Total Synthesis

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Isolation and Asymmetric Total Synthesis of Perforanoid A

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Abstract: *A novel limonoid, perforanoid A, was isolated, and an asymmetric total synthesis was achieved in 10 steps. The key steps are chiral tertiary aminonaphthol mediated enantioselective alkenylation of an aldehyde to an allylic alcohol, Pd-catalyzed coupling of the allylic alcohol with vinyl ether to form the γ-lactone ring, and cyclopentenone ring formation through a Rh-catalyzed Pauson–Khand reaction. Preliminary studies show that perforanoid A is cytotoxic towards HEL, K562, and CB3 tumor cell lines.*

Limonoids are a structurally diverse family of natural products. They have a wide range of biological activities and are used in agricultural and medicinal applications.[1]

Our research group is interested in Meliaceae and Simaroubaceae species. We have previously isolated from them a group of limonoids[2] featuring a polycyclic lactone fragment (**2**–**6**), and this work, we isolated the new limonoid **1** (Figure 1). These compounds have antifeedent,[1b] antileukemia,[3] anticancer,[4] antibacterial (including against multidrug-resistant bacteria),[5] and antimalarial activities.[6]

The gross structure of perforanoid A (**1**) was determined using NMR spectroscopy (see the Supporting Information for details). It has an all-carbon quaternary stereocenter at C13 and a novel BCD tricyclic ring system. However, the C10 configuration could not be determined from its ROESY spectrum because of free rotation about the C5−C10 single bond. We were unable to crystallize the compound because of the limited amount of product isolated, therefore X-ray crystallography could not be used.

Several methods have been reported for the synthesis of CD bicyclic ring systems,[7] but the total synthesis of this type of limonoid has not been reported.[8] Therefore, we initiated a program toward the total synthesis of perforanoid A (**1**). Our aim was to identify a pathway for rapid access to the tricyclic core, which would provide a foundation for the total synthesis of **1** and the modular construction of a library of analogues for medicinal chemistry studies. Herein, we report the asymmetric total synthesis of **1** and confirmation of its structure.

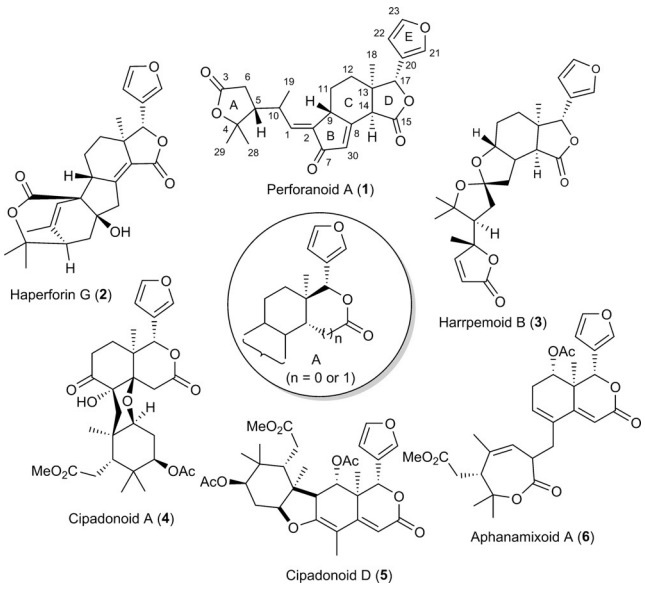
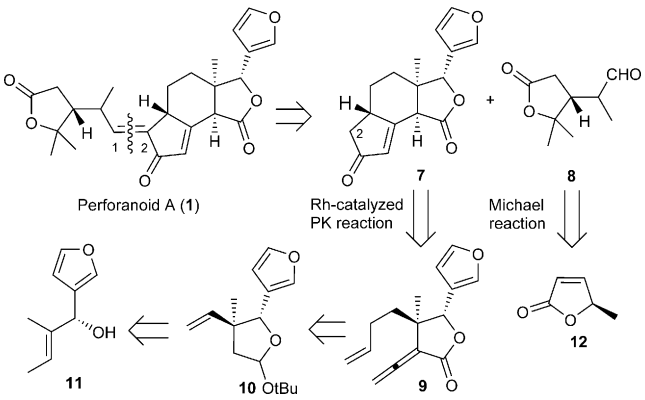


Figure 1. Examples of naturally occurring limonoids.

Scheme 1 shows our retrosynthetic analysis of **1**. We envisioned that **1** could be made from ketoester **7** and aldehyde **8** through aldol condensation to form a pair of diastereoisomers, which could help us to define the stereo-



Scheme 1. Retrosynthetic analysis of perforanoid A (**1**).

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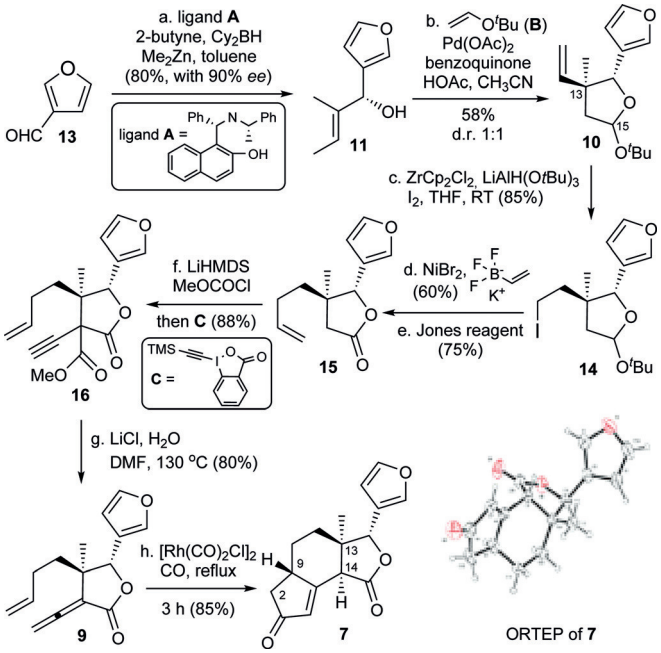
chemistry of **1** at C-10. The Pauson–Khand (PK) reaction is a powerful method for cyclopentenone synthesis, and has been used to synthesize complex natural products.[9] Therefore, we decided to explore the synthetic feasibility of constructing of **7** from allene **9**.[10,9e] Compound **9** was expected to be derived from cyclic acetal **10**, which has been used in the total synthesis of fraxinellone limonoids.[7d] Acetal **10** could be generated through Pd-catalyzed coupling[11] of allylic alcohol **11** with a vinyl ether. On the other hand, the γ-lactone side chain (A ring) would be prepared from the known optically pure butenolide, with a Michael reaction as a key step.[12]

Scheme 2 shows our asymmetric synthesis of intermediate **7**. The first step was the asymmetric synthesis of **11** through enantioselective alkenylation of an aldehyde. The reaction of furan-3-carbaldehyde **13** with 2-butenyl methyl zinc[13] (derived from the reaction of 2-butyne, Cy_2BH, and Me_2Zn) in the presence of chiral ligand **A** (1-[(*S*)-phenyl(((1′*S*)-1′-phenylethyl)methylamino)methyl]-2-naphthol)[14] gave **11** in 80% yield with 90% *ee*. With compound **11** in hand, we then adopted Morken's method[7d] for the synthesis of acetal **10**.



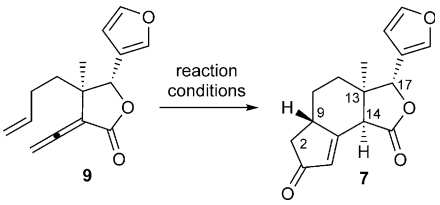
Scheme 2. Asymmetric synthesis of intermediate **7**. Reagents and conditions: a) aldehyde **13** (1.0 equiv), ligand **A** (15 mol%), 2-butyne (2.0 equiv), Cy_2BH (2.0 equiv), Me_2Zn (2.0 equiv), toluene, RT to −78 °C then −30 °C (80% with 90% *ee*); b) 2-methyl-2-(vinyloxy)-propane (**B**), $Pd(OAc)_2$ (0.1 equiv), BQ (3.0 equiv), AcOH (1.1 equiv), CH_3CN, RT, 20 h (58%); c) $ZrCp_2Cl_2$ (1.5 equiv), $LiAlH(OtBu)_3$ (1.5 equiv), THF, I_2 (2.0 equiv), RT (85%); d) $NiBr_2$ glyme (10 mol%), potassium vinyltrifluoroborate (1.1 equiv), bathophenanthroline, NaHMDS (3.0 equiv), *t*-BuOH/CPME (1:1), 60 °C (60%); e) Jones oxidation (75%); f) LiHMDS (2.5 equiv), $ClCO_2Me$ (2.0 equiv), THF, −78 °C to RT, then **C** (Waser's reagent, 2.0 equiv), TBAF (2.0 equiv), −78 °C to RT (88%); g) LiCl (5.0 equiv), H_2O (5.0 equiv), DMF, 130 °C, 2 h (80%); h) $[Rh(CO)_2Cl]_2$ (7%), CO (balloon pressure), toluene, reflux, 3 h (85%). THF = tetrahydrofuran, HMDS = hexamethyldisilazane, CPME = cyclopentyl methyl ether, DMF = *N*,*N*-dimethylformamide.

Pd-catalyzed coupling[11] of **11** with 2-methyl-2- (vinyloxy)-propane (**B**) in the presence of benzoquinone (BQ) and AcOH in CH_3CN gave **10** in 58% yield. The product was obtained as C15 anomers in a ratio of 1:1, and as diastereoisomers at the C13 quaternary center in a ratio of 20:1 in favor of the desired diastereosiomer.

Compound **15** was obtained by Zr-mediated iodonation[15] of **10** with $ZrCp_2Cl_2$ and $LiAlH(OtBu)_3$ and then reaction with I_2 to give **14** in 85% yield. We attempted to use Suzuki,[16] Negishi,[17] and Kumada reactions[18] to convert iodide **14** into its corresponding terminal olefin, but none of these reactions gave the desired product. A recently reported Ni-catalyzed coupling reaction[19] gave the desired olefin in 60% yield. Treatment of the olefin with Jones reagent gave γ-butyrolactone **15** in 75% yield. Intermediate **7** was obtained by treating **15** with lithium hexamethyldisilazide (LiHMDS) and then reacted sequentially with methyl carbonochloridate and Waser's reagent[20] (**C**) to give alkyne **16** in 88% yield with a d.r. ratio of 7:1. Both diastereomers of **16** were treated with LiCl in the presence of water in DMF at 130 °C to initiate decarboxylation, and allene **9** was obtained in 80% yield.[21]

We then evaluated the allene-based PK reaction for the synthesis of **7** with the desired stereochemistries at C9 and C14. Allene **9** was treated with $[Rh(CO)_2Cl]_2$ (10.0 mol%) in dichloroethane (DCE) or toluene at 80 °C under the conditions listed in Table 1, but the desired product was not observed in the reaction mixture (entries 1–3). We then ran the reaction at 120 °C, and product **7** was isolated in 5% yield

Table 1: Pauson–Khand reaction of allene **9** for the synthesis of tricyclic cyclopetenone **7**.



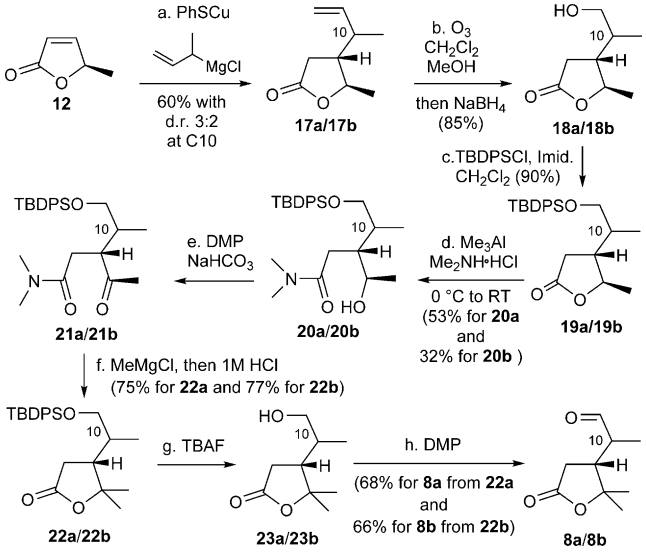
Entry	Rh^I	Solvent	temp. (°C)	conc.[b] (N)	cat. (mol%)	Yield[c] (%)
1	$[Rh(CO)_2Cl]_2$	DCE	80	0.1	10	–[a]
2	$[Rh(CO)_2Cl]_2$	DCE	80	0.01	10	–[a]
3	$[Rh(CO)_2Cl]_2$	toluene	80	0.1	10	–[a]
4	$[Rh(CO)_2Cl]_2$	toluene	120	0.1	10	5
5	$[Rh(CO)_2Cl]_2$	toluene	120	0.01	10	55
6	$[Rh(CO)_2Cl]_2$	toluene	120	0.008	10	84
7	$[Rh(CO)_2Cl]_2$	toluene	120	0.008	7	85
8	$[Rh(CO)_2Cl]_2$	CH_2Cl_2	reflux	0.008	10	–[a]
9	$[Rh(CO)_2Cl]_2$	CH_2Cl_2	reflux	0.008	7	–[a]
10	$[Rh(CO)_2Cl]_2$	CH_3CN	reflux	0.008	10	–[a]
11	$[Rh(CO)_2Cl]_2$	CH_3CN	reflux	0.008	7	–[a]
12	$[Rh(CO)_2Cl]_2$	benzene	reflux	0.008	10	–[a]
13	$[Rh(CO)_2Cl]_2$	benzene	reflux	0.008	7	–[a]
14	$[Rh(CO)_2Cl]_2$	toluene	120	0.005	7	75
15	$[Rh(CO)_2Cl]_2$	toluene	120	0.008	5	70
16	$[Rh(CO)(dppp)Cl]_2$	toluene	120	0.008	10	45
17	$[Rh(CO)(dppe)Cl]_2$	toluene	120	0.008	10	36
18	$[RhCl(cod)]_2$	toluene	120	0.008	10	18

[a] No reaction, recovery of starting material **9**. [b] Concentration of allene **9**. [c] Yield of isolated product.

(entry 4). To improve the reaction yield, we systematically evaluated the effects of the reaction parameters (catalyst, CO pressure, solvent, and reaction temperature and concentration) on the PK reaction (Table 1).

These results show that: 1) among the catalysts used ($[Rh(CO)(dppp)Cl]_2$, $[Rh(CO)(dppe)Cl]_2$, $[RhCl(cod)]_2$, and $[Rh(CO)_2Cl]_2$), $[Rh(CO)_2Cl]_2$ gave the best result (Table 1, entries 7, 10, 11 and 12); 2) toluene was the best solvent; 3) better yields were obtained at 120 °C than 80 °C; 4) a reaction concentrations of 0.008 M gave the best result (entries 6–7); 5) performing the reaction at a balloon pressure of CO did not improve the product yield; and 6) performing the reaction in the presence of different catalysts and solvents did not improve the results (entries 14–18). The optimum conditions, namely, 3 h at 120 °C in toluene at a reaction concentration of 0.008 M with $[Rh(CO)_2Cl]_2$ (7 mol %) as the catalyst, gave **7** in 85 % as a single isomer; the relative stereochemistry of **7** was determined by using single-crystal X-ray diffraction.[22]

We then focused on synthesizing **8a** and **8b** (Scheme 3). Treatment of furanone **12** with a Grignard reagent in the presence of PhSCu[23] gave **17a** and **17b** in a 60 % combined yield as a pair of C10 diastereoisomers in a ratio of 3:2. Without separation, **17a** and **17b** were treated with ozone followed by reduction with $NaBH_4$ to give alcohols **18a** and **18b**, which were converted into their corresponding silyl ethers **19a** and **19b** in 90 % combined yield by treatment with TBDPSCl in the presence of imidazole. Treatment of **19a** and **19b** with dimethylamine hydrochloride in the presence of trimethylaluminum gave **20a** and **20b** in 53 % and 32 % yield,

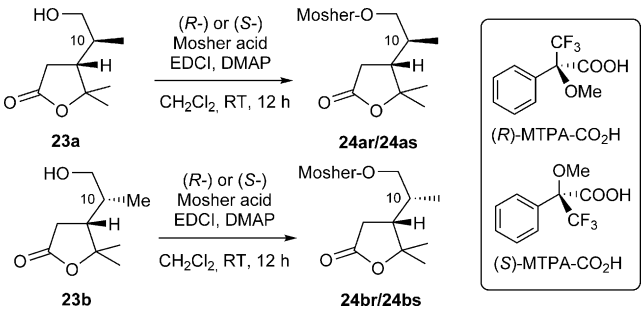


Scheme 3. Asymmetric syntheses of intermediates **8a**/**8b**. Reagents and conditions: a) PhSCu, then but-3-en-2-ylmagnesium chloride (60% for **17a** and **17b**, d.r. 3:2); b) O_3, CH_2Cl_2-MeOH (1:1), −78 °C, then $NaBH_4$, RT (85% for **18a** and **18b**, d.r. 3:2); c) imidazole, TBDPSCl, CH_2Cl_2, 0 °C to RT (90% for **19a** and **19b**); d) Me_3Al, dimethylamine hydrochloride, 0 °C to RT (53% for **20a** and 32% for **20b**); e) DMP, $NaHCO_3$, CH_2Cl_2, RT; f) MeMgCl, −20 °C then 1 M HCl (75% for **22a** and 77% for **22b**); g) TBAF, 50 °C; h) DMP, $NaHCO_3$, CH_2Cl_2, RT (68% for **8a** and 66% for **8b**, two steps). TBDPS = *tert*-butyldiphenylsilyl.

respectively.[12b] Our goal was the total synthesis of **1** and identification of the stereochemistry at C10, therefore, we needed to convert **20a** and **20b** into **8a** and **8b**, respectively, and then react them with substrate **7** to give the corresponding products, and one of which should match the natural product perforanoid A in terms of the stereochemistry at C10. Oxidation of **20a** with Dess–Martin periodinane (DMP) in the presence of $NaHCO_3$ in CH_2Cl_2 gave ketone **21a**, which was reacted with MeMgCl followed by an acid-mediated intramolecular lactonization to give lactone **22a** in 75 % overall yield.[24]

Under identical conditions, lactone **22b** was formed in 77 % yield from **20b. 22a** was treated with *tetra*-butylammonium fluoride (TBAF) to remove the silyl group; the resultant primary alcohol **23a** was oxidized to aldehyde **8a** in 68 % yield for the two steps. The same procedure was used to convert **22b** into aldehyde **8b** in 66 % yield. DMP oxidation gave the aldehyde without epimerization.

To determine the absolute stereochemistry at C10 in **8a** and **8b**, **23a** and **23b** were converted into their corresponding Mosher esters **24ar**/**24as** and **24br**/**24bs** (Scheme 4). ^1H NMR and ^{19}F NMR spectra (see the Supporting Information for details)[25] showed that the absolute stereochemistry at C10 in **8a** and **8b** was *S* and *R*, respectively.

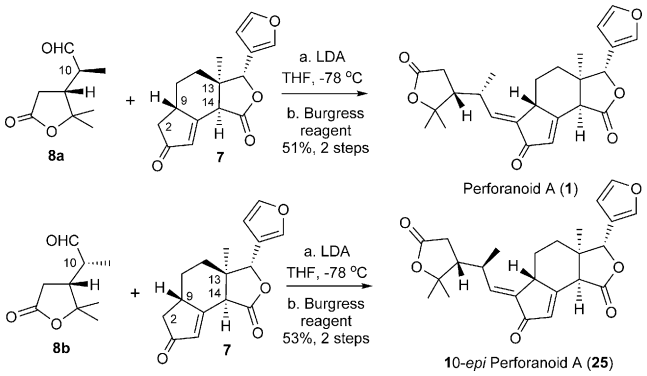


Scheme 4. Syntheses of Mosher esters **24ar**/**24as** and **24br**/**24bs**. EDCI = 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide.

To complete the total synthesis, enone **7** was treated with LDA in THF at −78 °C; the resultant enolate underwent an aldol reaction with aldehyde **8a** to give an alcohol, which was then dehydrated by treatment with Burgess reagent to give perforanoid A (**1**) in 33 % (51% brsm) overall yield (Scheme 5). Under identical conditions, 10-*epi* perforanoid A (**25**) was obtained in 36 % (53% brsm) overall yield.

The ^1H and ^{13}C NMR spectra and specific rotation of the synthesized **1** 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 **25** was assigned as 10-*epi* perforanoid A.

The biological activities of the synthesized perforanoids were investigated by using cytotoxicity assays. The compounds were tested against HEL, K562, CB3, DP17 ,and DM9 cell lines by using the standard method for the MTT proliferation assay.[26] Perforanoid A (**1**) showed cytotoxic



Scheme 5. Syntheses of perforanoid A and 10-*epi* perforanoid A. LDA = lithium diisopropylamide.

activity against HEL, K562, CB3 tumor cell lines, with half maximal inhibitory concentration (IC_{50}) values of 6.17, 4.24, and 3.91 μM, respectively. 10-*epi*-Perforanoid A (**25**) did not show any cytotoxic activity (see Table 2).

Table 2: Cytotoxic assay results for perforanoid A (**1**) and 10-*epi* perforanoid A (**25**) against different cell lines. The results are given as IC_{50} values (μM).

Compound	Cell lines				
	HEL	K562	CB3	DP17	WM9
1	6.17	4.24	3.91	25.96	11.01
25	>50	>50	>50	>50	>50

In summary, we isolated the novel limonoid perforanoid A (**1**) and achieved an asymmetric total synthesis in 10 steps. The key steps in the total synthesis are chiral tertiary aminonaphthol mediated enantioselective alkenylations of aldehydes for the asymmetric synthesis of allylic alcohol **11**, Pd-catalyzed coupling of **11** with a vinyl ether to form the γ-lactone ring, with stereoselective construction of the C13 all-carbon quaternary center, and formation of the cyclopentenone ring by a Rh-catalyzed Pauson–Khand reaction. Preliminary biological studies indicate that this type of natural product has cytotoxic activity against HEL, K562, and CB3 tumor cell lines.

Acknowledgements

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Keywords: asymmetric synthesis · cytotoxicity · limonoids · Pauson–Khand reaction · total synthesis

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