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Total Synthesis of Penostatin B

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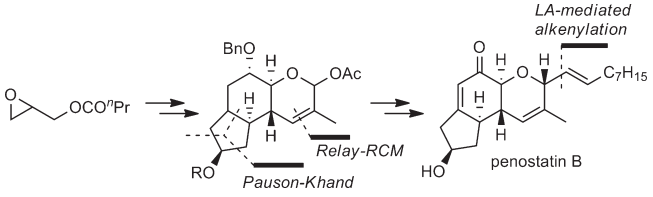
ABSTRACT



The first total synthesis of penostatin B has been accomplished by using a highly diastereoselective Pauson–Khand reaction and an efficient relay ring-closing metathesis for the construction of the basic carbon skeleton of the natural product as the key steps.

Penostatins A (**1**) and B (**2**) are representatives of nine molecules in this family that have been isolated from a strain of *Penicillium* sp. originally separated from the marine alga *Enteromorpha intestinalis* by Numata and co-workers in 1996.[1a] Except for penostatin D, these polyketide-derived penostatins all exhibited significant cytotoxicity against cultured P388 cells.[1] Their structures and absolute stereochemistry have been established on the basis of spectral analyses and chemical transformations. The penostatins A and B possess a synthetically challenging array of structural features: five tertiary stereogenic centers, a densely functionalized hexahydrocyclopenta-[*f*]chromenone skeleton, and the fascinating sigma linkage at C_{12} (a skipped diene) (Figure 1). To date, although the synthesis of (±)-5-deoxypenostatin A[2] has been reported, none of the natural penostatins have been synthesized. Herein, we present the first total synthesis of (±)-penostatin B (**2**), employing as the key steps a highly diastereoselective Pauson–Khand reaction[3] for the construction of the tetrahydroindenone segment, an efficient assembly of the dihydropyranone moiety using a relay ring-closing metathesis,[4] and a diastereoselective introduction of the alkenyl appendage at C_{12} on the dihydropyran ring.

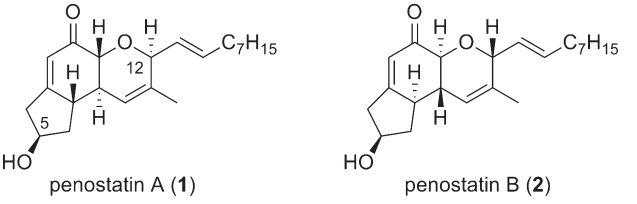


Figure 1. Penostatins A and B.

Our retrosynthetic strategy is illustrated in Scheme 1. We reasoned that the alkenyl side chain at C_{12} could be introduced at a late stage of the synthesis *via* a Lewis acid mediated alkenylation of the acetate **3**. The dihydropyran moiety in **3** would be assembled *via* the ring-closing metathesis (RCM) protocol of the corresponding diene precursor, which can be readily derived from **4**. The alkenyl alcohol **4** with four contiguous stereogenic centers would be constructed diastereoselectively by the Pauson–Khand

(1) (a) Takahashi, C.; Numata, A.; Yamada, T.; Minoura, K.; Enomoto, S.; Konishi, K.; Nakai, M.; Matsuda, C.; Nomoto, K. *Tetrahedron Lett.* **1996**, *37*, 655–658. (b) Iwamoto, C.; Minoura, K.; Hagishita, S.; Nomoto, K.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 449–456. (c) Iwamoto, C.; Minoura, K.; Oka, T.; Hagishita, S.; Numata, A. *Tetrahedron* **1999**, *55*, 14353–14368.

(2) Snider, B. B.; Liu, T. *J. Org. Chem.* **2000**, *65*, 8490–8498.

(3) For a review, see: (a) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, *17*, 2547–2570. (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289–5292. (c) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220–223. (d) Hoye, T. R.; Suriano, J. *J. Org. Chem.* **1993**, *58*, 1659–1660. (e) Mukai, C.; Kim, J. S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem.* **1999**, *64*, 6822–6832. (f) Ishikawa, T.; Shimizu, K.; Ishii, H.; Ikeda, S.; Saito, S. *J. Org. Chem.* **2001**, *66*, 3834–3847. (g) Nakayama, A.; Kogure, N.; Kitajima, M.; Takayama, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8025–8028.

(4) (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211. (b) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. *J. Org. Chem.* **2010**, *75*, 7052–7060.

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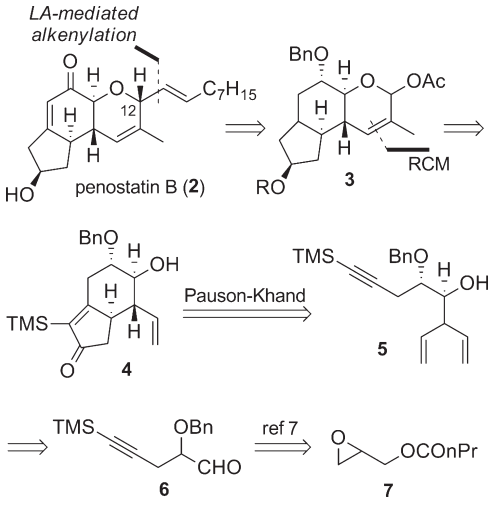
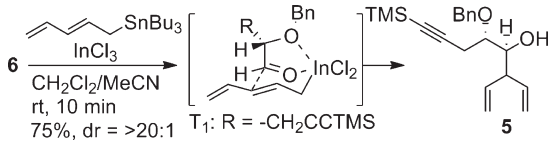
Scheme 1. Retrosynthetic Analysis



reaction of the dienyl alcohol **5**,[5] which in turn would be synthesized from the aldehyde **6** by metal-mediated diastereoselective pentadienylation.[6] The aldehyde **6** can be prepared from the glycidyl ester **7**,[7] which is readily available in both racemic and optically active forms (Scheme 1).

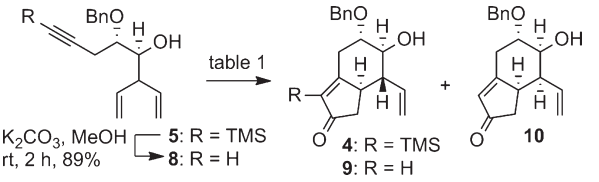
The aldehyde **6**, prepared from (±)-oxiran-2-ylmethyl butyrate **7** *via* a four-step sequence, was treated with (*E*)-tributyl(penta-2,4-dienyl)stannane in the presence of $InCl_3$[6] to give the pentadienylated alcohol **5** as a single product in 75% yield. The diastereoselectivity can be attributed to the indium-chelated chairlike transition state (T_1) as shown in Scheme 2.

Scheme 2. Diastereoselective Synthesis of **5**



We next examined the key Pauson–Khand cyclization for the construction of the tetrahydroindenone segment with four contiguous stereogenic centers. To evaluate the diastereoselectivity of the cyclization, the desilylated compound **8** was prepared and its cyclizations were explored. The results are shown in Table 1. Sequential treatment of a solution of the desilylated substrate **8** in CH_2Cl_2 with $Co_2(CO)_8$ and *N*-methylmorpholine *N*-oxide (NMO),[3b] gave a chromatographically separable 4:1 mixture of the diastereoisomers **9** and **10**, in 72% yield (entry 1). The stereostructures of both were determined by ^1H NMR

Table 1. Pauson–Khand Reaction



entry	substrate	conditions	product (ratio)	yield (%)
1	**8**	$Co_2(CO)_8$, CH_2, rt, 8 h, then NMO, CH_2Cl_2, rt, 8 h	**9/10** (4/1)	72
2	**5**	$Co_2(CO)_8$, CH_2, rt, 8 h, then NMO, CH_2Cl_2, rt, 8 h	**4** (>20:1)	86
3	**5**	$Co_2(CO)_8$, CH_2, rt, 8 h, then evaporation, add MeCN, 60 °C, 8 h	**4** (>20:1)	97

NOE experiments, and it was determined that the major diastereoisomer **9** was indeed the desired product (Figure 2). When compound **5** was subjected to the same reaction conditions as those for **8**, the bicycle **4** was produced in 86% yield as a single product (entry 2). A higher yield (97%) and complete diastereoselectivity of the product **4** were obtained under these conditions without an oxidizing agent (NMO) (entry 3).[3c–e]

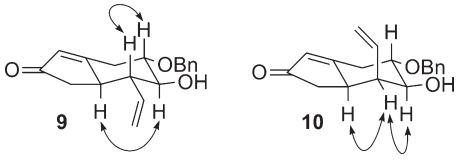


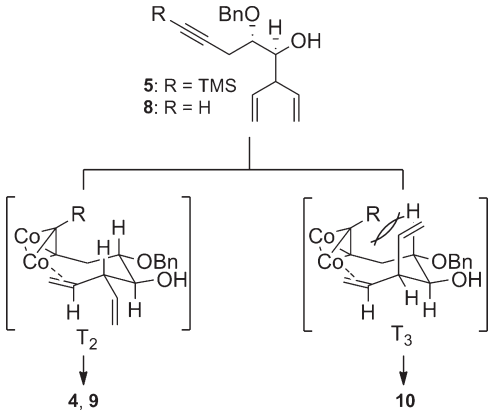
Figure 2. NOE experiments.

The diastereoselective formation of the requisite tetrahydroindenone **4** can be explained by considering the conformation of the transition states $\mathbf{T_2}$ and $\mathbf{T_3}$ for the Pauson–Khand reaction.[8] In the transition state $\mathbf{T_3}$, leading to the formation of the undesired isomer **10**, the R group on the cobalt complex moiety interacts with an axially oriented vinyl group so that the substrate **5** with a bulkier substituent (R = TMS) resulted in the exclusive formation of the desired bicycle **4** *via* $\mathbf{T_2}$ (Scheme 3).

After desilylation, the enone double bond in **4** was selectively reduced with DIBAH/MeLi in the presence of CuI in HMPA/THF[9] to give **11**, which was condensed with methacrylic acid in the presence of 2-methyl-6-nitrobenzoic

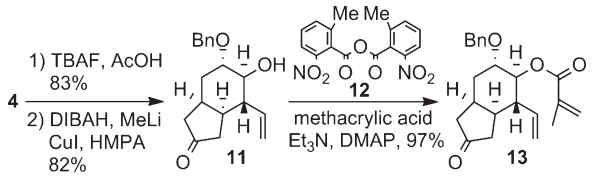
(5) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167–2213.
(6) Nishigaichi, Y.; Hanano, Y.; Takuwa, A. *Chem. Lett.* **1998**, 33–34.
(7) Trost, B. M.; Papillon, P. N.; Nussbaumer, T. J. *J. Am. Chem. Soc.* **2005**, *127*, 17921–17937.
(8) Magnus, P.; Principe, L. W. *Tetrahedron Lett.* **1985**, *26*, 4851–4854.
(9) Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 537–540.

Scheme 3. Plausible Mechanism of Pauson–Khand Reaction



anhydride (MNBA)[10] to provide **13** in excellent yield (Scheme 4).

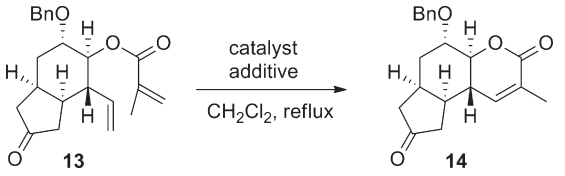
Scheme 4. Synthesis of the Substrate **13** for RCM



With the diene **13** in hand, we next examined the RCM for assembling the dihydropyranone ring in **14**.[11,12] Treatment of **13** with the Grubbs' second-generation catalyst **15** (15 mol %) in refluxing CH_2Cl_2 for 32 h provided only **14** in 11% yield (61% based on the recovered starting **13**) (entry 1, Table 2). When the reaction was conducted using 25 mol % of **15**, compound **14** was obtained in moderate yield (47%; 77% brsm) (entry 2). Using the Grubbs–Hoveyda catalyst **16** or **15** and $Ti(O^iPr)_4$[11] resulted in no reaction (entry 3) or the formation of **17**[13] in 46% yield (entry 4).

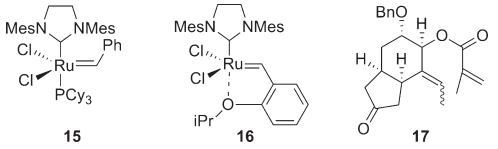
In an effort to improve the lower yield of **14**, we decided to use a relay ring-closing metathesis (RRCM).[4] Treatment of **11** with the carboxylic acid **18**, prepared from allyl alcohol *via* four steps, in the presence of MNBA **12**, triethylamine, and DMAP provided the ester **20** in 93% yield. When **20** was exposed to 50 mol % of **15** in refluxing CH_2Cl_2, **14** was produced in 78% yield. Much better results were obtained when the RRCM was conducted with the methyl homologue

Table 2. Attempted Ring-Closing Metathesis of **13**



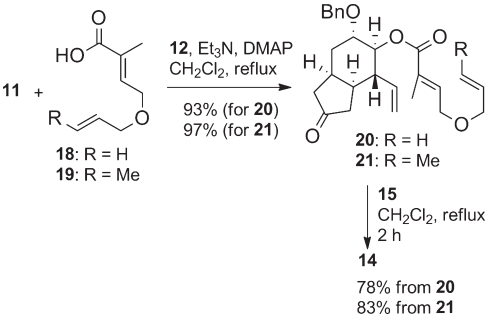
entry	catalyst (mol %)	additive	time (h)	yield (%)[a]
1	**15** (15)	–	32	11 (61)
2	**15** (25)	–	8	47 (77)
3	**16** (10)	–	32	0 (75)
4	**15** (5)	$Ti(O^iPr)_4$	6	–[b]

[a] The yield in parentheses is the yield based on the recovered starting material. [b] The compound **17** was obtained in 46% yield.



21, prepared from **19**. Thus, compound **21** was treated with 25 mol % of **15** in refluxing CH_2Cl_2 to give **14** in 83% yield. Thus, it was demonstrated that RRCM is a versatile method to obtain the functionalized dihydropyranones (Scheme 5).[14]

Scheme 5. Relay Ring-Closing Metathesis

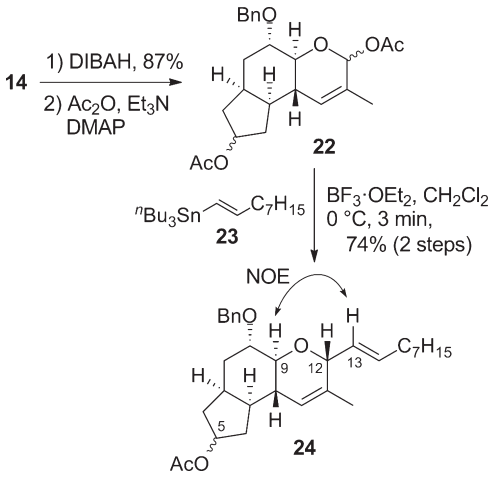


Having made the construction of the basic carbon framework, we next examined the introduction of the alkenyl appendage at C_{12}. Reduction of **14** with DIBAH (87%) followed by acetylation provided the diacetate **22**, as a mixture of diastereoisomers, which was treated with the vinyl stannane **23**[15] in the presence of $BF_3{\bullet}OEt_2$ to provide **24**, as an inseparable 9:1 mixture of diastereoisomers at C_5, in 74% (two steps from the diol).

(10) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, 286–287.
(11) For a review, see: (a) Monfette, S.; Fogg, D. F. *Chem. Rev.* **2009**, *109*, 3783–3816. (b) Prasad, K. R.; Anbarasan, P. *Tetrahedron: Asymmetry* **2007**, *18*, 2479–2483. (c) Pospíšil, J.; Markó, I. E. *Tetrahedron Lett.* **2008**, *49*, 1523–1526.
(12) (a) Fürstner, A.; Langeman, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136. (b) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651–4654. (c) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40*, 4187–4188.
(13) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865–1880.
(14) Druais, V.; Hall, M. J.; Corsi, C.; Wendeborn, S. V.; Meyer, C.; Cossy, J. *Tetrahedron* **2010**, *66*, 6358–6375.
(15) Amans, D.; Beronique, V.; Cossy, J. *Org. Lett.* **2007**, *9*, 4761–4764.

The stereochemistry at C_{12} was established by NOE experiments as shown in Scheme 6.

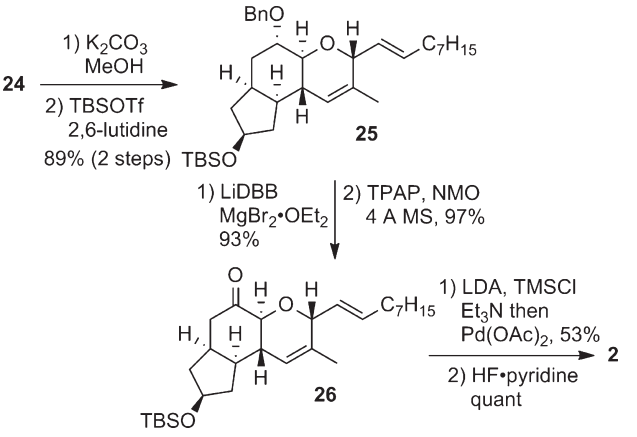
Scheme 6. Diastereoselective Alkenylation



Alkaline hydrolysis of **24** followed by silylation provided the TBS ether **25** in 89% in two steps, and at this stage the minor diastereoisomer with the 5*R** configuration could be separated. Debenzylation using LiDBB/$MgBr_2$•OEt_2[16] proceeded smoothly to give the alcohol, which was oxidized with TPAP/NMO in the presence of 4A MS to provide the ketone **26** in excellent yield. Finally, the Ito–Saegusa oxidation,[17] followed by desilylation of the TBS ether with HF•pyridine, provided (±)-penostatin B (**2**) in 53% yield. The ^1H and ^{13}C NMR properties of the synthetic material were identical with those of the natural penostatin B[1] (Scheme 7).

In summary, we have completed the first total synthesis of penostatin B in a longest linear sequence of 16 steps with an overall yield of 12% from compound **6**, which is known in the literature. The unique features of this work include the use of a highly diastereoselective indium-mediated pentadienylation and intramolecular Pauson–Khand cyclization, the successful application of an efficient RRCM for assembling the dihydropyranone moiety, and the diastereoselective introduction of the C_9 alkenyl side chain at C_{12}. The synthetic route developed here is general and efficient and could also be applied to the syntheses of other penostatins.

Scheme 7. Total Synthesis of Penostatin B (**2**)



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Supporting Information Available. Experimental procedures and characterization data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Fukuda, K.; Miyashita, M.; Tanino, K. *Tetrahedron Lett.* **2010**, *51*, 4523–4525.

(17) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.