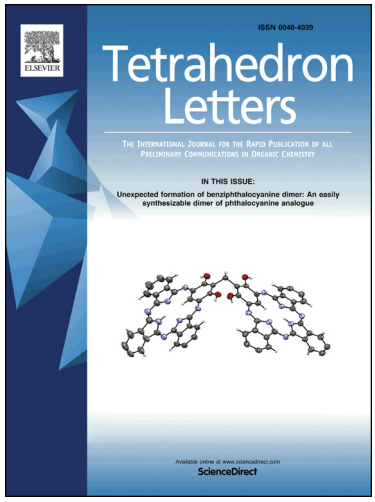


An Efficient Synthesis of the 1,6-Dioxaspiro[4.4]nonan-2-One Motif of the Immunosuppressive Triterpenoid Phainanoid F

Chen-Lu Zhang, Fa-Jun Nan

PII: S0040-4039(17)31248-0
DOI: https://doi.org/10.1016/j.tetlet.2017.09.091
Reference: TETL 49361

To appear in: *Tetrahedron Letters*

Received Date: 25 August 2017
Revised Date: 27 September 2017
Accepted Date: 29 September 2017

Please cite this article as: Zhang, C-L., Nan, F-J., An Efficient Synthesis of the 1,6-Dioxaspiro[4.4]nonan-2-One Motif of the Immunosuppressive Triterpenoid Phainanoid F, *Tetrahedron Letters* (2017), doi: https://doi.org/10.1016/j.tetlet.2017.09.091

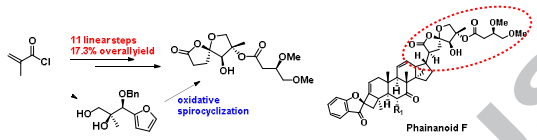
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

An Efficient Synthesis of the 1,6-Dioxaspiro[4.4]nonan-2-one Motif of the Immunosuppressive Triterpenoid Phainanoid F

Leave this area blank for abstract info.

Chen-Lu Zhang[†,‡] and Fa-Jun Nan[†,‡,*]



Tetrahedron Letters
journal homepage: www.elsevier.com

An Efficient Synthesis of the 1,6-Dioxaspiro[4.4]nonan-2-One Motif of the Immunosuppressive Triterpenoid Phainanoid F

Chen-Lu Zhang[†,‡] and Fa-Jun Nan[†,‡,*]

[†] *National Center for Drug Screening, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China*

[‡] *University of Chinese Academy of Sciences, No. 19A Yuquan Road, Beijing 100049, PR China*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Immunosuppressive triterpenoid
Phainanoid F
furan
oxidative spirocyclization

ABSTRACT

We describe an efficient synthesis of the 1,6-dioxaspiro[4.4]nonan-2-one motif of the immunosuppressive triterpenoid Phainanoid F and its C4 epimer. A furan oxidative spirocyclization for constructing the spiro center was used as the key step. Other important reactions involved Sharpless asymmetric dihydroxylation, Weinreb ketone synthesis and Yamaguchi esterfication. The synthesis was achieved in 11 linear steps with 17.3% overall yield.

Phainanoids A-F, endowed with two unprecedented motifs of 4,5- and 5,5-spirocyclic systems, were isolated from *Phyllanthus hainanensis* by Yue and co-workers (Figure 1).[1] They have been found to exhibit remarkable immunosuppressive activities, among which the most potent one, Phainanoid F, inhibit the proliferation of T cells with an IC_{50} of 2.04 ± 0.01 nM and B cells with IC_{50} of < 1.60 ± 0.01 nM. The intriguing chemical structures have attracted some synthetic chemists and a study towards the western part of molecule, 4,5-spirocyclic motif, has been achieved by Dong group recently. [2]

More recently, a series of congeners of Phainanoids A-F which also bearing a highly oxygenated 5,5-spirocyclic ketal lactone motif were reported by Yue's group.[3] A preliminary structure-activity relationship analysis showed that the substituent groups in the 5,5-spirocyclic motif and the configuration of the spiro-ring appeared crucial to the biological activity.[1, 3] As an intriguing structural unit present in variety of other bioactive natural products and [4-6], construction of such a skeleton is vital for further biological evaluation. Some flexible and asymmetric synthetic methods have been reported.[7] Herein, we describe our synthetic efforts towards the eastern part of the molecule, 5,5-spirocyclic motif of Phainanoid F.

The retrosynthetic analysis is illustrated in Scheme 1. We envisaged that the spiroketal lactone **2** could serve as the precusor of compound **1** through Yamaguchi esterfication and following hydrogenation. The spiro center in **2** could be established by oxidative spiroketalization of furan derivative **3**, utilizing *m*-CPBA and pyridinium dichromate (PDC).[8, 9] The Weinreb ketone synthesis was used to install the furan group and the known compound **5** was prepared by Sharpless asymmetric dihydroxylation of **6** according to previous procedures.[10]

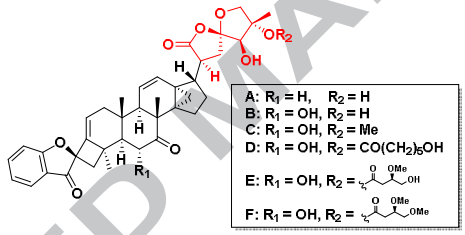
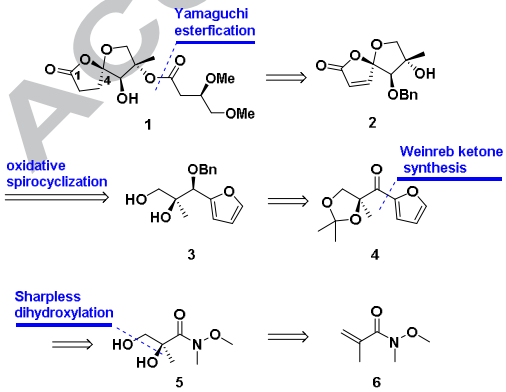
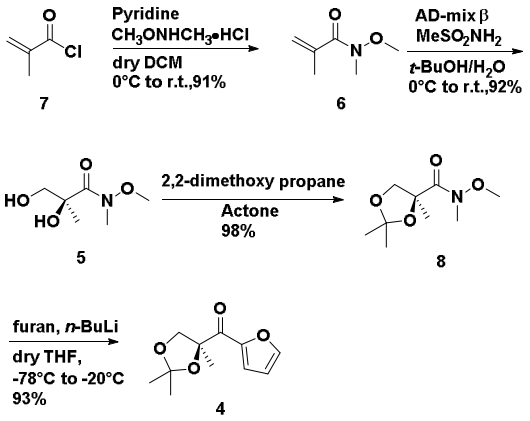


Figure 1. Structures of Phainanoids A-F

Our synthesis commenced with the preparation of the Weinreb ketone synthesis precursor **8** (Scheme 2). Treatment of commercially available acyl chloride **7** with methoxymethylamine and pyridine afforded **6**,[11] which was then subjected to Sharpless asymmetric dihydroxylation to gave (S)-**5** with 89% *ee* value.[10] The ee value of diol **5** was determined by formation of the corresponding Mosher's ester followed by quantification of NMR spectroscopy. After protected with ketal group to furnish **8**, Weinreb ketone synthesis was applied to construct the furan derivative **4** in 76% yield (four steps).



Scheme 1. Retrosynthetic analysis of **1**



Scheme 2. Synthesis of Intermediate **4**

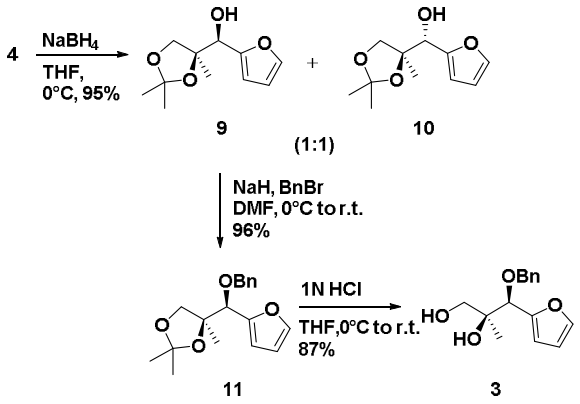
Attempts to reduce compound **4** using L-selectride reported by Hidenori and co-workers[12] failed to get the desired configuration (**9** and **10** as a 1:3 diastereomeric mixture) due to the steric effect of methyl group. Unfortunately, the Corey-Bakshi-Shibata reduction got compound **10** as the major product whether the (S)-CBS or (R)-CBS were used. We also used the sterically hindered reductant such as L-selectride but failed again. Finally we chose $NaBH_4$ although there's no stereoselectivity and got 1:1 diastereomeric mixture. (Table 1) Separation of the mixture was realized on column chromatography (Petroleum: EtOAc, 8:1 v/v), in 48% and 47% yield respectively and the configurations of **9** and **10** were elucidated through NOSEY cross peak shown in energy minimized structures in Figure 2 and further supported by the NOSEY results of compound **2** and **14**. The secondary hydroxyl group of compound **9** was then protected as its benzyl ether **11** and subsequent hydrolyzation with 1N HCl solution in THF afforded **3** as the precusor of oxidative spirocyclization.

reductant	solvent	temp(□)	**9/10** ratio
$NaBH_4$	MeOH	0	1:1
$NaBH_4/CeCl_3 \cdot H_2O$	MeOH	0	1:3
L-selectride	THF	0	1:3
(S)-CBS, $BH_3 \cdot Me_2S$	THF	-78	1:2
(S)-CBS, $BH_3 \cdot Me_2S$	THF	0	1:10
(R)-CBS, $BH_3 \cdot Me_2S$	THF	-78	1:20
(R)-CBS, $BH_3 \cdot Me_2S$	THF	0	1:99

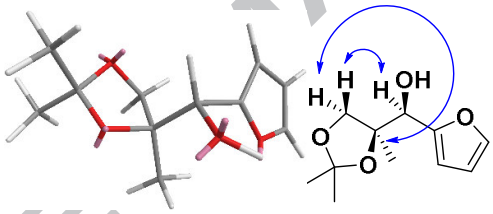
Table 1. Reduction conditions and results

With **3** in hand, the stage was set for a furan oxidative spirocyclization with *m*-CPBA to afford highly unstable lactol intermediate **12** and **13** (Scheme 4), followed by oxidation with PDC in DMF gave γ-spiroketal γ-lacton **2** and **14** as a 10:1 mixture, which was easily separated via column chromatography. Fortunately, the conformation of the major compound **2** was consistent with our desired isomer. Results of 1D and 2D NMR experiments also supported the assignment of the structure and stereochemistry. Owing to the difficulties encountered in esterfication of the hindered tertiary alcohol **2**, a variety of conditions were used to access the ester

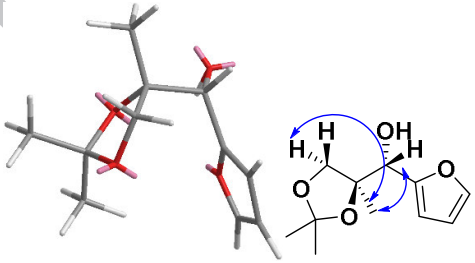
but all failed. Fortunately, Yamaguchi conditions worked well and enabled smooth esterfication of tertiary alcohol with highly oxygenated carboxylic acid **15**[1] to afford **16** and **17**.[13] Hydrogenation using $Pd(OH)_2/C$ and H_2 allowed the debenzylation and reduction of the double bond simultaneously, affording the desired product **1** and its C4 epimer **18**. The structure and stereochemistry was confirmed with the results of NMR (^1H, ^{13}C, 2D-COSY, 2D-HSQC, 2D-HMBC) and the key NOSEY correlations in **1** and **18** are shown in Figure 3.



Scheme 3. Synthesis of Intermediate **3**

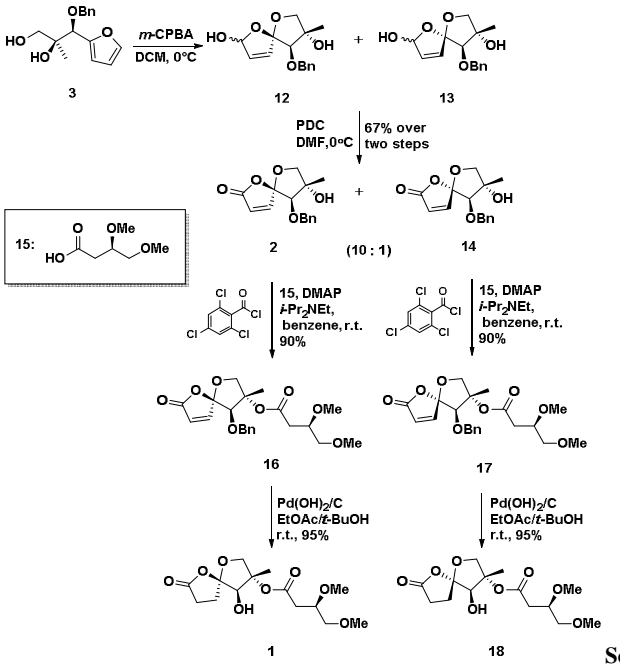


Compound **9**

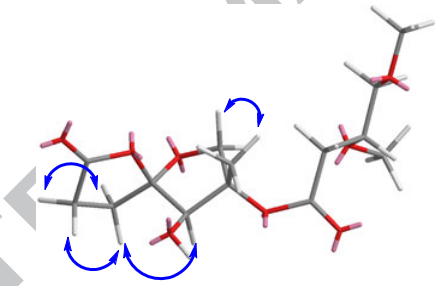


compound **10**

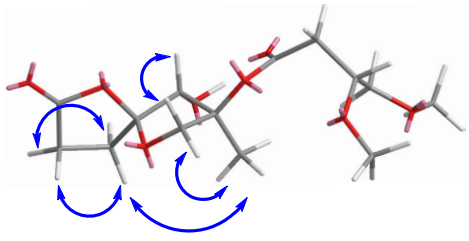
Figure 2. Energy-minimum structure and NOSEY interactions for compound **9** and **10**



Scheme 4. Synthesis of compound **1** and its C4 epimer **18**



Compound **1**



Compound **18**

Figure 3. Key NOSEY correlation in compound **1** and **18**

In summary, we developed an efficient synthesis of the 1,6-dioxaspiro[4.4]nonan-2-one motif of Phainanoid F, employing a furan oxidative spirocyclization as the key step, with 11 linear steps and 17.3% overall yield. However the stereoselectivity of reduction remains to be improved. Further medicinal chemistry derivatization and biological evalution of these simple spirocyclic lactones against the proliferation of T cell and B cell are still ongoing and will be reported in due course.

Supplementary data

Supplementary data (experimental precedure,characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds) can be found in the online version.

References and notes

1. Fan, Y.-Y.; Zhang, H.; Zhou, Y.; Liu, H.-B.; Tang, W.; Zhou, B.; Zuo, J.-P.; Yue, J.-M. *J. Am. Chem. Soc.* **2015**, *137*, 138-141.
2. Xie, J.; Wang, J.; Dong, G. *Org. Lett.* **2017**, *19*, 3017-3020.
3. Fan, Y.-Y.; Gan, L.-S.; Liu, H.-C.; Li, H.; Xu, C.-H.; Zuo, J.-P.; Ding, J.; Yue, J.-M. *Org. Lett.* **2017**, 19, 4580-4583.
4. Nukina, M.; Hirota, H. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1158-1159.
5. Tuchinda, P.; Munyoo, B.; Pohmakotr, M.; Thinapong, P.; Sophasan, S.; Santisuk, T.; Reutrakul, V. *J. Nat. Pro.* **2006**, *69*, 1728-1733.
6. Jing, S.-X.; Luo, S.-H.; Li, C.-H.; Hua, J.; Wang, Y.-L.; Niu, X.-M.; Li, X.-N.; Liu, Y.; Huang, C.-S.; Wang, Y.; Li, S.-H. *J. Nat. Pro.* **2014**, *77*, 882-893.
7. Yoneda, N.; Fukata, Y.; Asano, K.; Matsubara, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 15497-15500.
8. Yang, Z.; Tang, P.; Gauuan, J. F.; Molino, B. F. *J. Org. Chem.* **2009**, *74*, 9546-9549.
9. Thirupathi, B.; Reddy, P. P.; Mohapatra, D. K. *J. Org. Chem.* **2011**, *76*, 9835-9840.
10. Smith, N. D.; Goodman, M. *Org. Lett* **2003**, *5*, 1035-1037.
11. Avenoza, A.; Busto, J. H.; Corzana, F.; Garcia, J. I.; Peregrina, J. M. *J. Org. Chem.* **2003**, *68*, 4506-4513.
12. Hidenori, C.; Toshiki, N.; Hiromitsu, U.; Kazuyoshi, I. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2121-2123.
13. Wadsworth, A. D.; Furkert, D. P.; Sperry, J.; Brimble, M. A. *Org. Lett.* **2012**, *14*, 5374-5377.

Highlights

- An efficient synthesis of the 1,6-dioxaspiro[4.4]nonan-2-one motif of the immunosuppressive triterpenoid Phainanoid F
- A furan oxidative spirocyclization for constructing the spiro center was used as the key step.
- The synthesis was achieved in 11 linear steps with 17.3% overall yield.