Accepted Manuscript

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PII: S0040-4020(17)30329-0

DOI: 10.1016/j.tet.2017.03.072

Reference: TET 28578

To appear in: *Tetrahedron*

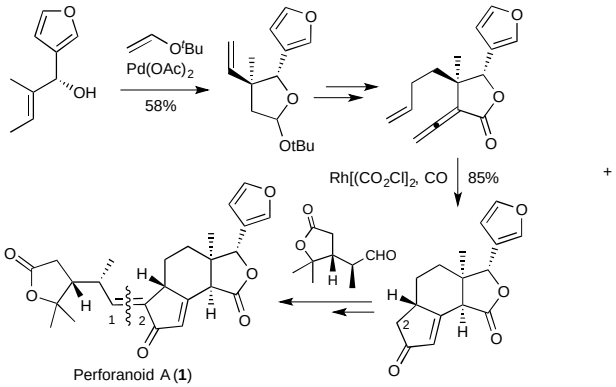
Received Date: 30 January 2017

Revised Date: 24 March 2017

Accepted Date: 26 March 2017

Please cite this article as: Lv C, Tu Q, Gong J, Hao X, Yang Z, Asymmetric total synthesis of (-)-perforanoid A, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.03.072.

Graphic abstract



Graphical Abstract

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Asymmetric Total Synthesis of (-)-Perforanoid A

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Tetrahedron
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
(-)-Perforanoid A
Lemonoids
Asymmetric total synthesis
Rhodium catalyzed
Intramolecular Pauson-Khand

ABSTRACT

Asymmetric total synthesis of (−)-perforanoid A, a novel limonoid isolated from the leaves of *Harrisonia perforata*, has been achieved. The key features of our total synthesis include the Rh-catalyzed intramolecular Pauson–Khand reaction of an allene and an alkene, the Pd-catalyzed lactonization of an allylic alcohol with a vinyl ether, and the enantioselective alkenylation of 3-furaldehyde.

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1. Introduction

The synthesis of natural products with interesting biological activity but low abundance in natural sources remains an important area of research in chemistry, chemical biology, and drug discovery.[1] In this context, the limonoids represent an important family of natural products that exhibit structural diversity and a broad spectrum of biological activities.[2] They have applications in agriculture and medicine as a result of their anti-feedent,[2] anti-multi-drug resistance (MDR) bacteria,[3] antimalarial,[4] anti-cancer,[5] and anti-leukemia[6] properties.

While isolating the limonoids from species of the Meliaceae and Simaroubaceae families in southern China, we isolated a group of ring-demolished imonoids, featuring a polycyclic lactone fragment (**1–3** in Figure 1)[7]. Perforanoid A (**1**), which is a novel type of limonoid, was isolated from the dried leaves of *Harrisonia perforata* (Blanco) Merr. of the Simaroubaceae family and is characterized by its fused bicyclic γ-lactone subunit. Structurally, perforanoid A consists of five rings, which contain six stereogenic centers; among these is an all-carbon quaternary chiral center (C13). The structural novelty of this compound and its cytotoxic activity against tumor cell lines (HEL, K562, CB3) render perforanoid A a compelling target for total synthesis..

From a synthetic point of view, we sought to design a unified strategy to enable the total synthesis of perforanoid A, and anticipated that the developed chemistry could also be used to synthesize other limonoids, such as haperforin G (**2**) and harrpemoid B (**3**). In a previous paper,[8] we presented our concise strategy for the construction of perforanoid A (**1**) using a Pauson–Khand reaction as a key step. This strategy enabled the total synthesis of perforanoid A to be achieved in 10 linear steps. In this full paper, we describe the details of our efforts that led to the asymmetric total synthesis of (−)-perforanoid A, which paves the way for the total synthesis of the other liminoid family members.

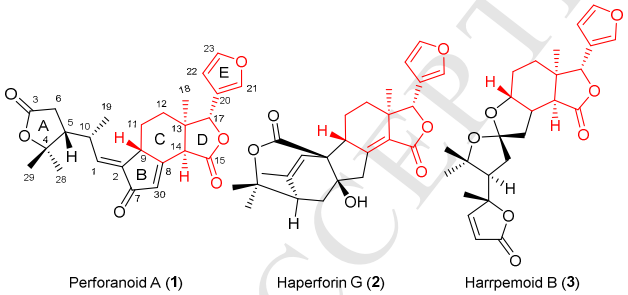
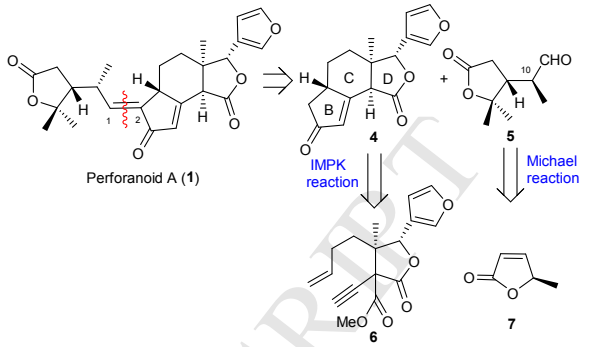


Fig. 1. Representitive liminoids from *Harrisonia perforate*.

2. Retrosynthetic analylisis

Retrosynthetically, perforanoid A (**1**) can be divided into two major pieces, **4** (right fragment) and **5** (left fragment), which could be combined in an aldol condensation. Right ketoester fragment **4**, which contains the BCD tricyclic core of perforanoid A (**1**) could in turn be constructed from enyne **6** in an intramolecular Pauson–Khand (IMPK) reaction, a powerful instrument used in the total synthesis of complex natural products.[9] The γ-lactone side chain (A ring) in left fragment **5** could be generated from known optically pure butenolide **7** through a Michael reaction.[10]

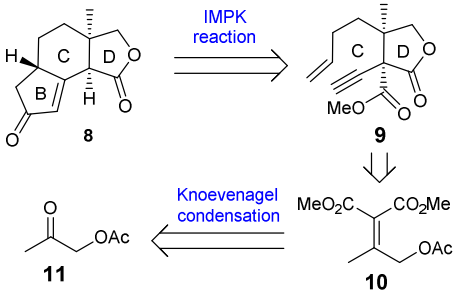
Scheme 1. Retrosynthetic analysis for perforanoid A.



3. Model study

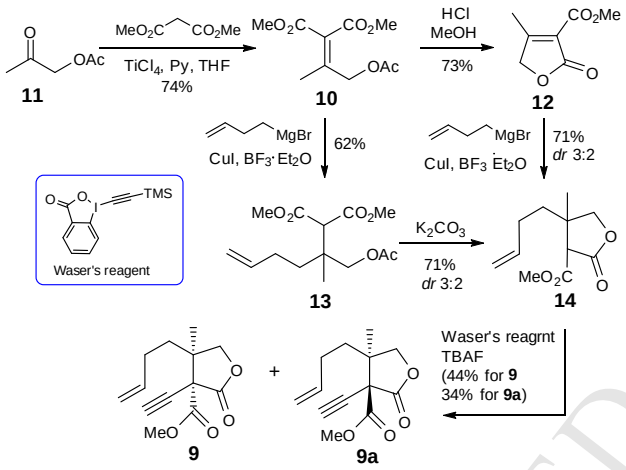
To explore the synthetic feasibility of the proposed IMPK reaction, compound **8**, which bears the BCD ring system of perforanoid A (**1**), was chosen as a synthetic model. Scheme 2 illustrates our retrosynthetic analysis of **8**. We envisaged that **8** could be assembled from enyne **9** by an IMPK reaction followed by a decarboxylation.[11] In 2010, Waser's group reported the ethynylation of keto, cyano, and nitro esters using Waser's reagent ([(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one, TMS-EBX). We envisioned that enyne **9** could be accessed from diester **10** by sequential Michael addition,[12] intramolecular lactonization, and Waser's ethynylation.[13] Ester **10** could in turn be prepared from ketone **11** and dimethyl malonate in a Knoevenagel reaction.[14]

Scheme 2. Retrosynthetic analysis for model compound **8**.



Scheme 3 illustrates the synthesis of key intermediate **9**. The synthesis commenced with a $TiCl_4$-mediated Knoevenagel

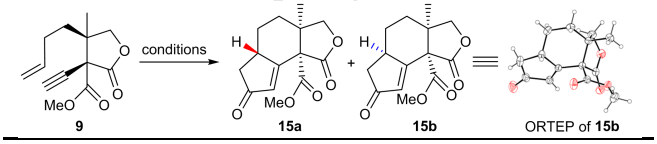
reaction of ketone **11** with dimethyl malonate in THF to afford α,β-unsaturated ester **10** in 74% yield. With compound **10** in hand, we then adopted two protocols for the synthesis of lactone **14**. Substrate **10** was converted to corresponding lactone **12** by treatment with HCl in MeOH, followed by reaction with but-3-enylmagnesium bromide in the presence of CuI and BF_3•Et_2O to give **14** in 71% yield as a pair of diastereoisomers in a ratio of 3/2. Alternatively, product **14** could also be prepared by reaction of **10** with but-3-enylmagnesium bromide in the presence of CuI and BF_3•Et_2O to give diester **13**, which was then treated with K_2CO_3 to afford lactone **14** in 44% yield in two steps as a pair of diastereoisomers in a ratio of 3/2. It is worth mentioning that BF_3•Et_2O was more effective than other Lewis acids (such as $TiCl_4$, TMSCl, and $AlCl_3$) as an additive in the Michael reaction, and that in the absence of a Lewis acid, the addition product was not observed.[12]



Scheme 3. Synthesis of key intermediate **9**.

We then worked on the synthesis of compounds **9** and **9a**. To this end, lactone **14** was directly reacted as a pair of diastereisomers with Waser's reagent in the presence of tetrabutylammonium fluoride (TBAF), and resultant enynes **9** and **9a** could be separated by flash chromatography on silica gel to give **9** and **9a** in 44% and 34% yield, respectively.

Table 1. Optimization results of the Pauson-Khand reaction.



entry	solvents	additive	T(°C)	results[a]
1	PhMe	-	80	**15a** (5.7%)+**15b** (4.3%)
2	PhMe	-	95	**15a** (14.1%)+**15b** (10.9%)
3	PhMe	-	110	**15a** (16.8%)+**16b** (11.2%)
4	THF	-	reflux	NR
5	CH_3CN	-	reflux	NR
6	Benzene	-	reflux	NR
7	PhMe	NMO	110	**15a** (19.6%)+**15b** (5.4%)
8	PhMe	TMAMO	110	**15a** (10%)+**15b** (5%)
9	PhMe	Me_2S	110	**15a** (21.4%)+**15b**(8.6%)
10	PhMe	TMTU	110	trace

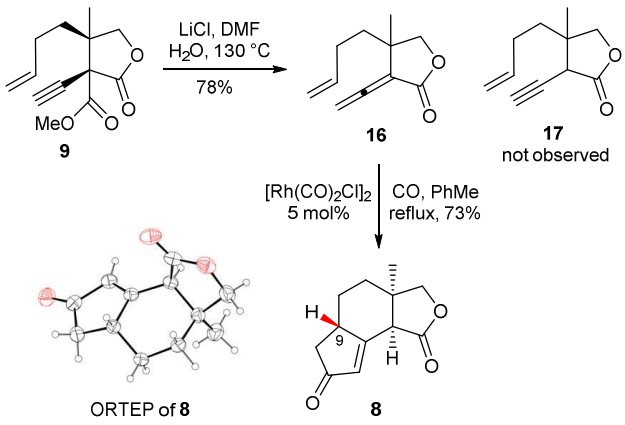
[a] Isolated yield.

With substrates **9** and **9a** in hand, we began to investigate the Pauson–Khand reactions. Initially, we carried out the reaction in the presence of a stoichiometric amount of $Co_2(CO)_8$ in toluene at 80 °C, and expected products **15a** and **15b** were obtained in yields of 5.7% and 4.3%, respectively (Table 1, entry 1). To improve the yields, we performed the reaction at a higher temperature, and the yields increased to 16.8% and 11.2%, respectively (entry 3). We also attempted to improve the outcome by changing the reaction solvent from toluene to THF, acetonitrile, and benzene; however, none of these solvents gave the expected products (entries 4–6). The structure of **15a** was confirmed by NOESY experiments, and that of **15b** was confirmed by X-ray crystallographic analysis. Thus, the relative stereochemistry of **15a** was in agreement with that of the natural product perforanoid A (**1**).

To further improve the yield, we next added additives to the annulation. However, no significant improvement was observed when Me_2S, *N*-methylmorpholine-*N*-oxide (NMO), trimethylamine-*N*-oxide (TMANO), or tetramethyl thiourea (TMTU) (entries 7–10) were added.[15]

We reasoned that the quaternary carbon center in the substrate might provide steric hindrance that could interfere with the desired annulation. We therefore decided to remove the ester group from its quaternary center. To this end, we treated lactone **9** with LiCl in the presence of water in DMF at 130 °C. To our surprise, expected enyne **17** was not obtained; however, allene **16** was obtained in 78% yield. Thus, under similar conditions, **9a** was also converted to **16** (Scheme 4).

Scheme 4. Synthesis of model compound **8**.



In 2006, Mukai and co-workers reported rhodium-catalyzed Pauson–Khand reactions of allenenes for the formation of bicyclo[4.3.0]non-1(9)-en-8-ones,[16] and applied the method in the total synthesis of sesquiterpene-based natural products.[16b] Inspired by this chemistry, we attempted to adopt this protocol

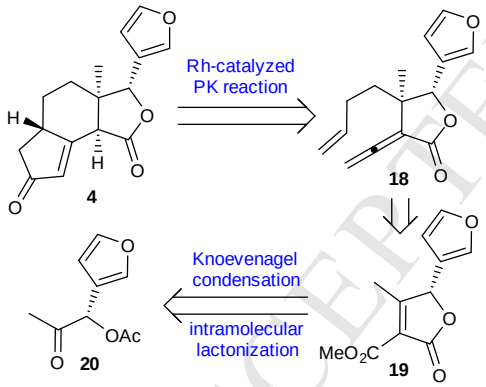
for the formation of enone **8** from allene **16**. When we treated allene **16** with $[Rh(CO)(dppp)Cl]_2$ (5 mol%) in refluxing toluene under a balloon pressure of CO, enone **8**, which has the desired stereochemistry at C9, was formed in 50% yield as a single isomer,[16b] and its stereochemistry was confirmed by X-ray crystallographic analysis. To further improve the yield, we tested other rhodium catalysts, such as $[Rh(CO)_2Cl]_2$, $[Rh(CO)(dppp)Cl]_2$, $[Rh(CO)(dppe)Cl]_2$, and found that enone 8 could be obtained in 73% yield when $[RhCl(cod)]_2$ was used as the catalyst in refluxing toluene under a balloon pressure of CO.

4. First-Generation for the synthesis of right fragment

Having established a way to construct the BCD tricyclic ring system of perforanoid A (**1**), we decided to apply it to the synthesis of the right fragment (BCDE ring system) of **1**.

As illustrated in Scheme 5, enone motif **4** was expected to be obtained from the Rh-catalyzed IMPK reaction of allenene **18**, which, in turn, could be prepared from α,β-unsaturated ester **19** through Michael addition, alkynylation, and decarboxylation. The relative stereochemistry of the methyl group and the furyl ring in **4** could be controlled by the chirality of the furyl ring, to make the nucleophile approach the α,β-unsaturated ester from the back of the furyl ring. Thus, our retrosynthetic analysis leads back to the formation of α,β-unsaturated ester **19**, which, in turn, is expected to be formed through a Knoevenagel reaction of ketone **20** followed by intramolecular lactonization.

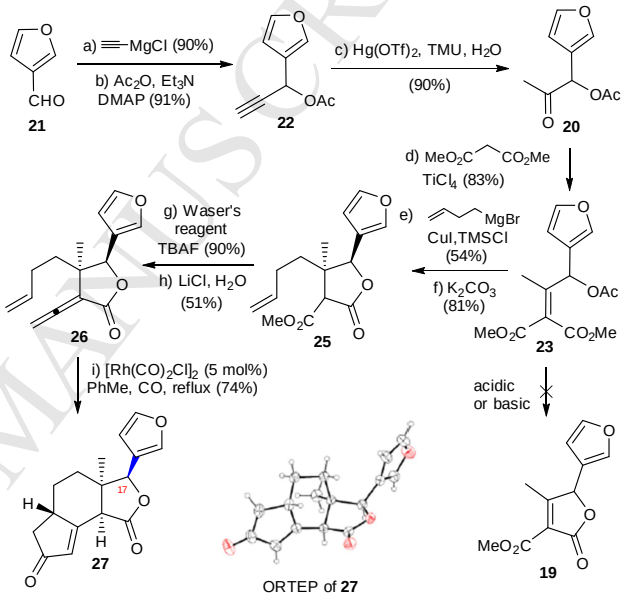
Scheme 5. First-generation retrosynthetic analysis of right fragment.



Scheme 6 shows our synthesis of compound **27**. Commercially available furan-3-carbaldehyde **21** was reacted with ethynylmagnesium chloride to generate the alcohol, which was then converted into acetate **22** in 82% yield in two steps. Further treatment of **22** with H_2O in the presence of a catalytic amount of $Hg(OTf)_2$-TMU afforded ketone **20**, which in turn underwent a $TiCl_4$-mediated condensation to give **23** in 75% yield in two steps.

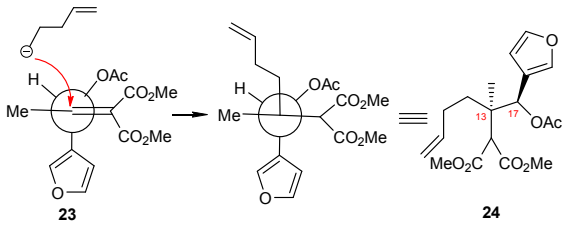
With **23** in hand, we then proceeded to prepare lactone **19** through an intramolecular lactonization. Initially, we treated **23** with various acids or bases; however, lactone **19** was not formed, presumably because of the double bond in substrate **23** which prevented the lactonization. We therefore treated ester **23** with but-3-enylmagnesium bromide in the presence of CuI-TMSCl, and the expected lactonization of resultant dimethyl malonate **24** proceeded to afford **25** in 44% yield in two steps. It is worth mentioning that TMSCl was effective as a Lewis acid additive in the Michael reaction, but other Lewis acids (such as BF_3•Et_2O, $TiCl_4$, and $AlCl_3$) failed to give the desired product.[12]

Scheme 6. Synthesis of **27**.



To complete the synthesis of **27**, ester **25** was first reacted with Waser's reagent in the presence of TBAF, and the resultant enyne was then subjected to decarboxylation by treatment with LiCl–H_2O in DMF at 130 °C to give allenene **26** in 46% overall yield. Thus, under the optimized IMPK reaction conditions, allenene **26** was treated with $[RhCl(CO)_2]_2$ (5 mol%) under a balloon pressure of CO at 120 °C in toluene to give enone **27** in 74% yield as a single isomer. However, X-ray crystallographic analysis revealed that the stereochemistry at C17 in enone **27** was opposite to the desired stereochemistry. To account for this observation, we built a Felkin–Ahn model,[17] which indicated that the nucleophile approached the α,β-unsaturated double bond in ester **23** from the less hindered side. As a result, ester **24** was generated as the major product (Scheme 7).

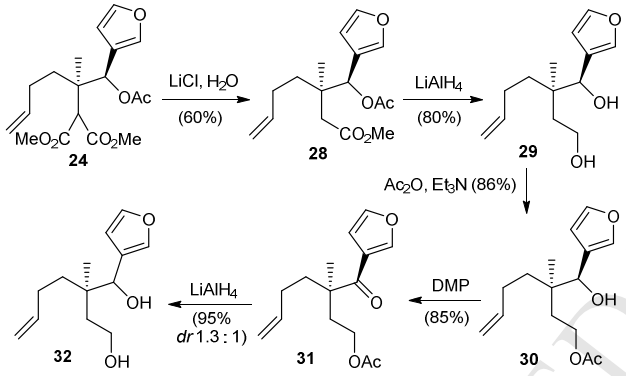
Scheme 7. Felkin-Ahn model to rationalize the stereochemical outcome.



Although this synthetic route failed to afford right fragment **4**, the Rh-catalyzed IMPK reaction for the stereoselective formation of **27** from allenene **26** might provide a concise route to the core structure of perforanoid A (**1**).

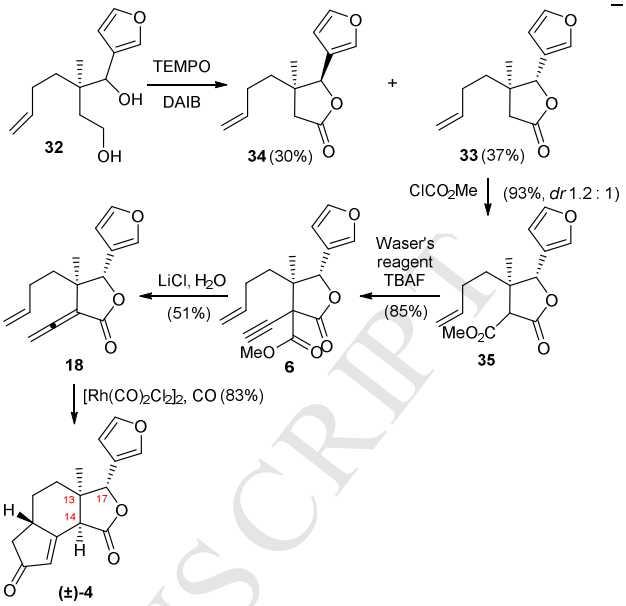
We then attempted to develop a strategy to invert the stereochemistry at C17. To this end, substrate **24** was subjected to decarboxylation by reaction with LiCl–H_2O in DMF at 130 °C, and resultant monoester **28** was reduced with $LiAlH_4$ to give diol **29** in 48% overall yield.

Scheme 8. Synthesis of diol **32**.



To invert the C17 stereogenic center, diol **29** was first treated with Ac_2O/Et_3N, and resultant monoacetate **30** was then oxidized with DMP to afford ketone **31** in 73% yield for the last two steps. However, attempts with various reducing agents, including $NaBH_4$, $LiAlH_4$, Me_4NBH_4, $Zn(BH_4)_2$, $LiHBEt_3$, $Li(OtBu)_3AlH$, Bu_4NBH_4, $NaBH_4/CaCl_2$, $NaBH_4/CeCl_3•7H_2O$, and $LiBH_4$, to achieve the diastereoselective reduction of ketone **31** were unsuccessful. The best result was obtained when $LiAlH_4$ was used as the reductant, and gave diol **32**[18] in 95% yield with a diastereoselectivity ratio of 1.3:1 (Scheme 8).

Scheme 9. Synthesis of (±)-**4**.

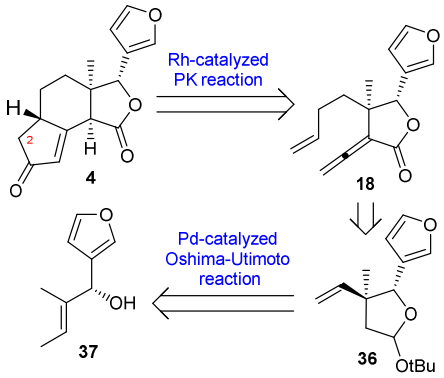


Further oxidation of inseparable diol **32** with TEMPO-DAIB afforded lactones **34** and **33** as separable diastereoisomers[19] in 37% and 30% yields, respectively. By comparing the ^1H NMR spectra of **33** and **34** with lactone **25**, we confirmed that **33** was our desired lactone. Thus, the enolate obtained after treatment of lactone **33** with lithium hexamethyldisilazide (LiHMDS) was reacted with methyl carbonochloridate to give ester **35** in 93% yield as a pair of diastereoisomers in a ratio of 1.2:1. The pair of diastereoisomers of **35** was further reacted without separation with Waser's reagent in the presence of TBAF, followed by decarboxylation with LiCl–H_2O to afford allene **18** through intermediate **17** in 68% overall yield. $[RhCl(CO)_2]_2$-catalyzed (5 mol%) reaction of allene **18** with CO at 120 °C in toluene gave enone (±)-**4** in 83% yield. In this way, we successfully constructed desired right fragment (±)-**4** of perforanoid A in 15 steps (Scheme 9).

5. Second-Generation for the synthesis of right fragment

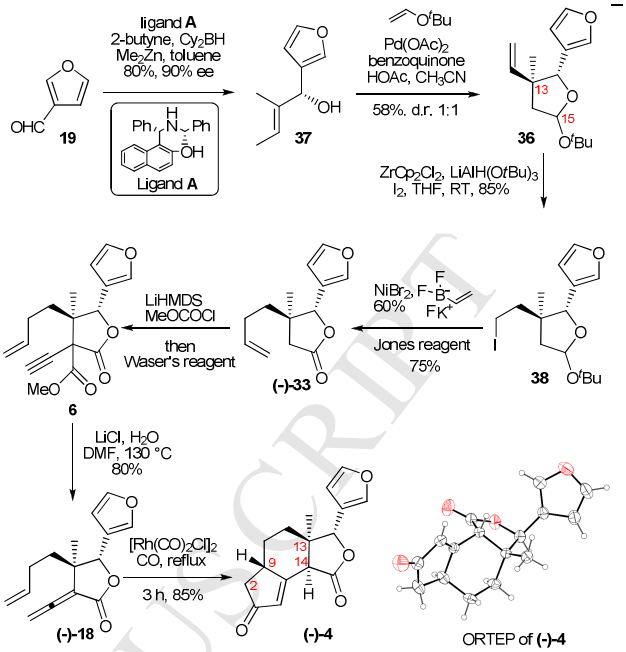
Having established a strategy for the racemic synthesis of the right fragment of perforanoid A (**1**), we next aimed to determine an asymmetric strategy with a Rh-catalyzed IMPK reaction as the key step. To achieve this goal, we needed to find a method for the asymmetric synthesis of key intermediate **37** (Scheme 10), which would ensure that we could construct the right fragment of perforanoid A (**1**) in an asymmetric fashion according to the chemistry presented above.

Scheme 10. Second-generation retrosynthetic analysis of right fragment.



Scheme 10 illustrates the retrosynthetic analysis for our second generation, asymmetric synthesis of intermediate **4**. Accordingly, we expected intermediate **4** to be derived from cyclic acetal **36** through intermediate **18**, and cyclic acetal **36** was in turn expected to be generated from chiral allylic alcohol **37** by a Pd-catalyzed Oshima–Utimoto reaction.[20]

Scheme 11 illustrates our asymmetric synthesis of right fragment **4**. The synthesis began with the asymmetric construction of allylic alcohol **37** in an asymmetric allylation in the presence of 1-[(*S*)-phenyl{[(1′*S*)-1′-phenylethyl]methyl-amino}-methyl]-2-naphthol.[21] When furan-3-carbaldehyde **19** was reacted with 2-butenyl methyl zinc [derived from the reaction of 2-butyne, dicyclohexylborane (Cy_2BH), and Me_2Zn][22] in the presence of tertiary aminonaphthol, desired allylic alcohol **37** was isolated in 80% yield with 90% ee. Acetal **36** was furnished by adopting Morken's protocal in a Pd-catalyzed Oshima–Utimoto reaction from allylic alcohol **37**. In this reaction, treatment of **37** with $Pd(OAc)_2$ in the presence of benzoquinone and AcOH in CH_3CN gave acetal **36** in 58% yield as anomers with a *dr* value of 1:1, and diastereoisomers at the C13 quaternary center in a ratio of 20:1, in favor of the desired isomer. The reaction proceeded through a stereoselective carbopalladation of the tethered alkene via a chair-like transition state to afford a cyclic acetal bearing a defined quaternary carbon stereocenter. This cyclic acetal then underwent a β-hydride elimination to deliver the furan acetal product as well as palladium(0), which required reoxidation to continue the catalytic cycle.[20]



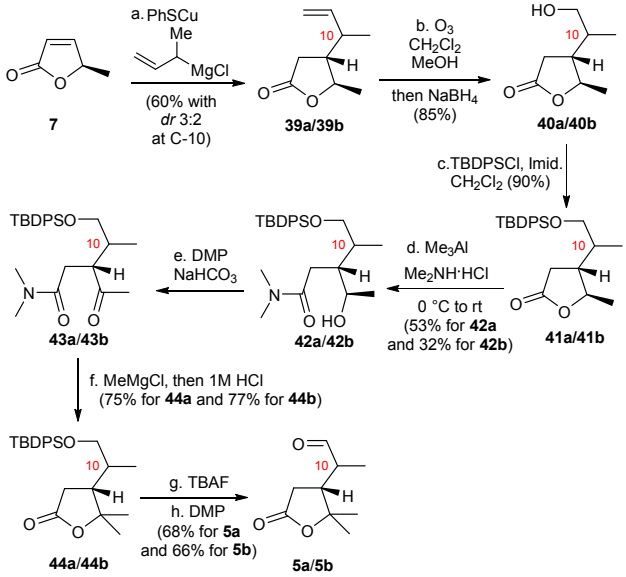
Scheme 11. Asymmetric synthesis of (-)-**4**.

To prepare lactone (−)-**33**, we intended to develop a synthetic protocol containing sequential iodination, metal-catalyzed cross-coupling,[23-24] and Jones oxidation reactions. To this end, acetal **36** was treated with $ZrCp_2Cl_2$ and $LiAlH(OtBu)_3$, and then quenched with I_2 to give iodide **38** in 85% yield. The ligation of iodide **38** with an olefin was achieved in a nickel-catalyzed coupling reaction developed by Molander and co-workers,[25] and the resultant product was then subjected to a Jones oxidation to give expected γ-butyrolactone (−)-**33** in 45% yield over two steps. Treatment of (−)-**33** with LiHMDS and reaction of the resultant enolate with methyl carbonochloridate, followed by acetylation by treatment with Waser's reagent gave enyne **6** in 88% yield as a pair of diastereoisomers at the newly generated stereogenic center at C14. Thus, treatment of enyne **6** with LiCl–H_2O in DMF at 130 °C, followed by an optimized Rh-catalyzed IMPK reaction[8] of resultant allenene (−)-**18** gave (−)-**4** in 68% overall yield as a single isomer. The relative stereochemistry of **4** was confirmed by X-ray crystallographic analysis.

6. Synthesis of left fragment

Having constructed the right fragment of **1**, we turned our attention to the synthesis of left fragments **5a** and **5b**; Scheme 12 lists the synthetic details. We attempted to prepare intermediate **39** using a Cu-mediated Michael reaction of known optically pure compound **7**. To this end, furanone **7** was reacted with a Grignard reagent in the presence of (phenylthio)copper (PhSCu) to give lactones **39a** and **39b** in 60% combined yield as a pair of diastereoisomers at C10 with a *dr* ratio of 3:2. PhSCu was essential for the success of the desired reaction; other cuprite reagents, including CuI, CuCl, and $CuBr_2$•Me_2S, with or without Lewis acids, did not furnish expected products **39a** and **39b**. Both diastereosiomers (**39a** and **39b**) were then treated with ozone, followed by reaction with $NaBH_4$ to give alcohols **40a** and **40b** in 85% yield.

Scheme 12. Asymmetric synthesis of **5a**/**5b**.

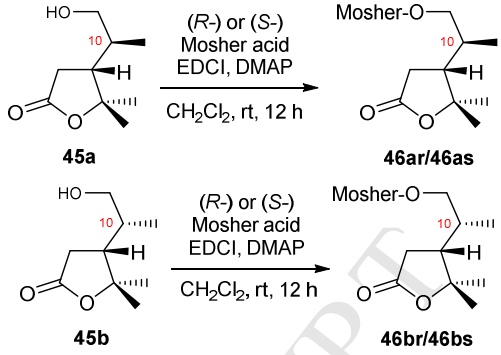


Alcohols **40a** and **40b** were protected as the silyl ethers using TBDPSCl in the presence of imidazole to furnish **41a** and **41b** in 90% yield. To separate the diastereoisomers, **41a** and **41b** were treated with the hydrochloride salt of dimethylamine in the presence of trimethylaluminum to afford hydroxyamides **42a** and **42b** as separable products in 53% and 32% yields, respectively.[26] Because one of the objectives of our asymmetric total synthesis of perforanoid A was to confirm the stereochemical assignment at C10, we needed to convert **42a** and **42b** into left fragments **5a** and **5b**, and react them both with right fragment (−)-**4** to afford the corresponding aldol condensation products. One of these condensation products should match the natural product with the desired stereochemistry at C10.

Oxidation of **42a** with DMP in the presence of $NaHCO_3$ in CH_2Cl_2, and treatment of resulting ketone **43a** with MeMgCl followed by an acid-mediated intramolecular lactonization[27] afforded lactone **44a** in 75% overall yield. Under similar conditions, lactone **44b** was obtained in 77% yield from alcohol **42b**. Finally, treatment of **44a** with TBAF to remove the silyl protection group and oxidation of the obtained primary alcohol gave corresponding aldehyde **5a** in 68% yield over two steps. Alcohol **44b** was converted to aldehyde **5b** in 66% yield by following the same procedure. Notably, DMP oxidation was effective for the preparation of aldehydes **5a** and **5b** without epimerization.

7. Completion of total synthesis

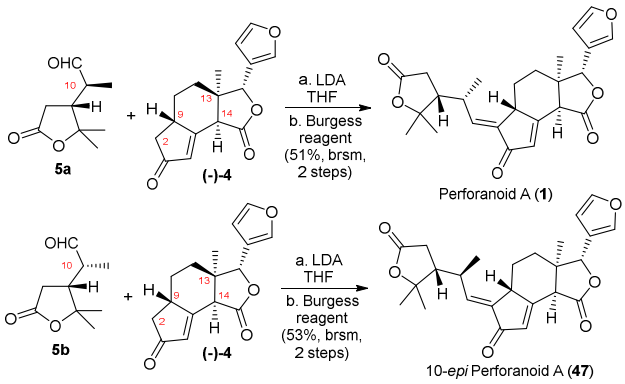
To establish the absolute stereochemistry at C10 in **5a** and **5b**, **45a**, and **45b** were converted into corresponding Mosher esters **46ar**/**46as** and **46br**/**46bs** (Scheme 13). The absolute stereochemistry at C10 in **5a** and **5b** was determined to be *S* and *R*, respectively, by comparison of the ^{1}H NMR and ^{19}F NMR spectra.[28]



Scheme 13. Synthesis of mosher's esters **46ar**/**46as** and **46br**/**46bs**.

To complete the total synthesis, enone (-)-**4** was treated with LDA in THF at -78 °C; the resulting enolate underwent an aldol reaction with aldehyde **5a** to give an alcohol, which was then dehydrated by treatment with Burgess reagent[29] to give perforanoid A (**1**) in 33% (51% brsm) overall yield (Scheme 14). Under identical conditions, 10-*epi* perforanoid A (**47**) was obtained in 36% (53% brsm) overall yield. The ^{1}H and ^{13}C NMR spectra and specific rotation of the synthesized perforanoid A were in agreement with those of natural perforanoid A (synthetic perforanoid A: $[\alpha]_D^{22}$ = -183.5 (c = 0.18, MeOH); natural perforanoid A: ($[\alpha]_D^{22}$ = -199.2 (c = 0.09, MeOH)). Our results show that the structure of perforanoid A is **1**, and compound **47** was assigned as 10-*epi* perforanoid A.

Scheme 14. Completion of the total synthesis.



8. Conclusion

In summary, we have achieved a concise total synthesis of limonoid perforanoid A (**1**) in 10 steps by developing a unified synthetic strategy. The key features of our approach include the chiral tertiary aminonaphthol-mediated enantioselective alkenylation of aldehydes for the asymmetric synthesis of allylic alcohol **37**, Pd-catalyzed coupling of **37** with a vinyl ether to form the *γ*-lactone ring with stereoselective construction of the C13 all-carbon quaternary center, and a Rh-catalyzed Pauson–Khand reaction to form the polycyclic cyclopentenone ring system in perforanoid A. The developed chemistry may be modified to facilitate the total synthesis of other limonoid natural products.

Experimental section

*8.1. Synthesis of Compound (±)-**33** and (±)-**34**:*

To a solution of diol **32** (113 mg, 0.5 mmol) in dry CH_2Cl_2 (3 mL) was added TEMPO (2,2,6,6-tetramethylpiperidinooxy, 23.4 mg, 0.15 mmol, 0.3 equiv.), and the resultant mixture was stirred at room temperature for 5 min. To this solution was added DAIB (Iodobenzene diacetate, 209.3 mg, 6.5 mmol, 1.3 equiv.), and the mixture was then stirred at room temperature for 12 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (10 mL), and the mixture was extracted with EA (5 × 10 mL), the combined organic extract was dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the residue was purified by a flash column chromatography (hexane/EA = 30/1) on silica gel to give lactones **33** (40.5 mg, 37% yield) and **34** (33.5 mg, 30% yield) as colorless oil.

(±)-**33**: IR (neat, ν cm^{-1}): 2936, 1781, 1503, 1460, 1164, 1029, 875, 800, 602; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.42 (s, 1H), 6.34 (t, *J* = 1.3 Hz, 1H), 5.80 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.13 (s, 1H), 5.09 – 4.94 (m, 2H), 2.54 (d, J = 16.9 Hz, 1H), 2.41 (d, *J* = 16.9 Hz, 1H), 2.16 (dtdd, *J* = 13.6, 7.3, 4.5, 3.1 Hz, 1H), 2.10 – 1.93 (m, 1H), 1.65 – 1.52 (m, 2H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 143.5, 140.0, 137.5, 120.3, 115.4, 108.8, 83.3, 43.8, 42.2, 37.7, 29.1, 20.0; HRMS (ESI) $(M+Na)^+$ calcd for $C_{13}H_{16}O_3Na^+$: 243.0992, found: 243.0992.

(±)-**34**: IR (thin film, ν cm^{-1}): 2936, 1781, 1164, 1029, 874, 800; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 1.7 Hz, 1H), 7.43 – 7.40 (m, 1H), 6.32 (dd, *J* = 1.7, 0.7 Hz, 1H), 5.67 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.13 (s, 1H), 5.02 – 4.80 (m, 2H), 2.60 (d, *J* = 17.1 Hz, 1H), 2.38 (dd, *J* = 17.1, 0.6 Hz, 1H), 2.10 – 1.81 (m, 2H), 1.43 – 1.04 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 143.8, 140.1, 137.8, 120.5, 115.1, 108.8, 84.7, 43.4, 41.0, 34.3, 28.7, 23.3; HRMS (ESI) $(M+Na)^+$ calcd for $C_{13}H_{16}O_3Na^+$: 243.0992, found: 243.0998.

*8.2. Synthesis of Compound (±)-**35**:*

To a solution of lactone **33** (2.83 g, 12.83 mmol) in dry THF (60 mL) was added LiHMDS (32.1 mL, 32.1 mmol, 2.5 equiv) at -78 °C in a drop-wise manner, and the resultant mixture was stirred at the same temperature for 2 h. To this solution was added $ClCO_2Me$ (2.42 g, 25.66 mmol, 2.0 equiv) at -78 °C in a drop-wise manner, and the resultant mixture was first stirred at the same temperature for 1 h, and then at room temperature for 11 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (100 mL), and the mixture was extracted with EA (5 × 100 mL), and finally dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography (hexane/EA = 30/1) on silica gel to give lactone*(±)*- **35** (3.32 g，yield 93%, dr 1.2:1) as colorless oil.

(±)-**35**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.36 (m, 2H), 6.36 (dd, *J* = 8.6, 0.8 Hz, 1H), 5.86 – 5.60 (m, 1H), 5.52 and 5.18 (2s, 1H), 5.11 – 4.94 (m, 2H), 3.79 and 3.78(2s, 3H), 3.65 and 3.42 (2s, 2H), 2.09 (dddd, *J* = 20.3, 15.6, 10.5, 3.7 Hz, 2H), 1.68 (dd, *J* = 10.1, 6.8 Hz, 1H), 1.55 (dddd, *J* = 17.7, 13.9, 10.3, 6.4 Hz, 1H), 0.97 and 0.92 (2s, 3H), 0.92; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 167.4, 167.1, 143.6, 140.7, 140.5, 137.4, 137.2, 119.3, 119.2, 115.6, 115.3, 109.1, 109.1, 82.4, 81.5, 58.7, 55.9, 52.8, 52.5, 48.1, 47.7, 37.2, 33.4, 28.6, 28.3, 20.7, 17.5; HRMS (ESI) $(M+Na)^+$ calcd for $C_{15}H_{15}O_5Na^+$: 301.1046, found: 301.1045.

*8.3. Synthesis of Compound **(±)-6***

To a solution of ester **35** (134 mg, 0.48 mmol, 1.0 equiv.) in dry THF (3 mL) was added Waser's reagent (332 mg, 0.96 mmol, 2.0 equiv.) at -78 °C, and the resultant mixture was stirred at the same temperature for 5 min. To this solution was added TBAF (1M in THF, 0.96 mL, 0.96 mmol, 2.0 equiv.) at -78 °C in a drop-wise manner, and the resultant mixture was stirred first at -78 °C for 1 h, and then at room temperature for 9 h. The reaction was quenched with brine (10 mL), and the mixture was extracted by EA, then the combined organic extracts were dried over Na_2SO_4. The solvent was removed under vacuum, the residue was purified by a flash column chromatography (hexane/EA = 20/1) on silica gel to give enyne **6** (128 mg, yield 85%) as colorless oil.

(±)-**6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.39 (m, 2H), 6.48 – 6.23 (m, 1H), 5.88 – 5.59 (m, 1H), 5.44 and 5.37 (2s, 1H), 5.01 (dddd, *J* = 13.4, 10.2, 2.8, 1.5 Hz, 2H), 3.89 and 3.86 (2s, 3H), 2.72 and 2.69 (2s, 1H), 2.49 – 2.35 (m, 0.6H), 2.26 – 2.02 (m, 2H), 1.92 (ddd, *J* = 14.0, 11.5, 6.5 Hz, 0.4H), 1.57 – 1.42 (m, 2H), 1.11 and 0.95 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 168.6, 166.4, 166.2, 143.7, 141.1, 140.9, 137.7, 137.6, 118.9, 118.6, 115.3, 115.2, 109.4, 109.3, 82.2, 81.5, 77.9, 77.9, 76.0, 74.5, 61.5, 59.3, 53.9, 53.5, 52.0, 51.7, 34.7, 34.5, 27.7, 27.6, 18.3, 16.7; HRMS (ESI) $(M+Na)^+$ calcd for $C_{17}H_{18}O_5Na^+$: 325.1046, found: 325.1046.

*8.4. Synthesis of Compound **(±)-18***

To a solution of enyne **6** (0.228 g, 0.76 mmol, 1.0 equiv) in DMF (4 mL) was sequentially added H_2O (28 μL, 0.76 mmol, 2.0 equiv) and LiCl (96 mg, 2.28 mmol, 3.0 equiv), and the resultant mixture was degased with N_2 for 6 times. The reaction mixture was stirred at room temperature for 5 min, and then transferred to a preheated oil bath at 110 °C for 2 h. After cooling to room temperature, then reaction mixture was quenched by addition of water (10 mL), and the mixture was extracted with Et_2O, and the combined organic extracts were dried over anhydrous Na_2SO_4. After removal of the solvent under vacuum, the residue was purified by a flash column chromatography (hexane/EA :30/1) on silica gel to give allene (±)-**18** (95 mg, 51%) as wax.

(±)-**18:** IR (neat, *ν* cm^{-1}): 3439, 2929, 1971, 1759, 1641, 1329, 1140, 1025, 874, 783, 601; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 0.7 Hz, 1H), 7.45 (t, *J* = 1.7 Hz, 1H), 6.36 (d, *J* = 0.9 Hz, 1H), 5.64 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.55 – 5.37 (m, 2H), 5.18 (s, 1H), 4.90 (ddd, *J* = 8.6, 3.3, 1.6 Hz, 2H), 2.07 – 1.82 (m, 2H), 1.45 (ddd, *J* = 13.7, 11.9, 4.8 Hz, 1H), 1.31 (s, 3H), 1.22 (ddd, *J* = 13.7, 11.9, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 169.0, 143.9, 140.2, 137.7, 119.6, 114.9, 108.6, 103.5, 83.8, 83.5, 46.4, 34.8, 27.9, 21.7; HRMS (ESI) $(M+Na)^+$ calcd for $C_{15}H_{16}O_3Na^+$: 267.0992, found: 267.0990.

*8.5. Synthesis of Compound **(±)-4***

To a solution of allene **(±)-18** (49 mg, 0.2 mmol) in dry toluene (20 mL) was added $[Rh(CO)_2Cl]_2$ (3.9 mg, 5 mol%) at room temperature, the resultant mixture was degased with N_2 and CO for 6 times, respectively, and the resultant mixture

was stirred at 120 °C under CO atmosphere for 3 h. After cooling to room temperature, the mixture was concentrated under vacuum, and the residue was purified by a flash column chromatography (hexane/EA = 1/1) on silica gel to give enone **(±)-4** (45 mg, yield 83%) as white solid.

(±)-4: IR (neat, *v* cm^{-1}): 3440, 2929, 1768, 1705, 1625, 1461, 1274, 1134, 1002, 793; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.41 (s, 1H), 6.30 (s, 1H), 6.12 (s, 1H), 5.15 (s, 1H), 3.70 (s, 1H), 2.73 (dd, *J* = 11.8, 5.6 Hz, 1H), 2.64 (dd, *J* = 18.8, 6.5 Hz, 1H), 2.16 – 2.06 (m, 1H), 2.06 – 1.88 (m, 2H), 1.81 (d, *J* = 12.8 Hz, 1H), 1.32 (ddd, *J* = 26.3, 13.3, 3.0 Hz, 1H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 173.1, 173.0, 144.2, 140.1, 133.6, 120.9, 108.6, 83.2, 49.5, 46.6, 41.7, 39.2, 34.3, 29.8, 19.5; HRMS (ESI) $(M+H)^+$ calcd for $C_{16}H_{17}O_4^+$: 273.1121, found: 273.1127.

*8.6. Synthesis of Compound **37***

To a solution of dicyclohexylborane (1.42 g, 8.0 mmol, 2.0 equiv.) in toluene (5 mL) was added 2-butyne (0.63 mL, 8.0 mmol, 2.0 equiv.) in one portion, and the resultant mixture was first stirred at room temperature for 1 h, and then cooled to -78 °C. To this solution was added a solution of dimethylzinc (8 mL, 8.0 mmol, 1 M in toluene, 2.0 equiv.) at -78 °C slowly, and the resultant mixture was then stirred at the same temperature for 1 h. To this solution was added a solution of ligand **A** (212 mg, 0.6 mmol, 0.15 equiv.) in toluene (8 mL), and the resultant mixture was then gradually warmed up to -30 °C during 30 min with stirring. To this solution was added aldehyde **19** (346 μL, 4.0 mmol, 1.0 equiv.) slowly, and the resultant mixture was stirred at -30 °C for 12 h. The reaction mixture was quenched by slowly addition of water (10 mL), and the mixture was extracted with EA (3 × 20 mL), and the combined extracts were washed with brine, and dried over Na_2SO_4. The solvent was removed under vacuum,[1] and the residue was purified by a flash chromatography on silica gel (hexane/EA : 20/1 to 10/1) to give product **37** (486 mg, 80%, 90% ee) as bright oil.

37: $[\alpha]_D^{22}$ = -10.4, (c = 0.35, MeOH); IR (thin film, *v* cm^{-1}): 3365, 2920, 1502, 1445, 1380, 1158, 1023, 875, 787, 758; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 2H), 6.27 (s, 1H), 5.62 (q, *J* = 6.7 Hz, 1H), 5.04 (s, 1H), 2.20 (brs, 1H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 139.4, 137.1, 127.6, 121.0, 109.0, 73.0, 13.0, 11.5; HRMS (ESI) $(M+H-H_2O)^+$ calcd for $C_9H_{11}O$: 135.0804, found: 135.0806.

*8.7. Synthesis of Compound **36***

To a solution of alcohol **37** (1.0 g, 6.6 mmol, 1.0 equiv) in acetonitrile (8 mL) was sequentially added *t*-butyl vinyl ether (3.5 mL, 26.4 mmol, 4.0 equiv.), benzoquinone (2.1 g, 19.8 mmol, 3.0 equiv.), palladium (II) acetate (157 mg, 0.7 mmol, 0.1 equiv.) and glacial acetic acid (0.38 mL, 6.7 mmol, 1.1 equiv.), and the resultant mixture was stirred at room temperature for 20 h. To this solution was added pyridine (1.2 mL, 14.5 mmol, 2.2 equiv.) followed by addition of a solution of hexane and Et_2O (3/1, v/v, 100 mL). The reaction mixture was filtered off through a pad of Celite, and the pad was then rinsed with a second portion of hexane and Et_2O (3/1, v/v, 100 mL). The filtrate was concentrated under vacuum and the residue was suspended in hexane, and the suspension was then filtered off through a Buchner funnel to remove more benzoquinone, which was then washed with hexane. The filtrate was concentrated under vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/EA = 1000/1 to 50/1) to give acetal **36** (957 mg, 58%, colorless oil) as a mixture of diastereoisomers (*dr* = 1:1).

36: IR (thin film, *v* cm^{-1}): 2975, 2870, 1640, 1502, 1391, 1365, 1162, 1034, 922, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H) , 6.35 and 6.27 (2 s, 1H), 5.95 – 5.83 (m, 1H), 5.53 and 5.45 (t, *J* = 5.4 Hz and dd, *J* = 6.4, 2.8 Hz, 1H), 5.09 – 4.99 (m, 2H), 4.85 and 4.66 (2s, 1H), 2.21, 2.09 – 1.97 and 1.80 (dd, *J* = 13.1, 6.4 Hz, m and dd, *J* = 13.1, 2.8 Hz, 2H), 1.27 and 1.26 (2 s, 9H), 0.99 and 0.85 (2s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 143.0, 142.4, 142.3, 140.0, 139.5, 124.2, 122.7, 113.9, 113.1, 109.8, 109.2, 98.1, 97.6, 82.2, 79.2, 74.2, 74.2, 48.5, 48.3, 46.9, 46.4, 29.0, 28.9, 19.8, 19.0; HRMS (ESI) $(M+Na)^+$ calcd for $C_{15}H_{22}O_3Na^+$: 273.1461, found: 273.1461.

*8.8. Synthesis of Compound **38***

To a solution of alkene **36** (1.5 g, 6.0 mmol, 1.0 equiv.) and $ZrCp_2Cl_2$ (2.63 g, 9.0 mmol, 1.5 equiv.) in THF (15 mL) was added a solution of $LiAlH(OtBu)_3$ (9.0 mL, 9.0 mmol, 1 M in THF, 1.5 equiv.) at room temperature. The resulting mixture was then stirred at room temperature for 2 h. To this solution was added a solution of iodine (3.0 g, 12.0 mmol, 2.0 equiv) in THF (10 mL) in a drop-wise manner, and the resultant mixture was then stirred at room temperature for 3 h. The mixture was quenched by addition of a solution of HCl (1M, 20.0 mL) carefully, and the resultant mixture was extracted with Et_2O (3 × 50 mL). The combined organic extract was washed successively with saturated aqueous Na_2SO_3 solution (2 × 20 mL) and brine (2 × 30 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (shield from light) (hexane/EA : 50/1) to give the iodoalkane **38** (1.93 g, 85%, colorless oil) as a mixture of diastereoisomers (*dr* = 2.2:1).

38: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.32 (m, 2H), 6.40 (d, *J* = 1.1 Hz, 0.32H), 6.34 (d, *J* = 1.0 Hz, 0.69H), 5.50 (dd, *J* = 5.9, 4.5 Hz, 0.62H), 5.44 (dd, *J* = 6.3, 2.9 Hz, 0.32H), 4.71 (s, 0.71H), 4.55 (s, 0.34H), 3.20 (dddd, *J* = 12.2, 9.2, 5.4, 3.4 Hz, 1H), 3.10 (dddd, *J* = 12.4, 9.3, 7.1, 5.4 Hz, 1H), 2.20 – 1.96 (m, 3H), 1.85 – 1.77 (m, 1H), 1.27 (s, 3H), 1.25 (s, 6H), 0.90 (s, 1H), 0.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 142.7, 140.3, 139.9, 124.1, 122.5, 110.0, 109.4, 97.8, 97.1, 82.5, 79.6, 74.3, 47.3, 46.5, 46.4, 45.4, 45.3, 43.9, 29.0, 20.0, 20.2, 20.2, 0.1; HRMS (ESI) $(M+Na)^+$ calcd for $C_{15}H_{23}IO_3Na^+$: 401.0584, found: 401.0582. It should be noted that the iodoalkane **14** was unstable.

*8.9. Synthesis of Compound **(-)-33***

To a flame-dried flask with a stirring bar was added bathophenanthroline (33 mg, 0.1 mmol, 10 mol %), potassium vinyltrifluoroborate (148 mg, 1.1 mmol, 1.1 equiv.) and compound **38** (378 mg, 1.0 mmol, 1.0 equiv.), and the flask was then moved into a glove box. To this flask was added $NiBr_2$•glyme (31 mg, 0.1 mmol, 10 mol %) and NaHMDS (550 mg, 3.0 mmol, 3 equiv), and the flask was took out from the glove box. To this flask was added a mixture of dry cyclopentyl methyl ether (CPME, 2 mL) and *t*-BuOH (2 mL) *via* syringe, and the resultant mixture was degased with N_2 for 8 times then stirred at room temperature for 0.5 h, and the mixture was stirred at 60 °C, the reaction was monitored by

TLC until the compound **38** was consumed off. After completion, the reaction was worked up by filtration of the reaction mixture through a silica pad, which was then washed thoroughly with CH_2Cl_2 (3 × 20 mL) and EA (3 × 20 mL).[2] The filtrate was concentrated under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/EA : 500/1 to 50/1) to afford alkene **38a** (167 mg, 60%, as colorless oil) as a mixture of diastereoisomers (*dr* = 3:1).

38a: IR (thin film, *v* cm-1): 2974, 2933, 1641, 1501, 1458, 1391, 1197, 1162, 1010, 764; 1H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.30 (m, 2H), 6.42 (d, *J* = 1.0 Hz, 0.26 H), 6.35 (s, 0.79H), 5.93 – 5.73 (m, 1H), 5.59 – 5.48 (m, 0.77H), 5.45 (dd, *J* = 6.3, 3.0 Hz, 0.28H), 5.09 – 4.89 (m, 2H), 4.73 (s, 0.84H), 4.57 (s, 0.27H), 2.19 – 1.97 (m, 3H), 1.91 – 1.75 (m, 1H), 1.59 – 1.39 (m, 2H), 1.27 (d, *J* = 6.5 Hz, 9H), 0.90 (s, 1H), 0.76 (s, 2H); 13C NMR (100 MHz, CDCl3) δ 142.6, 142.5, 140.3, 139.8, 139.0, 138.9, 124.9, 123.1, 114.5, 114.4, 110.2, 109.6, 98.1, 97.4, 83.2, 80.6, 74.1, 47.4, 46.0, 45.3, 44.1, 39.5 37.9, 29.8, 29.6, 29.1, 29.0, 21.0, 20.8; HRMS (ESI) $(M+Na)^+$ calcd for $C_{17}H_{26}O_3Na^+$: 301.1774, found: 301.1770.

To a solution of acetal **38a** (350 mg, 1.26 mmol, 1.0 equiv) in acetone (10 mL) was added Jones reagent (4.2 mL, 5.0 mmol, 1.2 M, 4.0 equiv) at 0 °C, and the resultant reaction mixture was first stirred at 0 °C for 1 h, and then at room temperature for 2 h. The reaction mixture was worked up by addition of a saturated solution of $NaHCO_3$ slowly until the pH of the mixture reached 7. The reaction mixture was filtered through a pad of Celite, and then rinsed with EA (50 mL). The filtrate was concentrated under vacuum, and the residue was extracted with EA (3 × 50 mL). The combined extracts were washed with brine (3 × 50 mL), dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash chromatography on silica gel (hexane/EA : 30/1) to deliver the lactone **(-)-33**(208 mg, 75% yield) as colorless oil.

(-)-33: $[\alpha]_D^{22}$ = -24.7 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.42 (s, 1H), 6.34 (t, *J* = 1.3 Hz, 1H), 5.80 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.13 (s, 1H), 5.09 – 4.94 (m, 2H), 2.54 (d, *J* = 16.9 Hz, 1H), 2.41 (d, *J* = 16.9 Hz, 1H), 2.16 (dtdd, *J* = 13.6, 7.3, 4.5, 3.1 Hz, 1H), 2.10 – 1.93 (m, 1H), 1.65 – 1.52 (m, 2H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 143.5, 140.0, 137.5, 120.3, 115.4, 108.8, 83.3, 43.8, 42.2, 37.7, 29.1, 20.0; HRMS (ESI) $(M+Na)^+$ calcd for $C_{13}H_{16}O_3Na^+$: 243.0992, found: 243.0992.

*8.10. Synthesis of Compound **6***

To a solution of lactone **(-)-33** (506 mg, 2.3 mmol, 1.0 equiv.) in dry THF (15 mL) was added LiHMDS (5.8 mL, 5.8 mmol, 1.0 M in THF, 2.5 equiv.) at -78 °C, and the mixture was stirred -78 °C for 2 h. To this solution was added $ClCO_2Me$ (0.35 mL, 4.6 mmol, 2.0 equiv.) at -78 °C, and the mixture was stirred at the same temperature for 12 h, and at the end of the reaction, the reaction temperature of the mixture was warmed to room temperature. To this solution, Waser's reagent (**C**) (1.6 g, 4.6 mmol, 2.0 equiv.) was added at -78 °C, and the resultant mixture was then stirred for 5 min. To this solution was added a solution of TBAF (11.5 mL, 11.5 mmol, 1 M in THF, 5.0 equiv.) at -78 °C in a drop-wise manner, the mixture was then stirred at the same temperature for another 10 h, during which time the temperature was return to room temperature slowly. Then additional 3.0 equiv of TBAF solution was added in a drop-wise manner at 0 °C then stirred for 30 min. The mixture quenched with brine (50 mL), and extracted with Et_2O (3 × 100 mL). The combined extract was washed with brine (3 × 50 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/EA = 30/1) to give alkyne **6** (611 mg, 88%) as colorless oil.

*8.11. Synthesis of Compound **(-)-18***

To a solution of alkyne **6** (151 mg, 0.5 mmol, 1.0 equiv.) in a mixed solvent of DMF (2.5 mL) and H_2O (45 μL, 2.5 mmol, 5.0 equiv.) was added LiCl (105 mg, 2.5 mmol, 5.0 equiv.) at room temperature, and the mixture was degased with N_2 for 8 times, and the resultant mixture was first stirred at the same temperature for 5 min, and then transferred to a preheated bath oil at 130 °C for 2 h with stirring. After cooling to room temperature, the reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL), and then diluted with H_2O (30 mL). The mixture was extracted with Et_2O (3 × 100 mL), and the combined extracts were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography (hexane/EA : 30/1) on silica gel to give the allene compound **(-)-18** (98 mg, 80%) as wax.

(-)18: $[\alpha]_D^{22}$ = -18.4 (c = 0.56, $CHCl_3$); IR (neat, *v* cm^{-1}): 3439, 2929, 1971, 1759, 1641, 1329, 1140, 1025, 874, 783, 601; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 2H), 6.30 (s, 1H), 5.79 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.52 – 5.40 (m, 2H), 5.25 (s, 1H), 5.09 – 4.94 (m, 2H), 2.23 – 2.04 (m, 2H), 1.78 – 1.70 (m, 2H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 169.1, 143.7, 140.2, 137.4, 121.5, 115.2, 108.7, 103.4, 83.6, 81.4, 46.3, 39.3, 28.4, 22.0; HRMS (ESI) $(M+Na)^+$ calcd for $C_{15}H_{17}O_3Na^+$: 267.0992, found: 267.0990.

*8.12. Synthesis of Compound **(-)-4***

To a solution of the allene **(-)-18** (49 mg, 0.2 mmol, 1.0 equiv.) in dry toluene (25 mL, 0.008M) was added $[Rh(CO)_2Cl]_2$ (5.4 mg, 0.014, 7 mol %), and the resultant mixture was degased with N_2 for 8 times and with CO for 8 times, the mixture was then stirred at 120 °C for 3 h under CO atmosphere.[3] After the reaction was completed, the solvent was removed under vacuum, and the residue was purified by a flash column chromatography (hexane/EA : 1/1) on silica gel to obtain **(-)-4** (46 mg, 85%) as colorless crystal.

(-)-4: $[\alpha]_D^{22}$ = -155.3 (c = 0.35, $CHCl_3$); IR (neat, *v* cm^{-1}): 3440, 2929, 1768, 1705, 1625, 1461, 1274, 1134, 1002, 793; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.41 (s, 1H), 6.30 (s, 1H), 6.12 (s, 1H), 5.15 (s, 1H), 3.70 (s, 1H), 2.73 (dd, *J* = 11.8, 5.6 Hz, 1H), 2.64 (dd, *J* = 18.8, 6.5 Hz, 1H), 2.16 – 2.06 (m, 1H), 2.06 – 1.88 (m, 2H), 1.81 (d, *J* = 12.8 Hz, 1H), 1.32 (ddd, *J* = 26.3, 13.3, 3.0 Hz, 1H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 173.1, 173.0, 144.2, 140.1, 133.6, 120.9, 108.6, 83.2, 49.5, 46.6, 41.7, 39.2, 34.3, 29.8, 19.5; HRMS (ESI) $(M+H)^+$ calcd for $C_{16}H_{17}O_4^+$: 273.1121, found: 273.1127.

*8.13. Synthesis of perforanoid A (**1**)*

To a solution of (-)-**4** (9.8 mg, 0.036 mmol, 1.0 equiv.) in THF (1 mL) was LDA (55 μL, 0.11 mmol, 2 M in THF, 3.0 equiv.) in a drop-wise manner at -78 °C, and the resultant

mixture was then stirred the same temperature for 2 h, during this time the temperature was warmed to c. To this solution was added a solution of aldehyde **5a** (30.6 mg, 0.18 mmol, 5.0 equiv.) in THF (1 mL) slowly, and and the resultant mixture was stirred at -78 °C for 10 h, during which time the temperature was warmed to room temperature. The reaction mixture was quenched by addition of a saturated solution of NH_4Cl in a drop-wise manner, and the water phase was extracted with EA (6 × 20 mL) and CH_2Cl_2 (3× 20 mL). The combined extracts were washed with brine, and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was used in next step without further purification.

To a solution of the alcohol in dry toluene (3 mL) was added Burgess reagent (42.9 mg, 0.18 mmol, 5.0 equiv.), and the resultant mixture was stirred at 70 °C for 2 h. After cooling to the room temperature, the reaction mixture was quenched with brine, extracted with EA, and finally dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a silica gel column chromatography on silica gel (hexane/EA : 5/1 to 1/1) to give perforanoid A(**1**) (5.1 mg, 33%, 51% brsm, white solid) and 3.4 mg recovery of compound **(-)-4**. **1:** R_f = 0.3 (silica, hexane/EA : 1/1); $[\alpha]_D^{22}$ = -183.5 (c = 0.18, MeOH). IR (thin film, ν cm^{-1}): 2926, 1736, 1662, 1236, 1155, 1035, 904, 873, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 11.1, 9.4 Hz, 2H), 6.44 – 6.27 (m, 3H), 5.19 (s, 1H), 3.73 (s, 1H), 3.23 (dd, *J* = 12.3, 5.3 Hz, 1H), 2.58 – 2.41 (m, 2H), 2.33 – 2.15 (m, 3H), 2.08 (td, *J* = 13.9, 3.2 Hz, 1H), 1.86 (dd, *J* = 14.1, 1.5 Hz, 1H), 1.55 (s, 3H), 1.49 – 1.41 (m, 1H), 1.35 (s, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 174.0, 173.0, 166.6, 144.4, 140.2, 137.9, 136.6, 134.5, 120.7, 108.6, 85.9, 83.3, 50.7, 49.7, 46.7, 41.9 35.2, 34.5, 34.1, 29.4 28.0 21.9, 19.7,19.4; RMS(ESI) $(M+Na)^+$ calcd for $C_{25}H_{28}O_6Na^+$: 447.1778, found: 447.1776.

*8.14. Synthesis of Compound 10-epi perforanoid A (**47**)*

To a solution of (-)-**4** (9.5 mg, 0.035 mmol, 1.0 equiv.) in THF (1 mL) was added LDA (53 μL, 0.105 mmol, 3.0 equiv., 2M in THF) at -78 °C in a drop-wise manner, and the resultant mixture was then stirred at the same temperature for 2 h, during this time the temperature was warmed to -30 °C. To this solution was added a solution of aldehyde **5b** (30.0 mg, 0.175 mmol, 5.0 equiv.) in THF (1 mL) in a drop-wise manner, and the resultant mixture was stirred at -30 °C for 10 h, during which time the temperature was warmed to rt. The reaction mixture was quenched by addition of a saturated solution of NH_4Cl (5 mL), and the water (5 mL), the mixture was extracted with EA (6 × 20 mL) and CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with brine, and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was used in next step without further purification.

To a solution of the residue made above in dry toluene (3 mL) was added Burgess reagent (41.7 mg, 0.175 mmol, 5.0 equiv.), and the resultant mixture was stirred at 70 °C for 2 h. After cooling back to room temperature, the reaction mixture was quenched with brine, and extracted with EA (3 x 5 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (hexane/EA = 5/1 to 1/1) to give 10-*epi* perforanoid A (**47**) (5.3 mg, 36%, 53% brsm, white solid) and 3.0 mg recovery of compound **(-)-4**.

47: IR (thin film, ν cm^{-1}): 2972, 1772, 1696, 1654, 1620, 1459, 1271, 1127, 986, 874, 734, 602; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 1.7 Hz, 1H), 7.45 (d, *J* = 0.6 Hz, 1H), 6.53 (dd, *J* = 10.0, 1.5 Hz, 1H), 6.33 (s, 2H), 5.20 (s, 1H), 3.73 (s, 1H), 3.23 (dd, *J* = 12.3, 5.1 Hz, 1H), 2.71 (dd, *J* = 16.3, 7.2 Hz, 1H), 2.56 (td, *J* = 9.7, 6.9 Hz, 1H), 2.45 – 2.29 (m, 3H), 2.05 (td, *J* = 13.7, 3.2 Hz, 1H), 1.88 (dd, *J* = 14.2, 1.7 Hz, 1H), 1.47 (s, 3H), 1.45 – 1.30 (m, 2H), 1.23 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 174.4, 173.1, 166.7, 144.4, 140.2, 138.8, 136.7, 134.3, 120.7, 108.6, 86.3, 83.2, 51.6, 49.7, 46.9, 41.2, 34.6, 34.2, 34.2, 28.9, 28.1, 22.5, 19.8, 19.5. HRMS (ESI) $(M+Na)^+$ calcd for $C_{25}H_{28}O_6Na^+$: 447.1778, found: 447.1781.

Acknowledgments

We thank the National Science Foundation of China (Grant Nos.21372016,21572009 and 21402002), Guangdong Natural Science Foundation (Grant Nos.2014A030312004 and 2016A030306011), Shenzhen Basic Research Program (Grant Nos. ZDSYS20140509094114168, JSGG20140717102922014, JCYJ20150629144231017, JCYJ20160226105337556 and JCYJ20160330095629781), and the Shenzhen Municipal Development and Reform Commission (Disciplinary Development Program for Chemical Biology) for financial support.

Appendix A. Supplementary data

Supplementary data related to this article can be found at??

References

1. Bisson J, McAlpine JB, Friesen JB, et al. *J Med Chem* 2015; 59: 1671.
2. Tan Q-G, Luo X-D. *Chem Rev.* 2011; 111: 7437.
3. Rahman AKMS, Chowdhury AKA, Ali H-A, et al. *J Nat Med.* 2009; 63: 41.
4. Lee S-E, Kim M-R, Kim J-H, et al. *Phytomedicine*. 2008; 15: 533.
5. (a) Cui J, Deng Z, Xu M, et al. *Helv Chim Acta*. 2009; 92: 139; (b) Brandt GEL, Schmidt MD, Prisinzano TE, et al. *J Med Chem.* 2008; 51: 6495;
6. Rahman AKMS, Chowdhury AKA, Ali HA, et al. *J Nat Med*. 2009; 63: 41.
7. (a) Fang X, Di Y-T, He H-P, et al. *Org Lett*. 2008; 10: 1905; (b) Fang X, Zhang Q, Tan C-J, et al. *Tetrahedron.* 2009; 65: 7408; (c) Yan X-H, Di Y-T, Fang X, et al. *Phytochemistry.* 2011; 72: 508.
8. Lv C, Yan X, Tu Q, et al. *Angew Chem Int Ed.* 2016; 55:7539.
9. Selected examples for natural product synthesis by PK reactions: (a) Xiao Q, Ren W-W, Chen Z-X, et al. *Angew Chem Int Ed.* 2011; 50: 7373; (b) Yang Y, Fu X, Chen J, et al. *Angew Chem Int Ed*. 2012; 51: 9825; (c) Liu Q, Yue G, Wu N, et al. *Angew Chem Int Ed.* 2012; 51: 12072; (d) Huang J, Fang L, Long R. et al, *Org Lett.* 2013; 15, 4018; (e) Jørgensen L, McKerrall SJ, Kuttruff CA, et al. *Science* 2013;

341: 878; (f) You L, Liang X-T, Xu L-M, et al. *J Am Chem Soc* 2015; 137: 10120; (g) Shi L,Yang Z. *Eur J Org Chem* 2016; 2016: 2356.

10. van den Broek SAMW, Rensen PGW, van Delft FL, et al. *Eur J Org Chem*. 2010; 2010: 5906.
11. Ok T, Jeon A, Lee J, et al. *J Org Chem*. 2007; 72: 7390.
12. (a) Posner GH. *Org Rec*. 1972; 19: 1; (b) Kozlowcki JA. *Comp Org Synth.* 1991; 4: 169.
13. Fernández González D, Brand JP, Waser J. *Chem Eur J*. 2010; 16: 9457.
14. Matsumoto T, Imai S, Yamaguchi T, et al. *Bull Chem Soc Jpn*. 1985; 58: 346.
15. Shi L-L, Shen H-J, Fang L-C, et al. *Chem Commun*. 2013; 49: 8806.
16. (a) Inagaki F, Mukai C. *Org Lett*. 2006; 8: 1217; (b) Hayashi Y, Miyakoshi N, Kitagaki S, et al. *Org Lett*. 2008; 10: 2385.
17. Piancatelli G, Scettri A, D'Auria M. *Tetrahedron Lett*. 1977; 18: 2199.
18. Zhang W-B, Lin G, Shao W-B, et al. *Chem Asian J*. 2015; 10: 903.
19. Yadav JS, Reddy PAN, Ather H, et al. *Synthesis.* 2012; 44: 579.
20. (a) Evans MA,Morken JP. *Org Lett.* 2005; 7: 3367; (b) Evans MA, Morken JP. *Org Lett.* 2005; 7: 3371.
21. Ji JX, Qiu LQ, Yip CW, et al. *J Org Chem*. 2003; 68: 1589.
22. Sofiyev V, Navarro G, Trauner D. *Org Lett*. 2008; 10: 149.
23. For sp_3-sp_2 Suzuki reaction see : (a) Chemler SR, Trauner D, Danishefsky SJ. *Angew Chem Int Ed*. 2001; 40: 4544; (b) Ohba M, Kawase N, Fujii T. *J Am Chem Soc.* 1996; 118: 8250; (c) Meng DF, Danishefsky SJ. *Angew Chem Int Ed.* 1999: 38: 1485; (d) Trauner D, Schwarz JB, Danishefsky SJ. *Angew Chem Int Ed.* 1999; 38: 3542; (e) Johnson CR, Miller MW, Golebiowski A, et al. *Tetrahedron Lett.* 1994; 35: 8991.
24. Negeshi reaction: (a) Hatakeyama T, Nakagawa N, Nakamura M. *Org Lett.* 2009: 11: 4496; (b) Zhou J, Fu GC, *J Am Chem Soc*. 2003; 125: 12527; (c) Wiskur SL, Korte A, Fu GC, *J Am Chem Soc*. 2004: 126: 82.
25. Molander GA, Argintaru OA. *Org Lett*. 2014; 16:1904.
26. Haynes SW, Sydor PK, Corre C, et al. *J Am Chem Soc.* 2011; 133: 1793.
27. Álvarez S, Khanwalkar H, Álvarez R, et al. *ChemMedChem.* 2009; 4: 1630.
28. Seco JM, Quiñoá E, Riguera R, *Chem Rev*. 2004; 104: 17.
29. Gu YQ, Zhang PP, Fu JK, et al. *Adv Synth Catal*. 2016; 358: 1392.