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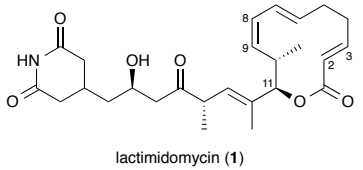
A formal total synthesis of the cytotoxic natural product lactimidomycin has been achieved in nine steps from (*E*)-2-methyl-2-pentenoic acid. The 12-membered lactone was efficiently formed via a copper-catalyzed ene-yne coupling/alkyne reduction tandem reaction.

The glutarimide-containing macrolide lactimidomycin (**1**, Fig. 1), isolated from *Streptomyces amphibiosporus* ATCC 53964, displays a wide spectrum of biological effects including cytotoxicity, antifungal activity, and inhibition of DNA/protein biosynthesis.[1,2] Further biological studies also identified it as a potent cell-migration inhibitor,[3] although this was contradicted by a more recent report suggesting that no significant cell-migration inhibition was observed at sub-toxic doses.[4] Nonetheless, lactimidomycin is still considered to be a potential anticancer drug lead because of its potent and selective antiproliferative effect on tumor cells both in vitro and in vivo.[1,5] Recently, details of its mechanism of action were reported when a lactimidomycin co-crystal structure with the 80S ribosome of *Saccharomyces cerevisia* revealed that the natural product binds to the tRNA E-site, thereby preventing the binding of tRNA.[5c] In addition, kinetic experiments showed that lactimidomycin targets the first elongation cycle.[5c]



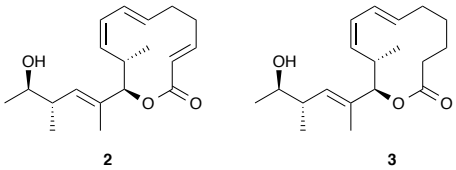
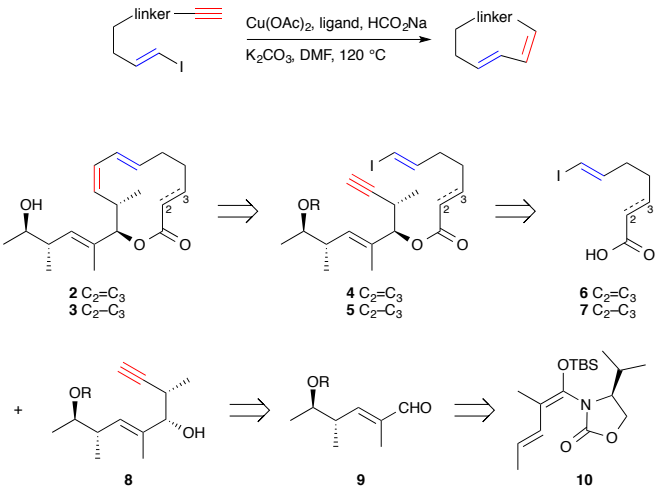


Fig. 1 Lactimidomycin (**1**) and its synthetic precursors **2** and **3**.

In addition to continuing interest in its biological activity, lactimidomycin has also attracted attention from the organic chemistry community. Two total syntheses and two formal total syntheses of lactimidomycin have been reported,[6] all with efforts focused on the construction of the unsaturated 12-membered lactone subunit. In the context of our continued exploration of natural produced-based drug discovery, we recently developed a methodology for the synthesis of macrocycles bearing an *E*,*Z*-1,3-diene structure within a macrocyclic ring via a Castro-Stephens coupling/alkyne reduction tandem reaction (Scheme 1). This method is particularly efficient for the formation of 12-membered rings.[7] We describe herein the application of this method to the enantiospecific formal total synthesis of lactimidomycin.

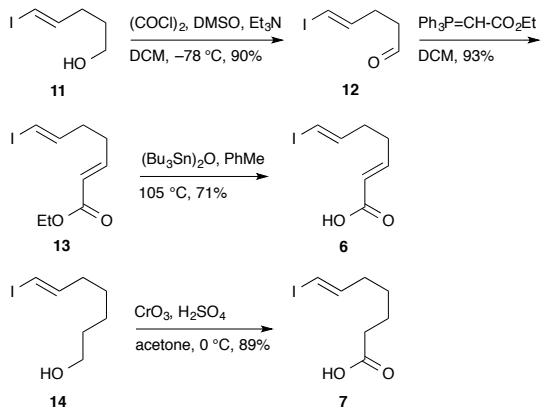


Scheme 1 Castro-Stephens coupling/alkyne reduction tandem reaction and retrosynthesis.

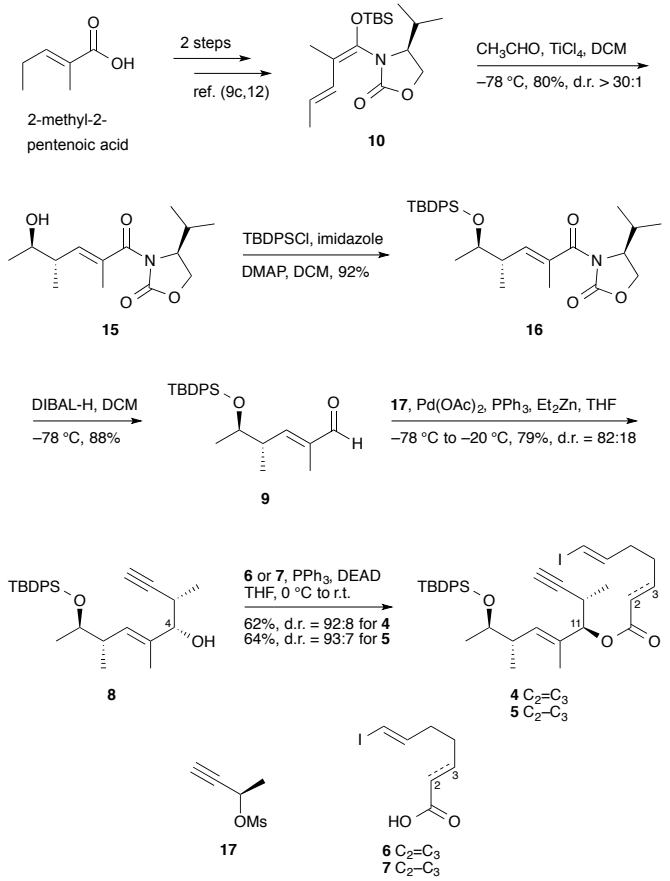
We selected truncated macrolides **2** and **3** (Fig. 1) as our target compounds, since both have been converted to lactimidomycin in Fürstner's synthesis.[4,6a] The retrosynthetic analysis is depicted in Scheme 1. We expected that the 12-membered macrocycles **2** or **3**

could be obtained from iodides **4**/**5** via our coupling/reduction tandem reaction. Esters **4**/**5** could be readily prepared from propargyl alcohol **8** and the carboxylic acids **6**/**7** using Mitsunobu conditions. Enantioenriched alcohol **8** was envisioned to be obtained from aldehyde **9** using Marshall's asymmetric propargylation reaction.[8] An *anti*-selective Kobayashi vinylogous aldol reaction of compound **10** could deliver aldehyde **9**.[9]

The preparation of acid **6** from alcohol **11**[10] is shown in Scheme 2 and involved a 3-step sequence including Swern oxidation, Wittig olefination and tin-promoted ester cleavage. Common basic saponification conditions failed to convert ester **13** to acid **6**. Acid **7** was prepared from alcohol **14**[11] via Jones oxidation.

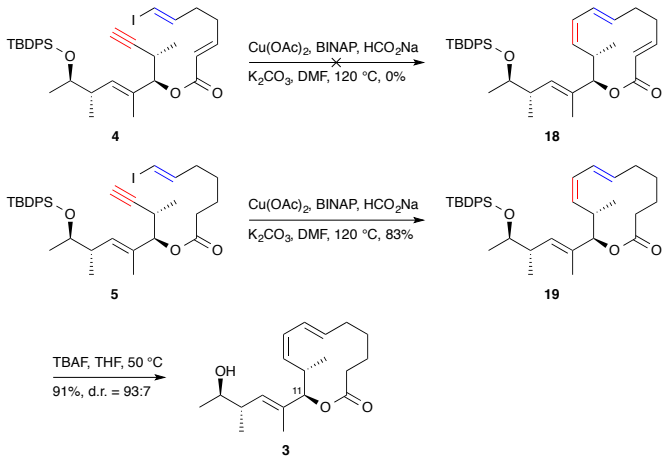


Scheme 2 Preparation of acids **6** and **7**.



Scheme 3 Synthesis of ester **4**/**5**.

The syntheses of esters **4**/**5** started from the commercially available (*E*)-2-methyl-2-pentenoic acid, which was converted to the known vinylketene silyl *N*,*O*-acetal **10** in two steps following literature reports (Scheme 3).[9c,12] Kobayashi's vinylogous aldol reaction of compound **10** with acetaldehyde afforded alcohol **15**. Maintaining the low reaction temperature was crucial for achieving high diastereoselectivity (d.r. > 30:1). Silyl protection of alcohol **15** followed by reductive removal of the chiral auxiliary provided aldehyde **9**. The aldehyde underwent Marshall's propargylation reaction with chiral allenylzinc reagent *in situ* formed from mesylate **17**[13] to furnish alcohol **8** as an inseparable mixture of epimers. The diastereomeric ratio was 82:18 in favor of the (4*S*)-alcohol.[15] Another version of the Marshall propargylation using a chiral allenylstannane[14] gave the (4*R*)-alcohol as the major stereoisomer, however, with low selectivity (d.r. = 56:44). Finally, esters **4** and **5** were obtained by Mitsunobu esterification of alcohol **8** with acids **6**/**7**, along with 20% of the dehydration products. A diastereomeric ratio of 90:10, preferring the (11*R*)-ester (lactimidomycin numbering), was observed, which is presumably due to the higher propensity of the minor (4*R*)-epimer of alcohol **8** to generate the dehydration products. The esters **4**/**5**, we then subjected to the macrocyclization method based on the Castro-Stephens coupling and the *in situ* alkyne reduction (Scheme 4). The reaction of ester **4** resulted in complete decomposition to form a complex, unidentifiable mixture. We hypothesized that the *E*-double bond might reduce the flexibility of the molecular so that it could not adapt a conformation in which the reacting centers were close enough to facilitate the macrocylization. In contrast, ester **5** without the conjugated double bond reacted smoothly to produce the expected lactone **19** in a yield of 83%. Completion of the formal total synthesis of lactimidomycin was achieved after desilylation of compound **19** to yield the known alcohol **3** and its C_{11}-epimer (d.r. = 93:7, separable). Spectra data and optical rotation ($[\alpha]_D^{22}$ = –85 (*c* 0.10, $CHCl_3$)) of the major isomer were in excellent agreement with those of the same compound reported by Fürstner ($[\alpha]_D^{20}$ = –86 (*c* 0.9, $CHCl_3$)).[6a]



Scheme 4 Macrocyclization and deprotection.

In summary, the synthesis of macrolactone **3**, an advanced intermediate in the synthesis of lactimidomycin, has been realized from commercially available starting materials in a total of nine steps (longest linear sequence) using minimal functional group protection. This is to our knowledge the shortest route to lactimidomycin intermediates with similar structure. The key step was a copper-catalyzed ene-yne coupling/alkyne reduction tandem reaction that formed the 12-

membered *E,Z*-diene macrocycle. Other featured reactions included a Kobayashi vinylogous aldol reaction and a Marshall propargylation reaction to generate the four stereocenters.

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Notes and references

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15 The diastereomeric ratio of **8** was determined by ^{1}H NMR. The major epimer was identified as the (4*S*)-alcohol by comparing the relative chemical shifts of C_4-*H* to those of structurally related compounds reported in Reference 8, and the fact that it led to the correct final product.