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Concise Synthesis of the Bacterial DNA Primase Inhibitor (+)-Sch 642305

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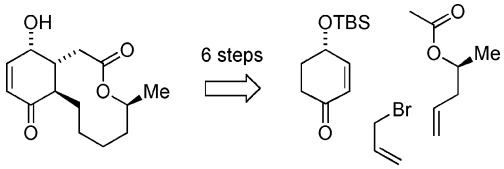
ABSTRACT

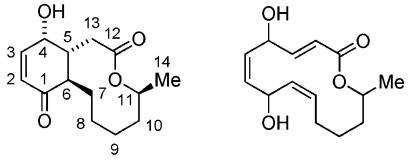


(+)-Sch 642305

A highly convergent, enantioselective synthesis of (+)-Sch 642305 is presented, which features a Mukaiyama–Michael addition followed by allylation to establish the syn–anti relationship of the three contiguous stereocenters. The 10-membered macrolactone was formed through ring-closing metathesis.

Bacterial DNA primase is an integral component of the prokaryotic DNA replication machinery and is structurally orthogonal to the analogous eukaryotic system. The primase initiates replication of the lagging DNA strand by synthesizing a short RNA primer, to which new nucleotides can be added by DNA polymerase. The exact mechanistic details of the initiation and regulation of the primase, however, are only beginning to be elucidated by both crystallographic and biochemical methods.[1]

Inhibitors of bacterial DNA primase are highly desirable because they represent a novel class of antibiotics and would be useful tools to study the DNA replication system in bacteria. In 2003, a group from Schering-Plough disclosed the structure of the 10-membered macrolide (+)-Sch 642305 (**1**) (Figure 1), isolated from *Penicillium verrucosum*.[2] The compound was found to inhibit bacterial DNA primase with an EC_{50} value of 70 μM. The mode of interaction with the bacterial primase complex, however, remains to be determined. Interestingly, Sch 642305 was reisolated from the fungus *Septofusidium* sp. by Merck scientists, who also reported that **1** inhibits HIV-1 Tat with an IC_{50} value of 1 μM.[3]



(+)-Sch 642305 (**1**) nigrosporolide (**2**)

Figure 1. Sch 642305 and its congener.

Our group has become interested in the synthesis of Sch 642305 to facilitate biochemical and mechanistic studies on the bacterial primase. Sch 642305 is of a size and complexity that an efficient synthesis could deliver significant quantities of enantiopure material for comprehensive biological evaluation. In addition, such a synthesis could be designed to procure libraries of derivatives and "diverted" compounds for SAR and affinity labeling studies.

With its four stereocenters and unusual decalactone trans fused to a cyclohexenone, Sch 642305 poses interesting challenges for total synthesis. Indeed, the compound has received immediate attention from several synthetic groups.

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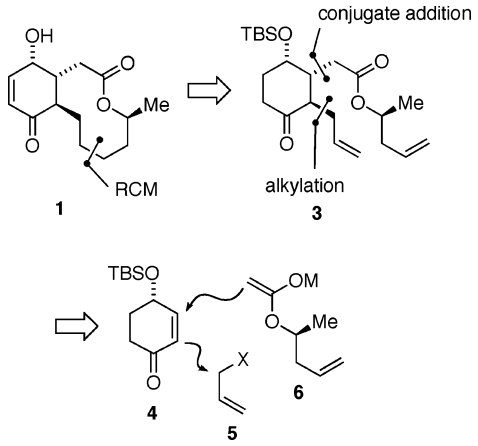
Mehta and Shinde reported an asymmetric total synthesis that featured a lipase-mediated enzymatic desymmetrization and ring-closing metathesis (RCM) along the C8−C9 bond.[4] Watanabe's synthesis was based on a highly functionalized enantiopure cyclohexanone derivative obtained through an enzymatic reduction.[5] More recently, Snider and Zhou proposed that Sch 642305 could be formed from an isomer of the related macrolactone nigrosporolide (**2**) through a transannular Michael reaction. This proposal was supported through a biomimetic total synthesis.[6]

We reasoned that Sch 642305 (**1**) could be retrosynthetically traced back to simple building blocks in the highly convergent manner shown in Scheme 1. Disconnection of

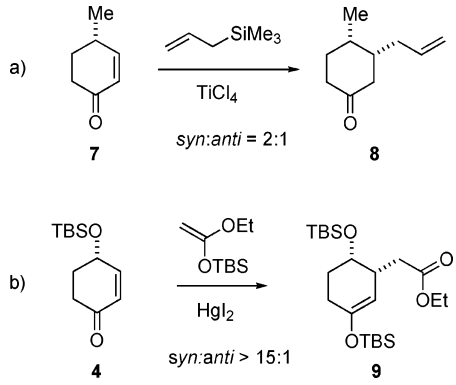
Scheme 1. Retrosynthetic Analysis



the 10-membered lactone through retro RCM along the C8−C9 bond and functional group manipulations could afford **3**. This compound, in turn, could be retrosynthetically disassembled to afford silyloxy cyclohexenone **4**, allyl halide **5**, and enol ether (or enolate) **6**. These three components are readily available from commercial material.

In the forward direction, the conjugate addition of **6** would have to proceed with syn selectivity. This seemingly counterintuitive proposal is based on literature precedent. In 1983, Heathcock reported that Sakurai reactions of 4-methyl cyclohexenone (**7**) preferentially afford the syn diastereomer (Scheme 2a).[7] This result was attributed to a lower-energy chairlike transition state leading to the syn product. Subsequently, in a system more relevant to our synthetic plan, Danishefsky reported that 4-silyloxy cyclohexenones such as **4** undergo highly diastereoselective Lewis acid catalyzed Mukaiyama−Michael and Sakurai reactions to form primarily the syn isomer (Scheme 2b).[8] Danishefsky postulated

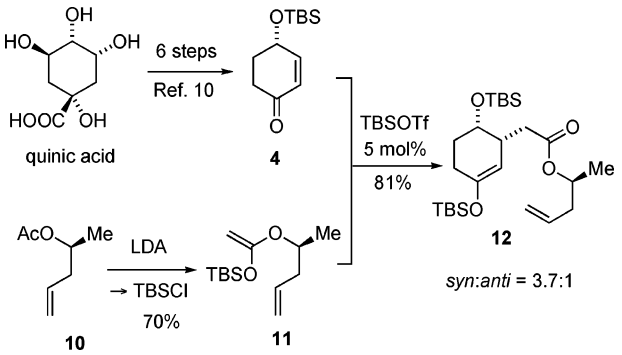
Scheme 2. Heathcock's and Danishefsky's Precedence for Syn-Selective Conjugate Addition to 4-Substituted Cyclohexenones



that this selectivity was due to a Cieplak effect of the 4-alkoxy group.[9]

Our synthesis of Sch 642305 started with the preparation of the known cyclohexenone **4**, which is most conveniently available from quinic acid (Scheme 3).[10] In parallel, the

Scheme 3. Synthesis of Silyl Enol Ether Key Intermediate **12**



known acetate[11] of commercially available (*S*)-4-penten-2-ol (**10**) was converted into silyl ketene acetal **11**. In the presence of a catalytic amount of TBSOTf, **11** underwent a Mukaiyama−Michael addition to enone **4** with concomitant silyl transfer.[12] This afforded an inseparable 3.7:1 mixture of *syn*-silyl enol ether **12** with its anti isomer (not shown).

Interestingly, preliminary results established that the same reaction conditions using the TBS enol ether of isopropyl acetate yield a 5:1 mixture of syn/anti isomers. These results in combination with Danishefsky's data suggest that there is a trend for decreasing selectivity of the reaction with increasing steric bulk of the silyl ketene acetal. In our case, the use of TBSOTf as a catalyst was found to provide

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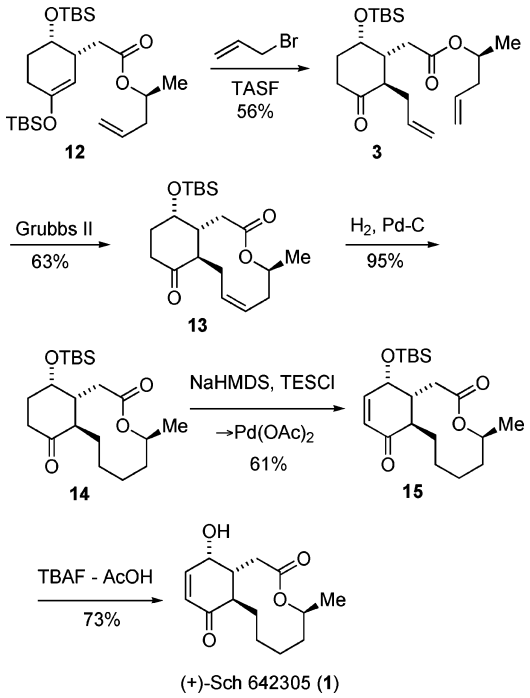
superior selectivity to the HgI_2-catalyzed conditions described by Danishefsky.[8]

With silyl enol ether **12** in hand (which could not be separated on a preparatory scale from its anti isomer), we proceeded to study the subsequent stereoselective alkylation. Unfortunately, attempts to allylate silyl enol ether **12** with palladium catalysis, as described by Tsuji,[13] were met with little success. However, this transformation could be performed using more classical conditions. Treatment of **12** with allyl bromide and TASF[14] gave cyclohexanone **3** in good yield and with excellent diastereoselectivity (Scheme 4).

Scheme 4. Synthesis of (+)-Sch 642305



The 10-membered ring of Sch 642305 was formed through ring-closing metathesis using the second-generation Grubbs catalyst. Only pure isomer **13** was isolated, although all previous steps were performed on inseparable mixtures of syn and anti isomers with respect to the C4−C5 stereocenters. The corresponding anti isomer was presumably lost in the RCM step. The resulting *cis*-alkene **13** underwent hydrogenation to afford the saturated 10-membered lactone **14**.

At this stage, a dehydrogenation and deprotection were required to complete the synthesis. In Mehta's endgame, the TBDPS analogue of **14** was dehydrogenated by oxidation of the aryl selenide derivative. In our hands, the analogous reaction, as well as an IBX-mediated dehydrogenation, were found to be unsatisfactory.[15] The Saegusa−Ito unsaturation through an intermediate TES enol ether, however, provided the desired unsaturated TBS-protected natural product **15** in good yield.[16] This compound had been previously reached in Watanabe's synthesis. In the final step of the synthesis, **15** was carefully deprotected with buffered TBAF to provide the target molecule Sch 642305. The physical properties of our synthetic material fully matched the reported data for the natural product.

In summary, we have developed a highly convergent, concise, and practical synthesis of Sch 642305. Our synthesis proceeds in six linear steps from the readily available chiral cyclohexenone **4**. Attempts to diversify the synthesis and cocrystallize our synthetic material with its target are currently underway and will be reported in due course.

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Note Added After ASAP Publication: Reference 4b was missing from version published on March 6, 2007; the correct version was published on March 14, 2007.

Supporting Information Available: Spectroscopic and analytical data and experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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