterial activity against anaerobic bacteria, but do not show antibacterial activity against aerobic bacteria.[8,9] In contrast, Nodusmicin (**3**)[10,11] and Nargenicin (**4**),[12,13] which possess a similar C(1–9–16) framework, are the reverse, showing antibacterial activity against aerobic bacteria but not against anaerobic bacteria.[14] We thus became interested in which functional groups of **1** play a key role in determining the type of bioactivity shown by the compound.

One of the most difficult tasks in the synthesis of the 14-membered macrolactone framework of **1** is construction of enol ether directly connecting the maleic anhydride unit. Therefore we created a simplified 14-membered skeleton compound (**5**), with a C(16–21–29) component, including maleic anhydride conjugated with vinyl ether as a model compound, in order to establish a convenient reliable procedure to access the framework as well as investigate structure–activity relationships. Herein we describe a concise 14-membered lactone assembly, which allows investigation of key antibacterial properties of **1**, together with antibacterial assay of **5** and its analogues.

From the retrosynthetic strategy (Scheme 1), we envisioned **5** to be constructed via oxidation of the furan (**6**) at the final stage, accomplished through macrolactonization of the seco acid (**7**). A Stille coupling between the iodofuran ester (**8**) and the stannyl alkyl ether (**11**) would be expected to produce the enol ether carbon–carbon bond of **7**. The required ether (**11**) could be formed

* Corresponding authors. Tel.: +81 3 5791 6101; fax: +81 3 3444 8360 (S.Ō.); tel./fax: +81 3 5791 6340 (T.S.).
E-mail addresses: omuras@insti.kitasato-u.ac.jp (S. Ōmura), sunazuka@lisci.kitasato-u.ac.jp (T. Sunazuka).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.03.098

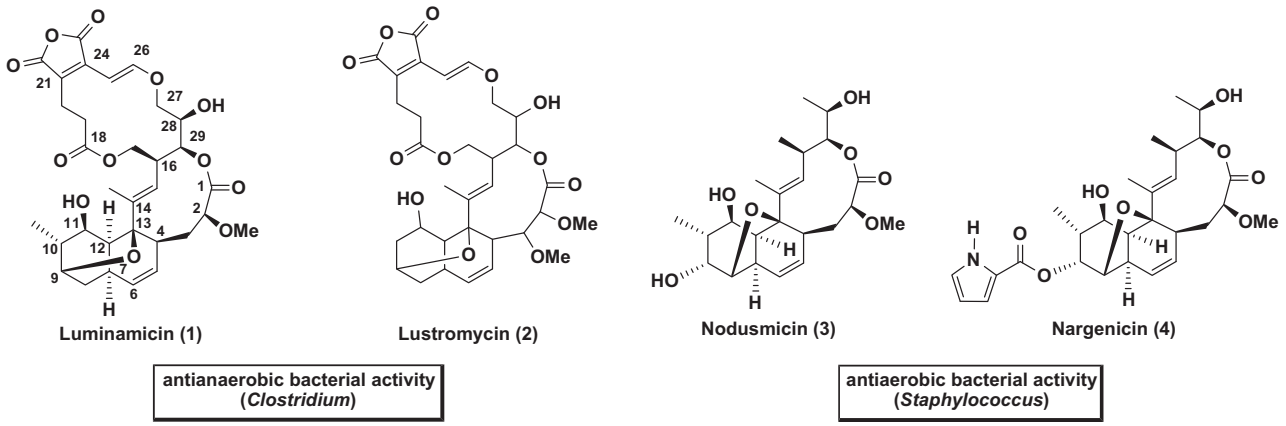
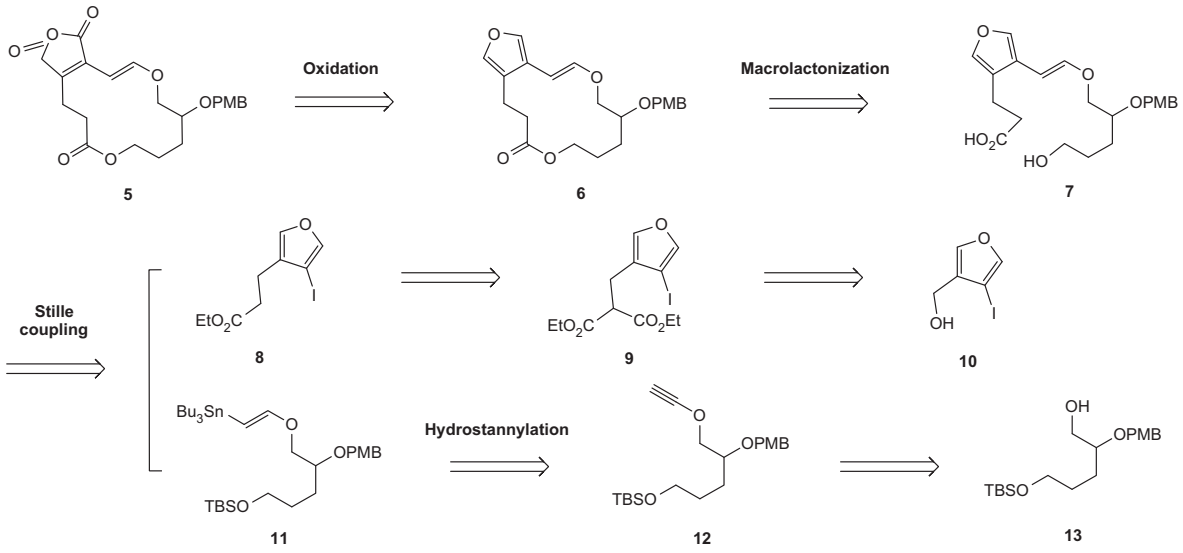


Figure 1. Structures of Luminamicin (**1**), Lustromycin (**2**), Nodusmicin (**3**), and Nargenicin (**4**).



Scheme 1. Retrosynthetic analysis of model compound **5**.

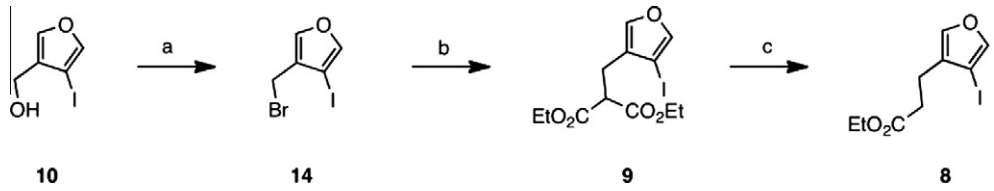
by regioselective hydrostanylation of the ethynyl ether (**12**), which can be converted from the alcohol (**13**).[15,16] The necessary **8** can be converted from commercially available **10**.

Substitution of the bromide functionality of **10**, which is prepared by modified Keay protocol,[17] with PPh_3 and CBr_4 resulted in the formation of bromomethylfuran (**14**)[18] in quantitative yield, followed by a diethylmalonate substitution reaction to produce **9** in 99% yield. Krapcho decarboxylation[19] (NaCl and DMAP in H_2O and DMSO) of **9** provided the coupling precursor **8** in 88% yield (Scheme 2).

Construction of the macrolactone (**6**), including enol ether with furan began with introduction of the ethynyl group to **13**,[20] followed by hydrostannylation of **12** to yield both β-*O*-vinyltin (**11**) and α-*O*-vinyltin (**11′**) (**11**/**11′**/**11″** = 5/4/0), using $PdCl_2(PPh_3)_2$, Bu_3SnH condition (run 1, Table 1), which are determined by ^1H NMR of the crude product. Although the use of $Pd(PPh_3)_4$,[21] led to a similar result (**11**/**11′**/**11″** = 1/1/0; run 2), the use of AIBN and Bu_3SnH predominantly provided the *Z* selective product (**11**/**11′**/**11″** = 0/1/20; run 3). However, the desired **11** appeared in low regioselectivity accompanying the formation of **11′** under most conditions.

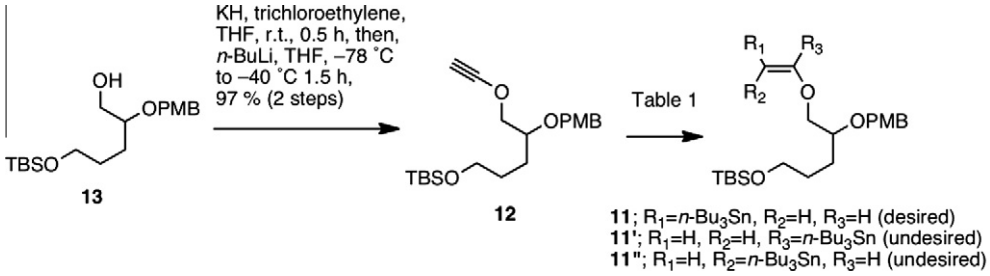
Due to instability of **11** and **11′**, the resulting crude product was immediately subjected to Stille coupling with **8** in the presence of $PdCl_2(PPh_3)_2$ and Et_4NCl to yield the coupling product **15** in 37% yield over two steps from **12** [67% as a theoretical yield given the ratio of the hydrostannylation (Table 1; run 1)] (Scheme 3). Incidentally, a Stille coupling using *Z*-β-vinyl stannane (**11″**) provided the corresponding furan vinyl ether in 29% yield (not shown), suggesting that the yield of a Stille coupling was found to be significantly low, despite the high selectivity of the hydrostannylation (Table 1; run 3). With **15** in hand, deprotection of the TBS group with TBAF afforded ethyl ester (**16**), which was hydrolyzed under basic condition to produce the seco acid (**7**), which upon Shiina macrolactonization[22] yielded the desired macrolide compound (**6**) in good yield. Toward construction of the oxidative stage of the model compound **5**, we investigated the two-step oxidation of **6** to the corresponding maleic anhydride. To obtain lactol **17**, a single oxygen protocol[23–25] with *hv*, O_2, DBU, and Rose Bengal at −78 °C, resulted in decomposed products. Likewise, $CO(NH_2)_2{\cdot}H_2O_2$, $ReMeO_3$ oxidation protocol[26] provided the same result . Pleasingly, $NaClO_2{\cdot}NaH_2PO_4$ oxidation protocol, reported by Clive,[27,28] afforded the desired lactol **17** in 64% yield as a single regioisomer, which upon the second oxidation of **17** with Dess–Martin periodinane[29] afforded a desired maleic anhydride functionality of **5** in 60% yield.

We then turned our attention to antibacterial activity of compounds **5, 6, 8, 12**, and **17** against *Clostridium perfringens* using a paper disc agar diffusion protocol.[1] Although Luminamicin (**1**)



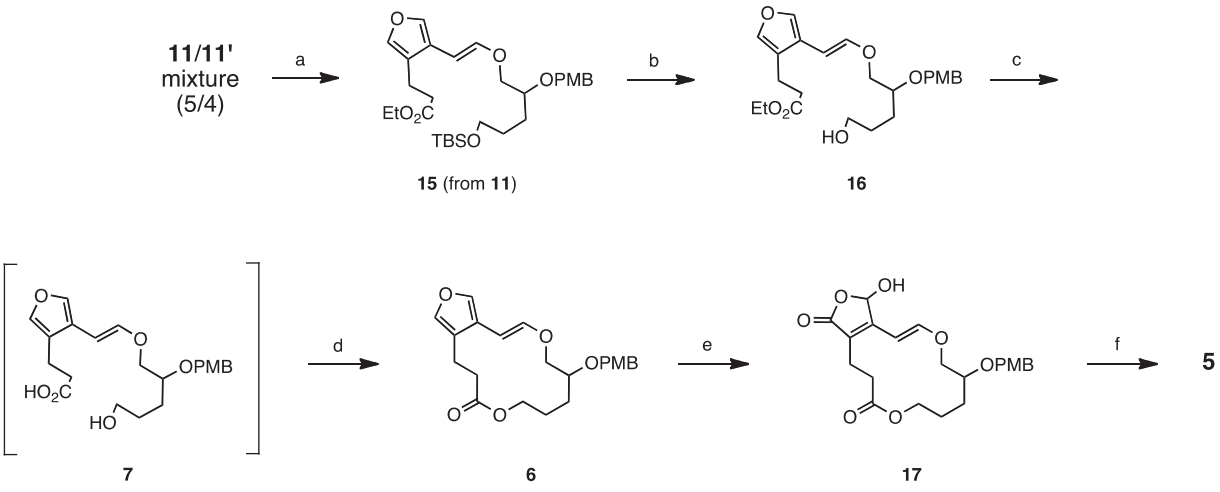
Scheme 2. Synthesis of iodofuran ester **8**. Reagents and conditions: (a) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 15 min, quant.; (b) diethyl malonate, DMF, THF, rt, 2 h, 99%; (c) NaCl, DMAP, H_2O, DMSO, 180 °C, 19 h, 88%.

Table 1
Results of hydrostannylation of ethynyl ether (**12**), prepared from **13**



Run[a]	Reagents	Solvents	Temp.; Time	Products (ratio)[b] **11**:**11′**:**11″**
1	$PdCl_2(PPh_3)_2$ (0.05 equiv), Bu_3SnH	CH_2Cl_2	rt; 0.5 h	5:4:0
2	$Pd(PPh_3)_4$ (0.05 equiv), Bu_3SnH	CH_2Cl_2	rt; 1.5 h	1:1:0
3	AIBN (0.2 equiv), Bu_3SnH	Toluene	80 °C; 40 min	0:1:20

[a] All the runs were carried out by using 1.05 equiv of Bu_3SnH.
[b] Products ratio was calculated by ^1H NMR.



Scheme 3. Synthesis of the model compound **5**. Reagents and conditions: (a) Iodofuran (**8**), $PdCl_2(PPh_3)_2$, Et_4NCl, DMF, 80 °C, 1 h, 37% from **12** (67% theoretical yield from **11**); (b) TBAF, THF, rt, 2 h, 86%; (c) 0.2 M NaOH, MeOH, THF, H_2O, rt, 1 h; (d) MNBA, DMAP, CH_2Cl_2, 0 °C, slow addition of **7** over 20 min to a reagents solution, 89% from **16**; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 2-PrOH, H_2O, rt, 8 h, 64%; (f) DMP[O], CH_2Cl_2, rt, 5 h, 60%.

exhibited antibacterial activity against *Clostridium perfringens* as a positive control, none of the compounds demonstrated any activity at all. Based on these results, the C(16–21–29) framework was deemed not to be responsible for creating bioactivity against anaerobic bacteria, thereby suggesting the whole framework of **1** and **2** is necessary for bioactivity against anaerobic bacteria.

In conclusion, we have achieved the synthesis of the simplified model compound **5**, possessing vinyl enol ether conjugated with maleic anhydride functionality, utilizing Stille coupling to construct the furan moiety conjugated with vinyl ether, together with Shiina macrolactonization to form the 14-membered macrolactone. Additionally, we found that the simplified molecules (**5**, **6**, **8**, **12**, and **17**) do not exhibit antibacterial activity against anaerobic bacteria. Further studies toward the total syntheses of **1** and **2** are now in progress.

Acknowledgements

This work was supported by a Grant for the 21st Century COE Program, Ministry of Education Culture, Sports, Science and Technology (MEXT) (Grant No. 18790022), a Grant-in-Aid for Scientific Research (Grant No. 16590012), Grant-in-Aid for Research Activity Start-up (Grant No. 22890175), the JSPS Research Fellowships for Young Scientists (T.M.), the Uehara Memorial Foundation (T.H.), and the

Kitasato University Research Grant for Young Researchers (A.S.). We also thank Ms. A. Nakagawa and Ms. N. Sato (School of Pharmacy, Kitasato University) for various instrumental analyses.

Supplementary data

Supplementary data (representative experimental procedure and characterization data of compounds **5**, **6**, **8**, **12**, **14**, **15**, **16**, and **17**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.098.

References and notes

1. Ōmura, S.; Iwata, R.; Iwai, Y.; Taga, S.; Tanaka, Y.; Tomoda, H. *J. Antibiot.* **1985**, *38*, 1322–1326.
2. Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Fernandes, P. B.; Semon, R. C.; Kohl, W. L. *J. Antibiot.* **1987**, *40*, 1375–1382.
3. Rasmussen, R. R.; Scherr, M. H.; Whittern, D. N.; Buko, A. M.; McAlpine, J. B. *J. Antibiot.* **1987**, *40*, 1383–1893.
4. Gouda, H.; Sunazuka, T.; Ui, H.; Handa, M.; Sakoh, Y.; Iwai, Y.; Hirono, S.; Ōmura, S. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 18286–18291.
5. Evans, J. M.; Kallmerten, J. *Synlett* **1992**, 269–271.
6. Gössinger, E.; Schwartz, A.; Sereinig, N. *Tetrahedron* **2000**, *56*, 2007–2014.
7. Sunazuka, T.; Handa, M.; Hirose, T.; Matsumaru, T.; Togashi, Y.; Nakamura, K.; Iwai, Y.; Ōmura, S. *Tetrahedron Lett.* **2007**, *48*, 5297–5300.
8. Tomoda, H.; Iwata, R.; Takahashi, Y.; Iwai, Y.; Ōiwa, R.; Ōmura, S. *J. Antibiot.* **1986**, *39*, 1205–1210.
9. Handa, M.; Ui, H.; Yamamoto, D.; Monma, S.; Iwai, Y.; Sunazuka, T.; Ōmura, S. *Heterocycles* **2003**, *59*, 497–500.
10. Magerlein, B. J.; Mizsak, S. A. *J. Antibiot.* **1982**, *35*, 111–112.
11. Whaley, H. A.; Chidester, C. G.; Mizsak, S. A.; Wnuk, R. J. *Tetrahedron Lett.* **1980**, *21*, 3659–3662.
12. Celmer, W. D.; Chmurny, G. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203–4209.
13. Magerlein, B. J.; Reid, R. J. *J. Antibiot.* **1982**, *35*, 254–255.
14. Shong, J. K.; Yamaguchi, T.; Seong, C. N.; Baik, K. S.; Park, S. C.; Lee, H. J.; Jang, S. Y.; Simkhada, J. R.; Yoo, J. C. *Arch. Pharm. Res.* **2008**, *31*, 1339–1345.
15. Ramesh, D.; Rajaram, S.; Prabhakar, P.; Ramulu, U.; Reddy, D. K.; Venkateswarlu, Y. *Helv. Chim. Acta* **2011**, *94*, 1226–1233.
16. Hirose, T.; Sunazuka, T.; Tsuchiya, S.; Tanaka, T.; Kojima, Y.; Mori, R.; Iwatsuki, M.; Ōmura, S. *Chem. Eur. J.* **2008**, *14*, 8220–8238.
17. Bures, E. J.; Keay, B. A. *Tetrahedron Lett.* **1988**, *29*, 1247–1250.
18. Grainger, R. S.; Owoare, R. B.; Tisselli, P.; Steed, J. W. *J. Org. Chem.* **2003**, *68*, 7899–7902.
19. Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *8*, 215–217.
20. Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919–2922.
21. Du, X.; Chu, H. V.; Kwon, O. *Tetrahedron Lett.* **2004**, *45*, 8843–8846.
22. Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822–1830.
23. Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773–2776.
24. Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425–12431.
25. Hagiwara, H.; Inome, K.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 757–764.
26. Finlay, J.; Mckervey, M. A.; Gunaratne, H. Q. N. *Tetrahedron Lett.* **1998**, *39*, 5651–5654.
27. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
28. Clive, D. L. J.; Ou, L. *Tetrahedron Lett.* **2002**, *43*, 4559–4563.
29. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.