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Tetrahedron Letters 45 (2004) 1351–1353
Tetrahedron Letters

Applications of chiral allenylzinc additions and Noyori asymmetric reductions to an enantioselective synthesis of a C3–C13 precursor of the polyketide phosphatase inhibitor cytostatin

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Received 4 December 2003; accepted 11 December 2003

Abstract—A 12-step synthesis of a C3–C13 precursor of the protein phosphatase inhibitor cytostatin is described. Key stereocenters were introduced by a chiral allenylzinc addition and Noyori asymmetric-transfer hydrogenation.

The polyketide cytostatin, a potent and selective inhibitor of protein phosphatase PP2A, was isolated from a strain of Streptomyces in 1994 by Ishizawa and co-workers.[1] These investigators established the basic constitution of the natural product, but did not elaborate the stereochemistry. Some years later, Bialy and Waldmann deduced a likely stereostructure by analogy with related natural products of established structure and through analysis of ^{1}H NMR coupling constants. They subsequently completed a total synthesis of a compound with this proposed structure.[2] The ^{1}H, ^{13}C, and ^{31}P NMR spectra of the synthetic and natural material were comparable, but the presence of inseparable impurities in the sample of the later prevented an unambiguous confirmation (Fig. 1). However, the synthetic material showed selective nanomolar in vitro inhibition of serine–threonine phosphatase PP2A comparable to that reported for natural cytostatin in support of its identity with the natural product.[3]

In their synthesis, Bialy and Waldmann employed Evans oxazolidinone-directed alkylation and aldol reactions to introduce the stereocenters at C4–C6 and C9–C10 (Fig. 1). Enantioselective reduction of a C10 alkynyl ketone with the Corey oxazaborolidene reagent[4] established the sixth and final stereocenter of their synthetic cytostatin. Each of these methods is capable of introducing either

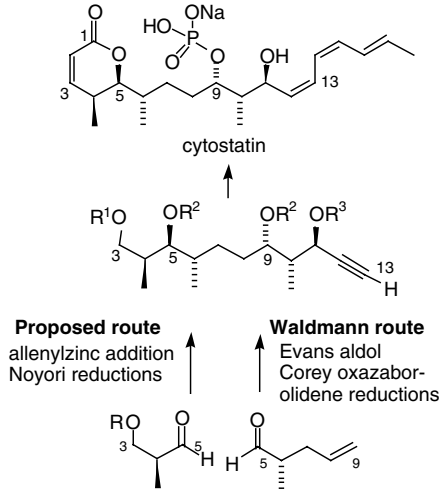

Figure 1. Alternative approaches to a C3–C13 precursor of cytostatin.

(*R*)- or (*S*)-chirality thus providing flexibility for analog synthesis.

In our approach, we utilize chiral allenylzinc methodology to control the stereochemistry at C5 and C6.[5] The C4 and C10 stereocenters originate with (*S*)-3-hydroxy-2-methylpropionic acid and the C9 and C11 hydroxyl centers are introduced through Noyori asymmetric-transfer hydrogenation of alkynone precursors.[6,7] This route is also capable of total stereochemical flexibility.

Our assemblage of the stereotriad homopropargylic alcohol segment **2** was effected in 71% yield (>95:5

Keywords: Allenylzinc; Asymmetric reduction; Polyketide; Hydrogenation.

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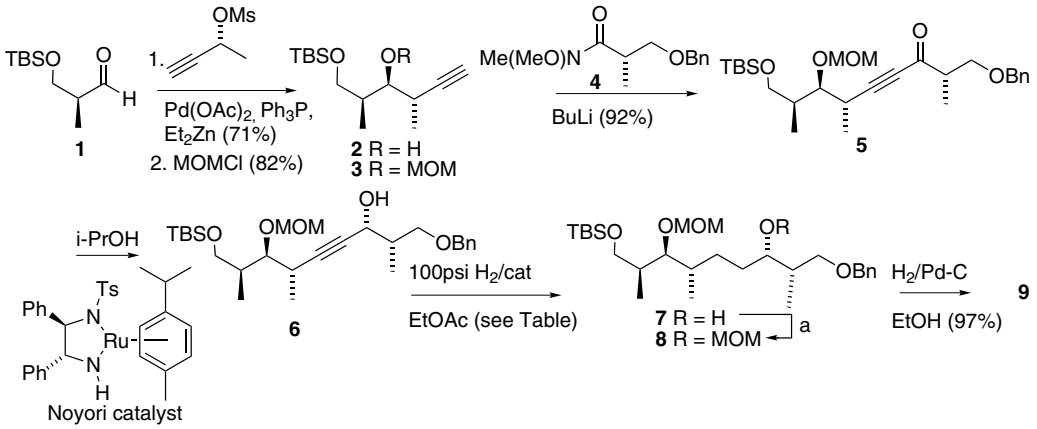
doi:10.1016/j.tetlet.2003.12.067

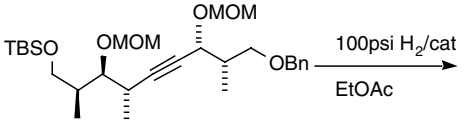


Scheme 1. Reagents and conditions: (a) MOMCl, TBAI, $(i\text{-Pr})_2$NEt (91%).

anti:*syn*) from aldehyde **1**[8] through addition of the allenylzinc reagent generated in situ from the mesylate of (*R*)-3-butyn-2-ol[9] and Et_2Zn in the presence of a Pd(0) catalyst (Scheme 1). The protected alkynyl adduct **3**, was next lithiated and treated with the Weinreb amide (**4**) of (*S*)-3-benzyloxy-2-methylpropionic acid[10] to afford alkynone **5** in 92% yield. Reduction of this ynone with the Noyori (*R*,*R*)-ruthenium/*p*-cymene catalyst proceeded in quantitative yield to afford the (*R*)-alcohol **6** as the only detectable isomer.

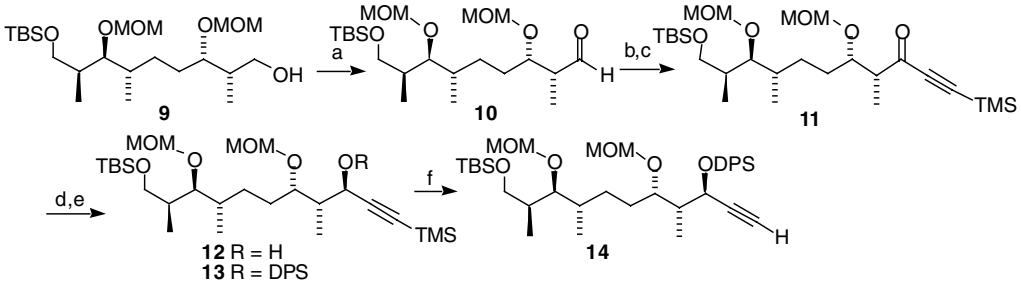
The next step of our synthesis, hydrogenation of the internal triple bond of alcohol **6**, proved surprisingly difficult. Stirring **6** with 20 mol% rhodium-on-alumina under 100 psi of hydrogen afforded only the (*Z*)-dihydro product (Table 1). Attempts to force this reaction by increasing the catalyst ratio and/or the reaction time caused extensive decomposition. The use of Pt-on-carbon effected partial cleavage of the MOM ether as well as decomposition. A similar result was seen with $Pd(OH)_2$. However, when triethylamine was added to this reduction, to neutralize what we presume to be acidic by-products, the tetrahydro product **7** was obtained in 97% yield.[11]

Table 1. Hydrogenation of Alkyne **7**



Catalyst	Result
Rh–alumina (20 mol%)	(*Z*)-Dihydro product
Rh–alumina (100 mol%)	Decomposition
Pt–C	Loss of MOM/decomposition
$Pd(OH)_2$	Loss of MOM/decomposition
$Pd(OH)_2$, Et_3N	Tetrahydro product **8** (97%)

Protection of this alcohol as the MOM ether **8**, then hydrogenolysis of the benzyl ether over palladium-on-carbon afforded the alcohol **9**, which was converted to aldehyde **10** with the Dess–Martin periodinane reagent buffered with $NaHCO_3$.[12] Addition of lithio TMS acetylene and a second Dess–Martin oxidation led to alkynone **11**. The Noyori transfer-hydrogenation methodology was again employed to reduce the alkynone carbonyl, affording the (*R*)-propargylic alcohol **12** as the sole isolable product in 62% yield (unoptimized). Protection of the alcohol as the DPS ether **13** and removal of the TMS grouping afforded the terminal alkyne **14**, an intermediate in Bialy and Waldmann's synthesis of cytostatin. Comparison of the optical rotation, ^{1}H NMR, and ^{13}C NMR spectra of this sample to the reported values confirmed the identity of the two substances (Scheme 2).



Scheme 2. Reagents and conditions: (a) Dess–Martin, $NaHCO_3$ (~100%); (b) lithio TMS acetylene; (c) Dess–Martin, $NaHCO_3$ (90%, two steps); (d) Noyori reduction (62%); (e) DPSCI, Im, DMF (~100%); (f) K_2CO_3, MeOH (89%).

A noteworthy feature of the present synthesis is the seamless integration of the allenylmetal and Noyori transfer-hydrogenation methodology to access relatively complex polyketide structural segments. As was previously shown,[7] the Noyori methodology is remarkably insensitive to the stereochemical environment of the carbonyl group. Our route, like that of Bialy and Waldmann, offers the potential for facile reversal of any or all stereocenters of the natural product for possible structure–activity studies.

Acknowledgements

This study was supported by research grant R01 CA090383 from the National Cancer Institute. We thank Professor Herbert Waldmann for a copy of a manuscript in press.

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