ORGANIC LETTERS

2012
Vol. 14, No. 21
5484–5487

Enantioselective Synthesis of the *ent*-Lomaiviticin A Bicyclic Core

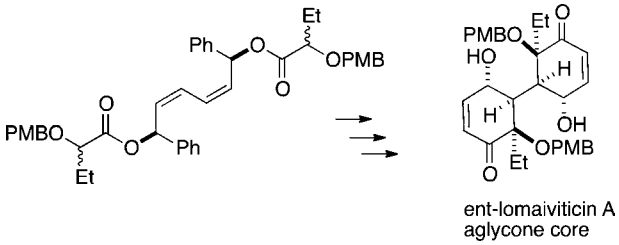
Ken S. Feldman* and Brandon R. Selfridge

Chemistry Department, The Pennsylvania State University, University Park, Pennsylvania 16802, United States

ksf@chem.psu.edu

Received September 18, 2012

ABSTRACT



The bicyclic core of *ent*-lomaiviticin A was prepared in 11 operations from (*S*)-1-phenyl-2-propyn-1-ol in a two-directional route that features (1) a double Ireland Claisen rearrangement and (2) a double olefin metathesis reaction to form the key C−C bonds of the target.

Lomaiviticins A and B are glycosylated dimeric marine actinomycetes isolates that extend the growing family of diazoparaquinones originally formulated around the structurally related but monomeric kinamycins (Figure 1).[1,2] The lomaiviticins exhibit remarkably potent cytotoxicity against several cancer cell lines, and the observation that they induce dsDNA cleavage under reducing conditions may underscore their biological mechanism-of-action, and perhaps that of the other structurally related diazoparaquinones as well.[2,3] The challenging structural intricacies of the lomaiviticin core and their intriguing biological activity has fueled several synthesis projects,[4] eventually culminating in a landmark 11-step total synthesis of the lomaiviticin aglycone along with its C(2)−C(2′) diastereomer (~2:1 mixture, lomaiviticin numbering) via a late-stage dimerization reaction.[5] Several of the other lomaiviticin synthesis approaches also recognized the expedience, and likewise the risk, of pursuing a formal dimerization strategy to this bipartite target,[4b,d,e] whereas other approaches that build outward from a central bicyclic core have been explored as well.[4a,c]

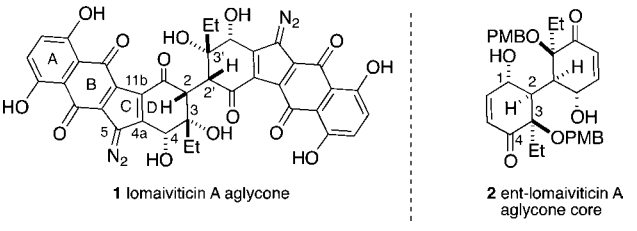


Figure 1. Lomaiviticin A aglycone and the bicyclic core synthesis target.

We speculated that relative stereochemical control in the sterically crowded C(3)−C(2)−C(2′)−C(3′) core region of

(1) (a) He, H.; Ding, W.-D.; Bernan, V. S.; Richardson, A. D.; Ireland, C. M.; Greenstein, M.; Ellstad, G. A.; Carter, G. T. *J. Am. Chem. Soc.* **2001**, *123*, 5362–5363. (b) Woo, C. M.; Beizer, N. E.; Janso, J. E.; Herzon, S. B. *J. Am. Chem. Soc.* **2012**, *134*, 15285–15288.

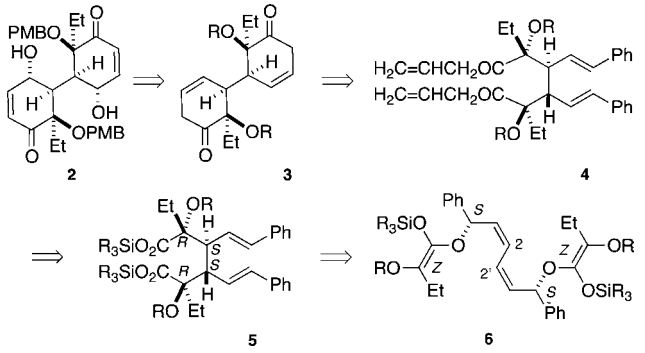
(2) Herzon, S. B.; Woo, C. M. *Nat. Prod. Rep.* **2012**, *29*, 87–118.

(3) (a) Moore, H. W. *Science* **1977**, *197*, 527–532. (b) Arya, D. P.; Jebaratnam, D. J. *J. Org. Chem.* **1995**, *60*, 3268–3269. (c) Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2002**, *124*, 1854–1855. (d) Feldman, K. S.; Eastman, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 15344–15345. (e) Feldman, K. S.; Eastman, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 12562–12573. (f) Hasinoff, B. B.; Wu, X.; Yalowich, J. C.; Goodfellow, V.; Laufer, R. S.; Adedayo, O.; Dmitrienko, G. I. *Anti-Cancer Drugs* **2006**, *17*, 825–837. (g) Zeng, W.; Ballard, T. E.; Tkachenko, A. G.; Burns, V. A.; Feldheim, D. L.; Melander, C. *Biorg. Med. Chem. Lett.* **2006**, *16*, 5148–5151. (h) O'Hara, K. A.; Wu, X.; Patel, D.; Liang, H.; Yalowich, J. C.; Chen, N.; Goodfellow, V.; Adedayo, O.; Dmitrienko, G. I.; Hasinoff, B. B. *Free Radical Biol. Med.* **2007**, *43*, 1132–1144. (i) Ballard, T. E.; Melander, C. *Tetrahedron Lett.* **2008**, *49*, 3157–3161. (j) Khdour, O.; Skibo, E. B. *Org. Biomol. Chem.* **2009**, *7*, 2140–2154. (k) Heinecke, C. L.; Melander, C. *Tetrahedron Lett.* **2010**, *51*, 1455–1458. (l) O'Hara, K. A.; Dmitrienko, G. I.; Hasinoff, B. B. *Chem.-Biol. Interact.* **2010**, *184*, 396–402. (m) Mulcahy, S. P.; Woo, C. M.; Ding, W.; Ellestad, G. A.; Herzon, S. B. *Chem. Sci.* **2012**, *3*, 1070–1074.

10.1021/ol302567f
Published on Web 10/17/2012

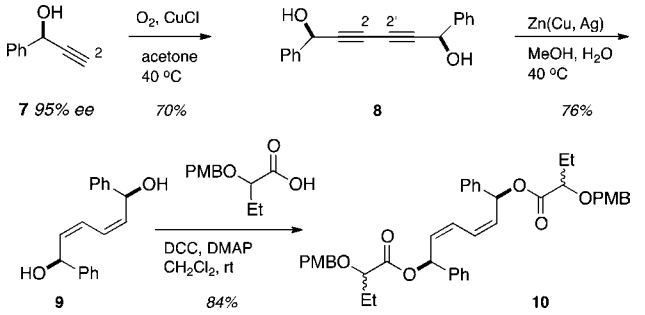
the lomaiviticins might be easier to achieve via the "inside-out" approach than through the "monomer dimerization" approach since the former chemistry focuses on establishing the C(2)−C(2′) bond early in the route. Toward this end, a synthesis plan for the lomaiviticin core, distinct from earlier approaches, can be developed (Scheme 1). In this plan, the bicyclic core **2** can be prepared by oxidation from the bis cyclohexenone **3**, which in turn should be available from a double ring-closing olefin metathesis reaction (RCM) on tetraene **4**.[6] Tetraene **4** should be available from two-directional chain extension of the bis ester **5**, the double Ireland Claisen rearrangement product of a bis silyl ketene acetal. Applying the standard chairlike transition state model[7] for this rearrangement with an equatorial phenyl ring anchor to these (sequential) Claisen rearrangements leads to the conclusion that a *Z*,*Z* diene **6** is required. In this plan, the Claisen rearrangements are responsible for setting the central C(3)−C(2)−C(2′)−C(3′) relative and absolute stereochemistry. This divergent synthesis plan, like any two-directional approach, has the advantage of halving the steps of the route while at the same time fighting the unavoidable disadvantage of the arithmetic demon, squared.

Scheme 1. Retrosynthesis of Bicycle **2**



The preparation of the key bis Ireland Claisen precursor **6** commenced with the (commercially available) chiral secondary alcohol **7**, which is prepared inexpensively in 10-g batches through the chiral auxiliary-mediated addition of zinc trimethylsilylacetylide to benzaldehyde (Scheme 2).[8] The cheaper of the two enantiomers of **7** was employed for convenience, even though the enantiomer of the natural core would result. Glaser coupling of this propargyl alcohol unites the two "halves" of the target by forging the C(2)/C(2′) bond within the product diyne **8**.[9] Reduction of the bis diyne **8** to a *Z*,*Z*-diene failed with Lindlar catalyst/H_2 under a variety of conditions/additives, as typically only an enyne product was isolated. The failure of the second alkyne reduction under Lindlar hydrogenation conditions, whereas disappointing, is not without precedent.[10] Hence, recourse was made to the more exotic Zn/Cu/Ag-mediated alkyne reduction protocol of Boland,[10] which in this instance worked splendidly to deliver only the *Z*,*Z*-diene containing product **9** in good yield. Double acylation of the crystalline diene diol **9** with the PMB ether of 2-hydroxybutanoic acid[11] proceeded uneventfully to deliver the Ireland Claisen precursor bis ester **10**.

Scheme 2. Synthesis of the *Z*,*Z*-diene Ireland Claisen Rearrangement Precursor



The Ireland Claisen rearrangement of **10** into the bis ester **12** required much optimization (on **10** and on related model systems[11]) in order to achieve the high yield shown (Scheme 3). The silyl source (TMSCl, TBSCl, TIPSCl, TMSOTF, TBSOTf, TIPSOTf), base (Li, Na, K salts of $N(TMS)_2$, LDA), Lewis acid additive (none, $SnCl_2$, $TiCl_4$, $ZnCl_2$), and solvent (THF, CH_3CN, Et_2O) defined the parameter space for this optimization. Whereas the formation of *Z*-silyl ketene acetals from simple 2-unsubstituted glycolate ethers via chelation-controlled enolization is well established,[12] the same level of predictability does not necessarily attend 2-substituted (i.e., 2-ethyl) versions such as **10**.[11,13] The double Claisen rearrangement depicted in transition state model **11** is illustrated as a convenience only; these rearrangements presumably occur sequentially.

(4) (a) Nicolaou, K. C.; Denton, R. M.; Lenzen, A.; Edmonds, D. J.; Li, A.; Milburn, R. R.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2076–2081. (b) Krygowski, E. S.; Murphy-Benenato, K.; Shair, M. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1680–1684. (c) Zhang, W.; Baranczak, A.; Sulikowski, G. A. *Org. Lett.* **2008**, *10*, 1939–1941. (d) Nicolaou, K. C.; Nold, A. L.; Li, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 5860–5863. (e) Lee, H. G.; Ahn, J. Y.; Lee, A. S.; Shair, M. D. *Chem.—Eur. J.* **2010**, *16*, 13058–13062.

(5) Herzon, S. B.; Lu, L.; Woo, C. M.; Gholap, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 7260–7263.

(6) (a) Bedel, O.; Haudrechy, A.; Langlois, Y. *Eur. J. Org. Chem.* **2004**, 3813–3819. (b) Français, A.; Bedel, O.; Picoul, W.; Meddour, A.; Courtieu, J.; Haudrechy, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1141–1155.

(7) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

(8) Qiu, L.; Wang, Q.; Lin, L.; Liu, X.; Jiang, X.; Zhao, Q.; Hu, G.; Wang, R. *Chirality* **2009**, *21*, 316–323.

(9) Smith, C. D.; Tchabanenko, K.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron Lett.* **2006**, *47*, 2309–3212.

(10) Boland, W.; Schroer, N.; Sieler, C. *Helv. Chim. Acta* **1987**, *70*, 1025–1040.

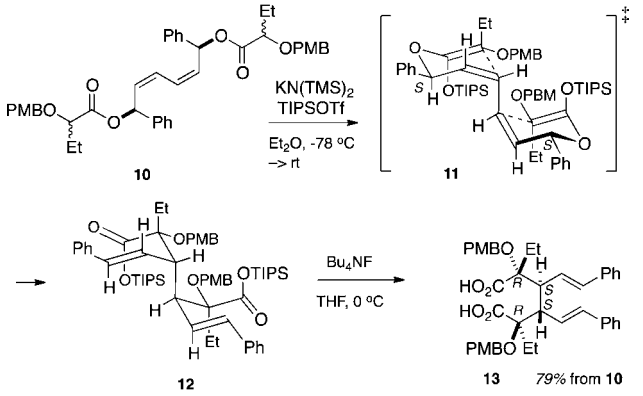
(11) Feldman, K. S.; Selfridge, B. R. *Tetrahedron Lett.* **2012**, *53*, 825–828.

(12) (a) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221–5228. (b) Gould, T. J.; Balestra, M.; Wittman, M. D.; Gary, J. A.; Rossano, L. T.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 3889–3901.

(13) Picoul, W.; Urchegui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797–4800.

The product diester **12** is isolated as a single stereoisomer without any evidence for a minor diastereomer (^{1}H NMR detection limit $< 5\%$).

Scheme 3. Ireland Claisen Rearrangement to Establish the Pivotal C(2), C(3), C(2′), C(3′) Stereochemical Tetrad

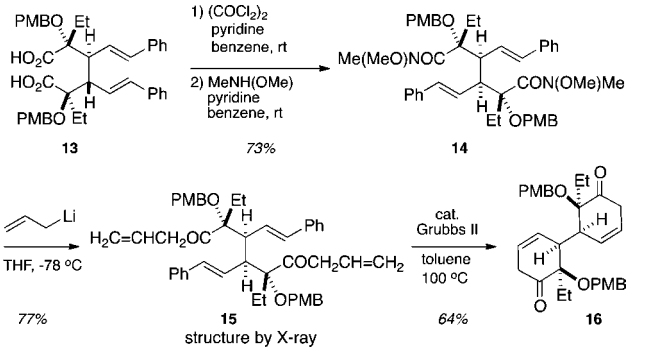


The relative stereochemistry of **12** was established via single crystal X-ray analysis of a downstream intermediate (vide infra). Thus the relative stereochemical outcome of this bis Claisen rearrangement is consistent with reaction through chairlike transition states with *Z*-silyl ketene acetal precursors, although boat-like transition states and *E*-silyl ketene acetals cannot be excluded. Facile desilylation of crude diester **12** provided the readily purified diacid **13**.

Continuation of the synthesis plan required double chain extension of diacid **13** to set up a double RCM sequence (Scheme 4). The sterically hindered acids of **13** simply cyclized into a seven-membered ring anhydride upon exposure to HN(OMe)Me and EDC-mediated amidation conditions, presaging what turned out to be a difficult transformation. Eventually, conversion of the bis acid **13** into the bis acid chloride and then acylation with NH(OMe)Me did suffice to form the bis Weinreb amide **14** in acceptable yield. Exposure of this bis amide to an allyl Grignard reagent led to monoaddition only. Fortunately, allyl lithium was servicable for this double chain extension, leading to a good yield of the bis allyl ketone product **15**. The structure and stereochemistry of **15** was firmly established by single crystal X-ray analysis (see Supporting Information).[14]

All that remained for this phase of the synthesis sequence was a double ring closing metathesis. Once again, extensive optimization studies were required to overcome problems with low yields in this transformation: Schrock's catalyst, Grubbs I, Grubbs II, and Hoyveda–Grubbs catalysts[15] were explored at a range of temperatures (rt–110 °C), concentrations (0.03–0.002 M), and solvents (CH_2Cl_2, $(ClCH_2)_2$, benzene, toluene). Eventually, reproducible, moderate yields of the bis cyclohexenone **16** were obtained by conducting the RCM reaction at 100 °C in a sealed tube (0.02 M in toluene) after thoroughly degassing the sample via three freeze–thaw cycles.

Scheme 4. Formation of the Bicyclic Structure by Double Olefin Metathesis



The conclusion of the *ent*-lomaiviticin A aglycone core synthesis involves a complicated solution to a seemingly simple oxidative transformation (Scheme 5). Conversion of the β,γ-alkenes of **16** into the requisite γ-hydroxy enones of **2** should have been no more challenging than alkene epoxidation followed by oxirane opening facilitated by enolization of the ketone.[16] Unfortunately, none of that planned chemistry worked. All efforts at alkene epoxidation within **16** (mCPBA, DMDO, peracetic acid, $Mn(ppei)_2(OAc)_6$) led to one of two equally unfortunate outcomes: no chemical reaction or compound destruction. Even a simple model system (half of **16**) was untouched by mCPBA and could only be epoxidized with DMDO. An initial workaround, which was designed to exploit hydroxyl-directed epoxidation methodologies, was set up by liberating the tertiary hydroxyls with TFA treatment of **16**. The caged compound **18** resulted.

A second approach to γ-hydroxylation focused on forming a bis dienyl silyl ether **19** from **16** with the hope that oxidation of this species could be directed to the γ-position. Attempts to epoxidize a simpler model dienyl silyl ether (i.e., half of **19**) led only to α-hydroxylation, presumably via an unisolated silyloxyepoxide (i.e., Rubottom oxidation). Fortunately, the electron-rich dienes of **19** were competent partners for singlet oxygen-mediated cycloadditions,[17] and the bis endoperoxide **20** as a stable single diastereomer was formed in modest overall yield from **16**. The structure and stereochemistry of **20** was determined by single crystal X-ray analysis (see Supporting Information).[14] Attempts to cleave the endoperoxide bond via various reductants (Me_2S, thiourea, tributylphosphine) proved fruitless, as only compound destruction ensued. However,

(14) Cambridge Crystallographic Data Centre deposition number for **15**: CCDC 867255; for **20**: CCDC 894557. The data can be obtained free from Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

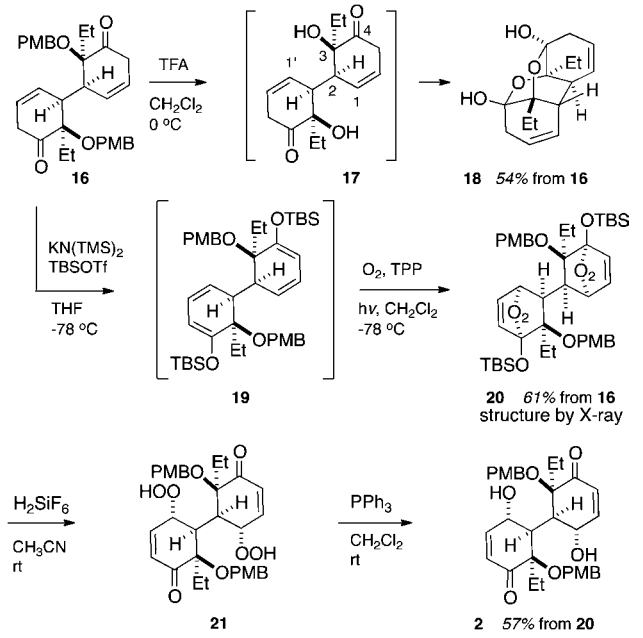
(15) Prunet, J. *Eur. J. Chem.* **2011**, 3634–3647.

(16) Crich, D.; Krishnamurthy, V. *Tetrahedron* **2006**, *62*, 6830–6840.

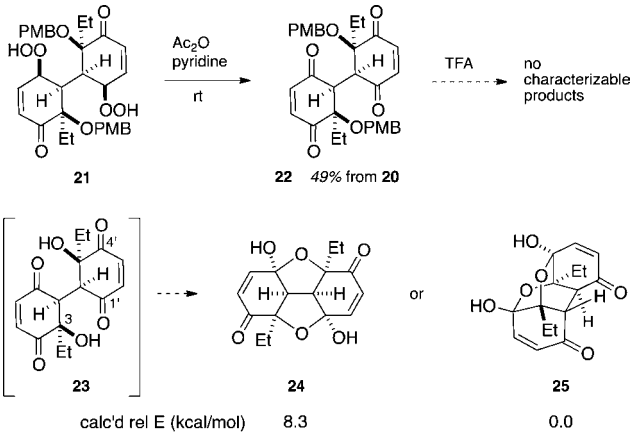
(17) Saito, I.; Nagata, R.; Kotsuki, H.; Matsuura, T. *Tetrahedron Lett.* **1982**, *23*, 1717–1720.

(18) He, J.; Tchabanenko, K.; Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Eur. J. Org. Chem.* **2006**, *17*, 4003–4013.

Scheme 5. Completion of the Bicyclic Core Synthesis



Scheme 6. Feasibility of Access to the Lomaiviticin B Core from a C(1)/C(4) Dione Precursor



desilylation under mild conditions with H_2SiF_6[18] did afford the bis peroxide **21**, which could be reduced easily to the diol **2** with PPh_3.

The bis peroxide **21** served as the launch point for an alternative thrust toward the lomaiviticin core (Scheme 6). The plan was to generate a bis enedione **22** by formal bis dehydration of the two peroxide moieties within **21** and then deprotect the hydroxyls (**22** – > **23**) in anticipation of a double cyclization event to form the lomaiviticin B core, **24**. This chemistry would pit the desired hemiketal-forming cyclization (**23** → **24**) against the undesired but now precedented (cf. **17** → **18**) alternative of C(3)–OH → C(4′) ketone cyclization to form **25**. With **23**, there is a C(1′) ketone to offer up a competition with C(3)–OH → C(4′) ketone cyclization; this C(1′) ketone was lacking in the **17** → **18** conversion. In the event, the enedione **22** was prepared from **21** by way of an intermediate bis acetate. All attempts to remove the PMB protecting groups from **22** met with compound destruction, so the cyclization selectivity of hypothetical lomaiviticin B core precursor **23** remains unknown. To the extent that such a cyclization might occur under thermodynamic control, density functional calculations[19] suggest that the undesired isomer **25** would be strongly favored. This calculational result, in conjunction with the **17** → **18** conversion, perhaps points out a potential weakness of any strategy to the core of lomaiviticin B that might proceed through a free C(4) ketone.

In summary, the bicyclic core of *ent*-lomaiviticin A has been prepared in enantiomerically enriched form over 11 chemical operations from a chiral alkynol starting material. Steric hindrance about the congested C(2), C(3), C(2′), C(3′) sector of various intermediate structures to some extent governed the success (or not) of several transformations. Eventually, key C–C bond forming steps (double Ireland Claisen rearrangement, double ring closing metathesis) were optimized to provide good yields of milestone intermediates along the way. The core bicycle **2** possesses useful functional handles by way of the γ-hydroxyenone units; these functionalities may serve as linkage points for attachment of the remaining aromatic portions of the lomaiviticin A aglycone in future synthesis studies.

Acknowledgment. Financial support from the National Science Foundation (CHE 0956458) is gratefully acknowledged. The X-ray facility is supported by NSF CHE 0131112.

Supporting Information Available. Full experimental procedures and copies of the ^1H and ^{13}C NMR spectra for **2**, **8**–**10**, **13**–**16**, **18**, **20**, and **22**; X-ray data for **15** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Spartan 10 was used with an initial MMFF force field conformational search and then density functional calculations (B3LYP/6-31G**) on the lowest-energy conformer.

The authors declare no competing financial interest.