J|A|C|S COMMUNICATIONS

Published on Web 09/10/2010

Concise Total Synthesis of the Potent Translation and Cell Migration Inhibitor Lactimidomycin

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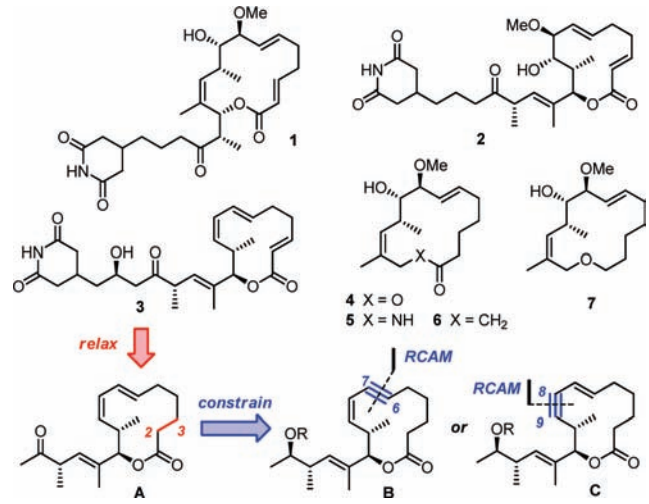
Abstract: An efficient total synthesis of the antiproliferative macrolide and cell migration inhibitor lactimidomycin (**3**) is reported, which relies on the performance of ring closing alkyne metathesis (RCAM). The strained 12-membered 1,3-enyne **21** as the key intermediate was forged with the aid of $[(Ph_3SiO)_3Mo{\equiv}CPh]\cdot OEt_2$ (**27**) as the most effective member of a new generation of powerful alkyne metathesis catalysts. **21** was elaborated to the target by a ruthenium catalyzed *trans*-hydrosilylation/proto-desilylation sequence and a highly diastereoselective Mukaiyama aldol reaction controlled by oxazaborolidinone **29** as strategic operations.

The family of macrolides derived from the parent compounds migrastatin (**1**) and isomigrastatin (**2**) includes some of the most promising cell migration inhibitors known to date.[1,2] Among them, the migrastatin core analogues **4**−**7** are particularly noteworthy as they were found to inhibit spreading of mammary tumors in mice without being noticeably cytotoxic.[1] These compounds were shown to selectively target the actin-bundling protein fascin, the overexpression of which in malignant tumors is often correlated with a poor prognosis.[3] If clinically viable as inhibitors of metastasis, these or functionally related small molecules might become an important second line of defense against cancer, complementing conventional chemotherapy.

The possible reward of this endeavor brought lactimidomycin (**3**) back on stage, a closely related macrolide isolated from *Streptomyces amphibisporus* as early as 1992.[4,5] Unlike isomigrastatin (**2**), compound **3** is not prone to ring expansion by allylic rearrangement. A detailed reinvestigation of its biological properties revealed the potent cell migration inhibitor capacity of **3**, which rivals the best migrastatin analogues.[6] Lactimidomycin is also cytotoxic and exhibits appreciable antiproliferative properties *in vivo* against various tumors including the highly invasive MDA MB 231 human breast adenocarcinoma.[4,7] Because nontumorigenic breast tissue was found to be much less sensitive to **3**, the compound holds an encouraging selectivity profile. In contrast to the fascin inhibitors **4**−**7**, compound **3** interferes primarily with protein synthesis, blocking the translation−elongation phase by binding to the 60S ribosome.[7] Hence, lactimidomycin and migrastatin differ fundamentally in their mode of action at the molecular level, despite an obvious structural relationship.

As part of our agenda concerning the chemistry and biology of small molecule anticancer agents,[8] we developed a concise approach to lactimidomycin as a first step of a more comprehensive investigation into the chemical space surrounding this lead compound. The major hurdle derives from the strain inherent to the 12-membered lactone, which incorporates no less than seven sp^2-hybridized C-atoms.[9] Problems caused by ring strain had already surfaced in the only synthesis of isomigrastatin (**2**) known to date[10]

Scheme 1. Glutarimide Macrolides and Retrosynthetic Analysis of Lactimidomycin (**3**)



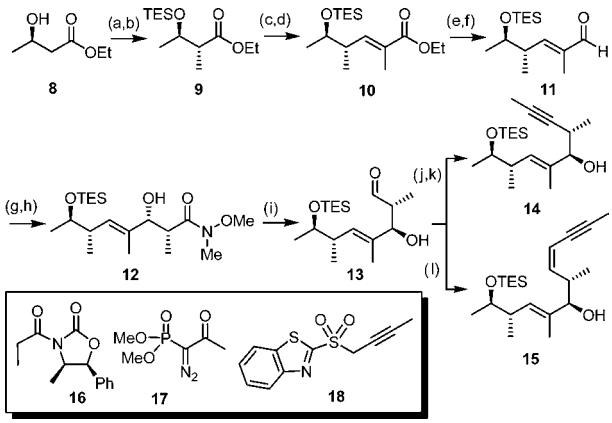
but are expected to become even more daunting in the case of **3**, which contains three rather than two alkenes within the macrocycle. Yet, we opted for a counterintuitive approach, in which the strain of the precursor is temporarily *increased* rather than decreased (Scheme 1). The enthalpic penalty for the formal replacement of one of the olefins by an alkyne, however, might be counterbalanced by building upon Danishefsky's pivotal finding that a late-stage installation of the enoate double bond was instrumental for the synthesis of **2**.[10] The projected incorporation of an alkyne into the cyclic frame trusts in the power of ring closing alkyne metathesis (RCAM)[11,12] and provides a stringent test for the latest generation of catalysts developed in our laboratory.[13−15] If successful, we might be rewarded with unambiguous olefin stereochemistry to be set by semireduction of the interim triple bond.[16] Of the two conceivable scenarios (Scheme 1), *Z*-enyne **B** seemed more promising than its *E*-enyne counterpart **C**,[17] but this analysis needed experimental verification. We were hence prepared to pursue both possible routes.

The required precursors were available in high yield from aldehyde **13** as a common intermediate, which in turn was derived from commercial **8** by standard operations, including a Frater−Seebach alkylation[18] and an Evans boron-aldol reaction[19] to set the chiral centers with exquisite selectivity (Scheme 2).[20] Extension of the carbon chain on reaction of **13** with the Ohira−Bestmann reagent **17**[21] followed by methylation gave alkyne **14** in good yield. Alternatively, **13** was subjected to a Julia olefination with sulfone **18**,[22] which furnished the required *Z*-enyne **15** in isomerically pure form.

Next, **14** and **15** were converted to the corresponding esters **19** and **20**, respectively, in preparation for ring closure via RCAM (Scheme 3). For this purpose, we chose the newly designed complex

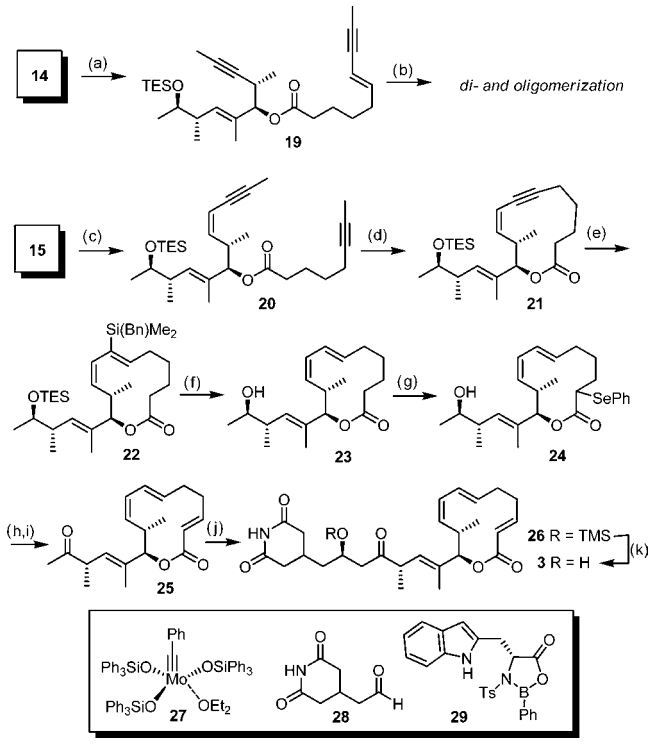
10.1021/ja107141p

Scheme 2[a]



[a] Reagents and conditions: (a) LDA (2 equiv), THF/HMPA, MeI, −78 °C → 0 °C, 94%; (b) TESCl, pyridine, CH_2Cl_2, 91%; (c) Dibal-H, CH_2Cl_2, −78 °C; (d) $Ph_3P{=}C(Me)COOEt$, THF, reflux, 92% (over two steps); (e) Dibal-H, CH_2Cl_2, −78 °C → 0 °C, 98%; (f) PCC, CH_2Cl_2, 79%; (g) **16**, Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C → RT, 90%; (h) MeNH(OMe)·HCl, Me_3Al, THF, −10 °C, 81%; (i) $LiAlH_4$, THF, −78 °C → 0 °C; (j) **17**, K_2CO_3, MeOH, 0 °C → RT, 61% (over two steps); (k) BuLi, MeI, THF, 73%; (l) **18**, KHMDS, THF, −55 °C, 59% (over two steps).

Scheme 3[a]



[a] Reagents and conditions: (a) dec-6*E*-en-8-ynoic acid, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), DMAP, CH_2Cl_2, 90%; (b) **27** (5 mol %), toluene; (c) 6-octynoic acid, EDC, DMAP, CH_2Cl_2, 0 °C → RT, 96%; (d) **27** (5 mol %), toluene, MS 5 Å, 80 °C, 95%; (e) $BnMe_2SiH$, $[Cp^*Ru(MeCN)_3]PF_6$ (10 mol %), CH_2Cl_2, 0 °C → RT; (f) TBAF, THF, 0 °C → RT, 64% (over both steps); (g) (i) LDA, THF, −78 °C → 0 °C; (ii) PhSeBr, −78 °C → 0 °C; (h) (i) *m*CPBA, CH_2Cl_2, −78 °C; (ii) *i*PrNEt$_2$, −78 °C → RT, 64% (over g−h); (i) Dess-Martin periodinane, CH_2Cl_2, 87%; (j) (i) LiHMDS, TMSCl, Et_3N, THF, −78 °C; (ii) **28**, EtCN, then **29**, −78 °C; (k) HF·pyridine, THF/pyridine, 0 °C, 60% (over three steps).

27 as the arguably most active and selective alkyne metathesis catalyst known to date.[13] The Ph_3SiO ligands temper the Lewis acidity of its Mo(+6) center while imparting outstanding reactivity on the operative alkylidyne unit. Nevertheless, diyne **19** could not be closed with the aid of this complex but furnished a mixture of (cyclic) dimers and oligomers. In stark contrast, the isomeric substrate **20** reacted cleanly under high dilution conditions to give the desired 12-membered enyne **21** as the only product, which was isolated in 95% (240 mg scale) and 84% (1.2 g scale) yield. The ring strain of the product is thought to account for the fact that the cyclization had to be performed at 80 °C, albeit catalyst **27** per se is fully operative at ambient temperature.[13] Since the cyclic enynes of type **B** and **C** are isomeric to each other, the different outcomes of the reactions of substrates **19** and **20** allow the upper limit of strain energy to be assessed which can be built-up by alkyne metathesis; this aspect is currently under investigation in our laboratory.[17] Of equal relevance is the exquisite chemoselectivity in the cyclization event, as catalyst **27** rigorously distinguished between the alkene- and alkyne π-bonds of compound **20**.

A *trans*-hydrosilylation/protodesilylation sequence was deemed ideal for the conversion of **21** to the required *E*,*Z*-configured 1,3-diene **23**.[23,24] Our previous observation,[25] however, that enynes are reluctant substrates in such transformations got confirmed when **21** was exposed to $(EtO)_3SiH$ and $[Cp^*Ru(MeCN)_3]PF_6$ as the catalyst. A mixture of regioisomeric alkenylsiloxanes was formed in low yield, and the workup of the mixture was plagued by competing siloxane polymerization. Gratifyingly, the use of $BnMe_2SiH$ nicely solved these problems.[26] The hydrosilylation was clean and regioselective, and the subsequent desilylation was effortless even with commercial TBAF, although this reagent had previously been found unsuitable for the cleavage of related alkenylsilanes carrying ordinary trialkylsilyl groups.[23−25,27,28]

The enoate moiety was then installed by quenching of the lithium enolate derived from **23** with PhSeBr and subsequent oxidative elimination, following Danishefsky's lead from the isomigrastatin series.[10,17b] Since **23** could be carried through without a protecting group for the secondary alcohol in the side chain, which had been liberated concomitantly with the C−Si bond cleavage, a standard oxidation sufficed to give ketone **25** in readiness for an aldol reaction with the known aldehyde **28**.[29] The kinetic lithium enolate of **25** furnished the desired product as a mixture of isomers (50%, dr =55:45); attempts to improve on this outcome by using the corresponding Ipc_2B-enolate met with failure.[30] Therefore we turned our attention to a Mukaiyama-aldol process.[31] After some experimentation it was found that the tryptophane-derived oxazaborolidinone **29** was the promoter of choice,[32] furnishing **26** as the only isomer, the *R*-configuration of which was confirmed by Mosher ester analysis.[33] In addition to providing excellent facial bias, the Lewis acidity of the boron center in **29** is properly adjusted such that it induces the reaction with ease but does not destroy the acid-labile product. The final deprotection step had to be carried out with HF·pyridine in buffered medium to account for the fact that lactimidomycin is quite sensitive to more basic fluoride sources. The spectral data of our synthetic samples were in excellent agreement with those reported for the natural product.[33]

The total synthesis of the translation and cell migration inhibitor lactimidomycin (**3**) outlined above illustrates the power of $[(Ph_3SiO)_3Mo{\equiv}CPh]\cdot OEt_2$ as a representative of the latest generation of alkyne metathesis catalysts.[13] The relevance of this methodology even for the formation of fairly strained compounds becomes obvious upon comparison of the RCAM-based approach to **3** with this RCM-based route to the closely related macrolide isomigrastatin **2**.[16] It is believed that the underlying blueprint provides a firm basis for a synthesis-driven evaluation of this promising lead compound, since the successful route is short, productive, and convergent and seems scalable as well as amenable

to structural diversification. Studies along these lines will be reported in due course.

Acknowledgment. Generous financial support by the MPG and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank our analytical department for excellent support, Prof. W. Thiel and Mr. T. Benighaus, Mülheim, for preliminary computational analyses, and Prof. B. Shen, University of Wisconsin, for sharing unpublished information on the chiroptical properties of **3** with us.

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

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(16) In this context it is noteworthy that the RCM en route to isomigrastatin (**2**) delivered only 21% of the desired *E*-olefin together with 36% of the unwanted *Z*-isomer. The reaction required a loading of 20 mol% of Grubbs-II catalyst and heating of the mixture to 110°C in toluene; cf. ref 10.

(17) (a) Intermediate **B** (R = $SiEt_3$) was computed to be 8.26 kcal/mol (B3LYP/TZVP) or 8.19 kcal/mol (B3LYP/TZVPP) less strained than isomer **C**. Likewise, the calculations suggest that the alkyne in **B** should be significantly less bent than that in **C**. (b) The strain energy of the analogous compounds with the enoate in place is prohibitively high, and all attempts to effect ring closure by RCAM with such substrates were indeed unsuccessful.

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JA107141P