A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

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Accepted Article

Title: Enantioselective Total Syntheses of Pallambins A-D

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201907523
Angew. Chem. 10.1002/ange.201907523

Link to VoR: http://dx.doi.org/10.1002/anie.201907523
http://dx.doi.org/10.1002/ange.201907523

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COMMUNICATION

Enantioselective Total Syntheses of Pallambins A-D

Xiwu Zhang, Xinxian Cai, Bin Huang, Lei Guo, Zhongrun Gao, and Yanxing Jia*

Abstract: The first enantioselective total syntheses of pallambins A-D have been achieved in 15 or 16 steps from known chiral cyclohexenone. Salient features of the work include a Pd-catalyzed oxidative cyclization to assemble the [3.2.1]-bicyclic moiety, an Eschenmoser-Claisen rearrangement/lactone formation sequence to construct the C ring, an intramolecular Wittig reaction to form the D ring. The described synthesis avoids protecting-group manipulations by designing highly chemo- and stereoselective transformations. During the course of this work, a Pd-catalyzed method for dehydrobromination of α–bromoketones was developed.

Since 1994, a group of extraordinary complex diterpenes with the common fused furofuranone rings have been isolated and characterized from the liverworts, such as pallavicinin (**1**), neopallavicinin (**2**), and pallambins A-D (**3-6**) (Figure 1A).[1-3] They contain 4-6 congested rings and 7-10 contiguous stereocenters including 1-2 all-carbon quaternary centers, representing formidable challenges for the total synthesis. However, this family of natural products exhibit no significant bioactivity,[2b] perhaps due to their scarce availability from natural sources that has limited their biological evaluation. Thus, the development of concise chemical synthesis of these diterpenoids can improve the availability of these molecules for full biological evaluation.

A plausible biosynthetic pathway for these natural products was proposed by Asakawa (Figure 1A).[3] The cleavage of C7-C8 bond of the labdane-type diterpenoid provides the common precursor **7**. **1** and **2** arise through the reconstruction of C2-C8 bond via an intramolecular aldol reaction. **3** and **4** are formed through demethylation followed by the C4-C8 bond reconstruction. Lou and coworkers have further demonstrated the photoinduced interconversion of **3** and **4** to **5** and **6** through a diradical rearrangement procedure.[2c]

The unprecedented and challenging molecular architectures of **1-6** have attracted considerable attention from synthetic chemists.[4-8] The group of Wong pioneered the first total syntheses of (±)-**1** to (±)-**4** from the Wieland-Miescher ketone.[5a,b] Carreira and coworkers have achieved the first total syntheses of (±)-**5** and (±)-**6** by the use of pentafulvene in an unprecedented Diels-Alder reaction in 2015.[6] In the same year, we have accomplished the first enantioselective syntheses of (−)-**1** and (+)-**2** from the known chiral cyclohexenone **8** (Figure 1B).[7] In 2016, the Baran group reported an elegant approach to (±)-**3** and (±)-**4** without any protecting-group manipulations.[8]

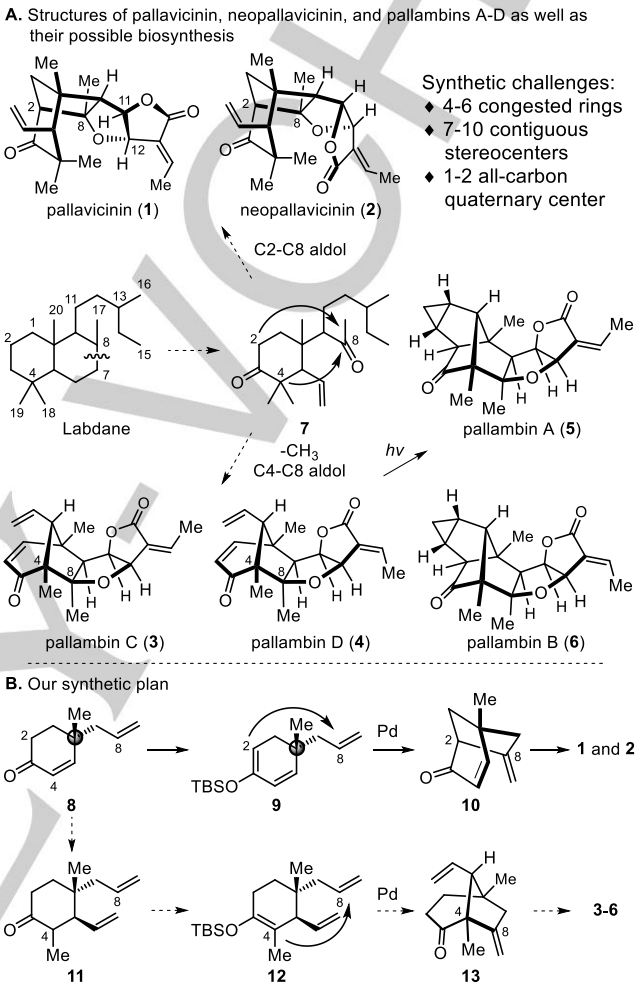

Figure 1. (A) Structures of pallavicinin, neopallavicinin, and pallambins A-D as well as their possible biosynthesis. (B) Our synthetic plan.

Encouraged by our recent success in the total synthesis of (−)-**1** and (+)-**2** from **8** and the aforementioned biogenetic hypothesis, we envisioned that **8** could serve as the common intermediate (corresponding to **7**) for the synthesis of **1-6** (Figure 1). Compound **8** could be easily transformed to **12**, which undergoes a Pd-catalyzed oxidative cyclization to afford the [3.2.1] bicyclic ketone **13**. Ketone **13** could be converted to **3-6** (Figure 1B). Thus, we could achieve the divergent synthesis of **1-6** in a bioinspired manner.[9] Herein we report the first enantioselective total syntheses of pallambins A-D (**3-6**) without the use of protecting groups.

Our retrosynthetic analysis of **3-6** is illustrated in Scheme 1. We envisioned that **5** and **6** could be readily accessed through Lou's photoinduced interconversion of **3** and **4**. In turn, **3** and **4** could be generated from tetracycle **14**, in which BCD three different ring systems are forged featuring three different cyclizations. Thus, D-ring is constructed by an intramolecular Wittig reaction from

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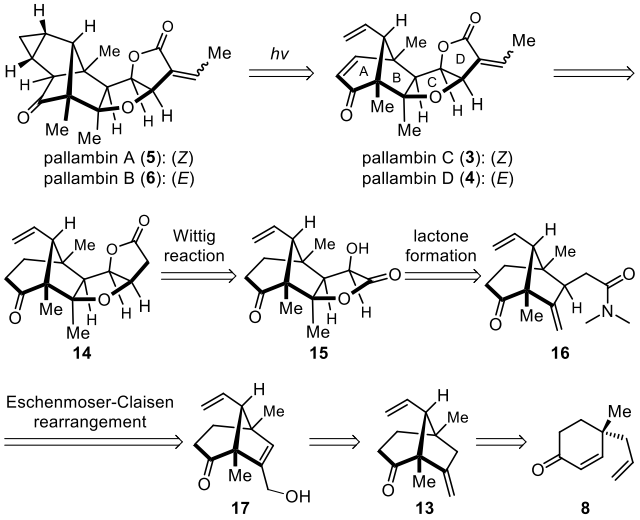
[b] Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

10.1002/anie.201907523

lactone **15**. The C-ring is forged by lactone formation from amide **16**. Amide **16** could be generated via a Claisen rearrangement of the allylic alcohol **17** which could be readily prepared from bicycle **13**. Bicycle **13** could be accessed from **8** (Figure 1B).



Scheme 1. Retrosynthetic analysis of pallambins A-D (**3**-**6**).

Our synthesis commenced with the known chiral **8** which could be readily prepared in 84% *ee* following the Stoltz's procedure (Scheme 2).[10] Conjugate addition of a vinyl group to **8** followed by methylation afforded the ketone **11** with a diastereomeric ratio (*dr*) of 3:1 at C5. Treatment of ketone **11** with Et_3N and TBSCl led to the corresponding thermodynamic TBS enol ether, which was subjected to our optimized Pd-catalyzed oxidative conditions to give the desired bicyclo[3.2.1]octane system **13** in 64% yield.[7] Chemoselective epoxidation of electron-rich double bond of **13** with *m*-CPBA gave the corresponding epoxide, which was subsequently treated with PTSA in the presence of 1,3-dimethylimidazolidin-2-one (**18**) to provide the desired allylic alcohol **17**.[11]

With a robust route to **17**, we focused on the construction of C-ring. Heating **17** and *N,N*-dimethylacetamide dimethyl acetal in toluene at 115 °C afforded the desired γ,δ-unsaturated amide **16** in 88% yield as a single diastereomer.[12] The remarkable stereoselectivity can be easily explained that the Claisen rearrangement would preferentially occur on the less sterically hindered *exo*-face. Treatment of **16** with H_2SO_4 in refluxing ethanol provided lactone **19** in 84% yield.

In order to install the hydroxyl group at C11, the ketone of **19** had to be protected. However, further visual inspection of the molecular models indicated that the free C3 ketone group might not affect the α-hydroxylation due to the sterically congested A/B ring system shielding α-position of C3 ketone group. Therefore, we audaciously opted to introduce the C11 hydroxyl group directly without protection of C3 ketone. After testing several conditions, we found that deprotonation of **19** with 3 equivalents of LiHMDS followed by addition of Davis oxaziridine (**20**) provided the α-hydroxylactone **21** as a single stereoisomer.[13] Owing to the highly constrained caged structure of **19**, the hydroxylation only occurred on the less hindered convex face, syn to the C8 methyl group. This is opposite to the stereochemistry required for the natural products. Thus, the inversion of the configuration of C11 hydroxyl group was performed by an oxidation/reduction strategy. Oxidation of **21** with DMP afforded the corresponding ketolactone which was subsequently underwent a complete chemo- and stereoselective reduction with $LiAlH(Ot\text{-}Bu)_3$ to give the desired alcohol **15** as a single stereoisomer in 99% yield.

With tricycle **15** in hand, the last ring was introduced. Heating **15** with (triphenylphosphoranylidene)ketene in *m*-xylene at 160 °C accomplished the acylation of the α-hydroxyl group and subsequent intramolecular Wittig reaction to afford tetronic ester **22**.[14] It is worth to note that the reaction temperature and the reaction time was critical for the high yield. Higher temperature and longer reaction time resulted in lower yield. Chemo- and stereoselective reduction of the tetronic ester double bond was then pursued. After extensive experimentation, we were delighted to find that reduction of **22** with CuH, generated in suit by reaction of CuI with Red-Al, provided the desired **14** in 94% yield.[15] The structure of **14** was verified by X-ray crystallography.[16]

At this stage, we needed to install C1,C2 double bond;[17] however, it proved exceptionally challenging. The one-step methods for direct dehydrogenation of ketones were investigated firstly. However, oxidation of ketone **14** with IBX,[18] and other methods such as Pd-catalyzed dehydrogenation did not give any **24**.[19,20] Thus, the two-step methods, such as silyl enol ethers/Saegusa reaction,[21] selenoxide and sulfoxide elimination reactions,[22,23] as well as bromination/dehydrobromination, were tested.[24] However, attempts to prepare the corresponding silyl enol ether and to introduce phenylselenide and phenylsulfide also failed. Gratefully, bromination of **14** with $Py{\cdot}HBr_3$ in HOAc gave **23** in 80% yield as a single stereoisomer.[25] Attempts to dehydrobromination of **23** with Li_2CO_3/LiBr, DBU or other bases were screened. The reaction did not occur at low temperature (< 80 °C), and the starting material was decomposed at high temperature (> 80 °C) and no desired product **24** was observed. These results indicated that **23** and(or) **24** might be sensitive to the bases at high temperature. Thus, a mild dehydrobromination method needed to be developed.

Inspired by the mild reaction conditions and reaction mechanism of Pd-catalyzed Heck reaction, we envisioned that oxidative addition of the α–bromoketone **23** to Pd(0) species could give the corresponding alkylpalladium species, which undergoes β–hydride elimination to provide the desired enone **24**. With this idea in mind and after extensive experimentation (the detailed information see SI), we found that treatment of **23** under the optimized conditions ($Pd(OAc)_2$, PPh_3, and Et_3N in DMSO) afforded the desired product **24** in 41% yield and the Heck-type product **25** in 38% yield. Installation of the ethylidene group on **24** provided the target molecule pallambin C (**3**) in 30% yield and pallambin D (**4**) in 51% yield. The physical data of our synthesized products **3** and **4** are identical to those reported in the literature.[1,2,5b,8]

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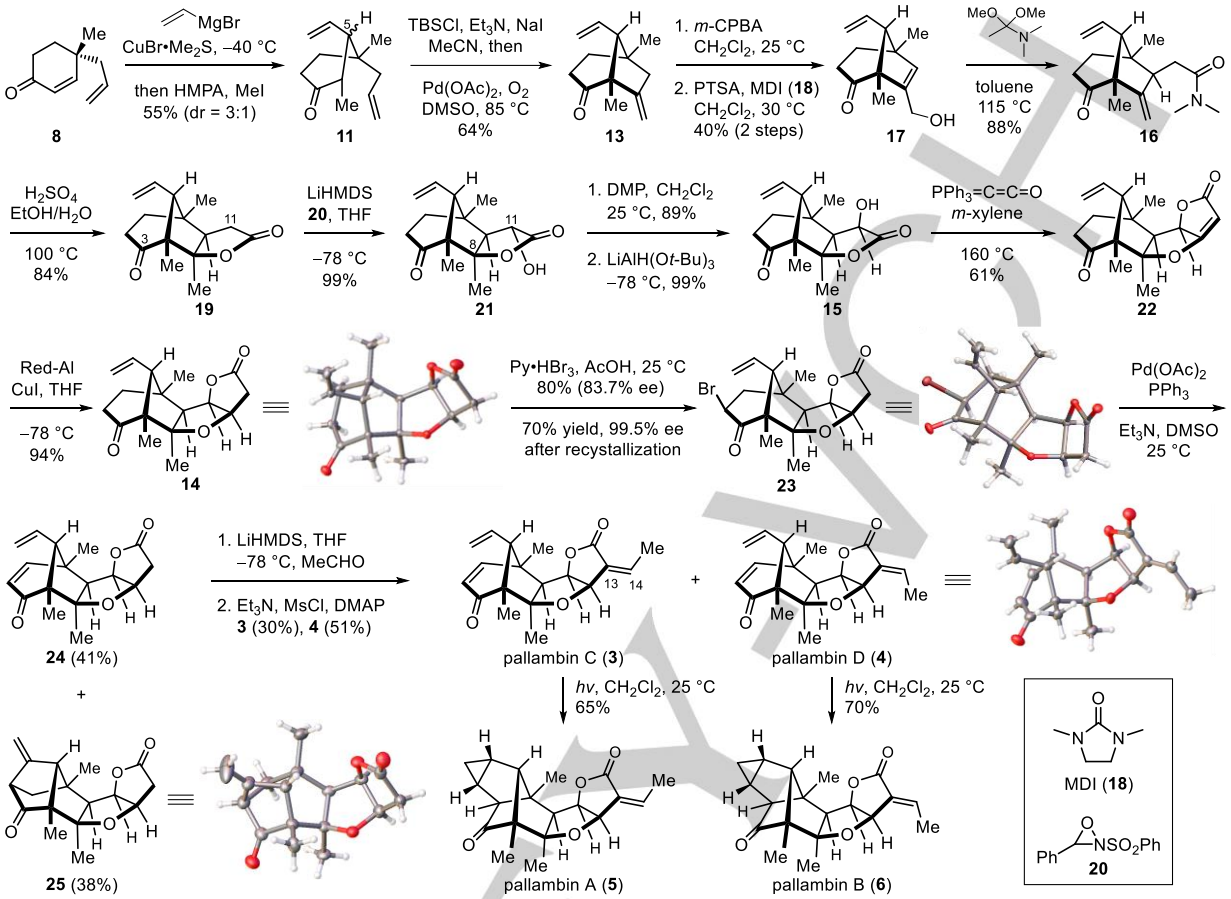
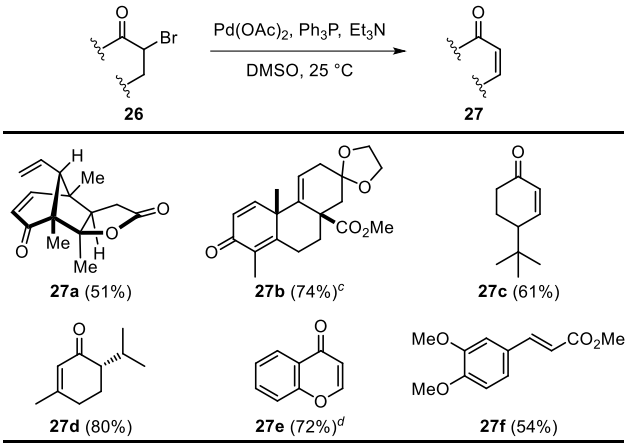


Scheme 2. Total syntheses of pallambins A-D (**3**-**6**). HMPA=hexamethylphosphoric triamide, TBS=*tert*-butyldimethylsilyl, DMSO=dimethyl sulfoxide, *m*-CPBA=*meta*-chloroperoxybenzoic acid, PTSA=*p*-toluenesulfonic acid, LiHMDS=lithium hexamethyldisilazide, THF=tetrahydrofuran, DMP=Dess-Martin periodinane, Red-Al=sodium bis(2-methoxyethoxy)aluminumhydride, Ms = methanesulfonyl, DMAP = 4-dimethylaminopyridine.

Finally, we sought to convert pallambins C (**3**) and D (**4**) to pallambins (**5**) and B (**6**) under UV light according to Lou's research.[2c] Interestingly, we serendipitously discovered that individual irradiation of **3** and **4** under milder conditions (UV lamp, 8W) in CH_2Cl_2 at 25 °C afforded **5** and **6**, respectively, without the *cis/trans* isomerization at $\Delta^{13(14)}$ between **5** and **6** as well as **3** and **4**. This result clearly indicated that the diradical rearrangement require lower energy than the *cis/trans* isomerization at $\Delta^{13(14)}$. The physical data of our synthesized products **5** and **6** are identical to those reported in the literature.[2,6]

As depicted in Table 1, this Pd-catalyzed dehydrobromination method proves to be general. Both cyclic and acyclic systems can be employed as the substrates to give α,β-unsaturated carbonyl compounds. Notably, the Pd-catalyzed enone formation under mild conditions should be valuable to synthetic community, which is difficult to achieve by other means (Supporting Information).

Table 1: Scope of dehydrobromination reaction.[a,b]



[a] Reaction conditions: **26** (0.5 mmol), $Pd(OAc)_2$ (0.15 mmol), PPh_3 (0.30 mmol), Et_3N (2.50 mmol) in DMSO (10 mL). [b] Isolated yield was given. [c] $Pd(OAc)_2$ (0.10 mmol) was used. [d] $Pd(OAc)_2$ (0.05 mmol) was used.

In summary, we have accomplished the first asymmetric total syntheses of pallambins A-D in 15-16 steps from the known cyclohexenone **8** without the use of protecting groups. The success of this protecting-group-free synthesis was mainly dependent on several highly chemo- and stereoselective reactions.[26] The present synthesis features a Pd-catalyzed oxidative cyclization to assemble the [3.2.1]-bicyclic moiety, a Claisen rearrangement/lactone formation sequence to construct the C ring, an intramolecular Wittig reaction to form the D ring. During the course of this work a mild method for dehydrobromination of α–bromoketones was developed.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (21572008) and the Drug Innovation Major Project (Grant No. 2018ZX09711-001-005-005).

Keywords: diterpenoids • palladium • protecting-group-free • total synthesis • natural products

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[16] CCDC 1916457 (**14**), CCDC 1916445 (**23**), CCDC 1917634 (**25**), CCDC 1917633 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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10.1002/anie.201907523

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Layout 2:

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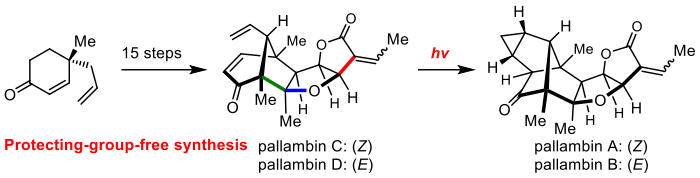

The first enantioselective total syntheses of pallambins A-D has been achieved without the use of protecting groups. Salient features of the work are the formation of three rings via three cyclizations. A palladium-catalyzed method for dehydrobromination of α–bromide ketone was developed.

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