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Formal Total Synthesis of Lactimidomycin

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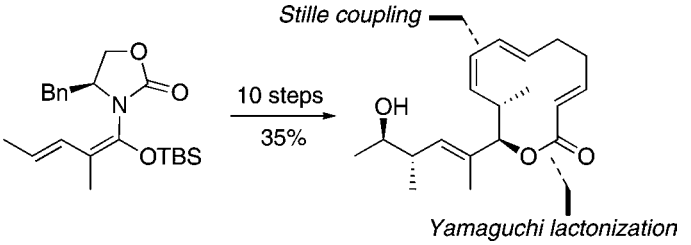
ABSTRACT



A concise synthesis of an intermediate of lactimidomycin, a glutarimide-containing macrocyclic polyketide produced by an actinomycete, has been accomplished in 35% overall yield from a known vinylketene silyl *N,O*-acetal by a 10-step sequence that involves two types of asymmetric aldol reactions to install all the stereocenters, the Stille coupling to set up the whole carbon famework, and the Yamaguchi lactonization to construct the 12-membered macrolactone ring.

Lactimidomycin (**1**) is a 12-membered macrolide bearing a glutarimide-containing side chain that was isolated from *Streptomyces amphibiosporus* ATCC 53964 by Sugawara and co-workers as a polyketide antibiotic exhibiting remarkably potent antifungal and antitumor activity as well as an inhibitory effect on DNA and protein biosynthesis (Figure 1).[1] Optimization of the fermentation conditions for lactimidomycin production was later implemented by Shen and co-workers, which led not only to improved yields of **1** but also to determination of its absolute stereochemistry and isolation of some new congeners.[2] Their reinvestigation of the biological activity of **1**, structurally related macrolide natural products including isomigrastatin (**2**)[3] and migrastatin (**3**),[4] and their semisynthetic derivatives concluded that **1** was an extremely potent cancer cell migration inhibitor with IC_{50} values of 0.60 nM against MDA-MB-231 human mammary adenocarcinoma cells and 5.03 nM against 4T1 mouse mammary adenocarcinoma cells in a standardized scratch wound healing (SWH) assay, and the potencies of **1** were much superior to those of **2** and **3**.[5] It was also reported that **1** and **2** exhibited potent cytotoxicity against the 4T1 and MDA-MB-231 cell lines at nanomolar levels.[5] Recent biological studies elucidated that **1** inhibited the elongation step of translation in protein synthesis by binding to the 60S ribosome and had an in vivo growth-inhibitory effect on MDA-MB-231 cells subcutaneously inoculated in mice.[6] The reported mode of action of **1**, which is likely to have no direct functional link to cell migratory ability, prompted a comprehensive biological re-evaluation of **1**, **2**, and their synthetic congeners by Fürstner and co-workers.[7] On the basis of their full dose–response assay, they most recently reached a contradictory conclusion that lactimidomycin (**1**) and isomigrastatin (**2**) had no appreciable effect on cancer cell migration at subtoxic doses.

In contrast to continuously disclosed biological and pharmacological studies on **1**–**3** including the above-mentioned controversial issue as well as their action mechanism and structure–activity relationship studies,[8,9] the

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last of which led successfully to the creation of some structurally simplified migrastin analogues as promising anticancer agents by Danishefsky and co-workers,[10] the total synthesis of **1**–**3** per se has scarcely been documented; for **2** and **3** each, two research groups have succeeded in total synthesis,[11,12] and only one group for **1**.[13] Furthermore, synthetic efforts toward analogues and partial structures of this family of natural products have been focused mainly on the 14-membered macrolide **3**,[9a,10a–10c,12c,14] while only two reports have so far appeared with regard to synthetic analogues of the 12-membered macrolactones **1** and **2**.[15] In this context and from its medicinally important biological activities, lactimidomycin (**1**) and its analogues would deserve more attention and synthetic endeavors. Hoping to further promote the chemistry and biology of **1** as a potential lead for antitumor drugs, we describe herein a concise enantioselective synthesis of truncated macrolide **4**, which has previously been transformed into **1** in four steps by Micoine and Fürstner.[7,13a]

Scheme 1 outlines our retrosynthetic analysis of **4**. The target molecule **4** would be derived by macrolactonization of seco acid **5** coupled with oxidative elimination of the seleno functionality at the C2 position. We then dissected **5** at its C7–C8 single bond into two segments **6** and **7**, with their connection by the Stille coupling reaction in mind. The vinyl iodide **6** would be prepared from **8** via stereoselective installation of a three-carbon unit based on

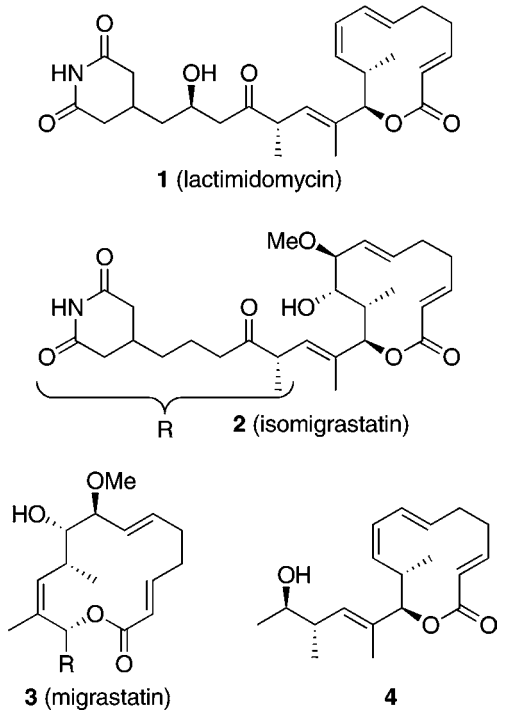

Figure 1. Lactimidomycin (**1**), related natural products (**2**, **3**), and target molecule **4** in the present synthesis.

asymmetric aldol methodology followed by *Z*-selective olefination, while the vinylstannane **7** would readily be obtainable from commercially available acetylenic alcohol **9**. The vinylogous aldol **8** bearing two stereogenic centers at its γ- and δ-positions should be accessible by applying Kobayashi's remote asymmetric induction to vinylketene silyl *N*,*O*-acetal **10** and acetaldehyde.[16,17]

Our three-step preparation of the vinylstannane segment **7** from **9** is shown in Scheme 2. Known *E*-stannyl alcohol **11**, obtained by palladium-catalyzed syn-hydrostannation of **9** according to Chong's protocol,[18] was converted into iodide **12**. Alkylation of ethyl 2-(phenylseleno)acetate with **12** afforded **7** as a racemic mixture.[19]

The vinyl iodide segment **6** to be coupled with **7** was obtained in six steps as shown in Scheme 3. The Kobayashi vinylogous aldol reaction of the known ketene silyl *N*,*O*-acetal **10** with acetaldehyde proceeded with excellent

(8) For isomigrastatin, see for examples: (a) Ju, J.; Lim, S.-K.; Jiang, H.; Seo, J.-W.; Shen, B. *J. Am. Chem. Soc.* **2005**, *127*, 11930–11931. (b) Ju, J.; Lim, S.-K.; Jiang, H.; Seo, J.-W.; Her, Y.; Shen, B. *Org. Lett.* **2006**, *8*, 5865–5868. (c) Feng, Z.; Wang, L.; Rajski, S. R.; Xu, Z.; Coeffet-LeGal, M. F.; Shen, B. *Bioorg. Med. Chem.* **2009**, *17*, 2147–2153. (d) Ma, M.; Kwong, T.; Lim, S.-K.; Ju, J.; Lohman, J. R.; Shen, B. *J. Am. Chem. Soc.* **2013**, *135*, 2489–2492 and references cited therein.

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(11) For **2**, see ref 7 and the following: Krauss, I. J.; Mandal, M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5576–5579.

(12) For 3, see ref 10a and the following: (a) Gaul, C.; Njardarson, J. T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 6042–6043. (b) Reymond, S.; Cossy, J. *Eur. J. Org. Chem.* **2006**, 4800–4804. (c) Reymond, S.; Cossy, J. *Tetrahedron* **2007**, *63*, 5918–5929. (d) Reymond, S.; Ferrié, L.; Guérinot, A.; Capdevielle, P.; Cossy, J. *Pure Appl. Chem.* **2008**, *80*, 1683–1691.

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(15) See ref 7 and the following: Dias, L. C.; Monteiro, G. C.; Amarante, G. W.; Conegero, L. S.; Finelli, F. G. *Tetrahedron Lett.* **2012**, *53*, 707–709.

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(17) For the Kobayashi vinylogous aldol reaction, see also: (a) Nicolaou, K. C.; Guduru, R.; Sun, Y.-P.; Banerji, B.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896–5900. (b) Nicolaou, K. C.; Sun, Y.-P.; Guduru, R.; Banerji, B.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 3633–3644. (c) Shinoyama, M.; Shirokawa, S.-i.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2009**, *11*, 1277–1280. (d) Wang, L.; Gong, J.; Deng, L.; Xiang, Z.; Chen, Z.; Wang, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2009**, *11*, 1809–1812. (e) Wang, L.; Xi, Y.; Yang, S.; Zhu, R.; Liang, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2011**, *13*, 74–77. (f) Symkenberg, G.; Kalesse, M. *Org. Lett.* **2012**, *14*, 1608–1611.

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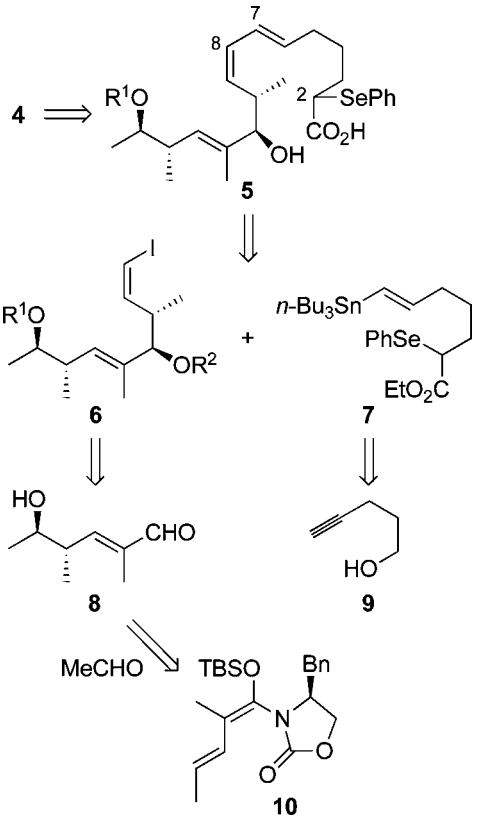
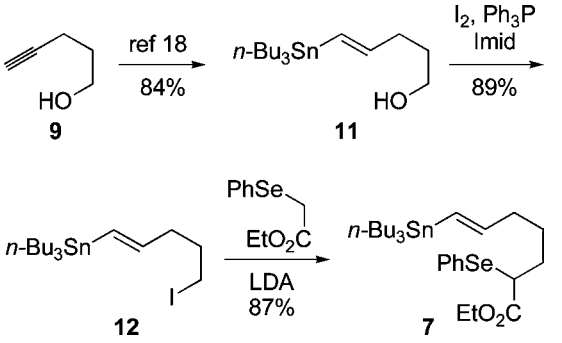
(19) Lebarillier, L.; Outurquin, F.; Paulmier, C. *Tetrahedron* **2000**, *56*, 7483–7493.

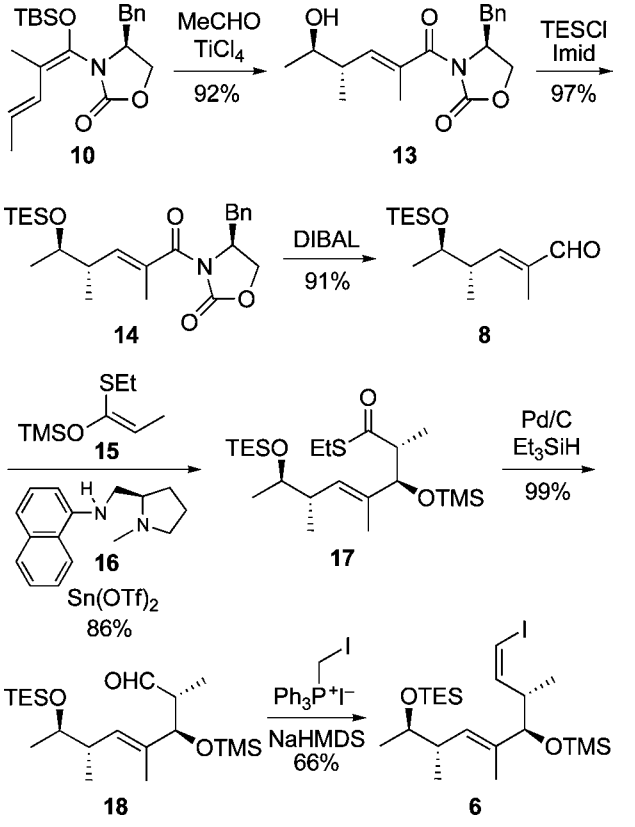
Scheme 1. Retrosynthetic Analysis of **4**



Scheme 2. Preparation of Vinylstannane Segment **7**



Scheme 3. Preparation of Vinyl Iodide Segment **6**



diastereoselectivity to give **13** (dr $>20:1$).[16,17] After protection of its hydroxy group as the corresponding TES ether, the resulting oxazolidinone **14** was reduced with DIBAL to directly give aldehyde **8**. Conversion of **8** into aldol **17** was best accomplished by exposing **8** to ketene silyl *S*,*O*- acetal **15** in the presence of catalytic amounts of $Sn(OTf)_2$ and chiral amine **16** in propionitrile according to the literature,[20] furnishing thiol ester **17** in 86% yield along with a small amount (ca. 10%) of an alcoholic product generated by deprotection of the TMS group. Reduction of **17** by Fukuyama's method gave aldehyde **18** almost quantitatively,[21] which was then subjected to a *Z*-selctive Witting olefination to afford **6** ($Z/E > 20:1$).[22]

With the two segments **6** and **7** in hand, we proceeded to the final stage of our synthesis of **4** (Scheme 4). The coupling of **6** and **7** was conducted according to Corey's modification of the Stille coupling reaction to give **19** in 89% yield.[23] The product **19** was considered to be generated as a 1:1 diastereomeric mixture at the C2 stereocenter, although the diastereomers were indistinguishable both in ^1H and ^{13}C NMR spectra. Gratifyingly, saponification of the ester **19** brought about concomitant selective removal of the TMS protecting group, giving directly the seco acid **5** in an excellent yield of 93%. Exposure of **5** to the Yamaguchi lactonization conditions proceeded smoothly to afford selenolactone intermediate **20**.[24,25] Interestingly, ^1H NMR analysis of crude **20** indicated that the selenolactone was obtained as a ca. 5:1 mixture of inseparable diastereomers with respect to the C2 position, which would probably be ascribable to the intervention of equilibrium

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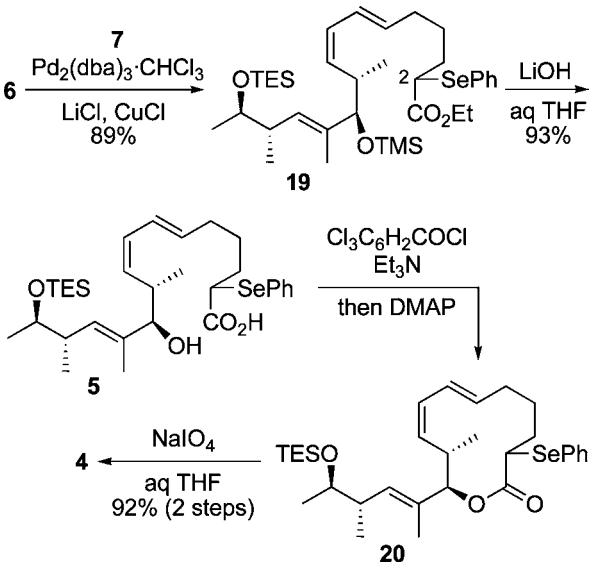
Scheme 4. Completion of the Synthesis of **4**



between the major and the minor diastereomers in the macrolactonization process. Finally, treatment of the epimeric mixture **20** with $NaIO_4$ in aqueous THF induced both the oxidative elimination of the seleno functionality and deprotection of the TES group,[26] furnishing the target molecule **4** with high *E*/*Z* selectivity (> 20:1) in 92% yield from the seco acid **5**.[27] The ^1H and ^{13}C NMR spectra of **4** were identical to those of an authentic sample, and the specific rotation of **4** [$[\alpha]^{24}_D$ −234 (*c* 1.12, $CHCl_3$)] showed good agreement with a reported value [$[\alpha]^{22}_D$ −232.7 (*c* 1, $CHCl_3$)].[13a]

In conclusion, the enantioselective synthesis of the lactimidomycin precursor **4** was accomplished from the known ketene silyl *N*,*O*-acetal **10** by the concise 10-step sequence (35% overall yield) that features the highly diastereoselective construction of the vinylogous aldol **13**, Sn(II)-catalyzed asymmetric aldol reaction to form the thiol ester **17**, the Stille coupling to assemble the whole carbon framework, and the Yamaguchi lactonization to install the 12-membered ring. In addition, the saponification and oxidative elimination steps (**19** → **5** and **20** → **4**) were accompanied by deprotection of the TMS and TES groups, respectively, as concomitant reactions, which enabled the shortening of our synthetic pathway. Our efforts directed toward the total synthesis of lactimidomycin **1**, beginning with a glutarimide-containing aldehyde (instead of acetaldehyde in the present formal synthesis), are now in progress and will be reported in due course.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(25) It is worth mentioning that the Yamaguchi lactonization of a seco acid which is identical to **5** except for the presence of a double bond at the C2−C3 position (instead of the PhSe group) as well as a TBSO group at the C15 position (instead of the TESO group) gave the corresponding 12-membered lactone (2,6,8,12-tetraene) in a poor yield of 22%. For the difficulty to prepare analogous unsaturated 12-membered macrolides, see refs 7 and 13a,13b.

(26) For deprotection of silyl ethers with $NaIO_4$, see: Wang, M.; Li, C.; Yin, D.; Liang, X.-T. *Tetrahedron Lett*. **2002**, *43*, 8727–8729.

(27) We are considering that both epimers of **20** were converted selectively into the *E*-configured macrolactone **4** on the basis of observations by Danishefsky and co-workers in their total synthesis of isomigrastatin. For details, see ref 11.