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Synthesis of Eukaryotic Translation Elongation Inhibitor Lactimidomycin via Zn(II)-Mediated Horner–Wadsworth–Emmons Macrocyclization

Brian J. Larsen, Zhankui Sun, and Pavel Nagorny*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States

nagorny@umich.edu

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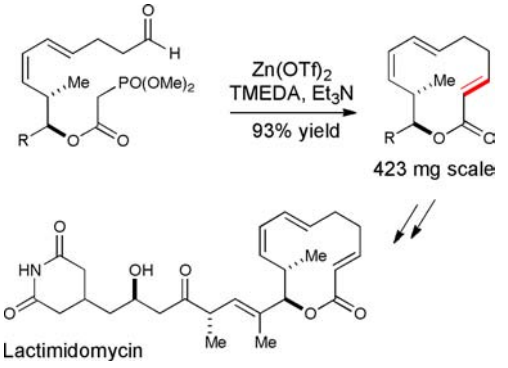
ABSTRACT



An enantioselective synthesis of potent eukaryotic translation elongation inhibitor lactimidomycin has been accomplished in 21 linear steps. This synthesis features a Zn(II)-mediated Horner–Wadsworth–Emmons reaction that could be executed on a large scale to provide the highly strained 12-membered lactimidomycin macrolactone.

The glutarimide-containing natural polyketides lactimidomycin (**1**),[1a] migrastatin (**2**),[1b] and isomigrastatin (**4**)[1c] (Figure 1) have attracted considerable attention due to their promising anticancer activity. Among this group, migrastatin (**2**) is by far the most well-studied member of this family. Recently, Danishefsky and co-workers synthesized migrastatin (**2**) and developed diverted total syntheses (DTS) of more simple, stable and potent analogues of **2**.[2] Subsequent in vivo studies demonstrated that some of these analogues, such as **3**, could serve as selective and nontoxic inhibitors of various types of breast cancer metastasis.[3]

While the initial reports indicated that 12-membered glutarimide-containing macrolides lactimidomycin (**1**) and isomigrastatin (**4**) could also inhibit cancer cell migration in vitro,[4a] a recent study suggests that **1** and **2** are acutely cytotoxic and do not inhibit migration of cancer cells at subtoxic doses.[4b] Nevertheless, being a very potent inhibitor of the translocation step in eukaryotic protein translation initiation, **1** has been identified as a promising

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antitumor agent with a strong antiproliferative effect on tumor cells in vivo.[1a,5]

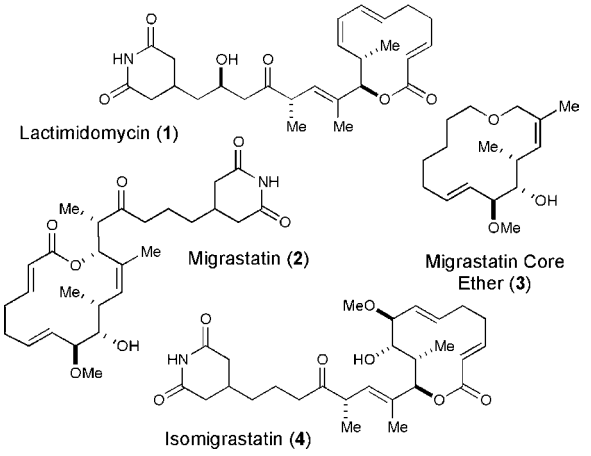
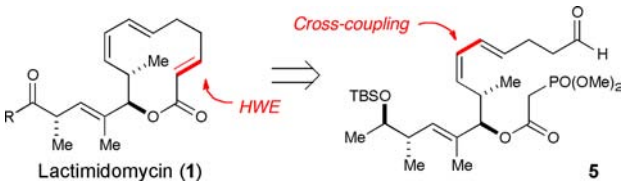


Figure 1. Glutarimide-containing natural products and their analogues.

A synthetic approach to **1** and its analogues could help in identifying new anticancer agents with improved stability and therapeutic properties; however, high ring strain energy associated with the unsaturated 12-membered macrolactone of **1** (vide infra) significantly complicates the preparation of this macrolide. As a consequence, only Fürstner group's approach could provide access to synthetic **1**.[4b,6] As part of our program directed to the discovery of new natural product-based agents for the treatment of human diseases, we undertook designing a general synthetic approach to **1** as well as to other 12-membered glutarimide-containing natural products. In developing a viable general strategy, the number of synthetic steps after the formation of the macrocyclic ring should be minimized in order to avoid the decomposition and isomerization reactions of the intermediates.[7] To accomplish this, we proposed to establish both the macrocyclization and installation of the enoate double bond in a single step via intramolecular Horner–Wadsworth–Emmons (HWE) cyclization of precursor **5** (Scheme 1). This manuscript summarizes our studies on stereoselective total synthesis of lactimidomycin (**1**).

While intramolecular olefination reactions could effectively be used for the construction of larger macrocycles,

Scheme 1. Retrosynthetic Analysis



E-selective cyclizations leading to 12-membered macrolactones have little precedence.[8] In addition, the presence of the (*E*,*Z*)-diene moiety decreases the overall flexibility of the macrocycle, which could affect the relative rates for the intermolecular and intramolecular pathways. To evaluate the feasibility of the approach depicted in Scheme 1, we initiated model studies with the unfunctionalized phosphonate **6** (Table 1). Intramolecular cyclization of **6** under standard conditions employing potassium carbonate (entry 1)[9] or lithium hexamethyldisilazide (entry 2)[8a] as bases did not result in the formation of **7**, and only diolide **8** was isolated. Subjecting **6** to the standard Masamune–Roush olefination protocol[10] provided only minor quantities of *E*-enoate **7** (13% yield) and mostly resulted in diolide **8** (60% yield). Encouraged by these results, we decided to evaluate other soft enolization conditions[11] surmising that the Lewis acidity of the counterion correlates with its ability to bring together the termini of **6**. Gratifyingly, the combination of zinc(II) trifluoromethanesulfonate, TMEDA, and triethylamine[12] (entry 4) promoted the *E*-selective formation of the macrolactone **7** (78% yield), and only a minor quantity of diolide **8** was observed (9% yield). Additional studies will be conducted to establish the origins of the strong templating effect exhibited by Zn^{2+}. One of the possible rationals for this effect is that the coordination to the larger in size and more polarizable Zn^{2+} cation, relative to the other cations (entries 1–3), is less dependent on the geometrical constrains posed by the macrocyclic ring in the transition state, leading to the desired macrolactone.

It is noteworthy that **7** was found to be unstable and could easily polymerize upon storage in neat state.[13] This instability could be attributed to the highly strained nature of the lactimidomycin macrocycle. Thus, our computational studies suggest that **7** is by 14.7 kcal/mol more

(5) (a) Schneider-Poetsch, T.; Ju, J.; Eyler, D. E.; Dang, Y.; Bhat, S.; Merrick, W. C.; Green, R.; Shen, B.; Liu, J. O. *Nat. Chem. Biol.* **2010**, *6*, 209. (b) Lee, S.; Liu, B.; Lee, S.; Huang, S.-X.; Shen, B.; Qian, S.-B. *Proc. Nat. Acad. Sci. U.S.A.* **2012**, *109*, 14728.

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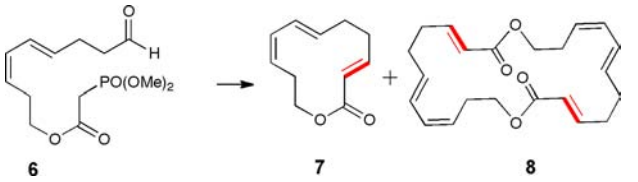
(12) Intermolecular version: (a) Schauer, D. J.; Helquist, P. *Synthesis* **2006**, 3654. Application to the formation of macrolactams: (b) Pirrung, M. C.; Biswas, G.; Ibarra-Rivera, T. R. *Org. Lett.* **2010**, *12*, 2402.

(13) Similar observations have been made for lactimidomycin (**1**): Schneider-Poetsch, T. Ph.D. Thesis, John Hopkins University, 2009, p 33.

strained than its fully saturated 12-membered macrolactone analog (cf. the Supporting Information).

With these encouraging model study results in hand, the synthesis of lactimidomycin (**1**) was pursued next (Scheme 2). These studies commenced with the known vinylogous aldol reaction of **9** and acetaldehyde to provide the corresponding aldol adduct (93% yield, > 20:1 dr).[14] Protection of this adduct (TBSCl, DMAP, ImH) followed by reductive removal of the auxiliary ($NaBH_4$, 84% yield, two steps) and Parikh–Doering oxidation of the resultant alcohol provided aldehyde **10**. Aldehyde **10** was then subjected to the Evans *syn*-selective aldol reaction[15] with chiral oxazolidinone **11** to provide the corresponding aldol adduct (> 20:1 dr), which was converted to silyl ether **12** (79% yield, three steps). With compound **12** in hand, the synthesis of the (*E*,*Z*)-diene was addressed next.

Table 1. Macrocyclization Optimization Studies



6 7 8

entry	conditions	**7** (yield, %)[a]	**8** (yield, %)[a]
1	K_2CO_3, 18-C-6,1.3 mM in toluene	0	65
2	LiHMDS, 1.3 mM in THF	0	36
3	LiCl, DBU, 1.3 mM in THF	13	60
4	$Zn(OTf)_2$, TMEDA Et_3N, 1.7 mM in THF	78	9

[a] Yields are measured over two steps (oxidation of an alcohol precursor to **6** followed by the HWE cyclization to **7** and **8**); 18-C-6 = 18-crown-6; LiHMDS = lithium hexamethyldisilazide; TMEDA = tetramethylethylenediamine.

Approaches based on cross-metathesis or Wittig olefination strategies to convert **12** into **17** were evaluated first; however, little success was achieved in these studies. Eventually, we pursued the assembly of the (*E*,*Z*)-diene moiety through a Suzuki cross-coupling strategy. Thus, the chiral auxiliary of **12** was removed through the formation of a thioester (EtSLi, 83% yield), which was reduced by DIBALH to provide the corresponding aldehyde.[16] The following Stork–Zhao olefination provided *cis*-vinyl iodide **13** as a 14:1 mixture of *Z*:*E* isomers (68% yield, two steps).[17] Compound **13** was next converted into phosphonate **15** (44–85%, two steps) by selective removal of the trimethylsilyl ether followed by the acylation of the resultant alcohol with acyl chloride **14** (DMAP, pyridine). The cross-coupling of the iodide **15** and boronic acid **16**, available in one step from 4-pentyn-1-ol, was evaluated next. It is known that such vinyl iodides could potentially undergo an intramolecular Heck cyclization, and that this pathway could be suppressed by an addition of thallium(I) ethoxide.[18] Indeed, subjecting the mixture of **15** and **16** to $Pd(PPh_3)_4$/TlOEt[19] resulted in the rapid formation of the desired cross-coupling product containing an *(E,Z)*-diene. In order to avoid stoichiometric quantities of highly toxic thalium(I) ethoxide, further optimization of this Suzuki reaction between **15** and **16** was pursued. Gratifyingly, extensive evaluation of various catalysts and additives resulted in identifying $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ in combination with sodium hydroxide as the catalyst and base of choice.[20] Thus, the resultant (*E*,*Z*)-diene-containing cross-coupling product was produced in 84% yield as the only product. This product was further oxidized under Dess–Martin conditions to provide macrocyclization precursor **17** (84% yield), which was then subjected to the Zn(II)-mediated intramolecular HWE reaction conditions determined previously. Remarkably, this cyclization resulted in the desired (*E*)-**18** (93% yield, 423 mg of product), with only minor quantities of the corresponding diolide observed (ca. 3% yield). The formal total synthesis was completed by TBS-group deprotection that resulted in macrolactone **19** (90% yield), which is the intermediate in the Furstner's group synthesis of lactimidomycin.[6a] The ^1H and ^{13}C NMR spectra as well as the optical rotation of **19** ($[\alpha]_D = -234$, $c = 1.16$, $CHCl_3$) matched the previously published physical characteristics ($[\alpha]_D = -233$, $c = 1$, $CHCl_3$). This compound was then elaborated to lactimidomycin following the previously published route.[6a] Thus, **19** was oxidized to produce unstable ketone **20**, which was noted to decompose in the neat state upon prolonged storage and was unstable to multiple purifications by column chromatography. The methyl ketone functionality of **20** was converted into the corresponding silyl enol ether (LiHMDS, Et_3N, Me_3SiCl). Without purification, this silyl enol ether was subjected to the Mukaiyama aldol addition reaction with aldehyde **21** catalyzed by oxazaborolidinone **22** (100 mol %, EtCN, −78 °C).

The resultant aldol adduct was treated with buffered HF·Py solution in pyridine/THF to remove the trimethylsilyl ether and produce lactimidomycin (**1**). The ^1H and ^{13}C NMR data of the synthetic lactimidomycin were in good accordance with those previously reported by the Shen[7d] and Fürstner[6b] groups. However, the optical rotation value for synthetic **1** ($[\alpha]_D = -20$, $c = 0.25$, DMSO) was consistent with the corresponding value reported by the Sugawara group ($[\alpha]_D = -20$, $c = 0.5$, DMSO)[1a] but varied from the optical rotation values of Shen ($[\alpha]_D = +23$, $c = 0.52$, DMSO)[21] and Fürstner ($[\alpha]_D = +6.9$,

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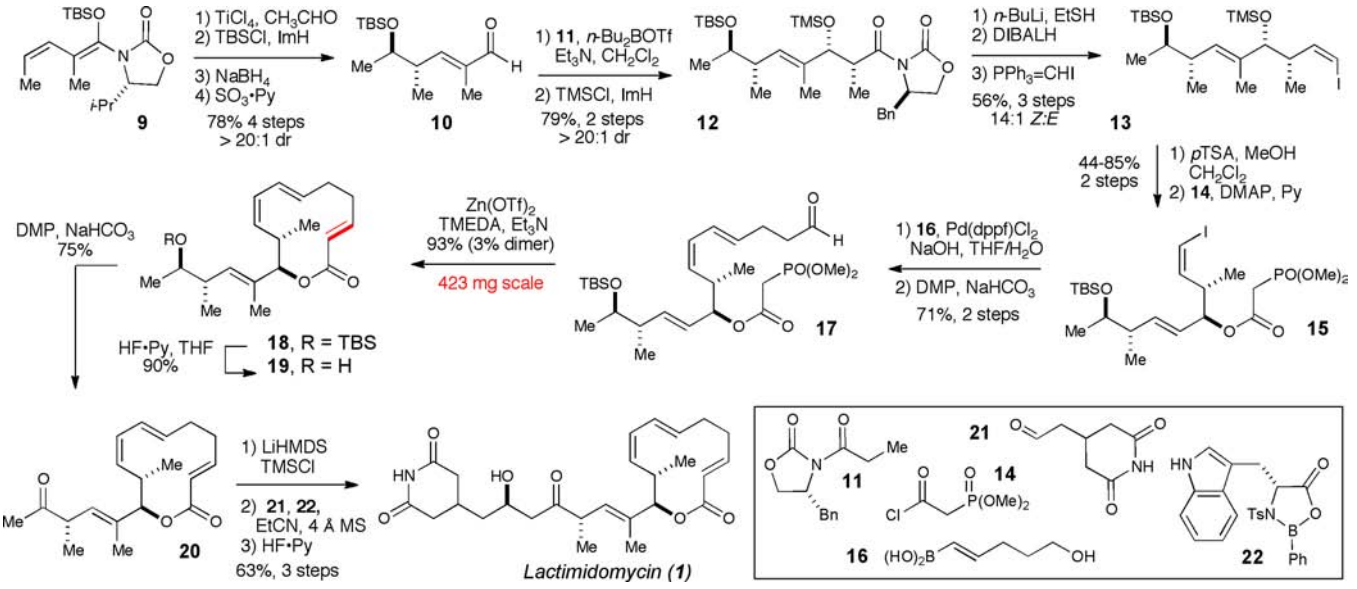
(21) The CD spectrum and optical rotation data for natural lactimidomycin were provided by Professor B. Shen and included with his permission (e-mail correspondence, February 6, 2013).

Scheme 2. Total Synthesis of Lactimidomycin



c = 0.5, DMSO)[6] groups.[22] In contrast, the CD spectrum of synthetic **1** was in good agreement with the corresponding spectrum of the natural sample.[22] The discrepancies in the optical rotation could be attributed to the presence of optically active impurities that arise from the decomposition of lactimidomycin. Consistent with our observations for macrolactone **7** as well as with our previous studies, **1** is unstable and could decompose upon storage in neat state (vide supra).[13]

In conclusion, a scalable enantioselective approach to eukaryotic translation elongation and cancer cell migration inhibitor lactimidomycin (**1**) has been developed. This synthesis relies on a Zn(II)-mediated *E*-selective Horner–Wadsworth–Emmons reaction to construct the strained 12-membered macrolactone of **1**. Synthesis of isomigrastatin (**2**) as well as the identification of more stable and active analogues of **1** and **2** are ongoing.

(22) Refer to the Supporting Information for the detailed comparison of ^{1}H and ^{13}C NMR spectra of synthetic and natural **1**.

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Note Added after ASAP Publication. Scheme 2 contained an error in the version published ASAP on June 3, 2013; the correct version reposted on June 21, 2013.

Supporting Information Available. Experimental procedures, description of computational studies to estimate the ring strain energy of **7**, and ^{1}H and ^{13}C NMR spectra for compounds **1** and **6**–**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.