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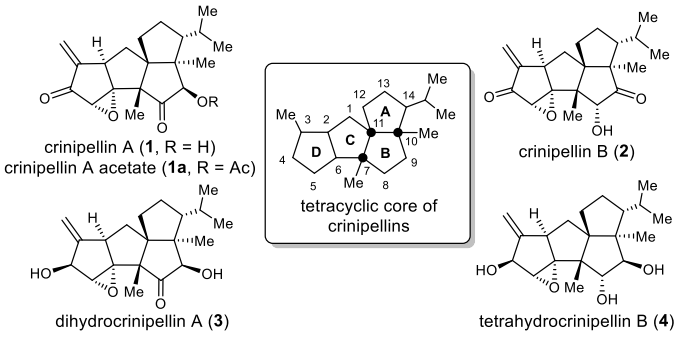
Concise Total Syntheses of Crinipellins Enabled by Co-Mediated and Pd-Catalyzed Intramolecular Pauson–Khand Reactions

Zhihui Huang[+], Jun Huang[+], Yongzheng Qu, Weibin Zhang, Jianxian Gong,* and Zhen Yang*

***Abstract**: Efficient total syntheses of the naturally occurring potent antibiotic compounds (−)-crinipellin A and (−)-crinipellin B are described. The key advanced intermediate, a fully functionalized tetraquinane core, was constructed via a novel thiourea/Pd-catalyzed Pauson–Khand reaction. This intermediate can serve as a common intermediate for the collective total synthesis of other members of the crinipellin family.*

Crinipellin A (1, Fig. 1) is one of several related diterpenoids[1] isolated from the fungus *Crinipellis stipitaria* (Agaricales) by Steglich and co-workers in 1979.[1a] It has an α-methylene ketone motif and a unique tetraquinane core, which bears eight stereogenic centers, of which three are contiguous all-carbon quaternary carbons (C7, C10, and C11).

Figure 1: Selected tetraquinane crinipellins

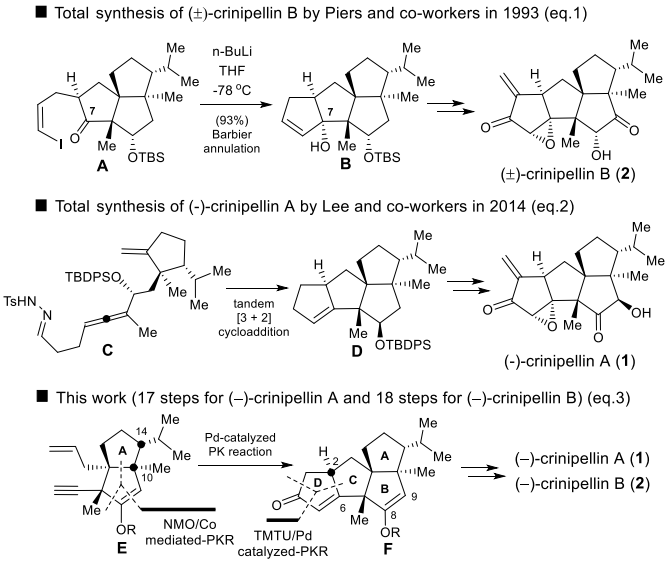


In terms of biological activity, **1** and **2** were originally reported to have antibiotic activities.[1,2] **1a** could completely inhibit the syntheses of DNA, RNA, and proteins in Ehrlich carcinoma cells at a concentration of 5 μg/mL. [1a] The α-methylene ketone motif in crinipellins A and B makes them as potential irreversible probes[3] in the field of drug discovery and chemical biology.

Synthesis of the densely packed array of stereogenic centers in these polyquinanes is a challenge to existing synthetic methods and has inspired the development of new synthetic methods and strategies.[4] The first total synthesis of racemic **2**, in 22 steps, was reported in 1993 by Piers' group; the key step was Barbier annulation[5] (Fig. 2, eq. 1). The first asymmetric total synthesis of **1** was accomplished by Lee's group in 2014, featuring a tandem [3+2] cycloaddition reaction to construct its tetraquinane core bearing three consecutive quaternary stereogenic centers[6] (Fig. 2, eq. 2).

In connection with our development of the Pauson–Khand (PK) reaction[7] as a powerful tool in natural product total synthesis,[8] we identified tetramethylthiourea (TMTU) as an effective ligand in the Co- and Pd-catalyzed PK reactions.[9] Herein we report our recent contribution using the thiourea/Pd-catalyzed PK reaction of enyne **E** as a key step in construction of the crinipellin scaffold **F** bearing the desired C2 stereogenic center. This strategy enabled the asymmetric total syntheses of crinipellin A (**1**) and crinipellin B (**2**) in 17 steps and 18 steps, respectively (Fig. 2, eq. 3).

Figure 2. Key steps for the synthesis of the tetraquinane core of crinipellins



Our synthesis began to stereoselectively construct the key intermediate **F** with the required C2 stereogenic center on its CD ring. Initial efforts focused on preparation of enyne **E**; its synthesis is shown in Scheme 1. Given the rigid, bicyclic nature of intermediate **10**, we expected to achieve diastereoselective installation of the quaternary stereogenic centers at C11 and C7 via an allylation and methylation sequence. We speculated that the synthesis of **10** bearing two *cis*-configured vicinal stereogenic centers at C10 and C14 could be achieved via an intramolecular PK reaction.[10]

Implementation of this approach required the enyne ester **9**, which was prepared via the Trost protocol[11] from known compound (*R*)-4-isopropyl-3-methylcyclohex-2-en-1-one **6**, which was prepared in 4 steps from commercially available 4-isopropyl-3-methylphenol **5**.[12] In the event, **6** underwent a diastereoselective Weitz−Scheffer-type epoxidation, [13] and the resultant ketone **7** was condensed with *p*-$NO_2ArSO_2NHNH_2$ and subsequently treated with $NaHCO_3$ to initiate

[*] Z. Huang[+], Dr. J. Huang[+], Y. Qu, W. Zhang, Prof. Dr. J. Gong, Prof. Dr. Z. Yang
State Key Laboratory of Chemical Oncogenomics, Key Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School, Shenzhen 518055, China
E-mail: gongjx@pku.edu.cn
zyang@pku.edu.cn
Prof. Dr. Z. Yang
Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Beijing National Laboratory for Molecular Science, College of Chemistry and Molecular Engineering, and Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China.
[+] These authors contributed equally to this work.
[**] Supporting information for this article can be found under: http://www.angewandte.org

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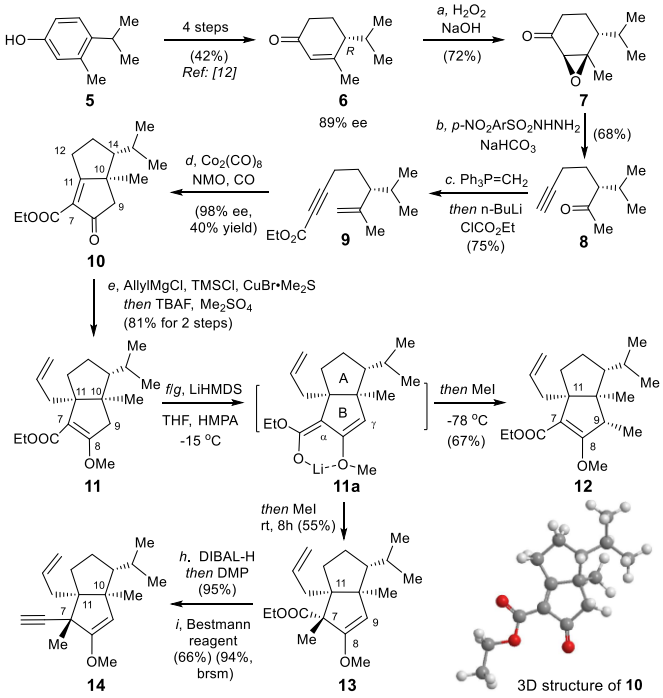
Eschenmoser fragmentation[14] to afford the acetylene ketone **8** in 68% yield. In the preparation of enyne ester **9**, ketone **8** was first subjected to a Wittig reaction, and the resultant enyne, without workup, was directly treated with BuLi and ethyl chloroformate sequentially to afford **9** in 75% yield. This one-pot transformation is essential to ensure a high yield because the intermediate enyne is volatile.

The preparation of enone **10** from enyne ester **9** was attempted via PK reactions in the presence of various metal complexes, namely $Co_2(CO)_8$,[15] $Co_2(CO)_8$/TMTU,[9a] $Mo(CO)_3(DMF)_3$[16] and $[Rh(CO)_2Cl]_2$.[17] However, none of these gave the expected product **10**. After considerable experimentation, we found that by treatment of **9** with a stoichiometric amount of $Co_2(CO)_8$ at room temperature for 1 h followed by gradual heating of the resultant enyne/Co complex to 76 °C in the presence of 4-methylmorpholine *N*-oxide (NMO) for 36 h, product **10** could be obtained in 40% yield with 98% ee after crystallizations. The erosion of ee value presumably occurred during the Wittig reaction. It is worth noting that pre-complexation of **9** with $Co_2(CO)_8$ at room temperature and gradual warming are essential for the desired reaction to occur; formation of the enyne/$Co_2(CO)_8$ complex is difficult because the electron-deficient alkyne is not a good ligand for $Co_2(CO)_8$.[18]

Scheme 1: Synthesis of enyne **14**.[a]



[a]*Reagents and conditions:* a) H_2O_2 (2.0 equiv), NaOH (0.3 equiv), MeOH, 0 °C to rt, 18 h, 72%; (b) *p*-NO_2-$ArSO_2NHNH_2$ (1.05 equiv), $NaHCO_3$ (3.0 equiv), THF, 30 h, -20 °C, 68%; (c) Ph_3PMeBr (2.2 equiv), *t*-BuOK (2.0 equiv), toluene, rt, 5h; then *n*-BuLi (3.5 equiv), ClCOOEt (4.0 equiv), -78 °C to 0 °C, 4 h, 75%; (d) $Co_2(CO)_8$ (1.05 equiv), NMO (3.5 equiv), CO (balloon pressure), DCE, rt to 76 °C, 66%, 69% ee (98% ee, 40% yield after crystallizations); (e) AllylMgCl (1.5 equiv), TMSCl (1.1 equiv), CuBr·Me_2S (1.5 equiv), THF, -78 °C; Me_2SO_4 (4.0 equiv), Cs_2CO_3 (4.0 equiv), 0 °C to rt overnight, then TBAF (0.75 equiv), Me_2SO_4 (4.0 equiv), 2 h, 81%; (f) LiHMDS (4.0 equiv), HMPA, THF, –15 °C, 20 min, then **11** (1 equiv), 1 h; MeI, -78 °C, 4 h, 67%; (g) LiHMDS (4.0 equiv), HMPA, THF, –15 °C, 20 min, then **11** (1.0 equiv), 1 h; MeI, rt, 8 h, **13** (55%), and **12** (18%) ; (h) DIBAL-H (2.5 equiv), DCM, 0 °C, 5 h, then *t*-BuOH (10.0 equiv), then $NaHCO_3$ (10.0 equiv), DMP (3.5 equiv), 0 °C, 3h, 95%; (i) Bestmann reagent (2.5 equiv), K_2CO_3 (5.0 equiv), MeOH, rt, 48 h, 66% (94% brsm).

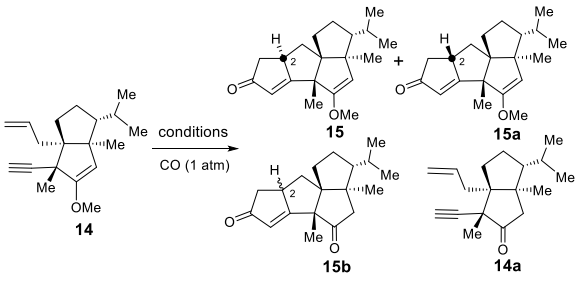
Having successfully implemented the PK reaction for the stereoselective synthesis of ketoester **10**, we next installed the two vicinal quaternary stereogenic centers at C7 and C11 in **13** (Scheme 1).

Ketoester **10** was reacted with an organocopper reagent (derived from allylmagnesium chloride and CuBr·Me_2S[19]) at −78 °C to give a highly diastereoselective conjugate addition reaction, and the resultant enolate was reacted with Me_2SO_4 in the presence of Cs_2CO_3 and tetrabutylammonium fluoride (TBAF) [20] to afford methyl vinyl ether **11** as a single isomer in 81% yield. This established the two all-carbon quaternary stereogenic centers at the ring junction.

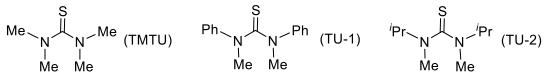
We next focused on synthesis of the key intermediate **13** via regio- and stereoselective installation of its C7 quaternary center.

Initially, we used Miyashita's procedure.[21] A THF solution of LHMDS was added to HMPA at −15 °C, followed by addition of a THF solution of **11**. The resultant enolate was reacted with MeI at room temperature, the expected product **13** was obtained in 55% yield, together with **12** in 18% yield. However, when we performed the reaction by treating the generated enolate with MeI at −78 °C, product **12** was obtained as the sole product in 67% yield. This regioselectivity depended on temperature, presumably because the enolate configuration was affected significantly by the reaction temperature, and a Curtin-Hammett situation was observed. [22] The enolate **11a** would form as 6-membered Li-chelated complex at low temperature, in which the α-position was sterically more congested than the γ-position. However, the enolate **11a** would stay chelated and unchelated at higher temperature, and the later would be more reactive at α-position. Reduction of ester **13** with DIBAL-H, followed by oxidation with the Dess–Martin reagent and reaction with the Bestmann reagent,[23] gave enyne **14** in 66% yield.

Table 1: Screening of conditions for the intramolecular PK reactions[a]



entry	conditions	yield (%)[b] 15	15a	15b	14a
1	$Co_2(CO)_8$ (10 mol%), TMTU (60 mol%) PhMe, 60 °C, 12 h	21	42		
2	$[Rh(CO)_2Cl]_2$ (10 mol%), DCE, 60 °C, 12 h,		45		
3	$[Rh(CO)_2Cl]_2$ (10 mol%), *t*-Bu_2O, 130 °C, 12 h,	6	30		
4	[RhCl(dppp)] (10 mol%), *t*-Bu_2O, 130 °C, 12 h,	trace	trace		
5	$PdCl_2$ (20 mol%), TMTU (20 mol%) THF, 50 °C, 50 h	trace	trace		
6	$PdCl_2$ (20 mol%), LiCl (1.2 eq), THF, 50 h, 50 °C				50
7	$PdCl_2(CH_3CN)_2$ (20 mol%), LiCl (1.2 eq) THF, 50 h, 50 °C			30	20
8	$PdCl_2$ (20 mol%), TMTU (20 mol%) LiCl (1.2 eq), THF, 50 °C, 50 h	30	20		
9	$PdCl_2$ (10 mol%), TU-1 (11 mol%) THF, 42 h, 50 °C	29	7	40	
10	$PdCl_2$ (30 mol%), TU-1 (33 mol%) THF, 18 h, 50 °C	14	2	17	30
11	$PdCl_2$ (10 mol%), TU-2 (10 mol%) THF, 18 h, 50 °C	10	8		
12	$PdCl_2$ (30 mol%), TU-1 (30 mol%) Na_2CO_3 (1.0 eq.), THF, 36 h, 50 °C	49	16		
13	$PdCl_2$ (30 mol%), TU-1 (30 mol%) $NaHCO_3$, THF, 36 h, 50 °C	61	16		



[a] [**14**] = 0.01 ~ 0.05 M. [b]Isolated yield after flash chromatography.

With enyne **14** in hand, we investigated the PK reaction for the construction of tetraquinane **15** (Table 1). Initially, enyne **14** was added to toluene solution of Co–TMTU catalyst, which was prepared

in situ by mixing $Co_2(CO)_8$ and TMTU.[9a] The resultant mixture was stirred at 60 °C under a balloon pressure of CO for 12 h. Product **15** was obtained in 21% yield, together with its undesired isomer **15a** in 42% yield (entry 1). Treatment of enyne **14** with Rh catalysts[17] under a balloon pressure of CO gave **15a** as the major product (entries 2–3).

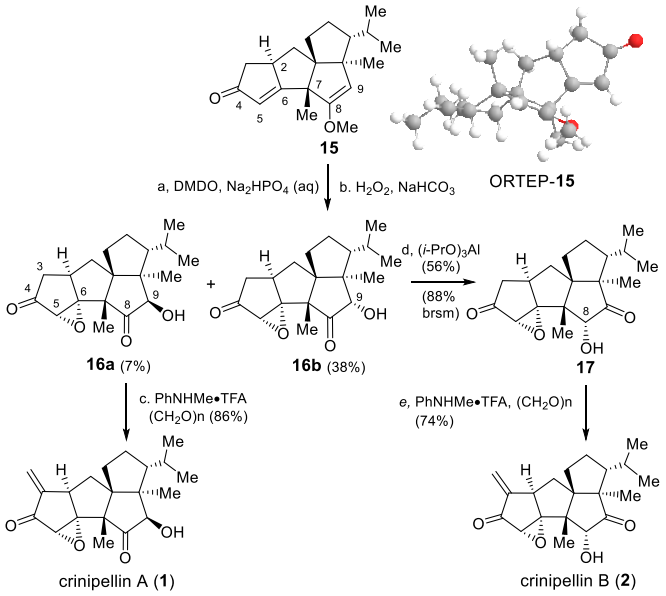
We then turned our attention to the Pd-catalyzed PK reaction. When the reaction was performed with enyne **14** in the presence of TMTU–$PdCl_2$ catalyst,[9b] which was prepared in situ by mixing $PdCl_2$ and TMTU in THF (entry 5), only trace amounts of the annulated products **15** and **15a** were observed after reaction under a balloon pressure of CO at 50 °C for 50 h.

Knowing the Pd-catalyzed PK reaction could be accelerated by addition of LiCl,[24] we decided to run the reactions in the presence of LiCl. In the event, the reaction was carried out the presence of $PdCl_2$, $PdCl_2(CH_3CN)_2$ as the catalysts (entries 6-8). To out delight, when the reaction was carried out in the presence of TMTU, the desired product **15** was obtained in 30% yield, together with its C2 diastereoisomer **15a** in 20% yield (entry 8).

Realizing the importance of the thiourea ligand in the annulation, we then ran the reaction in the presence of thioureas bearing phenyl and isopropyl substituents (entries 9–11). However, under these reaction conditions, the yields of products **15** and **15a** were significantly lower, and significant amounts of products **15b** and **14a** were formed in two cases because of hydrolysis of their enol ether moieties. Notably, the application of TU-1 ligand[25] could dramatically improve the diastereoselectivity (entries 9 and 10). We then performed the reactions in the presence of bases, namely Na_2CO_3 and $NaHCO_3$ (entries 12 and 13). The yield of the desired product **15** increased to 61%, and its C2 isomer **15a** was obtained in 16% yield, when $NaHCO_3$ was used (entry 13). The relative stereochemistry of compound **15** was unambiguously confirmed by X-ray crystallographic analysis.

With compound **15** in hand, we then investigated its elaboration for the syntheses of crinipellins A (**1**) and B (**2**) (Scheme 2).

Scheme 2: Total syntheses of crinipellins A (**1**) and B (**2**).



[a]Reagents and conditions: (a) **15** (1.0 equiv), DMDO (3.5 equiv), Na_2HPO_4 (1.07 equiv), acetone, rt, 21 h; (b) H_2O_2 (15 equiv), $NaHCO_3$ (10 equiv), THF/H_2O, rt, 40 min; **16a**, 7% for 2 steps; **16b**, 38% for 2 steps; (c) PhNHMe·TFA (5.0 equiv), $(CH_2O)_n$ (30 equiv), THF, 70°C, 4 h, 86%; (d) (*i*-PrO)$_3$Al (1.05 equiv), PhMe, rt, 42 min, 56%, (88% brsm); (c) PhNHMe·TFA (5.0 equiv), $(CH_2O)_n$ (30 equiv), THF, 70°C, 4 h, 74%.

Sequential treatment of **15** with dimethyldioxirane (DMDO) in a Na_2HPO_4 solution[26] and H_2O_2/$NaHCO_3$ gave epoxides **16a** and **16b** in 7% and 38% yields, respectively. The transformation proceeded via a sequence of reactions, namely a DMDO-mediated regioselective epoxidation at the C8–C9 double bond,[27] vinyl ether epoxide hydrolysis,[28] and a substrate stereoselective Weitz−Scheffer-type epoxidation. It is worth noting that Weitz−Scheffer-type epoxidation did not occur without the directed carbonyl group[29] at C8.

Compound **16a** has all the essential functional groups of crinipellin A (**1**) except the methylene group at C3, therefore we performed a modified Eschenmoser methylenation by reaction of **16a** with N-methylanilinium trifluoroacetate and paraformaldehyde in THF at 70 °C to give crinipellin A (**1**) in 86% yield. ^{1}H NMR, ^{13}C NMR and optical rotation data of synthetic **1** were in good agreement to those reported in the literature.[2a]

We next explored the total synthesis of crinipellin B (**2**) from **16b**. We envisaged that the thermodynamic stable compound **17** could be synthesized from **16b** via isomerization[30] of its α-hydroxy ketone moiety. Attempts to isomerize **16b** to **17** by treatment with various acidic and basic reagents, i.e., $MgBr_2$, $Al(Me)_3$, silica gel, HCl, KO^{t}Bu, and KOH, were unsuccessful. None of them afforded the desired isomerized product **17** and in most cases **16b** decomposed. We eventually achieved the proposed isomerization by treatment of **16b** with Al(^{i}PrO)$_3$ in toluene at room temperature for 42 min (desired product **17** would be decomposed dramatically when the reaction time was prolonged); **17** bearing the desired C8 stereogenic center was obtained as a single isomer in 56% yield (88%, brsm). Further treatment of **17** with N-methylanilinium trifluoroacetate and paraformaldehyde in THF at 70 °C, the natural product crinipellin B (**2**) was afforded in 74% yield. The structure of **2** was confirmed by comparison of its spectra (^{1}H NMR and ^{13}C NMR) and optical rotation data with those reported in the literature.[2a, 5]

In summary, we achieved the asymmetric total syntheses of (−)-crinipellin A (**1**) and (−)-crinipellin B (**2**) in 17 and 18 steps from the commercially available phenol **5**. The key features of our synthesis include use of our developed thiourea/Pd-catalyzed intramolecular PK reaction for diastereoselective construction of the tetraquinane core of the naturally occurring crinipellins. Tactical adjustments of substituents and functionalities will enable the protocol developed here to be used to synthesize tetraquinane cores with various substituents, therefore this strategy will be useful in the collective synthesis[31] of analogs of crinipellins.

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Natural Products

Zhihui Huang[+], Jun Huang[+], Yongzheng Qu, Weibin Zhang, Jianxian Gong, and Zhen Yang**

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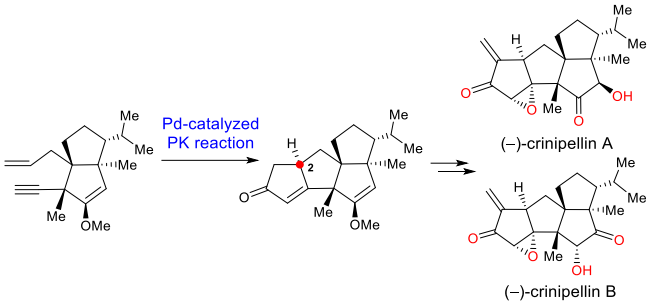
Concise Total Syntheses of Crinipellins Enabled by Co-Mediated and Pd-Catalyzed Intramolecular Pauson–Khand Reactions



Efficient total syntheses of the naturally occurring potent antibiotic compounds (−)-crinipellin A and (−)-crinipellin B are described. The key advanced intermediate, a highly functionalized tetraquinane core, was constructed via a novel thiourea/Pd-catalyzed Pauson–Khand reaction. This intermediate can serve as a common intermediate for the collective total synthesis of other members of the crinipellin family.