Tetrahedron Letters 54 (2013) 5826–5829

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Enantioselective synthesis of a potential 1,5-*syn*-polyol C1–C24 subunit of (−)-caylobolide A

Dripta De Joarder, Michael P. Jennings *

Department of Chemistry, 250 Hackberry Lane, The University of Alabama, Tuscaloosa, AL 35487-0336, United States

ARTICLE INFO

Article history:
Received 7 August 2013
Accepted 19 August 2013
Available online 27 August 2013

Keywords:
Allylation
Conjugate addition
Natural products
Cross-metathesis
Caylobolide

ABSTRACT

The synthesis of a possible 1,5-*syn*-polyol C1–C24 subunit resident in (−)-caylobolide A has been accomplished. The key reaction sequence was a repetitive protocol for the construction of the *syn*-1,5-diol segment by means of Ru-catalyzed cross-metathesis and boron-mediated allylation reactions.

Synthetic organic chemists are undoubtedly drawn to newly discovered biologically relevant and novel marine based natural products.[1] With the disclosures of challenging structures, the synthesis of such targets allows for further developments of known technologies and/or the invention of new strategies and thus new methodologies. One aspect that makes the total synthesis of natural products so challenging is the occasionally uncertain configuration of multiple stereogenic centers within a target compound. Along this line, caylobolide A (**1**), was isolated via bioassay-guided purification in 2002 from the marine cyanobacteria *Lyngbya majuscule* collected at Cay Lobos, Bahamas by Molinski and MacMillan.[2] As shown in Scheme 1, caylobolide A contains eight undefined stereocenters, thus 256 diastereomeric structural possibilities. Another interesting feature of **1** is the repeating 1,5-diol motif present along the 36-membered lactone core. In addition to its captivating macrocyclic structure, caylobolide A has revealed cytotoxic properties against the human colon tumor cell line HCT 116 (IC_{50} = 9.9 μM). Based on the synthetic challenge and underinvestigated biological profile of **1**, we wish to disclose our synthetic approach to a potential 1,5-*syn* polyol C1–C24 subunit of **1**.

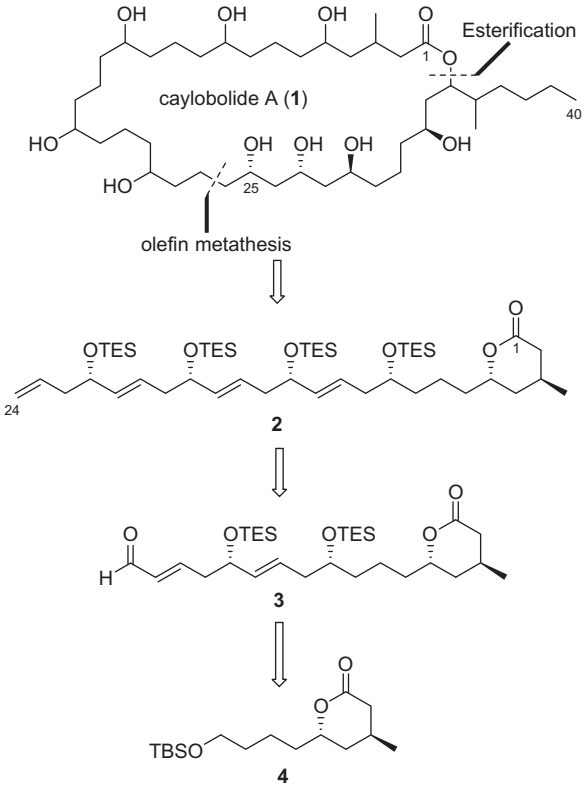
The retrosynthetic blueprint of caylobolide A focused on a convergent strategy as highlighted in Scheme 1. Thus, we envisioned an esterification at C35 (either standard or macrocyclic) and an olefin metathesis (either cross or ring-closing) process at C23–C24 to forge the 36-membered ring of **1**.[3]

With the unknown relative and absolute stereochemistry of the 1,5-diol repeating unit resident in C1–C24, we chose to focus on synthesizing the *syn*-polyol subunit **2** as delineated in Scheme 1. It is worth noting that the absolute configuration of **2** was selected arbitrarily, but other natural products suggest that the stereochemistry of the 1,5-diol subunits might be *syn* based on the biosynthetic polyketide assembly.[4] Thus, TES protected polyol **2** was imagined to be the product of two iterations of an asymmetric allylation, TES ether formation, followed by a chemo-and diastereoselective cross-metathesis of the pendent terminal olefin with acrolein in the presence of Grubbs' catalyst. Working further back, aldehyde **3** would be derived from the oxidized form of lactone **4** based on the allylation/TES-ether formation/cross-metathesis strategy as described for **2**. Lastly, lactone **4** would be the product of a diastereoselective conjugate addition of the methyl Gilman or Kharasch reagent to the applicable chiral α,β-unsaturated lactone.

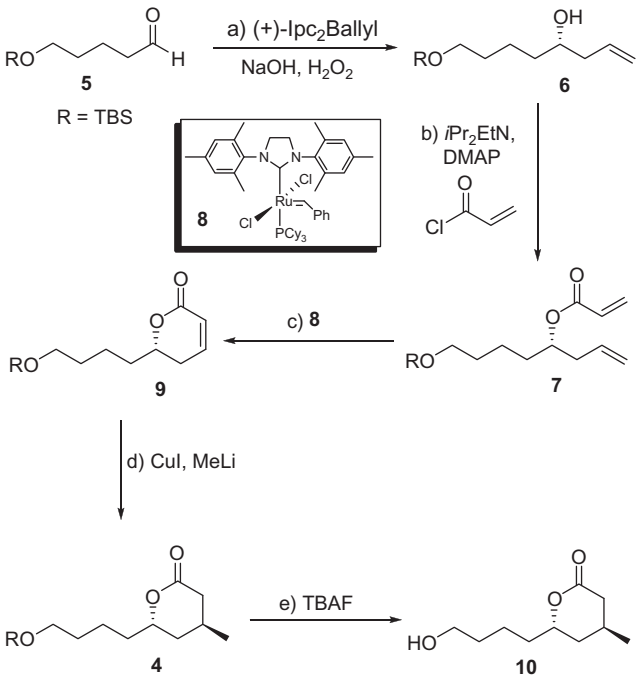
With the preliminary retrosynthetic blueprint in hand, our focus was turned to completing the β-methyl lactone **10**. As shown in Scheme 2, treatment of the known TBS protected aldehyde **7**[5] with (+)-Ipc_2Ballyl followed by a basic oxidation (NaOH, H_2O_2) as pioneered by Brown furnished the requisite homoallylic alcohol **6**.[6,7] An ensuing esterification of the free hydroxyl group with acryloyl chloride, Hunig's base, and DMAP provided acrylate ester **7** in 72% yield over two steps from **5**. Subsequent ring-closing olefin metathesis of diene 7 with Grubbs' second generation catalyst **8** under standard reaction conditions (toluene, 80 °C, 48 h) provided the α,β-unsaturated lactenone **9** in 82% yield.[8] With the required lactenone in hand, we envisioned a diastereoselective conjugate addition with an appropriate Gilman or Kharasch reagent *en route* to lactone **4**.[9] Unfortunately, the attempted addition of the modified dimethyl Kharasch reagent to **9** (derived from MeMgBr, 10 mol % of CuI·2LiCl, and TMSCl) provided lactone **4** in yields of

* Corresponding author. Tel.: +1 (205) 348 0351; fax: +1 (205) 348 9104.
E-mail address: jenningm@bama.ua.edu (M.P. Jennings).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.08.062

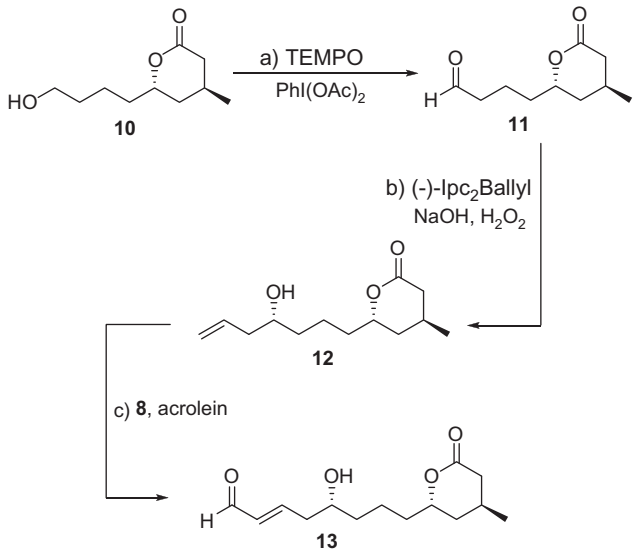


Scheme 1. Retrosynthetic analysis of caylobolide.



Scheme 2. Synthesis of hydroxy-lactone **10**: reagents and conditions: (a) (+)-Ipc_2BOMe (1.6 equiv), allyMgBr (1.5 equiv), Et2O, 0 °C to 78 °C to rt, 7 h, 89%; (b) acryloyl chloride (3.0 equiv), DMAP (0.2 equiv), ipr_2NEt (5 equiv), CH_2Cl_2, 0 °C to rt, 28 h, 81%; (c) **8** (0.15 equiv), toluene, 80 °C, 48 h, 82%; (d) CuI (2.0 equiv), MeLi (4 equiv), Et_2O, 0 °C, 85%; (e) TBAF (2.0 equiv), THF, 0 °C to rt, 87%.

50% or less after acidic hydrolysis.[10] Much to our delight, treatment of **9** with 2 equiv. of the dimethyl Gilman reagent (Me_2Cu^- Li^+) at 0 °C furnished the desired *anti*-TBS-protected lactone **4** in 85% yield coupled with excellent diastereoselectivity (~15:1 dr) as deduced by ^{1}H NMR.[11] Basic desilylation of the TBS ether with TBAF afforded the deprotected hydroxy-lactone **10** in 87% yield.



Scheme 3. Synthesis of intermediate **13**: Reagents and conditions: (a) TEMPO (15 mol %), $PhI(OAc_2)$ (1.1 equiv), CH_2Cl_2, rt, 24 h, 81%; (b) (−)-Ipc_2BOMe (1.6 equiv), allylMgBr (1.5 equiv), Et2O, 0 °C to −78°C to rt, 7 h, 90%; (c) **8** (0.05 equiv), acrolein (13.0 equiv), CH_2Cl_2, rt, 6 h, 70%.

Our outline to the C1–C24 segment of **1** required the synthesis of chiral aldehyde **13** as delineated in Scheme 3. Hence, oxidation of the hydroxyl group resident in **10** with TEMPO (15 mol %) and $PhI(OAc)_2$ furnished the desired aldehyde **11** in 81% yield.[12] Subsequent asymmetric allylation of **11** via Brown's (−)-Ipc_2Ballyl reagent afforded homoallylic alcohol **12** in 90% yield after basic oxidation with a dr of 10:1 favoring the *syn*-1,5 adduct. With **12** in hand, we focused our effort on the carbon chain elongation by means of a Ru-mediated diastereoselective cross-metathesis of the terminal olefin moiety. With this in mind, treatment of **12** with an excess of acrolein (13 equiv.) and Grubbs' second generation catalyst **8** (5 mol %) in CH_2Cl_2 provided the α,β-unsaturated aldehyde **13** in 70% yield with an *E*/*Z* ratio of >15:1 as determined by ^{1}H NMR.[13]

With the chiral aldehyde **13** completed and in multi-gram quantities, we next investigated homologating the carbon chain by a series of diastereo-and chemoselective cross-metatheses and asymmetric allylation reactions to forge the repeating *syn*-1,5-polyol chain as highlighted in Scheme 4. Thus, protection of the free hydroxyl group of aldehyde **13** with TESCl and 2,6-lutidine furnished triethylsilyl ether **14** in 86% yield. An ensuing allylation of the TES protected aldehyde **14** with (−)-Ipc_2Ballyl provided the corresponding homoallylic alcohol **15** after carefully buffered H_2O_2 mediated oxidation of the intermediate borinate ester in a respectable 60% yield and dr of ~10:1 for the *syn*-1,5-polyol subunit. Subsequent carbon chain elongation was accomplished upon treatment of the terminal olefin moiety of alcohol **15** with an excess of acrolein (13 equiv.) and catalyst **8** via a diastereo-and chemoselective cross metathesis reaction to furnish the α,β-unsaturated aldehyde **16** in 75% yield with an *E*/*Z* ratio of >20:1 for the newly formed conjugated alkene.

Silyl ether formation with TESCl, 2,6-lutidine, and **16** afforded the fully protected α,β-unsaturated aldehyde **3** in 90% yield.[14] A subsequent addition of (−)-Ipc_2Ballyl to **3** provided homoallylic alcohol **17** in 65% yield after buffered oxidation with a dr of >15:1 for the *syn* desired stereochemistry.