ORGANIC LETTERS

2013
Vol. 15, No. 20
5274–5277

Total Synthesis of (−)-18-*epi*-Peloruside A: An Alkyne Linchpin Strategy

Barry M. Trost,* David J. Michaelis, and Sushant Malhotra

Department of Chemistry, Stanford University, Stanford, California 94305-5080, United States

bmtrost@stanford.edu

Received August 30, 2013

ABSTRACT

A convergent synthetic route toward cytotoxic agent peloruside A that hinges on the use of an alkyne linchpin to assemble the natural product is described. Other highlights of this synthesis include an asymmetric desymmetrization reaction of a 1,3-diol, a one-pot conversion of a dibromoolefin to a stereodefined enone, and a diastereoselective aldol condensation. Misassignment of the absolute stereochemistry of the C18 stereocenter in our synthesis provided the natural product epimeric at the C18 ethyl stereocenter.

Alkynes are versatile functional groups in organic synthesis due to their ability to undergo catalytic transformations at the C−C triple bond and due to the inherent acidity of the acetylenic and propargylic C−H bonds. Our laboratory has taken advantage of this broad reactivity of alkynes in the context of total synthesis to perform alkene−alkyne[1] and alkyne−alkyne[2] coupling reactions, including for macrolactonizations; for hydrosilylation reactions to generate stereodefined trans olefins;[3] for asymmetric additions to aldehydes to generate enantioenriched propargylic alcohols;[4] and for metal-catalyzed alcohol additions to the triple bond to access pyran rings.[2,4f] In this report, we capitalize on the latent nucleophilicity of both propargylic and acetylenic C−H bonds and employ an alkyne as a linchpin for assembling the carbon framework of macrolide peloruside A. We then take advantage of the reactivity of the alkyne triple bond to construct the highly oxygenated pyran ring of the natural product.

Peloruside A (**1**) is a polyketide natural product isolated from a marine sponge *Mycale hentscheli*.[5] The impressive antimitotic activity of peloruside A,[6] which includes microtubule-stabilizing activity that is synergistic with paclitaxel,[7] has made it an attractive target for total synthesis.[8,9] Contained within the pyran ring of peloruside A is a masked α-hydroxyketone, which we recognized as an alkyne derivative. This observation forms the basis for our synthetic strategy, where a simple acetylene linchpin would enable assembly of the carbon framework.

Our retrosynthetic analysis deconstructs the final target into aldehyde **2** and alkyne **3**, which would allow us to assemble the right and left-hand portions of peloruside A via an aldehyde alkynylation reaction (Figure 1). The alkyne functional group would then enable construction of the pyran ring via metal-catalyzed alcohol-addition to the alkyne, followed by oxidation of the resulting vinyl ether to the fully oxygenated ring. We envisioned accessing alkyne **3** through a diastereoselective aldol reaction between enone **4** and aldehyde **5**. Enone **4** would be obtained

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(2) Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485–488.

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(5) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445–449.

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10.1021/ol4024997
Published on Web 10/04/2013

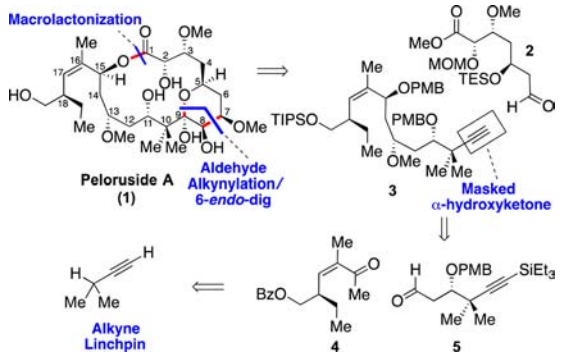
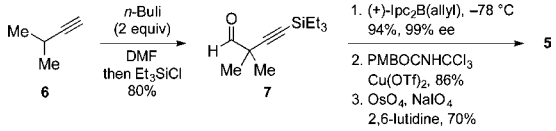


Figure 1. Retrosynthetic analysis of (+)-peloruside A.

by an asymmetric desymmetrization reaction of meso 1,3-diols previously developed in our laboratory.[10] We hypothesized that alkyne **5** could be readily accessed by the sequential treatment of the dianion of isopropylacetylene (our alkyne linchpin) with two different electrophiles, thereby taking advantage of the differential reactivity of the propargylic and acetylenic anions.

In the forward sense, treatment of commercially available alkyne **6** with 2 equiv of *n*-butyllithium to form the 1,3-dilithiated intermediate, followed by sequential trapping with *N,N*-dimethylformamide and chlorotriethylsilane, gave aldehyde **7** in good yield in a single transformation (Scheme 1). Allylation with (−)-Ipc_2B(allyl)borane provided the desired alcohol in high enantioselectivity,[11] and

Scheme 1. Synthesis of Aldehyde **5**



protection of the resulting alcohol as the PMB ether followed by oxidative cleavage of the olefin gave the requisite aldehyde **5**.

Further elaboration of the left-hand portion of the alkyne required the synthesis of enone **4** (Scheme 2). Asymmetric desymmetrization of 1,3-diol **8** using catalytic diethylzinc (*S,S*)-ProPhenol generated the enantioenriched monobenzoylated product **9** in quantitative yield and high enantioselectivity.[10] Enzymatic desymmetrizations of **8** have proven particularly challenging, and only the (*R*)-enantiomer of monoacetylated **8** can be obtained enzymatically in high enantioselectivity via monohydrolysis of the bisacetate substrate.[12] Our desymmetrization method, however, delivers either enantiomer of **9** in good yield and enantioselectivity simply by switching the enantiomer of catalyst. Subsequent oxidation of **9** to the beta-benzoylaldehyde, followed by immediate treatment with carbon tetrabromide and triphenylphosphine furnished dibromoolefin **10** without observable epimerization of the ethyl stereocenter or byproducts arising from β-elimination. Our original synthetic studies (see the Supporting Information) led us to believe that the desymmetrization reaction with (*S,S*)-ProPhenol generated the desired (*R*)-stereochemistry at the ethyl center. However, when the spectra of our final product did not match those of the natural product, we then obtained a crystal structure of dibromide **10**, which confirmed that we obtained the (S)-stereochemistry, as depicted in Scheme 2, leading ultimately to the epimeric stereocenter to that of the natural product. Nevertheless, *ent*-**9** (characterized as the dibromide *ent*-**10**) was obtained with the same level of enantioselectivity but opposite in configuration when (*R,R*)-ProPhenol was employed, verifying that the natural product could be obtained with equal ease through our synthetic route.

The conversion of dibromide **10** to enone *ent*-**4** was accomplished in a single step using a method developed by Miyashita and co-workers.[13] Treatment of **10** with dimethyl cuprate led to selective methylation of the less hindered bromide and formation of a (*Z*)-vinyl cuprate intermediate. Quenching with acetyl bromide provided the desired product. Retaining the geometrical integrity of the alkene in this process proved quite challenging. Key to its

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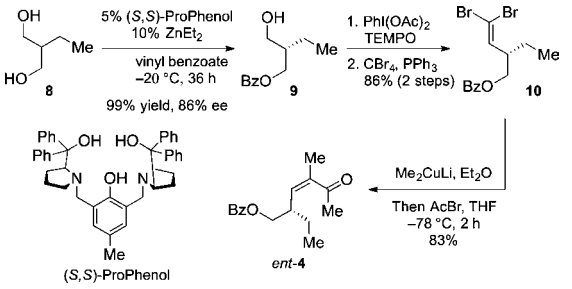
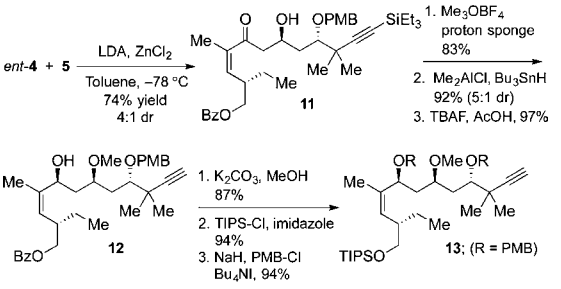
(13) Tanino, K.; Arakawa, K.; Satoh, M.; Iwata, Y.; Miyashita, M. *Tetrahedron Lett.* **2006**, *47*, 861–864.

Scheme 2. Synthesis of Enone *ent*-**4**



Scheme 3. Synthesis of Alkyne Partner

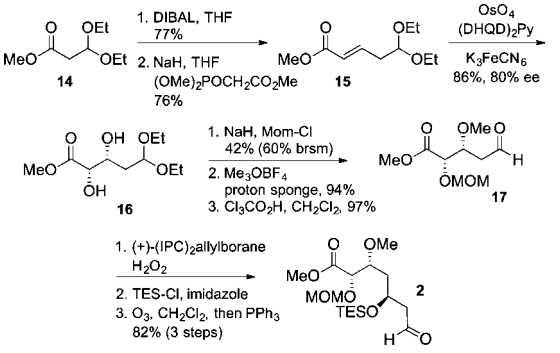


ultimate success was a reverse quench procedure where the intermediate (Z)-vinyl cuprate was added to excess acetyl bromide at low temperature, providing the enone in > 10:1 isomeric purity and 83% isolated yield of pure *ent*-**4**. The use of acetyl bromide in place of acetyl chloride also enabled reactivity with the vinyl cuprate at lower temperature, contributing to the success of the reaction.

The union of fragments *ent*-**4** and **5** was next accomplished with a diastereoselective aldol reaction (Scheme 3). The use of zinc chloride as a coordinating Lewis acid was essential in achieving 1,3-asymmetric induction (74%, 4:1 dr). The 1,3-trans relationship between the two oxygen centers was confirmed by formation of the cyclic PMP acetal via oxidation of the PMB ether with DDQ, then through NOE correlations (see the Supporting Information). Product **11** was then methylated, and a directed reduction of the carbonyl group with dimethylaluminum chloride and tributyltin hydride was used to establish the stereochemistry of the allylic alcohol with high diastereocontrol.[14] The newly created syn 1,3-stereochemistry was verified by mandelate ester analysis.[15] The terminal acetylene was then deprotected to provide intermediate **12** in preparation for the aldehyde addition reaction. At this stage, we found it necessary to remove the benzoyl protecting group as it interfered with the subsequent alkyne addition step. Thus, removal of the benzoate with potassium carbonate in MeOH, followed by selective formation of the TIPS ether of the primary alcohol[8b] and PMB protection of the allylic alcohol provided the necessary alkyne **13** for coupling to aldehyde **2**.

The synthesis of the right-hand portion of peloruside A (**2**) proceeded through a catalytic asymmetric dihydroxylation strategy (Scheme 4). Reduction of commercially available acetal **14**, followed by HWE olefination provided the substrate (**15**) for dihydroxylation. Osmium-catalyzed asymmetric dihydroxylation led to diol **16** in good yield and enantioselectivity with the desired syn stereochemistry. Selective protection of the α-hydroxyl group as the MOM ether, then methylation of the *β*-hydroxyl group and hydrolysis of the acetal all proceeded to give aldehyde

Scheme 4. Synthesis of Northern Fragment



17. Allylation with (+)-Ipc$_2$B(allyl)borane, TES protection of the resulting alcohol, and oxidative cleavage of the olefin gave aldehyde **2** in excellent yield (80%) over the three steps. The stereochemistry of the allylation product was again verified by mandelate ester analysis.[15]

The simple coupling of alkyne **13** with aldehyde **2** assembled the entire carbon framework of 18-*epi*-peloruside A and introduced the requisite functionality to construct the highly oxidized pyran ring (Scheme 5). Deprotonation of the terminal acetylene of **13** with *n*-butyllithium followed by transmetalation of the lithium acetylide to magnesium and addition to aldehyde **2** resulted in an 87% yield of propargylic alcohol **18** (~2:1 dr). The diastereoselectivity of the addition was inconsequential as we found it necessary to oxidize the propargylic alcohol prior to the metal-catalyzed alcohol addition to the alkyne. Thus, oxidation with manganese dioxide and then selective deprotection of the triethylsilyl ether provided intermediate **19**, which was poised to undergo metal-catalyzed cyclization onto the ynone. As little as 2.5 mol % of a gold(I) catalyst could facilitate efficient cyclization to form the pyranone ring (94% yield).[16] Final bis-deprotection of both PMB protecting groups generated the appropriate precursor (**20**) for macrolactonization.

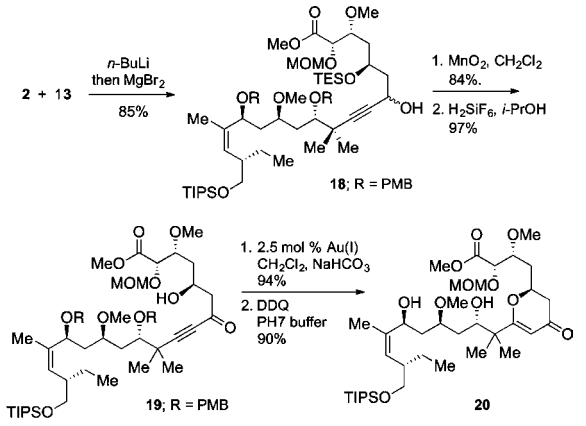
Intermediate **20** closely resembles an intermediate from the synthesis of peloruside A reported by the Taylor

(14) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840–10852.

(15) The 1,3-*syn* relationship of the oxygen centers was confirmed via formation of the (*R*)- and (*S*)-*O*-methylmandelate esters and then by analysis of the ^{1}H NMR spectra (see the Supporting Information).

(16) For a review on gold(I)-catalyzed C–X bond formation, see: Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657–1712.

Scheme 5. Alkyne Addition for Assembly of **2** and **3**



laboratory,[17,8b] and thus, our final sequence of reactions closely follows their reported route. We found it particularly troublesome to liberate the free acid by hydrolysis of the methyl ester without epimerizing the α center. Successful cleavage was accomplished using excess trimethyltin hydroxide at elevated temperatures.[18]

Our efforts toward macrolactonization were only successful under Yamaguchi conditions, and after extensive optimization we were able to obtain macrolactone **21** in a respectable yield (57%, 2 steps) (Scheme 6). Accessing 18-*epi*-peloruside A from intermediate **21** was most easily accomplished by performing the final four steps without intermediate characterization. Thus, reduction of the enone in **21** with sodium borohydride and cerium trichloride, followed by directed oxidation of the enol ether with *m*-CPBA, gave **22**.[19] Selective methylation of the equatorial hydroxyl group[6a] and global deprotection provided 18-*epi*-pelosuride A in an average of 70% yield per step over the final four steps. Very small discrepancies in the NMR spectra and the opposite sign of the optical rotation of our final compound from that of the natural product led us to question the stereoselectivity of our desymmetrization reaction since the stereochemistries of the other stereocenters were independently verified. The studies described above confirmed the identity of our product as (−)-18-*epi*-peloruside A.

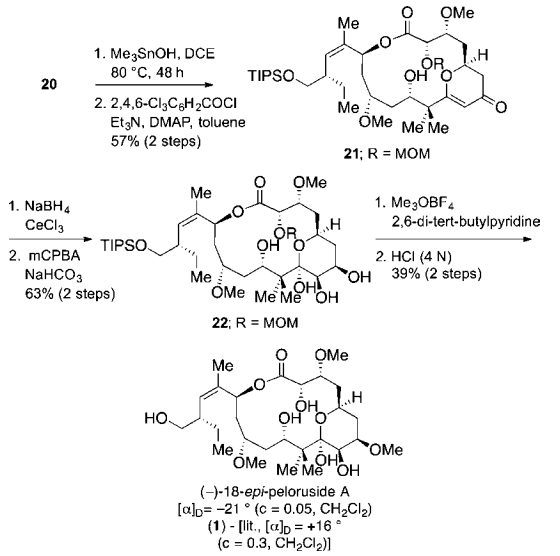
In conclusion, we have demonstrated that our alkyne linchpin strategy is an efficient method for assembling the carbon framework and oxidized pyran ring of peloruside A.

(17) Protection of **21** as the MOM ether allowed us to intercept an intermediate from the Taylor synthesis. Spectroscopic data from our product did not match what was previously reported, suggesting that a stereocenter formed previous to the final sequence of four reactions was incorrect (see the Supporting Information).

(18) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378–1382.

(19) The small coupling constant (2.5 Hz) between the C8 and C7 hydrogens on the pyran ring of (−)-18-*epi*-peloruside A confirms that the 1,2-*syn* stereochemistry was obtained in the reduction/directed oxidation sequence from **21** to generate **22**. See ref 5.

Scheme 6. Completion of (−)-18-*epi*-Peloruside A



Our strategy takes advantage of the latent nucleophilicity of both propargylic and acetylenic C−H bonds to perform key carbon−carbon bond-forming reactions. The utilization of the alkyne for metal-catalyzed intramolecular hydration and later oxidation to the α-hydroxy ketone further demonstrate the utility of the alkyne functional group in the context of total synthesis. While our end game strategy closely follows the sequence reported by the Taylor laboratory,[8b] our alkyne strategy allowed us to arrive at the required pyranone intermediate (**20**) in a significantly reduced number of steps. Interestingly, the efficiency of our prophenol-catalyzed diol desymmetrization proves to be significantly better than the reported enzymatic methods.[11] Although a misassignment of the absolute configuration of the product obtained in our desymmetrization reaction led to the synthesis of (−)-18-*epi*-peloruside A, the epimer corresponding to the natural product should also be accessed simply by preparation of **4** rather than *ent*-**4**, which we established can be done. Thus, this route readily supplies epimers of the natural product itself, which is of value to establish structure−activity relationships. This and additional synthetic studies will be reported in due course.

Acknowledgment. Funding was provided by the National Institutes of Health (GM033049). We thank the NSF for their generous support of our programs. D.J.M. wishes to thank the NIH for a postdoctoral fellowship (F32 GM093467).

Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.