ORGANIC LETTERS

2013
Vol. 15, No. 3
613–615

Total Synthesis of Paracaseolide A

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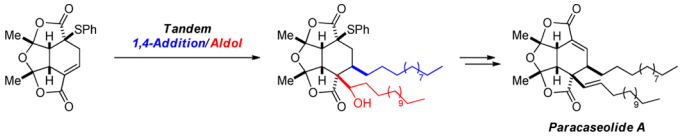
Received December 17, 2012

ABSTRACT

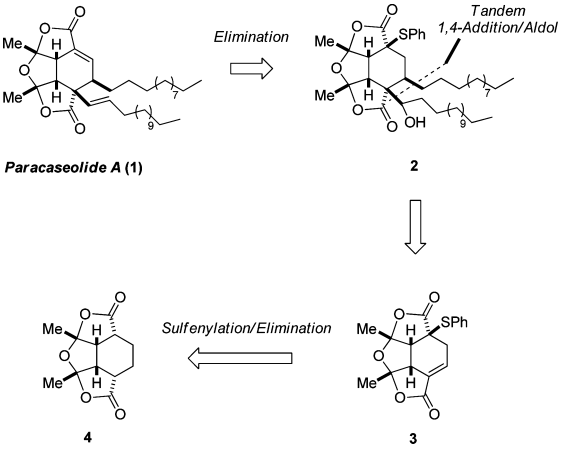


The total synthesis of paracaseolide A, a valuable cell-cycle progression inhibitor, was accomplished in 8 steps from known compounds, with 6.6% overall yield. The synthetic strategy creates strong potential for diversification.

Paracaseolide A (**1**) was isolated in 2011 from the stem bark of the Chinese mangrove *Sonneratia paracaseolaris* by the Guo group.[1] Their analysis identified **1** as an effective inhibitor against dual specificity phosphatase CDC25B with an IC_{50} value of 6.44 μM.[2] Cell division cycle 25 (CDC25) phosphatases play a crucial role in regulating cell-cycle progression.[2] Small molecule inhibitors such as quinones and thiazolones have already proven effective toward slowing the growth of cancerous cells.[2] With its unique tetracyclic molecular architecture compared to previously reported inhibitors, coupled with our earlier work in the area,[3] **1** attracted our attention as a synthetic challenge. Although a synthesis of **1** was recently described[4] based on the likely biosynthesis, our route is concise, strategically distinct, and flexible toward the generation of analogs. Obtaining suitable quantities of paracaseolide A and other analogs would greatly advance the creation of a structure–activity profile.

We recognized that the tetraquinane oxa-cage bis-lactone structure was characterized by a concave and convex surface, which we could use to our advantage to introduce functionality in a stereocontrolled manner. We envisioned that **1** would arise from a tandem vicinal difunctionalization of an α,β-unsaturated lactone **3** to form **2**, followed by elimination to install the requisite unsaturation (Scheme 1).

Scheme 1. Retrosynthetic Analysis



We utilized the symmetric bis-lactone **4**, prepared according to Wu and co-workers,[5] which was advantageous in the concise realization of **1**.

Our synthesis begins with enedione **5**, prepared by oxidation of 2,5-dimethylfuran (Scheme 2).[5] A Diels–Alder reaction of **5** with 1,3-cyclohexadiene followed by ozonolysis and oxidation of the hemiacetal with PCC provided the symmetrical bis-lactone **4** in 20% yield over three steps.[5] Functionalization of **4** via an enolate intermediate

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(2) (a) Huang, W.; Li, J.; Zhang, W.; Zhou, Y.; Xie, C.; Luo, Y.; Li, Y.; Wang, J.; Li, J.; Lu, W. *Bioorg. Med. Chem.* **2006**, *16*, 1905. (b) Lavecchia, A.; Giovanni, C. D.; Novellino, E. *Mini-Rev. Med. Chem.* **2012**, *12*, 62.

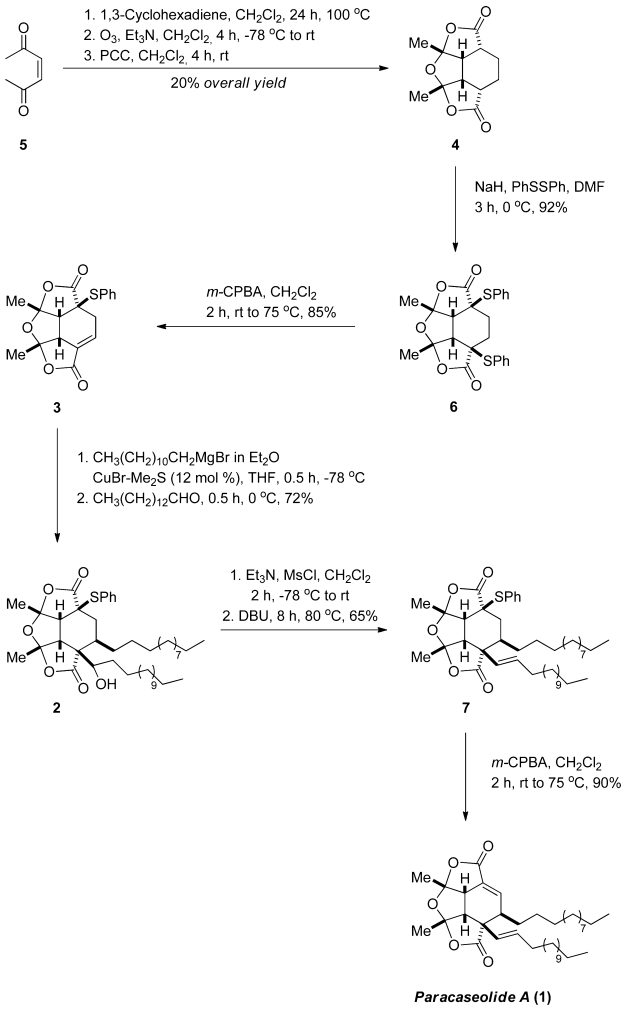
(3) Kraus, G. A.; Gupta, V.; Mokhtarian, M.; Mehanovic, S.; Nilsen-Hamilton, M. *Bioorg. Med. Chem.* **2010**, *18*, 6316.

(4) Noutsias, D.; Vassilikogiannakis, G. *Org. Lett.* **2012**, *14*, 3565.

(5) (a) Lin, C.-C.; Wu, H.-J. *J. Chin. Chem. Soc.* **1995**, *42*, 815. All ^{1}H and ^{13}C NMR characterization data matched their reported values. (b) Alternatively, MMPP can be used for the oxidation of 2,5-dimethylfuran: Dominguez, C.; Csaky, A. G.; Plumet, J. *Tetrahedron Lett.* **1990**, *31*, 7669.

10.1021/ol303447r
Published on Web 01/16/2013

Scheme 2. Synthesis of Paracaseolide A



presented multiple challenges, since the compound was only soluble in halogenated solvents and highly polar solvents such as DMF, but not in THF, diethyl ether, or acetonitrile. In addition to solubility difficulties, deprotonation was not straightforward since treating **4** with lithium diisopropylamide, lithium tetramethylpiperidine, potassium *tert*-butoxide, or potassium hydride led to either decomposition or recovery of starting material. Alternatively, forming the enol silyl ether with TMSOTf also led to a number of products, presumably due to fragmentation of the silylated intermediate. Fortunately, sodium hydride in DMF at 0 °C, after only 3 h, in the presence of excess diphenyl disulfide, afforded bis-sulfide **6** in 92% yield.

The subsequent oxidation/elimination step was designed based on the symmetric nature of **6**. We first tried using the mild oxidizing agent sodium periodate under standard conditions,[6] which only returned starting material, even after prolonged reaction times. In contrast, switching to *m*-CPBA cleanly resulted in the oxidation to yield the sulfoxide,[7] without any evidence of overoxidation to the sulfone. We planned to eliminate the sulfoxide immediately following the oxidation, but interestingly, we noticed that the sulfoxide was partially eliminated even at room temperature after 2 h, as observed by TLC and ^{1}H NMR. Heating the sulfoxide at 75 °C for 5 min was enough to induce the complete elimination to afford **3** in 85% yield.

The ensuing vicinal difunctionalization[8] allowed the introduction of both alkyl chains in a tandem 1,4-addition/aldol reaction. The normal addition involves adding **3** to a solution of the copper and organomagnesium compounds; however, in our system, a complex mixture resulted. The key to the success of the reaction was utilizing inverse addition, as described by other researchers.[9] In alignment with inverse addition, dodecyl magnesium bromide was added to a solution of **3** and $CuBr \cdot Me_2S$ at −78 °C, after which the solution was warmed to 0 °C before adding the aldehyde to produce a 72% yield of alcohol **2** as a single diastereomer.

The dehydration of **2** was unexpectedly problematic when we attempted a mesylation/elimination reaction utilizing excess triethylamine (10 equiv) and mesyl chloride (5 equiv) sequentially added at 0 °C, followed by warming the reaction mixture to 40 °C in dichloromethane over 12 h. Only 42% of the desired elimination product resulted, along with a diasteromeric mixture of mesylates and decomposition byproducts. After a number of trials, we found that regulating the temperature was critically important to reduce byproduct formation. Specifically, triethylamine and mesyl chloride were initially added at −78 °C, which was followed by bringing the temperature to 80 °C after DBU[10] addition to favor elimination and increase the yield of trans olefin **7** to 65%. The culmination of the synthesis involved a second simultaneous oxidation/elimination step, which converted **7** into parcaseolide A (**1**) in 90% isolated yield. The identity of **1** was confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectral characterization data which exactly matched those found in the literature.[1,4]

In summary, paracaseolide A (**1**) was expeditiously accomplished in 8 steps from known compounds, with 6.6% overall yield. Overcoming the initial solubility challenges and successfully pairing two transformations in single pot procedures greatly contributed to the overall efficiency of the total synthesis. Furthermore, the

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(7) For additional information on sulfoxide oxidation−elimination, see: (a) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363. (b) Rousch, W. R.; Walts, A. E. *J. Am. Chem. Soc.* **1984**, *106*, 721. (c) Nemoto, H.; Nagai, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1985**, *50*, 2764. (d) Krafft, M. E.; Kennedy, R. M.; Holton, R. A. *Tetrahedron Lett.* **1986**, *27*, 2087.

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distinctive framework of the tetraquinane oxa-cage bislactone structure allowed the stereocontrolled introduction of functionality. However, successfully optimizing conditions for the pivotal tandem 1,4-addition/aldol transformation amplifies the potential of our synthetic pathway for comprehensive functionalization.

Supporting Information Available. Experimental procedures, full spectroscopic data, and copies of ^{1}H 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.