ORGANIC LETTERS

2006
Vol. 8, No. 18
4105−4108

Pharmacophore Mapping in the Laulimalide Series: Total Synthesis of a Vinylogue for a Late-Stage Metathesis Diversification Strategy

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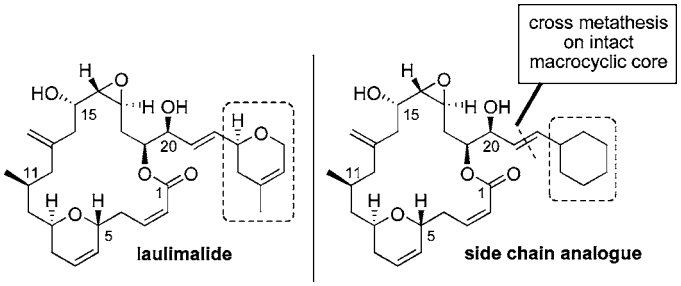
Received June 30, 2006

ABSTRACT



An efficient synthesis of the macrocyclic core of laulimalide with a pendant vinyl group at C20 is described, allowing for late-stage introduction of various side chains through a selective and efficient cross metathesis diversification step. Representative analogues reported herein are the first to contain modifications to only the side chain dihydropyran of laulimalide and des-epoxy laulimalide. This step-economical strategy enables the rapid synthesis of new analogues using alkenes as an inexpensive, abundantly available diversification feedstock.

The natural product laulimalide[1] (**1**, Figure 1) is a potent inhibitor of cancer cell proliferation with a mode of action similar to that of Taxol.[2] It stimulates the polymerization of purified tubulin and in cells causes mitotic arrest and initiation of apoptosis.[2] Significantly, however, it offers a distinct potential therapeutic advantage over Taxol due to its capacity to inhibit the proliferation of multidrug-resistant cell lines.[2,3] Moreover, laulimalide does not bind microtubules at the same site as Taxol,[3] and the two have been shown to synergistically stimulate the polymerization of tubulin in vitro.[4] Separate from its interaction with microtubules but equally as promising for the treatment of cancer is laulimalide's inhibition of two key pathways necessary for angiogenesis.[5] Recently, it has also been suggested that laulimalide and other microtubule stabilizers might hold promise for treatment of Alzheimer's and other neurodegenerative diseases.[6]

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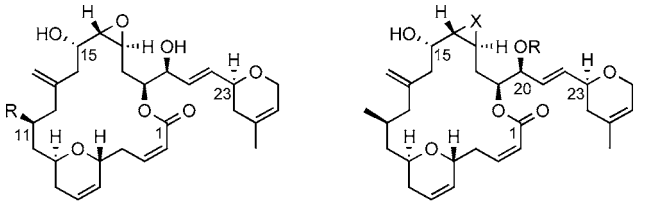
10.1021/ol061619u CCC: $33.50
Published on Web 08/12/2006



1 R = CH_3
IC_{50} (MDA-MB-435): 5.7 nM
2 R = H
IC_{50} (MDA-MB-435): 49.0 nM

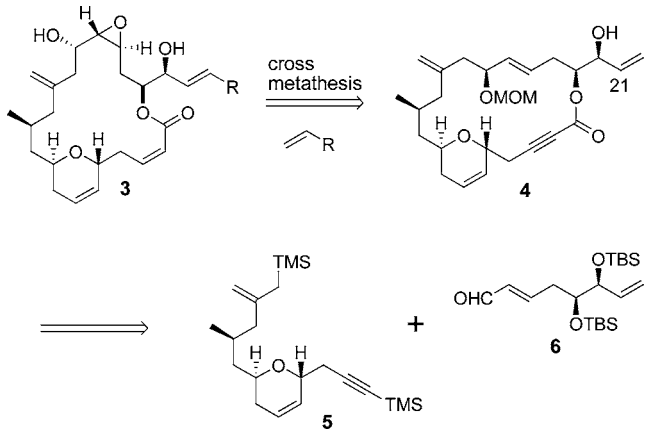
LA1 X = π-bond, R = H
IC_{50} (MDA-MB-435): 120 nM
LA2 X = O, R = CH_3
IC_{50} (MDA-MB-435): 240 nM

Figure 1. Laulimalide, selected analogues, and their potencies for inhibition of cancer cell proliferation.

Despite this unique therapeutic potential, laulimalide's scarce natural availability and instability are major obstacles to its clinical development. The first steps toward addressing these problems appeared in the form of several total syntheses of laulimalide.[7] Following this, the syntheses of various nonnatural analogues have appeared in the literature.[8] We have previously reported a uniquely short synthesis of laulimalide that provided the basis for accessing a first series of analogues. These analogues were designed to avoid the acid-catalyzed decomposition of laulimalide that leads to isolaulimalide, a less active compound.[8b] The most potent analogues, **LA1** and **LA2** (Figure 1), are more stable than laulimalide and retain its mode of action.[9] Significantly, they act synergystically with both paclitaxel and 2-methoxyestradiol *to a greater degree* than laulimalide itself.[10] More recently, we have focused on the identification of structurally simplified analogues that could be synthesized in a more step-economical and cost-efficient manner yet retain the potency and mode of action of the parent compound. We have recently reported, as our initial effort toward this goal, the synthesis of 11-desmethyllaulimalide[8g] (**2**, Figure 1).

Thus far, our efforts to define the pharmacophoric features of laulimalide that influence its activity have focused on modifications of the core macrocycle. However, little is known about the role of the dihydropyran side chain incorporating C23−C27 because so few analogues at this position exist.[8f] This subunit could contribute to the activity of laulimalide, but if not, variation of this unit could be used to modulate the pharmacokinetics and ADME of promising analogues. We sought to determine whether this ring could be replaced with a simpler moiety that would be beneficial with regard to both synthetic step count and biological activity. The ideal strategy for rapidly synthesizing numerous analogues at this position is to use a mild and selective reaction at a late stage in the synthesis that would draw on commercially available or easily prepared starting materials for structural variety. Such a reaction is the olefin cross metathesis process,[11,12] which would simply require an advanced laulimalide-like intermediate such as the C21−C22 alkene **4** and a partner alkene bearing the desired structural features of the new side chain (Scheme 1). We envisioned that such a reaction could be accomplished selectively at the C21 terminal alkene even in the presence of numerous other sites of unsaturation in the molecule. Although the synthesis of **4** would require a completely revised synthetic route, the opportunity to improve and generalize our earlier route and to access numerous analogues through late-stage diversification provided compelling justification for embarking on this effort. Drawing conceptually from our total syntheses of **1** and **2**, we expected that **4** would be convergently accessible from the less complex fragments **5** and **6** (Scheme 1). We provide herein the first report on this strategy for the synthesis of laulimalide side chain analogues.

Scheme 1. Retrosynthesis of Laulimalide Side Chain Analogues



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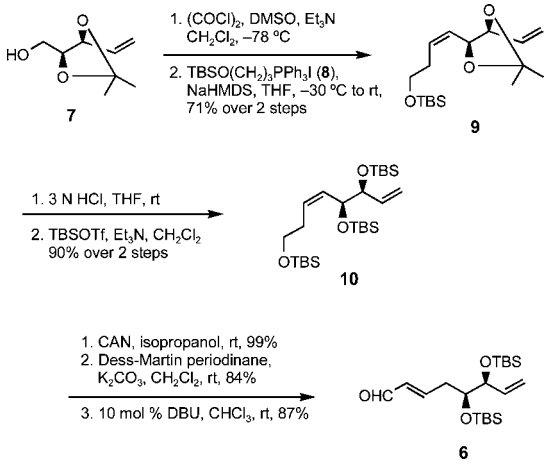
Enal **6** was prepared in seven steps starting from known primary alcohol **7**[13] using a sequence adapted from our earlier syntheses (Scheme 2). Swern oxidation of **7** followed by

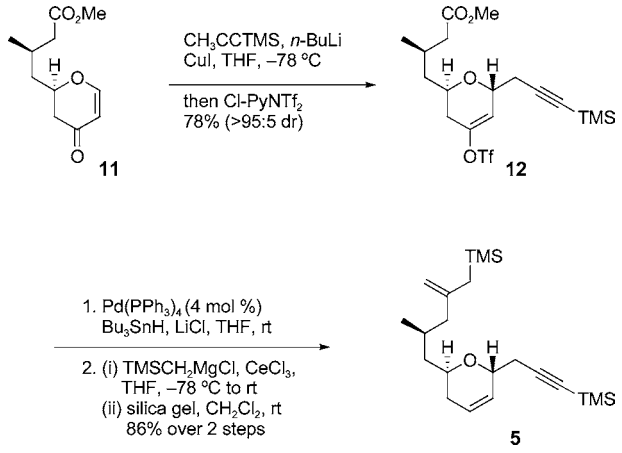
Scheme 2. Synthesis of Enal **6**



Wittig olefination with phosphonium salt **8** provided diene **9** in 71% yield over two steps. Global deprotection followed by silylation of the resulting triol afforded tris-TBS ether **10** in 90% yield over two steps. Selective deprotection of the primary TBS ether followed by Dess−Martin oxidation of the resulting alcohol and isomerization of the internal olefin with catalytic DBU gave enal **6** in high yield for the three-step sequence.

Allyl silane **5** was synthesized in accordance with our second-generation synthetic approach to the laulimalides (Scheme 3).[8g] Hetero Diels−Alder product **11**[7i] (prepared

Scheme 3. Synthesis of Allyl Silane **5**

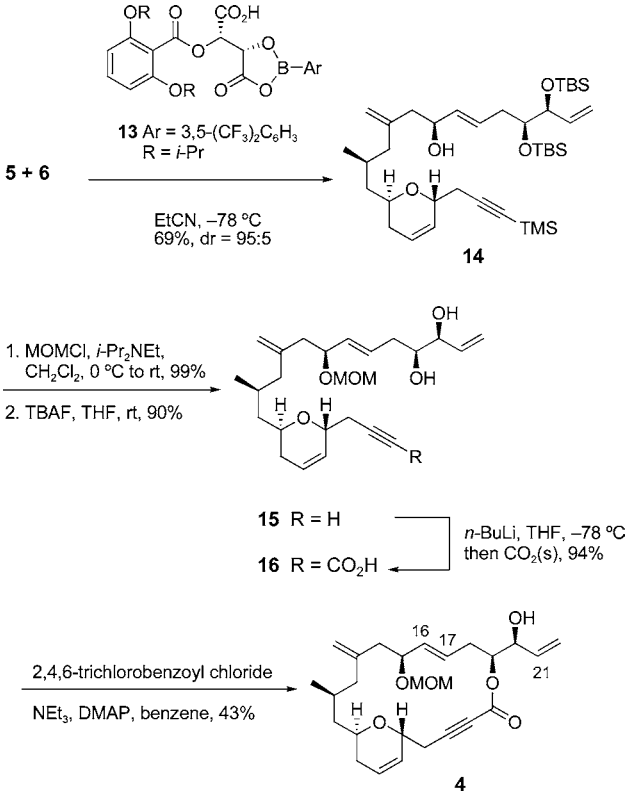


in four steps from (*R*)-citronellic acid) was subjected to a cuprate addition of the anion of 1-trimethylsilyl-1-propyne.[14]

The resulting enolate was trapped in situ with Comins' reagent, affording **12** (78%, >95:5 dr). Reduction of the enol triflate followed by treatment with excess $TMSCH_2MgCl$ and $CeCl_3$ and subsequent Peterson olefination provided allyl silane **5** (86% yield over two steps).

In the first stage of macrocycle formation, treatment of a solution of enal **6** and allyl silane **5** with Yamamoto's (acyloxy)-borane **13**[15] successfully promoted the asymmetric Sakurai reaction[16] of the two partners to yield the desired allylic alcohol **14** with high diastereoselectivity (up to 95:5 dr; Scheme 4). Protection of **14** as a MOM ether (99%)

Scheme 4. Synthesis of Cross Metathesis Precursor **4**



followed by cleavage of all three silyl groups with TBAF (90%) provided diol **15**. Gratifyingly, carboxylation of the lithium anion of the terminal alkyne proceeded in high yield (94%) in the presence of the unprotected 1,2-diol. This two-step sequence represents a further improvement to our synthetic route, replacing the former three-step sequence in which the TMS and TBS protecting groups were cleaved in separate steps.[8g] Finally, formation of the macrocycle under Yamaguchi conditions[17] selectively provided the 20-membered macrolactone **4**. Notably, the use of new allyl silane **5** coupled with the three-step formation of carboxylic acid **16** from allylic alcohol **14** resulted in a savings of four steps

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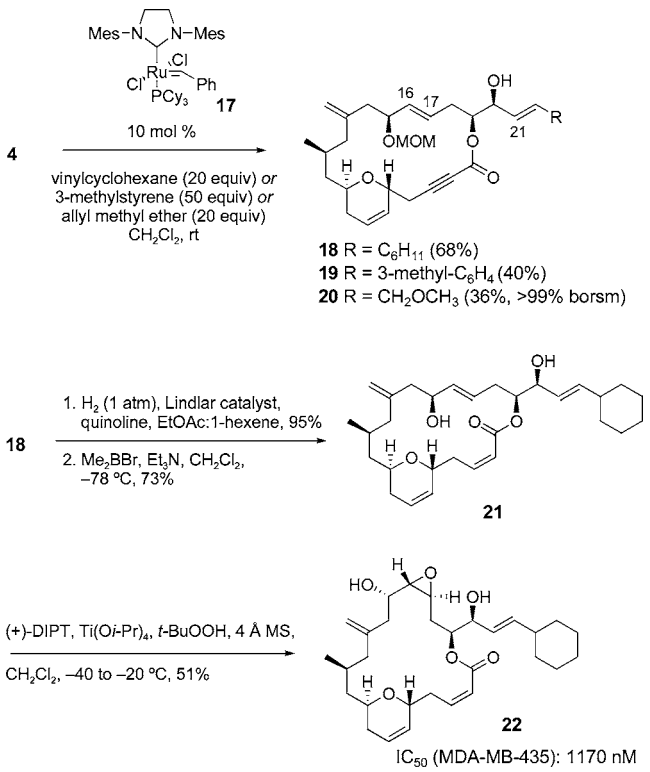
Scheme 5. Laulimalide Side Chain Analogue via Cross Metathesis



(longest linear) in the formation of **4** over the formation of the corresponding intermediate in our total synthesis of **1**.

Macrolactone **4** is the target intermediate from which we envisioned installing various new side chains using the cross metathesis reaction. This process is not without potential complication due to several sites of unsaturation in the substrate and the potential for intramolecular closure involving the C16−C17 alkene. Gratifyingly, the use of catalyst **17**[18] and 20 or 50 equiv of a variety of commercially available olefins at room temperature enables a highly selective functionalization of the C21 terminal olefin, allowing for installation of new side chains (Scheme 5). Illustrative of the exquisite selectivity for the C21 olefin, unreacted starting material was quantitatively recovered in one example (**20**). Only three additional synthetic steps are required to complete the synthesis of the target analogues. In one example, Lindlar reduction of cross metathesis product **18** (95%) followed by cleavage of the C15 MOM ether (73%) provided new des-epoxy side chain analogue **21**, analogous to active and stable analogues prepared in our earlier studies.[8b,g] Finally, selective epoxidation of the C16−C17 olefin using Sharpless conditions[7i] yielded completed cyclohexane side chain analogue **22** (51%).

The completion of the synthesis of these new analogues illustrates the generality of our synthetic approach to the laulimalides and introduces a cross metathesis strategy for rapid synthesis of new laulimalide side chain analogues. Although full biological evaluation of **21**, **22**, and other analogues will be disclosed in a more detailed future report, it is notable that analogue **22**, in which the hydropyranyl ring present in laulimalide is replaced with a cyclohexane, is roughly 200-fold less potent than the natural compound, with an IC_{50} of 1170 nM in the MDA-MB-435 cell line. This suggests an important role for the laulimalide side chain and is consistent with results obtained using the 11-desmethyl scaffold.[8f] Ongoing research in our laboratories is aimed at using this synthetic strategy to explore how the structural features of the laulimalide side chain affect both the potency and the biological function of analogues.

Acknowledgment. Support of this work provided by the National Institutes of Health (CA31841), the Joe and Jesse Crump Foundation (S.L.M.), the Carlsberg Foundation (postdoctoral support for P.R.S.), and the Swiss National Foundation (postdoctoral support for N.G.S.) is gratefully acknowledged.

Supporting Information Available: Experimental conditions and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061619U

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