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Rapid Assembly of the Bicyclo[5.3.1]undecenone Core of Penostatin F: A Successive Diels–Alder/Claisen Reaction Strategy with an Efficient Stereochemical Relay

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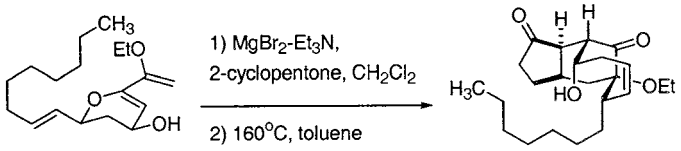
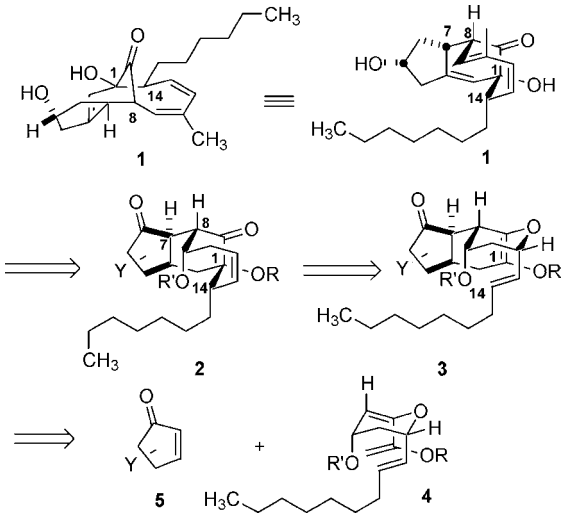
ABSTRACT



The first synthesis of the tricyclic core of Penostatin F (1) using a stereocontrolled Diels–Alder reaction and a Claisen rearrangement in succession has been achieved in nine steps from commercially available methyl acetoacetate and (*E*)-2-decenal. Penostatin F is a metabolite isolated from a fungal strain of *Penicillium sp.*, OUPS-79, separated from the marine alga *Enteromorphia intestinalis* and exhibits significant cytotoxicity against cultured P388 Leukemia cells (ED_{50} = 1.4 μmol/mL).

Penostatin F (**1**) is a metabolite isolated by Numata and co-workers from a fungal strain of *Penicillium sp.*, OUPS-79, separated from the marine alga *Enteromorphia intestinalis* (Scheme 1).[1] This natural product exhibits significant cytotoxicity against cultured P388 Leukemia cells (ED_{50} = 1.4 μmol/mL).[2] Its complex bicyclo[5.3.1]undecenone core is a structural motif that makes this molecule a formidable synthetic target. This is compounded by the paucity of efficient and stereoselective methods for their preparation.[3] To the best of our knowledge, no synthetic approaches for the synthesis of Penostatin F (**1**) have been reported in the literature. Herein, we report the first synthesis of the tricyclic core of **1** using a stereocontrolled Diels−Alder reaction and a Claisen rearrangement in succession as key steps.

Scheme 1



The key step in our retrosynthetic strategy has the γ-enone moiety of the core **2** resulting from a Claisen rearrangement

(1) Numata, A.; Iwamoto, C.; Minoura, K.; Hagishita, S.; Nomoto, K.; *J. Chem. Soc., Perkin Trans. 1* **1998**, 449.

(2) Numata, A.; Yang, P.; Takahashi, R.; Fujiki, M.; Nabae, M.; Fujita, E. *Chem. Pharm. Bull.* **1989**, *37*, 648.

(3) (a) For a detailed review on the synthesis of bicyclo[4.3.1]decenone of phomoidrides, see: Spiegel, D. A.; Njardason, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103*, 2691. For a review that summarizes different approaches for the synthesis of bicyclo[5.3.1]undecene of taxol, see: Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47−75. (c) Sheehan, S. M.; Lalic, G.; Chen, J. S.; Shair, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2714.

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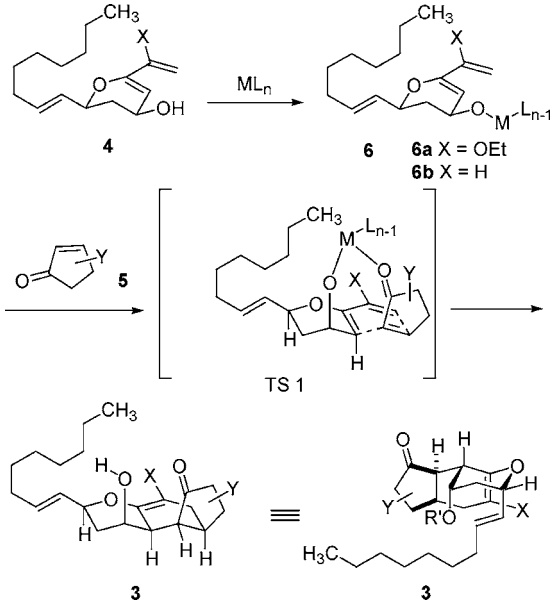
of a tricyclic species **3**. Such a species could arise from a Diels−Alder reaction between dihydropyranyl diene **4** and a five-membered carbocyclic dienophile **5**. Two stereocenters will be generated at the [3.4.0] ring junction, whose configuration will depend on the *endo*/*exo* selectivity of the reaction. However, it is of paramount importance that the facial selectivity be controlled in such a way that the [4.4.0] ring junction hydrogen is placed anti to the olefinic side chain of the pyran moiety.

By examining **3**, it can be seen that with the proper ring junction configuration, the exocyclic and endocyclic olefins can be placed in an orientation suitable for a Claisen rearrangement via a chairlike transition state (**3**→**2**).

Drawing inspiration from the work of Ward and Abaee,[4] we recently established the use of a temporary magnesium alkoxide tether to effect high levels of facial selectivity in Diels−Alder reactions of six-membered-ring semicyclic dienes.[5,6] We envisioned that a diene such as **4** with the hydroxyl placed syn to the olefinic side chain would undergo a hydroxy-directed Diels−Alder (HDDA) reaction through the transition state shown below (TS 1) giving the desired ring junction stereochemistry in **3** (Scheme 2).[4,5] Therefore our first challenge was to develop an efficient route to **4** with the required 1,3-syn relative configuration.

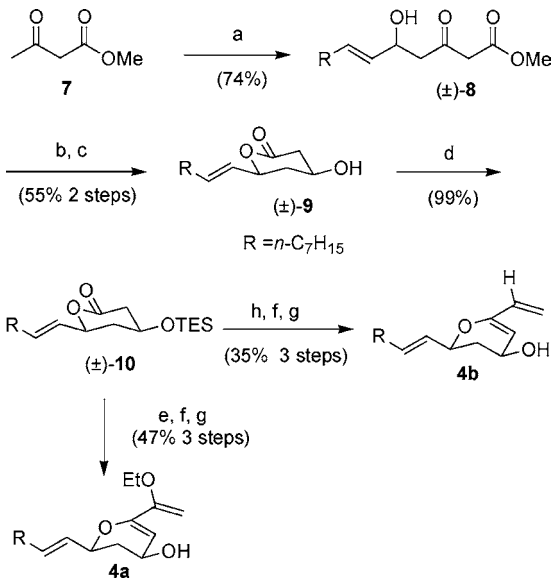
Scheme 2



The synthesis of dienes **4a** and **4b** commenced with a 1,2-addition of the Weiler dianion[7] of methylacetoacetate (**7**) to (*E*)-2-decenal in THF to give the racemic alcohol **8** in 74% yield (Scheme 3). The resulting β-hydroxy ketone **8** was diastereoselectively reduced[8] to the corresponding 1,3-anti diol, which upon treatment with trifluoroacetic acid in dichloromethane afforded lactone **9** in 55% yield (from **7**) as a single diastereomer.

The completion of dienes **4a** and **4b** required initial protection of the hydroxyl moiety in **9** as a triethylsilyl ether,

Scheme 3[a]



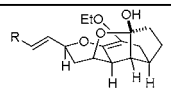
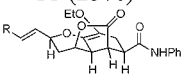
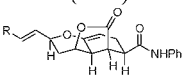
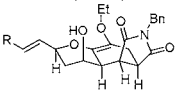
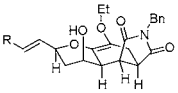
[a] Conditions and reagents: (a) NaH, BuLi, (*E*)-(*n*-C_7H_{15})CH═CHCHO, THF. (b) Me_4NBH_4 (4 equiv), AcOH, MeCN, −78 to −25 °C. (c) TFA (0.2 equiv), CH_2Cl_2. (d) TESCl, Et_3N, DMAP (0.1 equiv), THF. (e) *t*-BuLi, (EtO)CH═CH_2, THF, −78 °C. (f) $SOCl_2$, DMAP, CH_2Cl_2. (g) TBAF, THF. (h) CH_2═CHMgBr, THF, −78 °C.

which proceeded smoothly with chlorotriethylsilane (TESCl) to give **10** in quantitative yield. Addition of lithiated ethyl vinyl ether to **10** followed by dehydration and subsequent deprotection produced diene **4a** in 47% yield over three steps. A similar procedure was used to synthesize diene **4b** from lactone **10** in 35% yield over three steps. In only seven steps, with minimal use of protecting groups, the relative hydroxyl configuration is set correctly. The treatment of **4a** and **4b** with vinylmagnesium bromide (1.1 equiv) in toluene (method A) or $MgBr_2$−Et_3N[9] in dichloromethane (method B) generates in situ the corresponding magnesium alkoxides **6a** and **6b** (Scheme 2) poised to undergo a directed Diels−Alder reaction with *N*-phenylmaleimide (NPM), *N*-benzylmaleimide (NBM), and 2-cyclopenten-1-one (CP) (Table 1).

The HDDA between **4a** and CP using method B afforded the cycloadduct **20** in albeit 23% yield (entry 1). However,

(4) Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937.
(5) Barriault, L.; Thomas, J. D. O.; Clément, R. *J. Org. Chem.* **2003**, *68*, 2317.
(6) (a) For review on tether in cycloaddition, see: Shea, K. J.; Zandi, K. S.; Gauthier, D. R. *Tetrahedron* **1998**, *54*, 2289 and references therein. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478. (c) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578. (d) Sieburth, S.; Fensterbamk, L. *J. Org. Chem.* **1992**, *57*, 5279. (e) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595. (f) Olsson, R.; Bertozzi, F.; Fredj, T. *Org. Lett.* **2000**, *2*, 1283. (g) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450. (h) Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, Z.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653. (i) Shimada, S.; Osoda, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1254−1257. (j) Narasaka, K.; Shimada, K.; Osoda, N.; Iwasawa, N. *Synthesis* **1991**, 1171.
(7) Weiler, L.; Huckin, S. N. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(8) Evans, D. A.; Chapman, K. T.; Carreira, E. M *J. Am. Chem. Soc.* **1988**, *10*, 3560.
(9) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702.

Table 1. Hydroxy-Directed [4 + 2] Cycloaddition

entry	diene	method	dienophile	product (yield)[a]
1	**4a**	B	CP	 **11** (23%)
2	**4a**	B	NPM	 **12** (80%)
3	**4b**	B	NPM	 **13** (58%)
4	**4a**	A	NBM	 **14** (72%)
5	**4a**	B	NBM	 **14** (79%)

[a] Isolated yields, dr > 25:1 and R = *n*-C_7H_{15}.

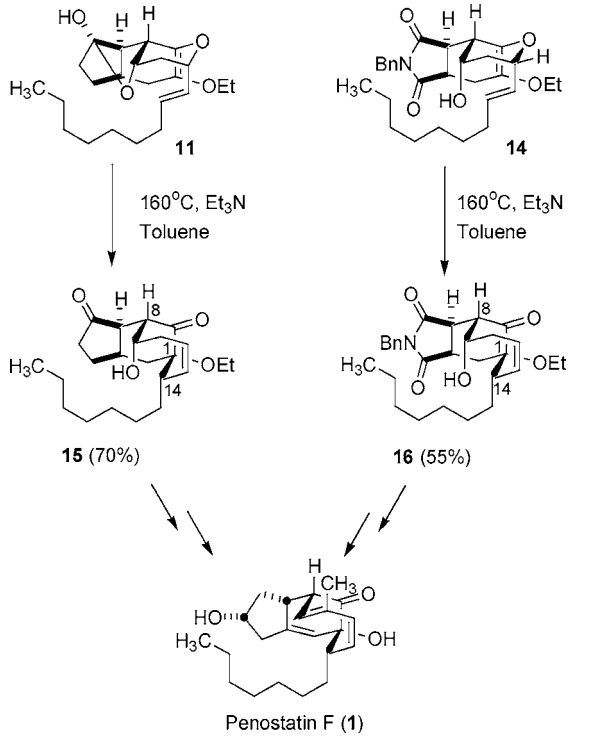
we were gratified to learn that the cycloaddition process produced the required stereochemistry at C8 (dr > 25:1). The relative stereochemistry in the product, as determined by COSY and NOESY analysis, is as expected for dienophile addition to the same face as the directing hydroxyl in an *endo* fashion. Given the low yield of the above Diels−Alder reaction, more active dienophiles were tested. Accordingly, cycloaddition of **4a** and **4b** with NPM and NBM under the above conditions (method B) proceeded smoothly to give the cycloadducts **12**, **13** and **14** in 80, 58, and 79% yields, respectively (entries 2, 3, and 5). Also, the HDDA reaction between **4a** and NBM was carried out where the magnesium alkoxide was formed by the initial reaction of **4a** with vinylmagnesium bromide (1.1 equiv) in toluene (method A).[10] This gave the adduct **14** in 72% yield in which no lactonization was observed (entry 4).

In all the Diels−Alder products, the desired stereochemistry resulting from correct *endo* facial addition was observed[11] and now could be subjected to the thermal conditions required for a Claisen rearrangement.

Cycloadducts **12** and **13** were heated in toluene with a trace of triethylamine yielding a complex mixture of products in which no Claisen products were isolated. It was believed that the lactone moiety in **12** and **13** was possibly hindering the conformational change necessary to bring the allyl and vinyl substituents within proximity of one another. Much to our delight, the heating of **11** and **14** in toluene at 160 °C with a trace of triethylamine produced the bicyclo[5.3.1]-undecenones **15** and **16** in 70 and 55% yields, respectively, resulting in the desired C1, C8, and C14 stereochemistry analogous to **1**.[11,12]

In conclusion, the architectural molecular complexity of **1** was readily assembled via a highly diastereoselective hydroxy-directed Diels−Alder/Claisen reaction sequence from simple structural dienes **4a** and **4b**. This demonstrates the effectiveness of the stereochemical relay established in this sequence starting with the anti-selective reduction of **8**. This process proves to be a powerful strategy for an expeditious formation of the bicyclo[5.3.1]undecenone core of Penostatin F in nine steps from commercially available β-ketoester **7** and (*E*)-2-decenal. The completion of the total synthesis of Penostatin F (**1**) is currently underway in our laboratory and will be reported in due course.

Scheme 4



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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR for compounds **4a**, **4b**, **8**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) No cycloadducts were isolated when using method A (entries 1−3). A complete degradation of dienes **4a** and **4b** was observed.

(11) Relative stereochemistry of **11**−**16** was established by ^{1}H NMR COSY and NOESY experiments.

(12) All attempts to perform this sequence in tandem resulted in the degradation of the Diels−Alder adduct.