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Total Synthesis of (−)-Spinosyn A via Carbonylative Macrolactonization

Yu Bai, Xingyu Shen, Yong Li, and Mingji Dai*

Department of Chemistry and Center for Cancer Research, Purdue University, West Lafayette, Indiana 47907, United States

Supporting Information

ABSTRACT: Spinosyn A (**1**), a complex natural product featuring a unique 5,6,5,12-fused tetracyclic core structure, is the major component of spinosad, an organic insecticide and an FDA-approved agent used worldwide. Herein, we report an efficient total synthesis of (−)-spinosyn A with 15 steps in the longest linear sequence and 23 steps total from readily available compounds **14** and **23**. The synthetic approach features several important catalytic transformations including a chiral amine-catalyzed intramolecular Diels−Alder reaction to afford **22** in excellent diastereoselectivity, a one-step gold-catalyzed propargylic acetate rearrangement to convert **28** to *α*-iodoenone **31**, an unprecedented palladium-catalyzed carbonylative Heck macrolactonization to form the 5,12-fused macrolactone in one step, and a gold-catalyzed Yu glycosylation to install the challenging *β*-forosamine. This total synthesis is highly convergent and modular, thus offering opportunities to synthesize spinosyn analogues in order to address the emerging cross-resistance problems.

Spinosyn A (**1**, Figure 1) is the major component of spinosad, an important organic and natural insecticide that is widely used around the world in agriculture.[1] Spinosad is also an FDA-approved agent for treating human head lice. Spinosyns A and D were produced by *Saccharopolyspora spinosa* in a roughly 17:3 ratio and were demonstrated to have novel mode of action.[2] They primarily target the insect nicotinic acetylcholine receptors of the nervous system. They also function as *γ*-aminobutyric acid neurotransmitter agonists. The overall effects make the insect hyperexcited, which ultimately leads to death. More importantly, in addition to spinosad's high efficacy and broad insect pest spectrum, it has very low mammalian toxicity as well as an excellent environmental profile. Unfortunately, cross-resistance has been observed for spinosad recently, which puts the usage life of this important insecticide at risk.[3] Thus, developing the next generation of spinosad insecticides becomes important and urgent. So far, the current biosynthesis approach is effective for producing the spinosyns in large scale, but cannot be adapted to make a large number of analogues with structural variations at different sites to target the emerging cross-resistance.

Structurally, spinosyns A and D consist of a unique 5,6,5,12-fused tetracyclic ring system with two carbohydrates attached: D-forosamine and tri-*O*-methyl-L-rhamnose. In addition to the synthetic challenges posed by the tetracyclic core, stereoselective installation of the *β*-D-forosamine, a 2-deoxy sugar, is nontrivial as well. So far, three total syntheses of spinosyn A have been

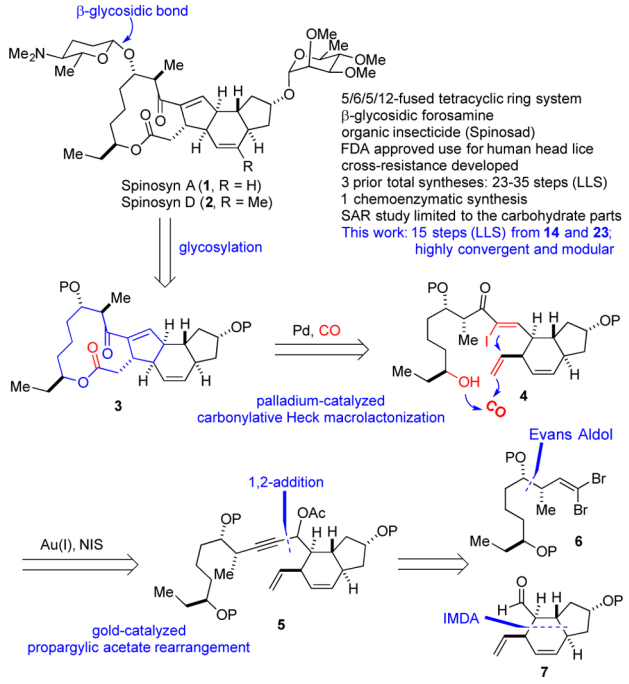

Figure 1. Spinosyn A and retrosynthetic analysis.

reported from the groups of Evans (31 steps in the longest linear sequence (LLS), 37 steps total),[4] Paquette (35 steps LLS, 44 steps total),[5] and Roush (23 steps LLS, 29 steps total).[6] One chemoenzymatic synthesis has been reported by Liu and coworkers.[7] This chemoenzymatic synthesis requires 23 steps (LLS) and 35 total steps, including one enzymatic step. Currently, most of the analogue exploration relies on semisynthesis and focuses on modifications of the tri-*O*-methyl-L-rhamnose moiety.[8] Structural modification of the tetracyclic core is important but highly challenging, and an efficient and modular synthetic approach toward the spinosyns is needed for this purpose. Herein, we report such a total synthesis of (−)-spinosyn A with 15 steps in the LLS and 23 steps total from readily available compounds **14** and **23**.

Our group[9] has an ongoing interest in developing novel catalytic carbonylative reactions[10] to streamline the synthesis of complex bioactive natural products with carbon monoxide (CO) as a one carbon linchpin. After carefully examining the structural features of the spinosyns, we envisioned the possibility of

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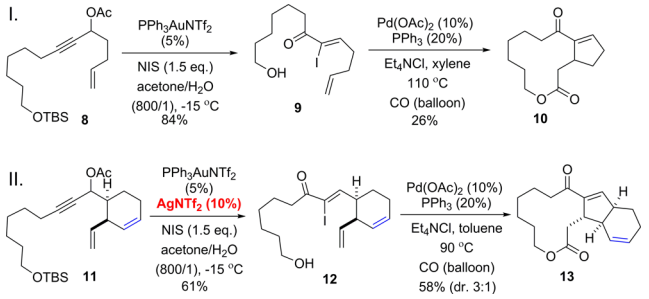
developing an unprecedented palladium-catalyzed carbonylative Heck macrolactonization to construct the spinosyn A aglycone (**3**) from (*Z*)-α-iodoenone **4**. Such a carbonylative Heck macrolactonization, while challenging, would significantly improve the synthetic efficiency and enable unique bond scission of the carbocycle and macrolactone moieties. Stereoselective synthesis of α-iodoenone **4** is not a simple task. The commonly used Wittig-type olefination is not suitable because of low stereoselectivity and the issues associated with the accessibility and stability of the corresponding α-iodo-ylide reagent.[11] Iodination of the corresponding acyclic enone is problematic as well.[12] Inspired by the recent discoveries by Zhang[13] and Shi[14] for the stereoselective rearrangement of propargylic acetates to *Z*- or *E*-α-iodoenones by using different gold(I) catalysts, we envisioned **5** as the precursor of **4**. Compound **5** could be assembled by 1,2-addition of an acetylide derived from dibromide **6** to aldehyde **7**, followed by in situ acetate formation. This bond disconnection is critical and strategic because it would cut **5** into two relatively simple pieces. Compound **6** could be readily synthesized with an Evans aldol reaction to construct the two contiguous carbon centers. Compound **7** could be assembled with an intramolecular Diels–Alder (IMDA) reaction.

So far, there have been no reports of palladium-catalyzed carbonylative Heck macrolactonization. Even for the sporadically reported intramolecular carbonylative Heck reactions,[15] issues such as over-carbonylation or no carbonylation are potential problems. In the proposed gold-catalyzed propargylic acetate rearrangement, there is a 1,6-enyne structural motif in substrate **5**, and a potential enyne cycloisomerization[16] may compete with the desired rearrangement. Under these circumstances, model studies were conducted (Scheme 1). We first prepared

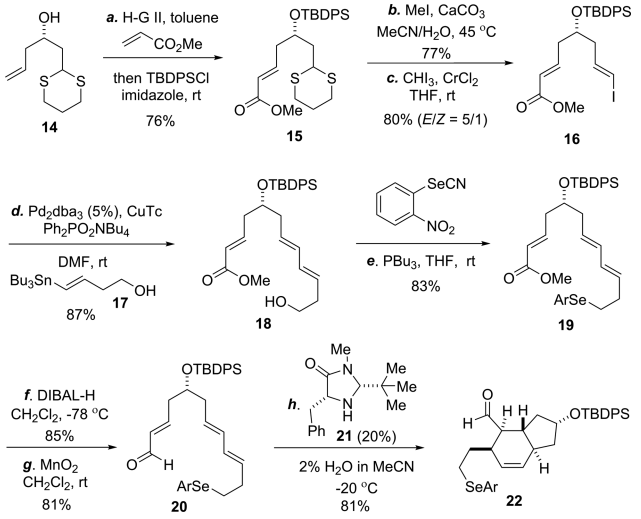
Scheme 1. Model Studies



propargylic acetate **8** with a 1,6-enyne moiety. To our delight, using Zhang's protocol,[13] the gold-catalyzed rearrangement in the presence of *N*-iodosuccinimide (NIS) provided α-iodoenone **9** in excellent yield and stereoselectivity without any detection of the corresponding cycloisomerization byproduct. The *tert*-butyldimethylsilyl (TBS) protecting group was removed as a bonus. We then explored the feasibility of using carbonylative Heck macrolactonization to build the 5,12-fused macrolide. After extensive investigations, we were able to obtain the desired product **10** in 26% yield with a catalytic amount of $Pd(OAc)_2$/PPh_3 under balloon pressure of CO. While the yield was not yet optimal, this result demonstrates the feasibility and efficacy of using a carbonylative Heck macrolactonization to build the 5,12-fused macrolide ring system. Encouraged by this simple model study, we prepared model substrate **11** to investigate four questions: (1) Will the internal double bond of the 6-membered carbocycle intercept the acyl-palladium species via a 5-*exo*-*trig* cyclization before it undergoes the macrolactonization with the tethered remote alcohol? (2) Will the 6-membered ring facilitate the carbonylative Heck macrolactonization via a Thorpe–Ingold-type effect to improve the reaction yield? (3) With the Thorpe–Ingold-type effect, will 1,6-enyne cycloisomerization become a problem since the terminal olefin and the alkyne are getting closer in comparison to the case of **8**? (4) What is the stereochemical outcome of the newly generated carbon center? With these questions in mind, substrate **11** was subjected to the gold-catalyzed rearrangement conditions. The reaction turned out to be quite complex, and α-iodoenone **12** was produced in trace amount. We then found that addition of 10% of $AgNTf_2$ to the reaction system is beneficial, and **12** was obtained in 61% yield, indicating some silver effect in this transformation.[17] More importantly, the carbonylative Heck macrolactonization was much more effective, and product **13** was produced in 58% yield with 3:1 diastereoselectivity favoring the desired stereochemical outcome. About 10% of the regular Heck reaction product was obtained as well. These results indicate the critical role of the 6-membered ring in facilitating the carbonylative Heck macrolactonization process.

We then embarked on the total synthesis. We planned to use a chiral amine-catalyzed IMDA reaction developed by the MacMillan group to control the relative stereochemistry of the *trans*-5,6-fused ring system,[18] since the substrate-controlled cases tend to give low stereoselectivity. Among the substrates reported in MacMillan's work, a conjugated triene substrate was shown to be ineffective; therefore, we decided to introduce the terminal olefin after the IMDA reaction and designed **20** as the IMDA precursor (Scheme 2). This choice also gives us an opportunity

Scheme 2. Synthesis of 22



to release the double bond at a later stage if it gets involved in the gold-catalyzed rearrangement process. The synthesis of **20** started with known compound **14**,[19] which can be prepared via a one-pot reaction from commercial starting materials (see the Supporting Information). Cross-metathesis with the Hoveyda–Grubbs second-generation catalyst followed by *tert*-butyldiphenylsilyl (TBDPS) protection gave **15** in 76% yield. Removal of the thioketal group followed by Takai olefination provided vinyl iodide **16** with good *E*/*Z* selectivity. Stille cross-coupling[20] of **16** with **17** afforded **18** in excellent yield, which was then advanced to the IMDA precursor **20** via a sequence of selenide formation, DIBAL-H reduction, and MnO_2 oxidation. The IMDA reaction

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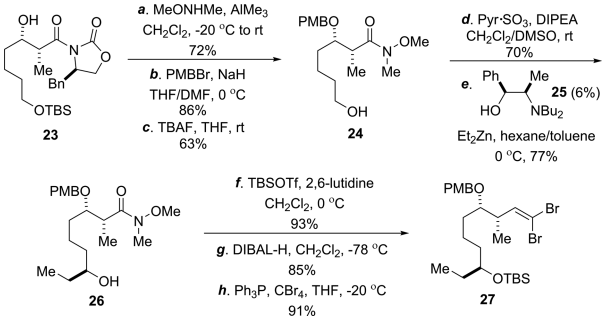
took place smoothly with a 20% loading of catalyst **21**, and **22** was produced in 81% yield as a single diastereomer. Notably, the IMDA reaction is sluggish and not selective in the absence of the chiral amine catalyst, even at elevated temperatures.

We then prepared dibromide **27** (Scheme 3). The synthesis is quite straightforward and started from known compound **23**,

Scheme 3. Synthesis of 27

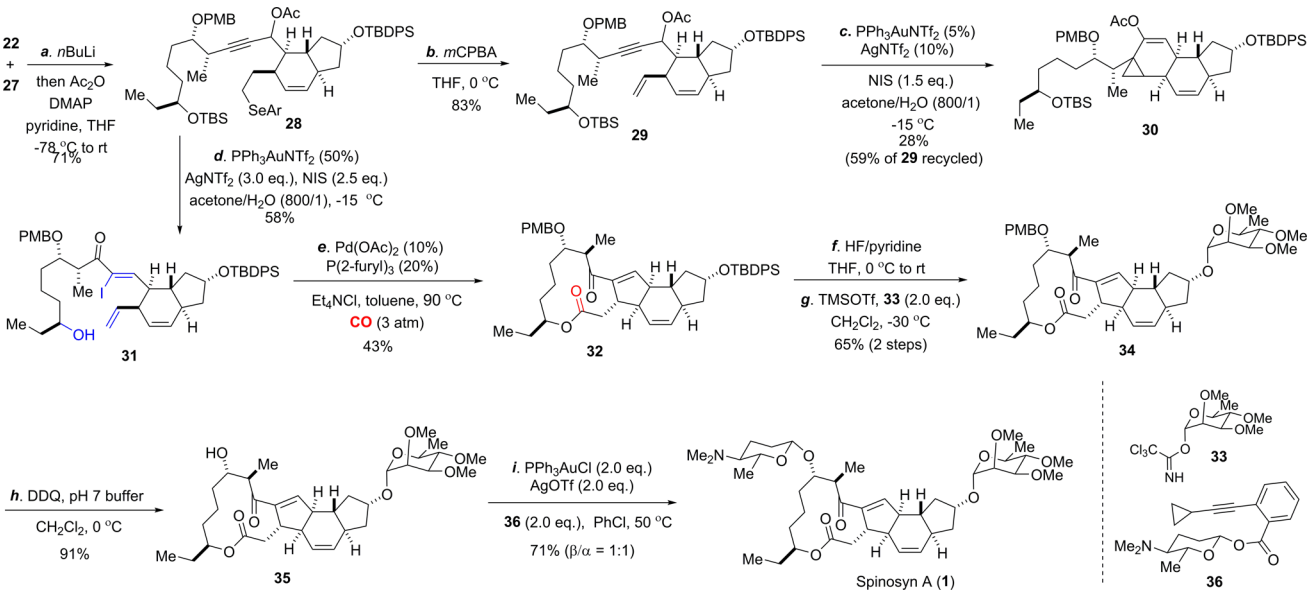


which can be prepared in three steps from cheap 1,5-pentanediol or one step from the more expensive 5-OTBS pentanal via an Evans aldol reaction.[21] After switching the Evans chiral auxiliary to a Weinreb amide and protecting the secondary alcohol as *p*-methoxybenzyl (PMB) ether, the TBS group was removed to give **24**. Oxidation of **24** to an aldehyde followed by an asymmetric 1,2-addition afforded **26**, which was then converted to **27** via a sequence of TBS protection, DIBAL-H reduction, and dibromide formation.

With both **22** and **27** in hand, we used the Corey–Fuchs protocol to unite them, and the resulting alkoxide was converted to acetate **28** in situ (Scheme 4). Compound **28** was obtained as a mixture of diastereomers in 71% yield from a 1:1.2 ratio of **22** and **27**. While this 1,2-addition was not stereoselective, the newly generated stereocenter will be eliminated at a later stage, so the effect is not permanent. *m*CPBA oxidative elimination converted **28** to **29** with a terminal olefin. To our surprise, despite the success of the two model substrates, rearrangement of **29** to the corresponding α-iodoenone did not take place. Instead, enyne cycloisomerization product **30** was produced in 28% yield, with 59% of **29** recycled. The structure of **30** was tentatively assigned on the basis of NMR studies. We then decided to explore the gold-catalyzed rearrangement with **28** directly, and only a trace amount of desired product was obtained using the conditions established in the model studies. Notably, both the selenide and the secondary TBS ether were found to be not stable under the rearrangement conditions, which further complicated the reaction process. However, we also saw an opportunity to realize the rearrangement, oxidative selenide elimination, and TBS removal in just one step. After extensive reaction condition optimizations, we learned that the ratio of $AgNTf_2$ and NIS is critical. When the amount of $AgNTf_2$ was less than the amount of NIS, the reaction was in general complex, and the desired product was produced in very low yield. The amount of water is critical as well. Eventually, desired product **31** was obtained in 58% yield with 3.0 equiv of $AgNTf_2$ and 2.5 equiv of NIS. Carbonylative Heck macrolactonization of **31** required tri(2-furyl)phosphine as ligand and 3 atm of CO; higher pressure was not beneficial and even showed an inhibitory effect. At last, **32** was produced in 43% yield as a single diastereomer. *The carbonylative Heck macrolactonization reaction built both the 5-membered ring and the 12-membered macrolactone in one step. Overall, a highly convergent and modular sequence was developed to convert* **22** *and* **27** *to tetracyclic intermediate* **32** *in only three steps!*

With the tetracyclic core structure assembled, the final stage was to install the two carbohydrate moieties. Installation of the α-tri-*O*-methyl-L-rhamnose proceeded smoothly. After removal of the TBDPS protecting group with HF/pyridine, Schmidt glycosylation gave **34** in 65% yield in two steps. The spectral data of **34** match those reported in the Roush synthesis.[6] Oxidative removal of the PMB protecting group gave the pseudoaglycon **35** in 91% yield. The last hurdle in our synthesis was to introduce the β-D-forosamine. The difficulty involved in a direct glycosylation with a D-forosamine-derived donor has been experienced by the previous pioneers, and no methods have been reported to stereoselectively introduce the β-linkage. The Evans group used a silver zeolite-catalyzed glycosylation of the **35** with a *N*-Fmoc-protected glycosyl bromide donor to give a 69% yield of

Scheme 4. Total Synthesis of (−)-Spinosyn A



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a 1:6 mixture of β/α-glycosides, but favoring the undesired α-isomer.[4] The Paquette group used AgOTf-catalyzed glycosylation with a glycosyl sulfide donor to give the glycosylation product in 17% yield as a 2:3 mixture of β/α-glycosides, again favoring the undesired isomer.[5] The Roush group used a 2-acetate glycosyl imidate donor to circumvent the stereoselectivity issue, but 11 steps were required to synthesize this donor and another five steps to convert the glycosylated product to spinosyn A. Recently, Yu and co-workers reported a gold-catalyzed glycosylation that favors β-selectivity.[22] We decided to investigate the Yu glycosylation in our synthesis by using donor **36**. To our delight, after finely tuning the reaction conditions, the glycosylation product was obtained in 71% yield along with 15% of recycled **35**. While the β/α-selectivity is only 1:1, it is still so far the most effective way to direct glycosylation with a D-forosamine derived donor. The β/α-glycoside isomers were separated by preparative TLC to complete the total synthesis of (−)-spinosyn A, the spectral data of which match with the ones of the natural product.

Overall, we have developed an efficient and modular total synthesis of (−)-spinosyn A with 15 steps in the longest linear sequence and 23 steps total from readily available compounds **14** and **23**. The synthetic approach features an organocatalyzed IMDA reaction to build the *trans*-5,6-fused ring in excellent diastereoselectivity, a one-step gold-catalyzed[23] propargylic acetate rearrangement, selenide elimination, and TBS removal to convert **28** to α-iodoenone **31**, an unprecedented palladium-catalyzed carbonylative Heck macrolactonization to form the 5,12-fused macrolactone, and a Yu glycosylation to install the challenging β-forosamine. This total synthesis is highly convergent and flexible, thus providing new avenues to access spinosyn analogues to address the cross-resistance problems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07585.

Experimental procedures and compound characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*mjdai@purdue.edu

Notes

The authors declare no competing financial interest.

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