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A Convergent and Enantioselective Synthesis of (+)-Amurensinine via Selective C−H and C−C Bond Insertion Reactions

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The development of mild and selective C−H and C−C bond insertion reactions for complex molecule synthesis has the potential to enable strategic disconnections that would be inconceivable using traditional methods.[1] Because of the sheer abundance of C−H and C−C bonds in most organic molecules and the general shortage of methods to perform selective reactions on these bonds, the application of C−H and C−C activation reactions in the context of natural product synthesis has been limited. Despite these challenges, the number of examples continues to rise.[2] In this communication, we present a convergent and enantioselective synthesis of the natural product amurensinine (**1**) that employs mild and selective C−H and C−C bond insertion reactions as key strategic maneuvers.

Amurensinine (**1**) is a member of the isopavine family of alkaloids, which are exemplified by a characteristic tetracyclic tetrahydroisoquinoline core structure consisting of a doubly benzannulated azabicyclo[3.2.2]nonane (Figure 1).[3,4] The isopavines exhibit important biological properties for the treatment of neurological disorders, such as Parkinson's and Alzheimer's disease.[5] To date, there has been only one reported enantioselective synthesis of amurensinine (**1**), which was based on a chiral auxiliary approach.[6]

Our retrosynthetic strategy for the preparation of amurensinine ((+)-**1**) commences with the disconnection of the bridging amine functionality, exposing hydroxyester **6** as a synthetic intermediate (Scheme 1). We reasoned that this chiral benzylic alcohol could be produced enantioselectively by application of the palladium-catalyzed oxidative kinetic resolution methodology, recently developed in our group.[7,8] Alcohol (±)-**6** could be accessed from ketoester (±)-**7**, which contains the benzosuberane core carbocycle, an ideal retron for an efficient and mild C−C bond insertion reaction involving the acyl alkylation of arynes, previously reported by our laboratories.[9,10] Thus, aryne **8** and β-ketoester **9** were revealed as substrates for the C−C bond insertion reaction. The former may be generated in situ from *o*-trimethylsilyl triflate **10**[11] and the latter by a position-selective Rh-catalyzed C−H bond insertion reaction of diazo compound **11**.[12]

We began our efforts toward amurensinine ((+)-**1**) with the preparation of β-ketoester **9** (Scheme 2). Functionalization of (3,4-dimethoxyphenyl)acetic acid (**12**) by standard methods produced diazo compound **11**, which was subjected to $Rh_2(OAc)_4$-catalyzed dediazotization.[13] Despite the possibility for intramolecular insertion into a number of C−H bonds at sp^3 and sp^2 carbon centers (i.e., H^{a-d}), as well as intermolecular reactions, we observed the product of a single C−H insertion event into the aryl C−H^a bond producing the desired β-ketoester **9** in 96% yield.

In the key bond-forming reaction of the synthesis, coupling of β-ketoester **9** and aryne precursor **10**[9] in the presence of CsF produced ketoester (±)-**7** in 57% isolated yield (Scheme 3). This single-step C−C insertion reaction generates the polycyclic carbon framework of amurensinine by direct acyl alkylation of **8**. From a strategic standpoint, the aryne/β-ketoester ring-expansive fragment coupling affords the concomitant production of the most synthetically challenging carbocycle of **1**, as well as the convergent union of the two major synthetic subunits.

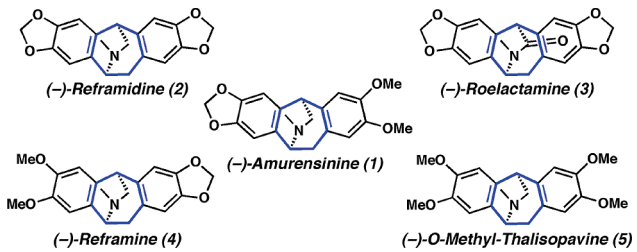
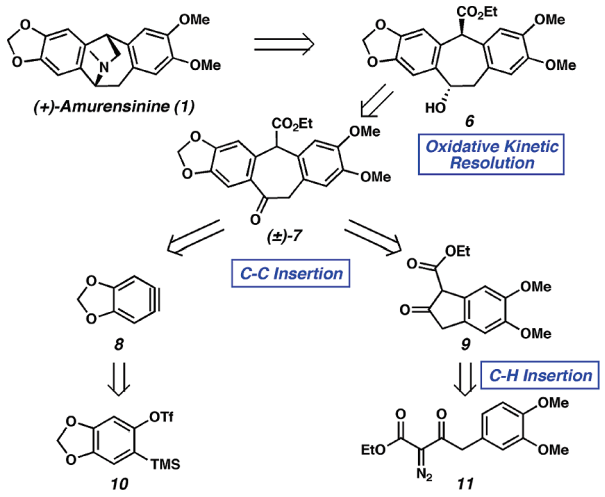
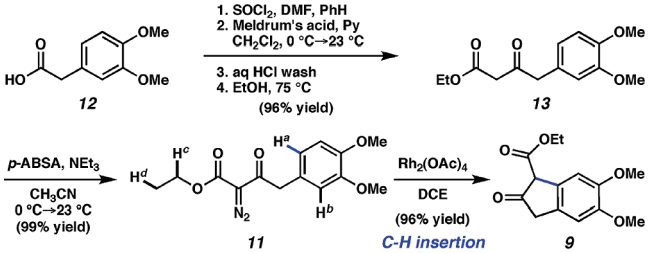


Figure 1. Representative isopavine natural products.

Scheme 1



Scheme 2



With the carbocyclic core structure of amurensinine (**1**) available (i.e., **7**), we implemented our strategy for kinetic resolution and completion of the synthesis. To that end, ketoester (±)-**7** was diastereoselectively converted to hydroxyester (±)-**6** by chemoselective carbonyl reduction with L-Selectride. Gratifyingly, application of our oxidative kinetic resolution technology to (±)-**6** using Pd(sparteine)Cl_2 and O_2 provided the enantioenriched intermediate (−)-**6** in 90% ee (s = 19, Scheme 4). Treatment of hydroxyester (−)-**6** with $(PhO)_2P(O)N_3$ in the presence of DBU,[14] followed by reduction with Pd/C under an atmosphere of H_2, spontaneously produced lactam (+)-**16**. Exhaustive reduction of the lactam with

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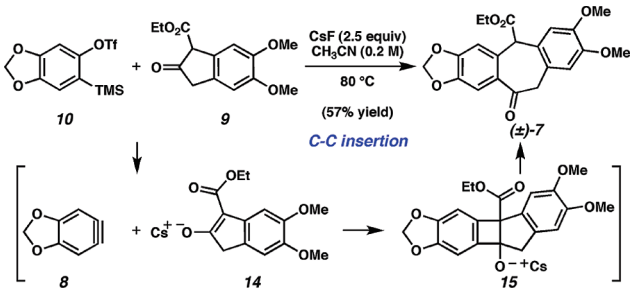
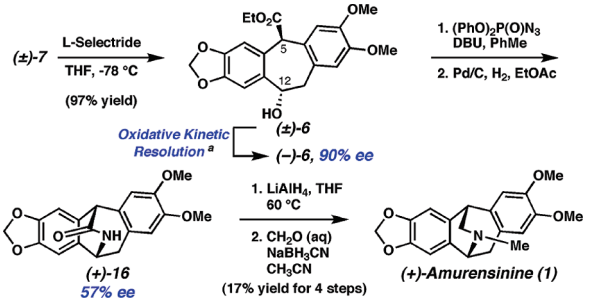
Scheme 3

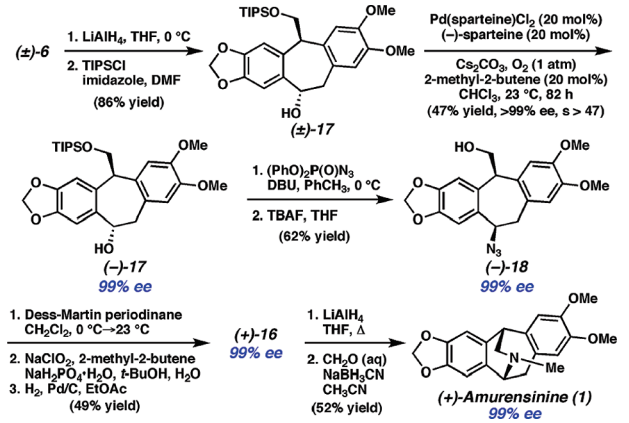


Scheme 4 [a]



[a] Pd(sparteine)Cl_2 (20 mol %), (−)-sparteine (20 mol %), Cs_2CO_3, O_2 (1 atm), $CHCl_3$, 23 °C, 36 h, (39% yield, 90% ee, $s = 19$).

Scheme 5



$LiAlH_4$ and subsequent reductive methylation yielded the natural product amurensinine ((+)-**1**).

Although this reaction sequence converted ketoester (±)-**7** to amurensinine ((+)-**1**) in a rapid fashion, the enantioenrichment produced by the oxidative kinetic resolution was degraded drastically. Most likely, this resulted from partial epimerization during the conversion of hydroxyester (−)-**6** to the corresponding azide due to the acidic nature of the C(5) position[15] and the propensity to produce achiral *o*-quinonedimethide intermediates following in situ activation of the C(12) hydroxyl.

To test this hypothesis and remedy the problem of racemization in our synthesis, we devised an alternate endgame strategy (Scheme 5). Hydroxyester (±)-**6** was reduced to a diol, and the primary alcohol was silylated to furnish hydroxysilane (±)-**17**. This racemic alcohol was then subjected to the oxidative kinetic resolution conditions to provide alcohol (−)-**17** in 47% yield and greater than 99% enantiomeric excess, corresponding to an associated *s*-factor of >47. Conversion of the enantioenriched alcohol (−)-**17** to azide (−)-**18** was straightforward and produced azido alcohol of greater than 99% ee. Azide (−)-**18** was then transformed to the desired secondary lactam (+)-**16** in three simple steps. Importantly, the lactam produced by this new synthetic sequence suffered no loss in optical purity and was converted to amurensinine ((+)-**1**) as a single enantiomer.

In summary, we have developed a convergent and enantioselective synthesis of amurensinine that takes advantage of sequential C−H and C−C bond insertion reactions to build the core structure of the isopavines in a rapid fashion. A palladium-catalyzed enantioselective aerobic oxidation of hydroxysilane (±)-**17** was utilized to generate enantioenriched amurensinine ((+)-**1**). Our work underscores the utility of selective C−H and C−C bond insertion reactions for strategic planning of multistep syntheses and provides the first demonstration of the oxidative kinetic resolution in the context of natural product synthesis. Development and applications of these powerful reactions are ongoing.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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