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Report

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Total Synthesis of UCS1025A via Tandem Carbonylative Stille Cross Coupling and Diels-Alder Reaction

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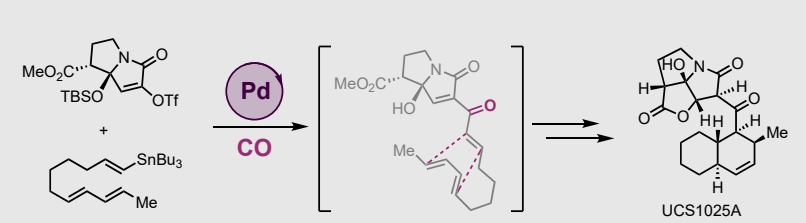
Keywords

Natural Products | Total Synthesis | UCS1025A | Carbonylation | Diels-Alder Reaction | Tandem Reaction

Comprehensive Summary



tandem carbonylative Stille coupling and Diels-Alder reaction

We report an efficient and convergent strategy for the total synthesis of UCS1025A and its diastereomer tetra-*epi*-UCS1025A. UCS1025A is a representative member of the naturally occurring pyrrolizidinone polyketides, from which members with potent antibacterial, antifungal, and anticancer activities have been identified. Our approach features a tandem carbonylative Stille cross coupling and Diels-Alder reaction to forge a key C–C bond and build the *trans*-decalin system. This tandem process utilizes carbon monoxide as a one-carbon linchpin to stitch a vinyl triflate and a vinylstannane together and form the desired enone moiety for the subsequent intramolecular Diels-Alder cyclization. Our synthesis also provides a versatile approach for the synthesis of other related pyrrolizidinone-containing polyketides.

Background and Originality Content

Pyrrolizidinone containing natural products are widespread in nature, exhibit diverse biological activities, and often have complex and novel structures.[1-4] One such example is UCS1025A (**1**, Figure 1A), which was isolated from the *Acremonium sp*. KY4917 fungus by Yamashita and co-workers in 2000.[5] UCS1025A was found to exhibit antiproliferative activity against human cancer cell lines by inhibiting the telomerase enzyme.[6] Structurally, UCS1025A consists of a compact pyrrolizidinone core connected by an acyl bond to a *trans*-decalin motif. Other antibiotics in this class include UCS1025B (**2**), CJ-16,264 (**3**), pyrrolizilactone (**4**), and myceliothermophins (**5-7**) (Figure 1A). In particular, CJ-16,264 (**3**: structure revised by Nicolaou and co-workers)[7] was isolated from fungus CL39457 and exhibited potent antibacterial activities against both Gram-positive and Gram-negative strains and cytotoxic properties.[8] Myceliothermophin E (**7**) was isolated from *Myceliophthora thermophila* and showed activity against various human cancer cell lines including hepatoblastoma (HepG2, IC_{50} = 0.28 μgmL^{-1}), hepatocellular carcinoma (Hep3B, IC_{50} = 0.41 μgmL^{-1}), lung carcinoma (A549, IC_{50} = 0.26 μgmL^{-1}), and breast adenocarcinoma (MCF-7, IC_{50} = 0.27 μgmL^{-1}).[9]

The complex structures and remarkable biological activities of the pyrrolizidinone polyketides have attracted significant synthetic attention.[1-3, 10-17] Several elegant total syntheses of UCS1025A (**1**) have been reported (Figure 1B). In 2005, Danishefsky and Lambert

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completed the first asymmetric total synthesis of UCS1025A in 11 steps (longest linear sequence, LLS).[12] Their synthesis started from readily available starting materials **8** and **9**, from which enantiopure bicyclic intermediate **11** was obtained via **10**. An iodolactonization then converted **11** to **12**. The salient feature of their synthesis is a remarkable boron-mediated Reformatsky-type fragment coupling to unite iodide **12** and aldehyde **13** (prepared from an organocatalyzed intramolecular Diels-Alder (IMDA)) and form advanced inter mediate **14**, which was then converted to UCS1025A via TBS removal with TBAF and Dess-Martin oxidation. In 2006, Hoye and co-workers reported an alternative strategy to complete their total synthesis of UCS1025A in 9 steps (LLS).[13] They used an acylation of the organomagnesium intermediate generated from magnesium- iodine exchange between **15** and *i*-PrMgCl with Weinreb amide **16** to form a key C–C bond and prepare **17**. The latter after removal of the two TIPS protecting group and oxa-Michael addition was converted to **18**, which underwent a biomimetic IMDA in water at pH 7.2 to form compound **20** with the *trans*-decalin moiety and its isomer (tetra-*epi*-**20**) in 1:1 ratio. Under the same aqueous condition, UCS1025A was later formed via an oxa-Michael addition. In 2007, Christmann and co-workers

developed a kinetic resolution strategy to synthesize **11** in high enantioselectivity.[14] Their key steps include a quinine-facilitated kinetic resolution to convert racemic **11** to enantio-enriched **22** and a trituration to further enhance the optical purity of **11**. They then followed the Danishefsky's approach to complete their total synthesis of UCS1025A in 9 steps (LLS). In 2012, Kan and co-workers developed a 30-step (LLS) stereo-controlled total synthesis of UCS1025A using a condensation strategy of pyrrolizidinone **26** and acyl benzotriazole **28**.[15] They used L-diethyl malate (**23**) as the starting material to prepare **26** and a camphorsultam-IMDA to synthesize **28**. The condensation product was then converted to UCS1025A shortly. In 2018, Uchiro and co-workers used a similar strategy to couple compound **32** and acyl benzotriazole **28**. The coupling product **33** was advanced to UCS1025A (16 LLS steps).[16] Overall, these reported routes utilized carbonyl chemistry (Reformatsky-type aldol or condensation with amide) to connect the pyrrolizidinone moiety and the other moiety. Thus, the carbonyl functionalities need to be installed first. Herein, we report our 12-step (LLS) total synthesis of UCS1025A which features a tandem

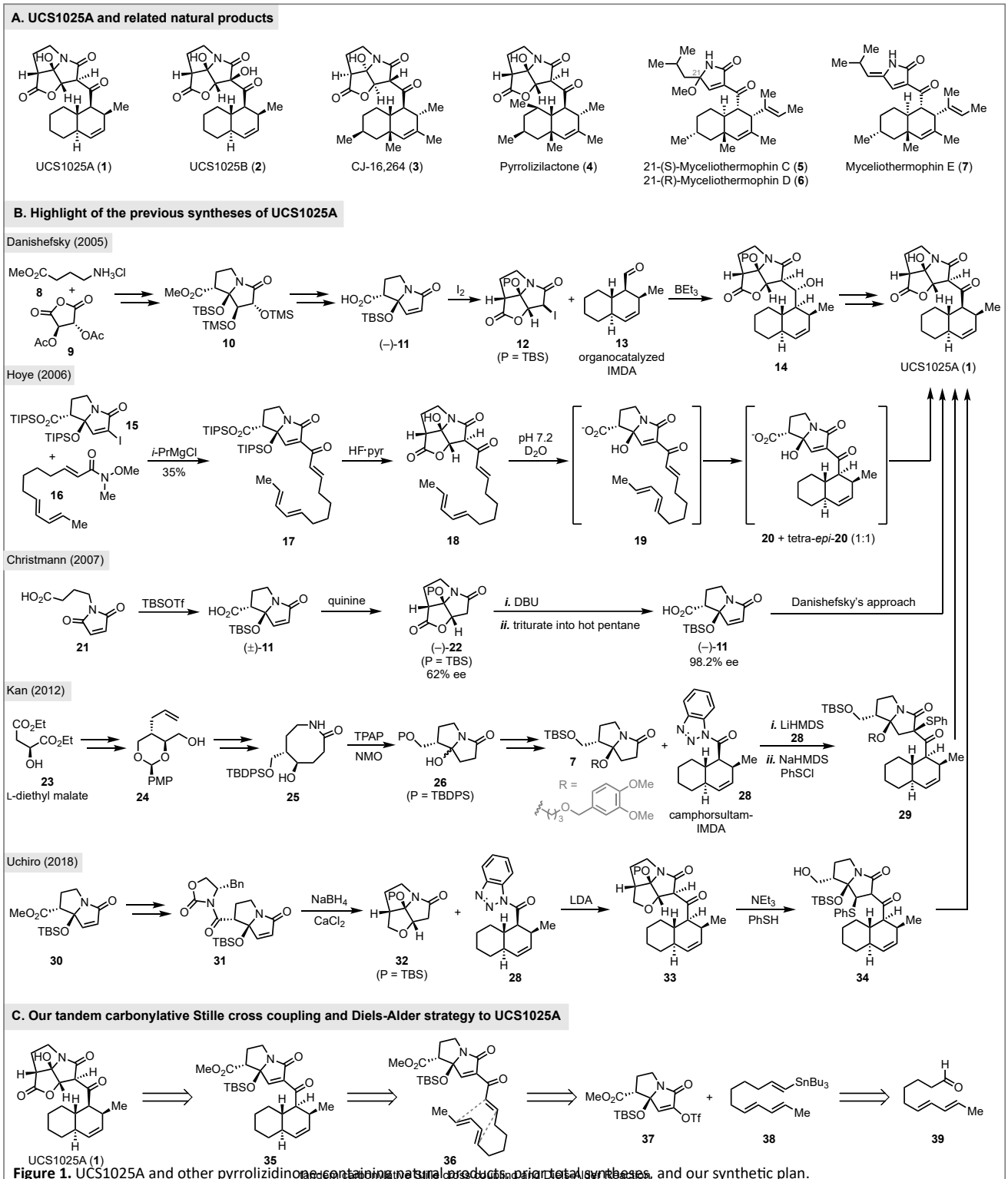


Figure 1. UCS1025A and other pyrrolizidinone-containing natural products, prior total syntheses, tandem carbonylative Stille cross coupling and Diels-Alder reaction, and our synthetic plan.

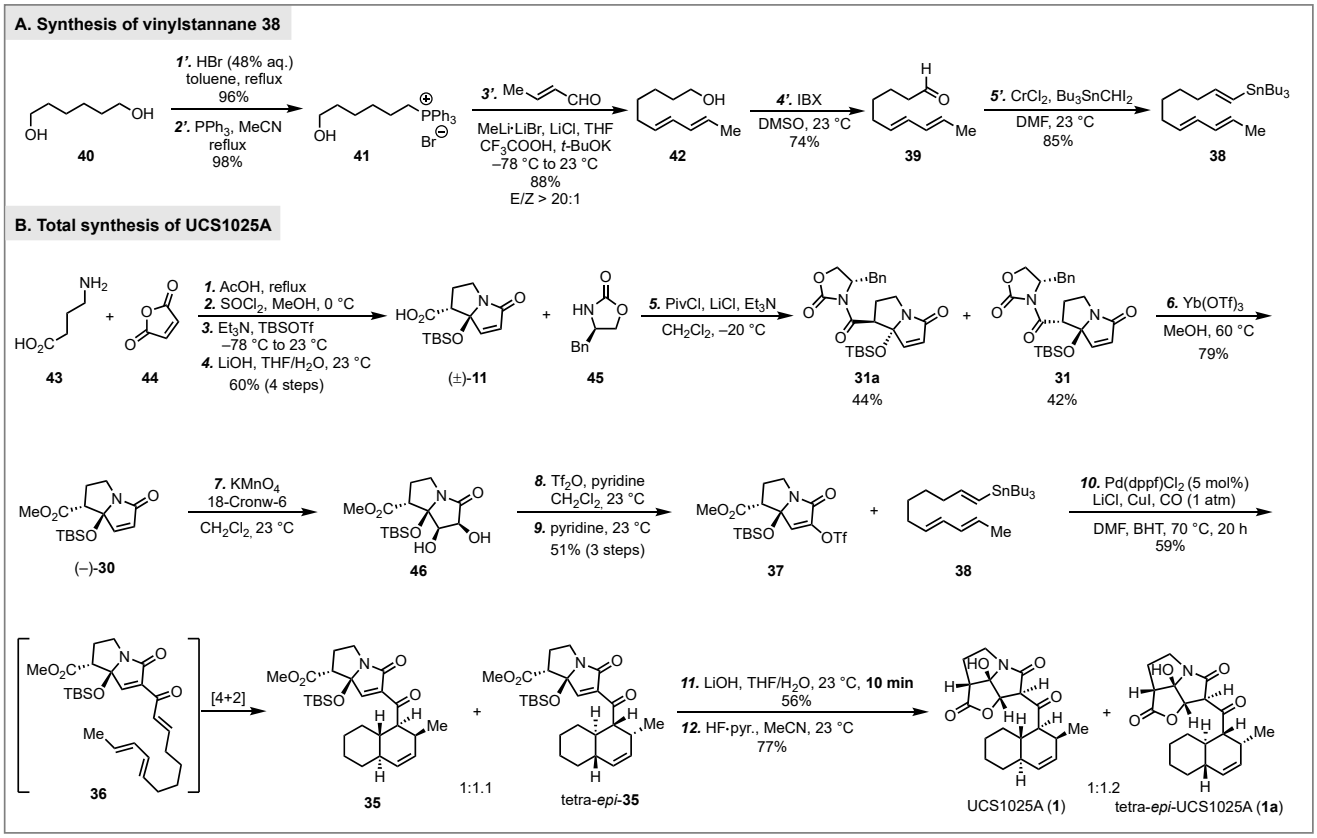
carbonylative Stille cross coupling and IMDA to forge a key C–C bond and build the required *trans*-decalin.

We have been developing palladium-catalyzed carbonylation methods and strategies for the total synthesis of complex natural products[18-20] and completed the total syntheses of a collection of terpene, alkaloid, and macrolide natural products with a broad spectrum of biological activities.[21-30] For the pyrrolizidinone polyketides (Figure 1A), we envisioned a tandem palladium-catalyzed carbonylative Stille cross coupling and Diels-Alder reaction sequence to install a key carbonyl functionality and build the *trans*-decalin moiety. To the best of our knowledge, such a tandem process has not yet been reported in the total synthesis of these natural products, and we hope that it would enable us to access a diverse collection of these natural products and their analogs for comprehensive biological evaluations. We chose UCS1025A (**1**) as the initial target molecule to test our hypothesis (Figure 1C). Retrosynthetically, USC1025A (**1**) could be prepared from advanced intermediate **35**, which could be prepared via the tandem carbonylative Stille cross coupling and Diels-Alder reaction from two key fragments **37** and **38** via enone **36**. Vinyl triflate **37** is a known compound[31] and vinylstannane **36** could be prepared from known aldehyde **39**.[32]

Results and Discussion

We first started to prepare vinylstannane **38** (Scheme 1A). We planned to use a Cr(II)-mediated Takai-Utimoto olefination to synthesize **38** from aldehyde **39**.[33-35] The latter could be synthesized from commercially available hexane-1,6-diol **40**.[32] Monobromination of **40** with 48% aqueous HBr in toluene followed by treating the monobromide with triphenylphosphine in acetonitrile under reflux gave phosphonium salt **41** in 94% yield over 2 steps. A Schlosser-modified Wittig reaction between **41** and crotonaldehyde afforded diene **42** in 88% yield and excellent stereoselectivity (E/Z > 20: 1). Oxidation of the primary alcohol of **42** with IBX in DMSO produced aldehyde **39** in 74% yield. We then used the Cr(II)-mediated Takai-Utimoto olefination between **39** and Bu_3SnCHI_2 to prepare vinylstannane **38** in 85% yield.

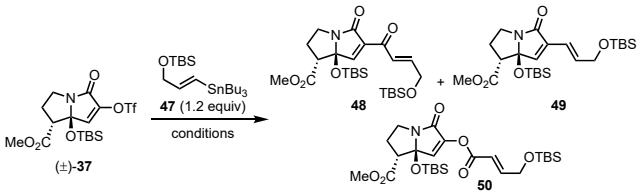
To synthesize vinyl triflate **37**, we decided to start from known compound (±)-**11**,[12] which was prepared from γ-aminobutyric acid **43** and maleic anhydride **44** (Scheme 1B). After treating **43** and **44** with acetic acid followed by thionyl chloride with methanol, the resulting maleimido methyl ester was then subjected to soft enolization conditions (TBSOTf and Et_3N in CH_2Cl_2) developed by Hoye and co-workers[36] to obtain the bicyclic pyrrolizidinone ester in high yield as a single diastereomer. Hydrolysis of the methyl ester with LiOH in THF/H_2O gave (±)-**11** in 58% yield over 4 steps. With (±)-**11** in hand, a kinetic resolution process was needed to prepare enantio-pure materials for the following synthesis. Thus, (±)-**11** was reacted with oxazolidinone **45** under the conditions of PivCl, LiCl, and Et_3N to generate an almost 1:1 mixture of **31a** and **31**, which were separated using chromatography.[11] Compound **31** was used for the following steps. Removal of the auxiliary group with $Yb(OTf)_3$ in MeOH gave 79% yield of (−)-**28**, which was further converted to vinyl triflate **37** in 51% yield via a three-step sequence: dihydroxylation with $KMnO_4$, bis-triflation of the resulting diol with Tf_2O and pyridine-promoted elimination sequences. It should be noted that removing the auxiliary under the basic conditions (LiOH, H_2O_2) resulted in the decomposition of the pyrrolizidinone motif. Additionally, compound **31a**, which was prepared during the resolution step, could be used for the synthesis of the pyrrolizidinone part of CJ-16,264 (**3**).



Scheme 1. Total synthesis of UCS1025A and tetra-*epi*-UCS1025A.

With both **37** and **38** in hand, we next focused on the carbonylative Stille cross coupling reaction. Model vinylstannane **47** was prepared and used to react with (±)-**37** for the reaction condition optimizations. Selected reaction conditions and the corresponding outcomes were listed in Table 1. The main competition process was a regular Stille cross coupling without carbon monoxide insertion. For example, with $Pd(PPh_3)_4$ as catalyst, LiCl as additive, in THF at 70 °C under 1 atm of carbon monoxide, no carbonylation product **48** was observed, but direct Stille cross coupling product **49** was obtained in 66% yield (entry 1). To our delight, switching $Pd(PPh_3)_4$ to $Pd(CH_3CN)_2Cl_2$ and THF to DMF gave the desired carbonylation product in 39% yield at 55 °C (entry 2). However, lowering the temperature to 23 °C and increasing the carbon monoxide pressure to 3.5 atm were detrimental and surprisingly product **50** was produced in 51% yield, which was presumably formed by hydrolysis of the triflate followed by carbonylative esterification (entry 3). The high carbon monoxide pressure may have inhibited the oxidative addition step and the triflate hydrolysis happened instead. Further optimizations showed that $Pd(dppf)Cl_2$ performed better than $Pd(CH_3CN)_2Cl_2$ and a trace amount of radical scavenger butylated hydroxytoluene (BHT) was beneficial for the carbonylative cross coupling (entry 4).[37,38] Addition of CuI (35 mol%) to facilitate the transmetalation step enhanced the yield of **46** to 71% yield (entry 4).[39,40]

Table 1. Model study for the carbonylative Stille reaction.



entry	reaction conditions	results
1	$Pd(PPh_3)_4$ (5 mol%), LiCl (3.0 equiv), THF, CO (1 atm), 12 h, 70 °C	**48** (0%), **49** (66%)
2	$Pd(CH_3CN)_2Cl_2$ (5 mol%), LiCl (3.0 equiv), DMF, CO (1 atm), 12 h, 55 °C	**48** (39%)
3	$Pd(CH_3CN)_2Cl_2$ (5 mol%), LiCl (3.0 equiv), DMF, CO (3.5 atm), 24 h, 23°C	**50** (51%)
4	$Pd(dppf)Cl_2$ (5 mol%), LiCl (3.0 equiv), BHT, DMF, CO (1 atm), 12 h, 70 °C	**48** (51%)
5	$Pd(dppf)Cl_2$ (5 mol%), LiCl (3.0 equiv), BHT, CuI (0.35 equiv), DMF, CO (1 atm), 12 h, 70 °C	**48** (71%)

We next investigated the tandem carbonylative Stille cross coupling and Diels-Alder reaction on real substrates **37** and **38**. To our delight, the carbonylation product **36** was produced smoothly with $Pd(dppf)Cl_2$ as a catalyst in the presence of LiCl, CuI and BHT under 1 atm of carbon monoxide at 70 °C. Under the same reaction condition, the IMDA reaction occurred to give desired product **35** and its tetraepimeric diastereomer tetra-*epi*-**35** as an inseparable mixture in 59% yield. Both diastereomers were formed from an *endo* IMDA cycloaddition, but as observed by Hoye and coworkers,[13] the rest of the stereocenters are too remote to control the facial selectivity for the diene moiety to approach the dienophile. Saponification of Diels-Alder adducts turned to be nontrivial at all and the saponification was very sensitive to the reaction time. Stirring the mixture of **35** and tetra-*epi*-**35** in LiOH in THF/H_2O in 10 min successfully generated the carboxylate anion in situ, which underwent an oxa-Michael addition spontaneously. Final desilylation with HF·Pyridine completed the total syntheses of UCS1025A (**1**) and tetra-*epi*-UCS1025A (**1a**). The data of our synthetic UCS1025A (**1**) and tetra-*epi*-UCS1025A (**1a**) matched well with those reported in the literature.[13,15]

Conclusions

In summary, we have developed an efficient and convergent approach for the total synthesis of UCS1025A, a naturally occurring pyrrolidinone polyketides. Our synthesis features a tandem palladium-catalyzed carbonylative Stille cross coupling and intramolecular Diels-Alder reaction to form one key C-C bond linkage and the *trans*-decalin in just one step. Further application of this novel approach to the total synthesis of other biologically active pyrrolidinone family members will be disclosed in due course.

Experimental

The general methods, detailed reaction procedures, all compound characterization data, and copies of ^1H and ^{13}C NMR spectra are found in the Supporting Information.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

Acknowledgement

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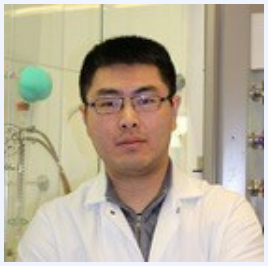


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Total Synthesis of UCS1025A via tandem carbonylative Stille cross coupling and Diels-Alder Reaction

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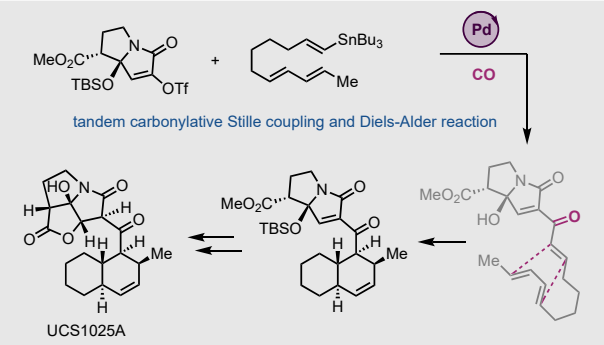

An efficient and convergent total synthesis of pyrrolidinone polyketide UCS1025A was achieved using a tandem palladium-catalyzed carbonylative Stille cross coupling and Diels-Alder reaction to form one key C-C bond linkage and the *trans*-decalin system.

