Natural Products

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Protecting-Group-Free Enantioselective Synthesis of (−)-Pallavicinin and (+)-Neopallavicinin

*Bin Huang, Lei Guo, and Yanxing Jia**

Abstract: *The first enantioselective synthesis of (−)-pallavicinin and (+)-neopallavicinin has been achieved in 15 steps. The described synthesis avoids protecting-group manipulations by synthesis designs predicated on highly chemo- and stereoselective transformations. Highlights of the synthesis include a palladium-catalyzed enantioselective decarboxylative allylation to form the chiral all-carbon quaternary stereocenter, a palladium-catalyzed oxidative cyclization to assemble the [3.2.1]-bicyclic moiety, and an unprecedented LiBHEt$_3$-induced fragmentation/protonation of an α-hydroxy epoxide to form the α-furan ketone with the desired configuration.*

Diterpenoids from liverworts often have interesting biological activities such as antifungal, antimicrobial, cytotoxic, insect antifeedant, insecticidal, and muscle relaxants.[1] (+)-Pallavicinin [(+)-**1**] and (−)-neopallavicinin [(−)-**2**], two structurally complex secolabdane-type diterpenoids, were first isolated by Wu and co-workers from the Taiwanese liverwort *Pallavicinia subciliata*, and then by Lou and co-workers from the Chinese liverwort *Pallavicinia ambigua* (Figure 1).[2,3] (+)-Pallavicinin (**1**), along with other biosynthesis-relative natural products had also been identified from the Japanese liverwort *Pallavicinia subciliata* by Asakawa and co-workers.[4] The absolute configurations of (+)-**1** and (−)-**2** were unambiguously assigned by single-crystal X-ray diffraction and circular dichroism (CD) analyses.[3] Their unique structures feature a novel ladder-shaped/cagelike [6-5-5-5] tetracyclic skeleton bearing seven contiguous stereogenic centers, including an all-carbon quaternary center, and a bridge ring of the left-part bicyclo[3.2.1] moiety. The unique structural features and potential bioactivities of (+)-**1** and (−)-**2** make them attractive targets for total synthesis.[5,6]

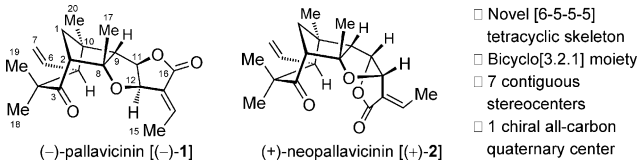
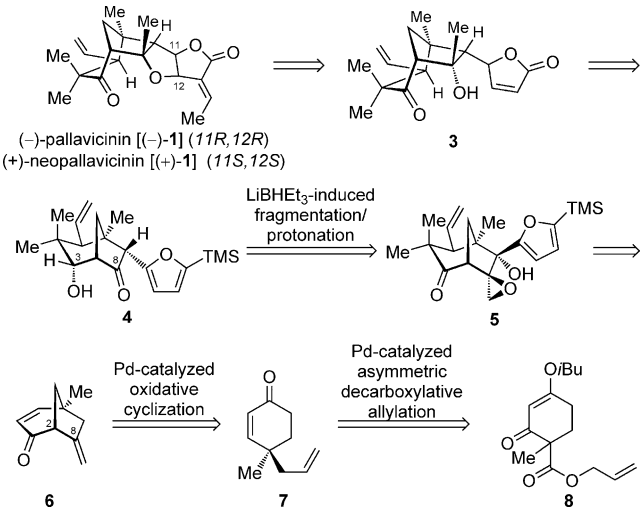


Figure 1. Structures of (−)-pallavicinin (**1**) and (+)-neopallavicinin (**2**).

In this context, the group of Wong reported the first, and thus far, the only total synthesis of (±)-**1** and (±)-**2** in a biomimetic manner from the (±)-Wieland-Miescher ketone in 2006.[5a]

Despite tremendous advances of new methodologies and strategies in organic chemistry, protecting-group-free (PGF) total syntheses of complex natural products still present a highly challenging task.[7,8] As a continuation of our ongoing projects focused on improving the efficiency of complex natural products synthesis,[9] herein we report the first asymmetric total synthesis of (−)-**1** and (+)-**2** without the use of protecting groups. Moreover, an unprecedented LiBHEt$_3$ (super hydride)-induced fragmentation/protonation of an α-hydroxy epoxide was discovered.

Our retrosynthetic analysis of (−)-**1** and (+)-**2** is illustrated in Scheme 1. We envisioned that both (−)-**1** and (+)-**2** could be generated from the lactone **3** by oxa-Michael addition and subsequent aldol condensation. The compound **3** could then be derived from the ketone **4** by nucleophilic methylation of the C8 carbonyl with subsequent peroxy acid oxidation of the furan moiety. The expeditious assembly of **4** with the desired α-C9 configuration of the furan substituent could be derived from the α-hydroxy epoxide **5** by an unprecedented LiBHEt$_3$-induced fragmentation/protonation,



Scheme 1. Retrosynthetic analysis of (−)-**1** and (+)-**2**. TMS = trimethylsilyl.

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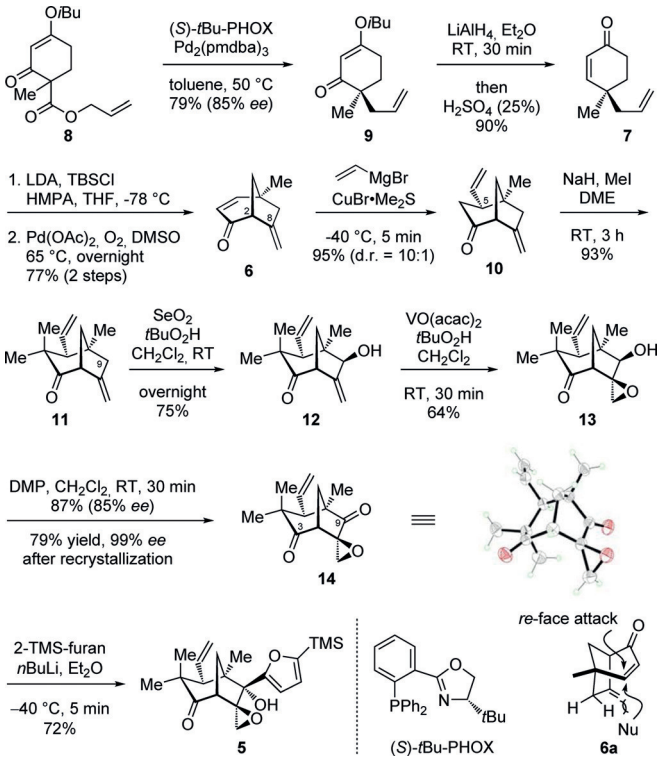
which was serendipitously discovered during attempts to utilize the $LiBHEt_3$-mediated Payne rearrangement of **5**.[10] It was very difficult to install the furan with the α configuration at the C9-position of **4** because the furan moiety is located on the *endo*-face of this concave skeleton, and nucleophilic attack or electrophilic attack would preferentially occur on the less sterically hindered *exo*-face.[6a,11] The epoxide **5** could be accessed from the [3.2.1]bicyclic ketone **6** by functional-group manipulations. Accordingly, the C2–C8 bond of **6** could be assembled by a palladium-catalyzed oxidative cyclization of the known chiral cyclohexenone **7**,[12,13] which has been prepared by a palladium-catalyzed enantioselective decarboxylative allylation of **8**, elegantly developed by Stoltz and co-workers.[14,15]

Our synthesis commenced with the preparation of the chiral cyclohexenone **7** in 85% *ee* following Stoltz's procedure, thus constructing the all-carbon quaternary stereogenic center (Scheme 2).[14a] Treatment of **7** with LDA and TBSCl

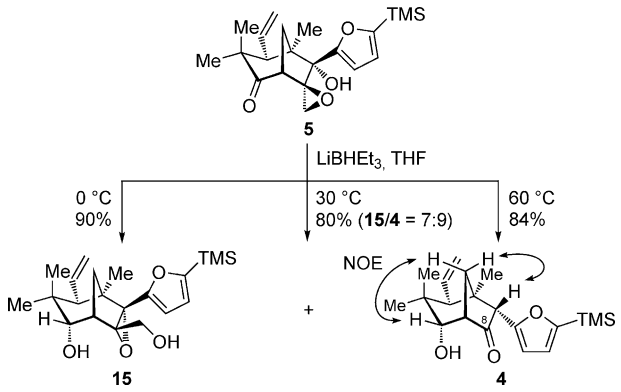


Scheme 2. Synthesis of **5**. LDA = lithium diisopropylamide, TBS = *tert*-butyldimethylsilyl, DME = ethylene glycol dimethyl ether, DMP = Dess–Martin periodinane, DMSO = dimethyl sulfoxide, HMPA = hexamethylphosphoric triamide, THF = tetrahydrofuran, $VO(acac)_2$ = vanadyl acetylacetonate.

led to the corresponding TBS enol ether, which underwent oxidative cyclization upon exposure to a catalytic amount of $Pd(OAc)_2$ under an atmosphere of O_2 to give the desired [3.2.1]bicyclic ketone **6** in 77% overall yield.[14] Conjugate addition of a vinyl group to **6** afforded the ketone **10** with a satisfactory diastereomeric ratio (d.r. = 10:1). The observed high preference for *re*-face attack can be easily explained by the steric hindrance between the allylic hydrogen atom and the nucleophile (**6a** in Scheme 2).[16] Double methylation of **10** produced the desired diene intermediate **11** in 93% yield.

Selective allylic oxidation at C9 of **11** with an excess of $tBuO_2H$ (TBHP) in the presence of a catalytic amount of SeO_2 afforded the corresponding allylic alcohol **12** as the sole stereoisomer (Scheme 2).[17] The hydroxy-directed epoxidation of **12** with $VO(acac)_2$/TBHP furnished the expected epoxide **13** as the only product.[18] The subsequent oxidation of **13** with Dess–Martin periodinane (DMP) provided the diketone **14** in 87% yield, and its structure was confirmed by the X-ray crystallography analysis.[19] Importantly, the optically pure diketone **14** (> 99% *ee*) could be readily obtained after one recrystallization, thus providing a basis for the enantioselective syntheses of (−)-**1** and (+)-**2**. Chemo- and stereoselective addition of trimethylsilyl furan lithium to the C9 carbonyl group of **14** delivered the desired epoxide **5** in 72% yield.[20,21]

With **5** in hand, $LiBHEt_3$-mediated Payne rearrangement was initially tested (Scheme 3). Surprisingly, treatment of **5**



Scheme 3. Unexpected $LiBHEt_3$-induced fragmentation of **5**.

with $LiBHEt_3$ at 30 °C not only afforded the epoxide migration product **15** in 35% yield, but also led to the isolation of an unexpected ketone (**4**) in 45% yield, and it is the key late-stage intermediate in our retrosynthetic design. Further optimizing the reaction conditions showed that **4** could be obtained as the sole product in 84% yield by increasing the reaction temperature to 60 °C. In contrast, decreasing the reaction temperature to 0 °C only gave the epoxide **15** in 90% yield. To the best of our knowledge, this $LiBHEt_3$-induced fragmentation of such α-hydroxy epoxide to the ketone has not been reported previously.[22]

To have preliminary insight on such an unprecedented fragmentation reaction, the epoxide **15**, resulting from the Payne rearrangement was subjected to the reaction conditions ($LiBHEt_3$ at 30 °C or 60 °C), but it did not react to give the desired ketone **4**. This result implied that the rearrangement product **15** was not the exact precursor of the fragmentation reaction. Based on the literature and the above facts, a plausible mechanism for the fragmentation/protonation cascade process is proposed in Scheme 4. Firstly, the ketone moiety on C3 is reduced and the C9 hydroxy group is deprotonated with $LiBHEt_3$ to form the alkoxide anion **A**. When the reaction is run at low temperature, the epoxide

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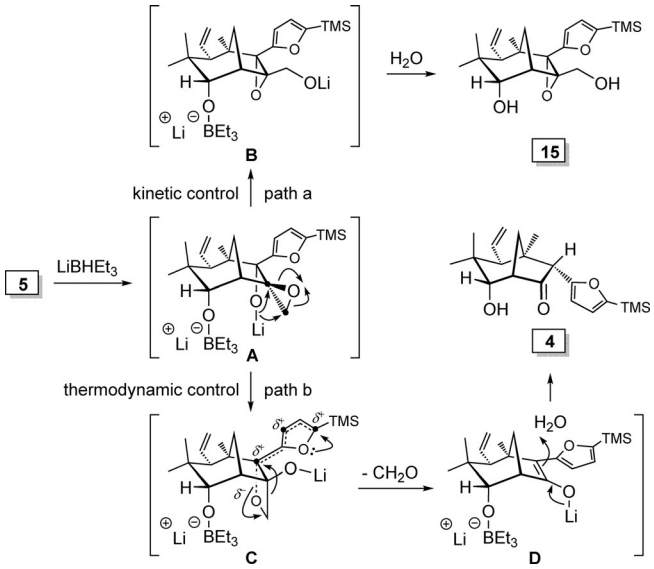
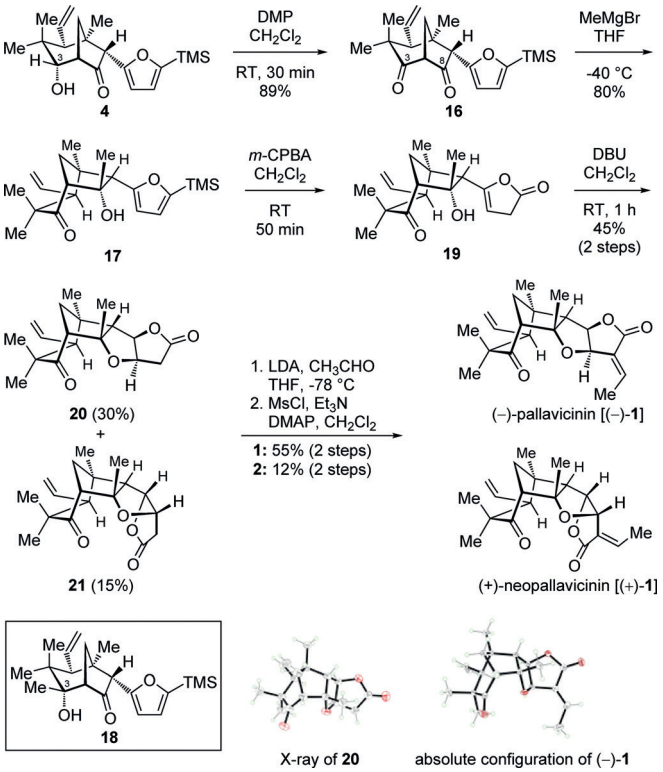


Scheme 4. Proposed mechanism for reaction of **5** with $LiBHEt_3$.

migration is under kinetic control, and Payne rearrangement occurrs to form **15** (path a). When the reaction is run at higher temperature, it is under thermodynamic control and the attack of the alkoxide anion at the less-substituted carbon atom of the epoxide formed the oxetane intermediate **C**,[23] which could readily undergo a fragmentation reaction to generate the enolate **D**. Finally, **D** is quenched with a proton from the less-hindered equatorial face (*exo*-face) of the concave skeleton to produce **4**.

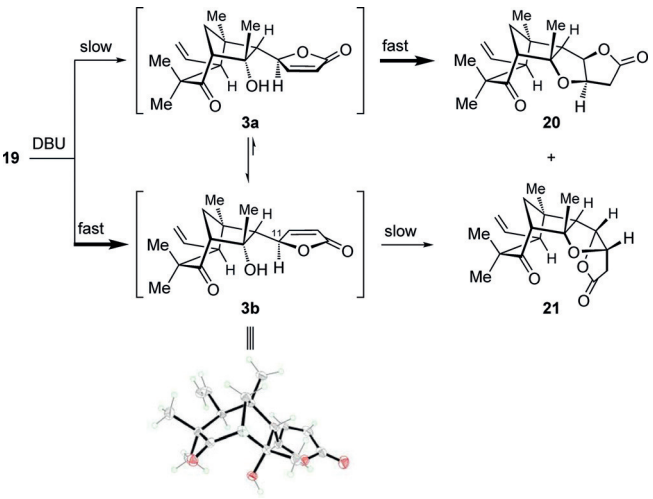
Having set the α configuration of the furan group at C9 of **4**, the completion of the syntheses of (−)-**1** and (+)-**2** is shown in Scheme 5. At this stage, attempts on direct methylation of **4** resulted in the decomposition of the starting material. Dess–Martin oxidation of **4** provided the diketone **16**. To pursue a protecting-group-free route, a challenging chemoselective monomethylation at the C8 carbonyl group of **16** was then examined. Initially methylation using 1.5 equivalents of MeLi in THF yielded the desired product **17** in 40% yield, accompanied by the undesired byproduct **18** in 12% yield, as well as the recovery of starting material **16** in 28% yield.[24] However, **17** and **16** could not be separated by column chromatography. An assortment of reaction conditions with various methylation reagents, solvents, additives, and temperatures were screened (see the Supporting Information), and it was found that reaction of **4** with 5.0 equivalents of MeMgBr in THF at −40 °C (two cycles) afforded the desired **17** in 80% yield.

Epoxidation of **17** with *m*-CPBA gave the unstable β,γ-butenolide **19**, which was subsequently treated with DBU and underwent a base-induced double-bond migration followed by intramolecular oxa-Michael addition to form the key tetracyclic compounds **20** and **21** in 30% and 15% yield, respectively (Scheme 5). Notably, the key intermediate α,β-butenolide **3b**, rather than its C11 epimer **3a**, could be readily isolated in 48% yield after column chromatography, when the reaction was quenched after 5 minutes, and its structure was unequivocally confirmed by X-ray crystallographic analysis



Scheme 5. Completing the total synthesis of (−)-**1** and (+)-**2**. *m*-CPBA = *meta*-chloroperoxybenzoic acid, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl.

(Scheme 6).[19] Further control experiments showed that **3b** could also be completely converted into the products **20** and **21** in 83% overall yield with the same ratio (**20**/**21** = 2:1) by prolonging the reaction time under the aforementioned basic conditions. These results indicated that the undetected intermediate **3a**, which could be formed in situ from a fast equilibration with **3b** in the presence of DBU, quickly underwent a subsequent intramolecular oxa-Michael addition to yield the stereodefined compound **20**.



Scheme 6. Conversion of **19** into **20** and **21**.

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Finally, the aldol reaction of **20** with acetaldehyde followed by treatment of the corresponding adduct with MsCl and Et_3N provided the target molecule (−)-**1** in 55% over two steps, and its absolute configuration was confirmed by X-ray crystallography (Scheme 5).[19] In the same manner, **21** can be transformed into the target molecule (+)-**2**, albeit only in 12% yield. The physical data of our synthesized products (−)-**1** and (+)-**2** are identical to those reported in the literature (see the Supporting Information).[2,3,5a]

In summary, we have accomplished the first asymmetric total synthesis of (−)-**1** and (+)-**2** in 15 steps from the known cyclohexenone **7** without the use of protecting groups. The success of this PGF synthesis was mainly dependent on several highly chemo- and stereoselective reactions. The present synthesis features a palladium-catalyzed enantioselective decarboxylative allylation to form the chiral all-carbon quaternary center, a palladium-catalyzed oxidative cyclization to assemble the [3.2.1]bicyclic moiety, and an unprecedented $LiBHEt_3$-induced fragmentation/protonation of an α-hydroxy epoxide to form the α-furan ketone with the desired configuration.

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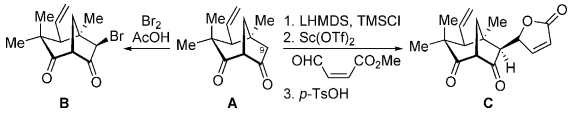

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