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Synthesis of (+)-Patulolide C via an Asymmetric Hydroformylation/ Macrocyclization Cascade

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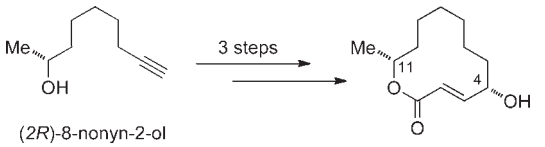
ABSTRACT



(2*R*)-8-nonyn-2-ol

(+)-Patulolide C (**1**)

A highly atom-economical total synthesis of (+)-patulolide C has been accomplished in three steps from the known (2*R*)-8-nonyn-2-ol in 49% overall yield and 93% de. A Rh(I)-catalyzed asymmetric hydroformylation (AHF)/ intramolecular Wittig olefination cascade was utilized to set the C4-hydroxyl stereochemistry and *E*-olefin geometry as well as form the macrolactone.

(+)-Patulolide C (**1**) was first discovered by Yamada and co-workers in 1985 from the culture filtrate of *Penicillium urticae* S11R59 mutant, along with its congeners patulolide A and B.[1a] Exhibiting both antifungal and antibacterial activities,[1b] the patulolides have been the targets of several total syntheses.[2] Some general strategies in these syntheses for macrolide formation include utilizing the Yamaguchi macrolactonization,[2a−f] Mitsunobu lactonization,[2g] Shiina lactonization,[2h] or ring-closing metathesis.[2i] The olefin has been constructed by various methods including Horner−Wadsworth−Emmons and Wittig olefinations[2d,e] and a photochemical rearrangement of an epoxydiazomethylketone.[2b,c] The C4-stereocenter has been established via a Sharpless asymmetric epoxidation[2b,c,i] or derived from the chiral pool.[1b,2a,2d] The C11-stereocenter has been constructed via a Jacobsen kinetic resolution,[2e,i] CBS-reduction,[2h] ring opening of (*R*)-propylene oxide,[2b,c] or other chiral pool sources.[1b,2d]

(+)-Patulolide C (**1**) has thus served to demonstrate a variety of approaches to macrocyclic lactone natural products. Many of the previously reported syntheses required 14 or more synthetic steps to produce (+)-patulolide C (**1**). Illustrated herein is a novel approach to this target based upon asymmetric hydroformylation (AHF), affording a very short, high-yielding synthesis of (+)-patulolide C (**1**).

The overall synthesis strategy is outlined in Scheme 1. We envisioned forming the C2,C3 alkene of **1** by intra molecular Wittig olefination from the stabilized ylide derived from **2** and (triphenylphosphoranylidene)ketene **4**, also known as the Bestmann ylide.[3] Two different, highly stereoselective rhodium(I) catalyzed reactions would be used to install both the oxygen (as an acetate) and the formyl group at the C4 position on the known alkyne **3**.[4] Specifically, alkyne **3** was seen as the substrate for a regio- and stereospecific addition of acetic acid to yield the *Z*-C4-enol acetate. This would be subjected to a catalytic asymmetric hydroformylation, envisioned to afford the

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(2) For previous total syntheses of (+)-patulolide C: (a) Yang, H.; Kuroda, H.; Miyashita, M.; Irie, H. *Chem. Pharm. Bull*. **1992**, *6*, 1616–1618. (b) Leemhuis, F. M. C.; Thijs, L.; Zwanenburg, B. *J. Org. Chem*. **1993**, *25*, 7170–7179. (c) Thijs, L.; Egenberger, D. M.; Zwanenburg, B. *Tetrahedron Lett*. **1989**, *30*, 2153–2156. (d) Takano, S.; Murakami, T.; Samizu, K.; Ogasawara, K. *Heterocycles* **1994**, *39*, 67–72. (e) Sabitha, G.; Chandrashekhar, G.; Yadagiri, K.; Yadav, J. S. *Tetrahedron Lett*. **2010**, *51*, 3824–3826. (f) Dorling, E. K.; Thomas, E. J. *Tetrahedron Lett*. **1999**, *40*, 471–474. (g) Kaisalo, L.; Koskimies, J.; Hase, T. *Synth. Commun*. **1999**, *29*, 399–407. (h) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett*. **2003**, *5*, 3021–3024. (i) Babu, K. V.; Sharma, G. V. M *Tetrahedron: Asymmetry* **2008**, *19*, 577–583.

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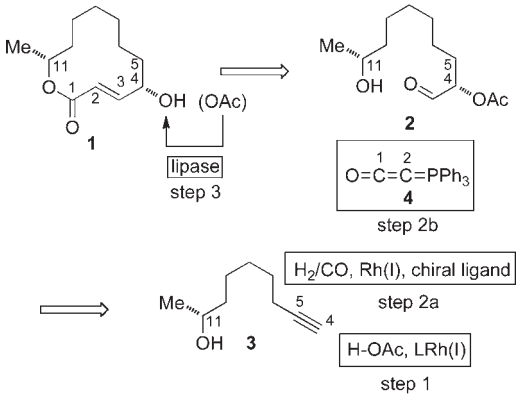
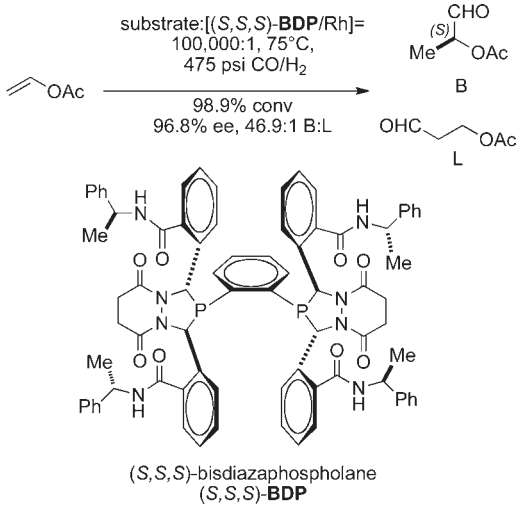
Scheme 1. Synthesis Strategy[a]



[a] Atom numbering throughout corresponds to that in (+)-patulolide C (**1**)

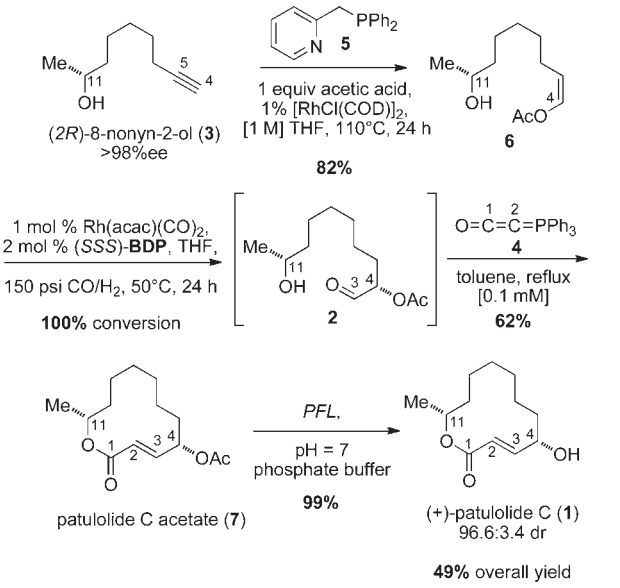
α-acetoxyaldehyde **2**. Reaction of the unprotected C11-hydroxyl in **2** with the Bestmann ylide (**4**)[3] was planned to occur in a cascade[5] with the AHF reaction (steps 2a and 2b) to directly afford patulolide C acetate.

Scheme 2. AHF of Vinyl Acetate



Hydroformylation converts olefins into valuable aldehydes with excellent atom economy, inexpensive reagents, and robust catalysts.[6] The Landis group has developed the (*S,S,S*)-bisdiazaphospholane [(*S,S,S*)-**BDP**] ligand which displays phenomenal activity with very high enantio- and regioselectivity for a variety of olefins.[7] For example, enol esters such as vinyl acetate react exceptionally well favoring the branched (B) aldehyde with high enantioselectivity over the linear (L) aldehyde as shown in Scheme 2.[7c] Furthermore, such chiral aldehydes can be transformed immediately into diverse functional groups, increasing molecular complexity from a variety of readily available alkenes. Hydroformylations in tandem with other reactions

Scheme 3. Total Synthesis of (+)-Patulolide C[a]



[a] Atom numbering throughout corresponds to that in (+)-patulolide C (**1**)

are known,[6] including hydroformylation/olefination.[8] It has been shown that stabilized ylides or phosphonate anions will not erode the stereochemical integrity of the newly formed asymmetric center in an *in situ* AHF/olefination tandem.[8]

In a forward sense (Scheme 3), alkyne **3**[4] underwent hydroacetoxylation in the presence of $[RhCl(COD)]_2$ and ligand **5** to afford the enol acetate **6** in 82% yield with >95% regio- and stereoselectivity.[9] This rhodium(I) catalyst system developed by Breit et al.[9] produces the *Z*-enol ester with remarkable anti-Markovnikov selectivity and excellent atom economy as well as without requiring protection of the C11-hydroxyl functionality. Since *Z*-1,2-disubstituted enamides react with higher regio- and enantioselectivity than their *E*-isomers, we expected *Z*-1,2-disubstituted enol esters to react analogously.[7e] Substrate **6** was subjected to AHF conditions using $Rh(acac)(CO)_2$ and (*S,S,S*)-**BDP** at 50 °C under 150 psi of syngas,[7] and within 24 h 100% conversion to the C11-hydroxy-C4-acetoxyaldehyde **2** was accomplished with complete

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regiocontrol and high diastereoselectivity. Only one aldehyde was observed by ^{1}H NMR as an equilibrium mixture with the hemiacetal.

The AHF reaction yielded a solution of aldehyde that is substantially pure, which was utilized directly without purification. The crude reaction mixture was simply diluted with toluene and transferred to a refluxing toluene solution of the Bestmann ylide (**4**).[3] This generated a stabilized ylide *in situ* from the unprotected hydroxyl attacking the electrophilic ketene carbon followed by concomitant intramolecular Wittig olefination of the α-acetoxyaldehyde to effect macrocyclization, affording the 12-membered lactone **7** in 62% yield with complete *E*-selectivity. Whereas traditional macrolactonizations typically require carboxylic acid activation and net dehydration, these requirements are built into the Bestmann ylide (**4**),[3] thus expediting the synthetic sequence. The absence of base and external nucleophile in the AHF/Bestmann ylide olefination cascade also avoided epimerization or olefin (*E*/*Z*) isomerization issues.[10] Neutral deacetylation of **7** with *Pseudomonas florescens* lipase[11] proceeded in quantitative yield to give (+)-patulolide C (**1**) in high dr, determined to be 96.6:3.4 by HPLC.

In summary, a concise total synthesis of (+)-patulolide C (**1**) has been accomplished in three steps from the known alkyne **3**.[4] Both Rh(I)-catalyzed reactions proceeded with outstanding atom economy and high regio- and stereoselectivity. An *in situ* reaction of the hydroxyaldehyde **2** with the Bestmann ylide directly afforded the 12-membered lactone **7**, and mild enzymatic deacetylation gave (+)-patulolide C (**1**) in 49% overall yield from **3**.

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Supporting Information Available. Experimental procedures and characterization data for new compounds. This material available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.

(10) Olefin isomerization was observed when macrolactonizations of the (+)-patulolide C seco-acid were performed with base present and will be described elsewhere.

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