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Asymmetric Total Syntheses of (+)-Penostatins A and C

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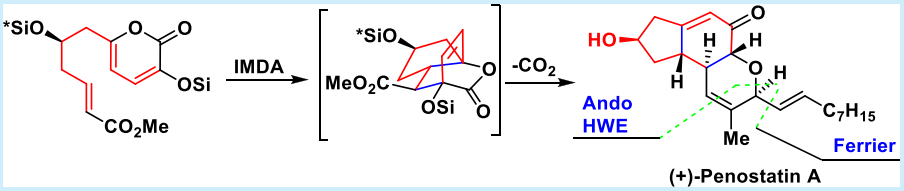

ABSTRACT: Penostatins A and C are cytotoxic natural products that show promising selective inhibitory activity against PTP1B. Here the first asymmetric total syntheses of (+)-penostatins A and C are reported. Our strategy features (i) a new method for the synthesis of 6-alkyl-3-hydroxy-2-pyrones, (ii) a cascade involving the intramolecular Diels–Alder reaction of 2-pyrone and a retro-hetero-Diels–Alder (decarboxylation) reaction, (iii) Ando–Horner–Wadsworth–Emmons olefination/lactonization, and (iv) selenoxide elimination. Our study confirmed the absolute configurations of penostatins A and C and laid the groundwork for further bioactivity studies.

Penostatins A and C along with other members of the penostatin family (Figure 1) were isolated by Numata et

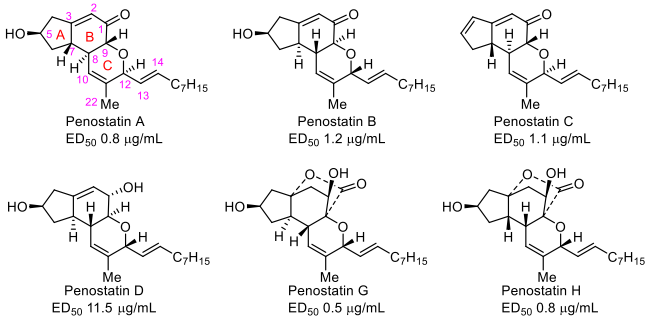

Figure 1. Representative members of the penostatin family.

al.[1] in the 1990s from *Penicillium* sp. of the marine green alga *Enteromorpha intestinalis*. They were found to be cytotoxic against P388 lymphocytic leukemia tumor cell lines with ED_{50} values of 0.8 and 1.1 μg/mL, respectively. Penostatin C was further tested against a panel of human tumor cell lines (39 kinds of human tumor cells) and showed significant cytotoxicity against seven kinds of tumor cells with ED_{50} values ranging from 1.6 to 2.5 μg/mL.[1c] In 2014, Luo and co-workers[2] reported the reisolation of penostatins A and C from cultures of the entomogenous fungus *Isaria tenuipes* and found that penostatins A and C significantly inhibited protein tyrosine phosphatase 1B (PTP1B) with IC_{50} values of 15.87 and 0.37 μM, respectively.

These preliminary bioactivity studies of penostatins sparked research interest from the synthetic community. Previous synthetic efforts were made by Snider,[3] Shishido,[4] Barriault,[5] Hoye,[6] and Mohapatra.[7] Nevertheless, among the 10 molecules of the penostatin family, only penostatins B (racemic) and E (bicyclic, not shown) were reported with total synthesis,[4] which was achieved by Shishido and co-workers, who employed the Pauson–Khand reaction to efficiently forge the A and B rings (Scheme 1a). Of note was Snider's elegant synthetic strategy for 5-deoxypenostatin A using an intramolecular hetero-Diels–Alder (IMHDA) cyclization to construct the tetrahydropyran (THP) ring (Scheme 1b). Unfortunately, this strategy could not be extended to the total synthesis of penostatin A.[3] To date, there is no publication on the total syntheses of cytotoxic penostatin A and the dehydrative congener penostatin C. Herein we report the first and asymmetric total syntheses of penostatins A and C, featuring an intramolecular Diels–Alder (IMDA) and retro-hetero-Diels–Alder (retro-HDA, decarboxylation) cascade to create the key A and B rings (Scheme 1c).

Our synthetic plan is depicted in Scheme 2. We believed that penostatin C (**2**) could be easily obtained from penostatin A (**1**) through dehydration. The enone functionality in the B ring could be derived from well-established PCC-mediated oxidation of tertiary allylic alcohol **3**. The side chain would be installed by Lewis acid-mediated alkenylation of lactone **4**-derived lactol with alkenylstannane reagent, and lactone **4** as the masked THP (C ring) could be prepared by olefination/

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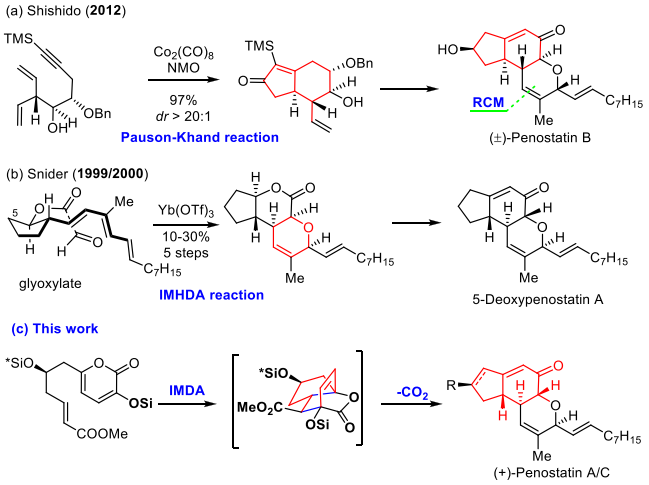
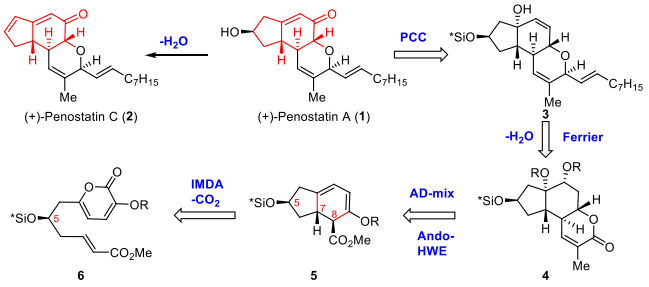
Scheme 1. Previous Syntheses of Penostatin B and 5-Deoxypenostatin A and Our Work on the Syntheses of Penostatins A and C



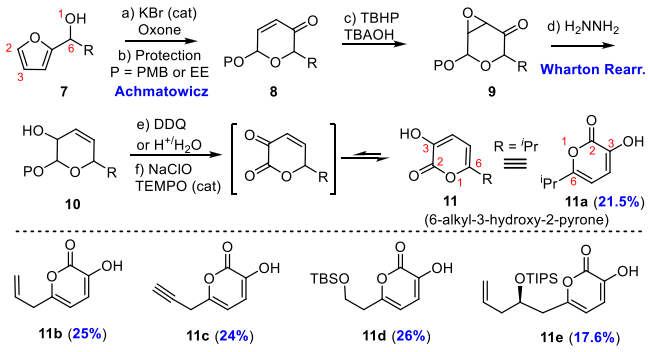
Scheme 2. Our Synthetic Plan (Revised Version)



lactonization with Ando's modification[8] of the Horner–Wadsworth–Emmons (HWE) reaction. We orchestrated a cascade involving the IMDA reaction of 2-pyrone **6**[9] and a retro-HDA (decarboxylation) reaction[10] to obtain the key A and B rings and believed that the chirality of the secondary silyl ether (C5) of **6** could control the formation of new chiral centers at C7 and C8 (**5**) in the Diels–Alder cyclization.

To verify the key IMDA/retro-HDA strategy, we needed an efficient synthesis of 2-pyrones with positional substituents identical or at least similar to those in **6**. However, there was no such example in the literature, and the majority of synthetic methods delivered 4-hydroxy-2-pyrones instead of our desired 3-hydroxy-2-pyrones.[11] The only two related methods for the synthesis of 3-hydroxy-2-pyrones (pyrolysis of mucic acid[12] and Tsuboi's seven-step synthesis[13]) were apparently not applicable or efficient for our synthesis of 6-alkyl-3-hydroxy-2-pyrone **6**. Therefore, we devised a new method for the synthesis of 6-alkyl-3-hydroxy-2-pyrones with positional substitution identical to that in **6** (Scheme 3). Inspired by our previous work on Achmatowicz rearrangement,[14] we envisioned that Achmatowicz rearrangement of substituted furfuryl alcohols (**7**) could provide the requisite THP ring of 2-pyrones and that subsequent epoxidation, Wharton rearrangement,[15] and double oxidation of the α-hydroxy lactol would deliver the desired 6-alkyl-3-hydroxy-2-pyrones (**11**). This new method was finally established after extensive efforts to identify the conditions for protection/deprotection and double oxidation of the resulting α-hydroxy lactol, which either decomposed (oxidative cleavage) or was mono-oxidized under many classical oxidation conditions. Notably, the 3-hydroxy-2-

Scheme 3. Synthesis of 6-Alkyl-3-hydroxy-2-pyrones



pyrones were unstable under the oxidation conditions, and the reaction should complete or otherwise be terminated within 4 h since overnight reaction resulted in decomposition. A small set of 2-pyrones **11a–e** were prepared successfully in 17–26% overall yield without column purification of intermediates **8–10** (see the Supporting Information for details). The preparation of 2-pyrone **11e** was scaled up for our total synthesis of penostatins.

To continue our synthesis of penostatins A and C (Scheme 4), 2-pyrone **11e** was converted to 2-pyrone **6** through silylation and olefin cross-metathesis with methyl acrylate. Heating 2-pyrone **6** in toluene to 100 °C resulted in the expected IMDA/retro-HDA cascade to produce bicyclic **5a** and **5b** in 84% yield as an inseparable mixture with a diastereomeric ratio of 2.3:1 favoring **5a**. Careful structural elucidation of the derivatives (**12a**/**12b** and **13a**) of **5a**/**5b** suggested that **5a** was derived from the slightly favored *endo* adduct while **5b** was derived from the *exo* adduct. Next, we focused on elaboration of **5a** to obtain penostatins A and C and encountered the first unexpected difficulty in converting the **5a**/**5b** mixture to the corresponding allylic alcohols **5c** and **5d**. We imagined that the silyl enol ether of **5a**/**5b** would be electron-rich for α-oxygenation. However, various Rubottom oxidation methods with *m*-CPBA, dimethyldioxirane (DMDO), PIDA, or Davis reagents failed to introduce the α-hydroxy group on the silyl enol ether. Unexpectedly, we found that Upjohn oxidation and Sharpless asymmetric dihydroxylation occurred on the trisubstituted alkene and that AD-mix-β effected the desired diastereoselective (dr > 20:1) dihydroxylation to provide a mixture of **12a** and **12b**. The structure of **12a** was subsequently confirmed by five-step conversion of **12a** to **13a**, single crystals of which were suitable for X-ray diffraction analysis. This unexpected result prompted us to revise our synthetic plan (**4** → **3** → **1**) as shown in Scheme 2, while our original route engaged intermediate **5c**. Therefore, diol **12a** was subjected to a three-step sequence (acetonide protection, desilylation, and $NaBH_4$ reduction) to produce *trans*-β-hydroxy ester **13**, whose relative and absolute stereochemistry were confirmed by the X-ray analysis of its silyl derivative **13a**. Reduction of ester **13** to alcohol **14** was realized with $LiAlH_4$ in 85% yield. TEMPO-mediated regioselective oxidation and olefination using Ando's modification[8] of the HWE reaction (1:10 *E*/*Z* selectivity) and spontaneous lactonization provided the key tricyclic lactone **4** in 74% yield over the two steps. Next, we installed the side chain of lactone **4** (72% yield over two steps with 8:1 dr) through DIBAL-H reduction and BF_3-mediated alkenylation with alkenylstannane[16] by following Shishido's procedure.[4] Removal

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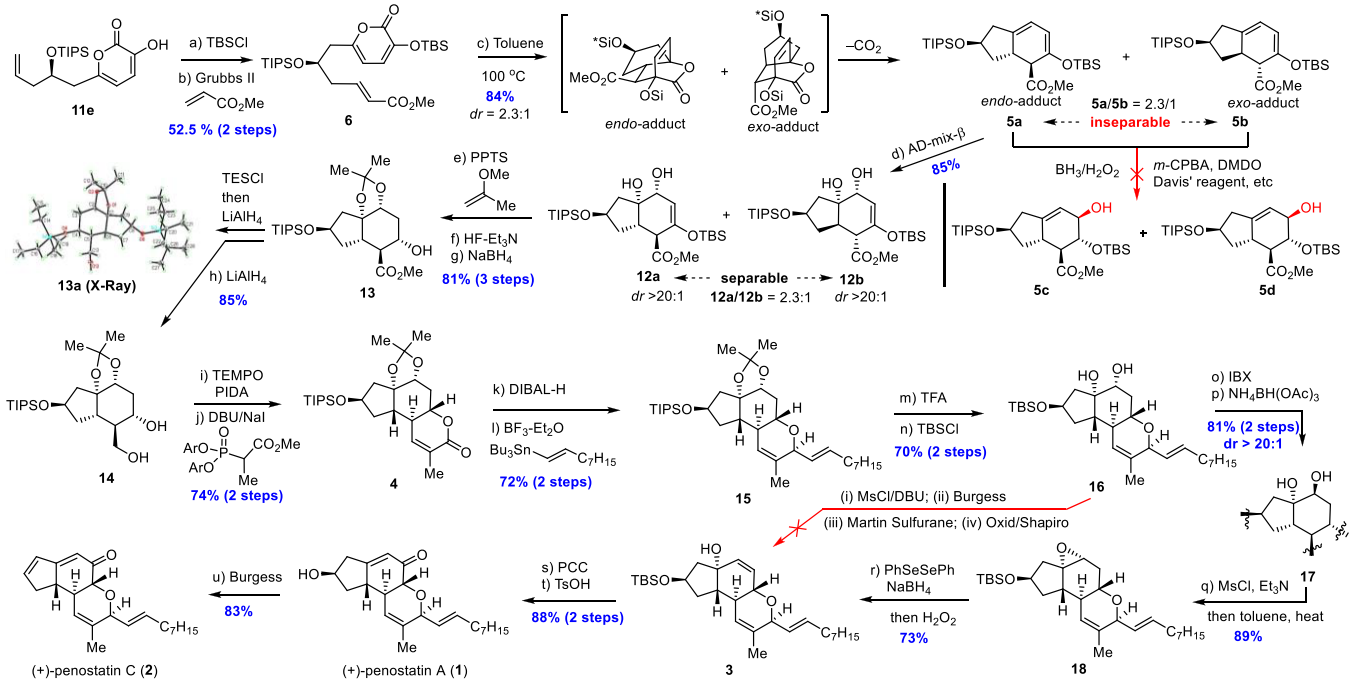
Scheme 4. Total Syntheses of (+)-Penostatins A and C[a]



[a]Conditions: (a) TBSCl (1.2 equiv), imidazole (1.33 equiv), CH_2Cl_2, 0 °C, 2 h, 89%; (b) Grubbs-II catalyst (5 mol %), methyl acrylate (3.3 equiv), CH_2Cl_2, rt, 2 days, 59%; (c) toluene, 100 °C, 2 h, 84%, **5a**/**5b** = 2.3/1; (d) $K_2OsO_2(OH)_4$ (0.05 equiv), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $(DHQD)_2PHAL$ (0.05 equiv), $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH/H_2O, rt, 2 days, 85% (**12a**/**12b** = 2.3:1; dr (**12a**) > 20:1); (e) PPTS (0.09 equiv), 2-methoxypropene (2.2 equiv), DMF, rt, 12 h, 99%; (f) HF-Et_3N (1.0 equiv), MeCN, rt, 12 h, 90%; (g) $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 2 h, 91%; (h) $LiAlH_4$ (2.2 equiv), THF, 0 °C, 2 h, 85%; (i) TEMPO (0.3 equiv), (diacetoxyiodo)benzene (PIDA) (1.05 equiv), CH_2Cl_2, 0 °C, 2 h; (j) Ando's phosphonate (1.27 equiv), DBU (1.6 equiv), NaI (1.6 equiv), THF, 0 °C, 2 h, 74% (two steps); (k) DIBAL-H (1.2 equiv), toluene, 0 °C, 1 h, 90%; (l) alkenyl stannane (3.0 equiv), BF_3-Et_2O (1.1 equiv), CH_2Cl_2, 0 °C, 2 h, 81%, dr 8:1; (m) TFA/MeCN/H_2O (1:20:20 v/v/v), rt, 12 h; (n) TBSCl (2.7 equiv), imidazole (4.2 equiv), CH_2Cl_2, 0 °C, 2 h, 70% (two steps); (o) IBX (2.0 equiv), DMSO, rt, 2 h, 91%; (p) $NH_4BH(OAc)_3$ (1.1 equiv), MeCN/AcOH(3:1 v/v), 0 °C, 1 h, 89%, dr > 20:1; (q) MsCl (1.5 equiv), Et_3N (3.0 equiv), DMAP (0.5 equiv), CH_2Cl_2, 0 °C, 1 h, then toluene, 70 °C, 1 h, 89%; (r) PhSeSePh (1.7 equiv), $NaBH_4$ (2.2 equiv), MeOH, 0 °C, 1 h, then H_2O_2 (3.0 equiv), acetone, 70 °C, 1 h, 73%; (s) PCC (2.0 equiv), NaOAc (3.0 equiv), CH_2Cl_2, 0 °C, 1 h; (t) TsOH (1.0 equiv), MeOH, 0 °C, 1 h, 88% (two steps); (u) Burgess reagent (2.0 equiv), toluene, 70 °C, 1 h, 83%. The ORTEP diagram of compound **13a** is shown with ellipsoids at the 40% probability level (CCDC 1995968).

of the acetonide using TFA resulted in desilylation, and subsequent regioselective silylation with *tert*-butyldimethylsilyl chloride (TBSCl) delivered diol **16** in 70% yield over the two steps. The elimination of the secondary alcohol of **16** to give allylic alcohol **3** posed another unexpected challenge: failure of all attempts using direct dehydrative elimination methods, including MsCl/DBU, TsCl/DBU, Burgess,[17] Martin's sulfurane,[18] etc. This might have occurred because the pseudoequatorial secondary alcohol derivative was unsuitable for E2 elimination. Oxidation of the secondary alcohol of **16** followed by Shapiro reaction[19] gave a trace amount of allylic alcohol **3**. Finally, we tried to invert the stereochemistry of the secondary alcohol with the expectation that dehydrative elimination might occur smoothly when the alcohol was in a pseudoaxial position. Thereafter, *trans*-1,2-diol **17** was prepared through IBX oxidation and subsequent Evans–Saksena reduction.[20] However, dehydrative elimination of the mesylate of diol **17** in toluene at 70 °C did not occur. Instead, epoxide **18** was isolated in 89% yield. Notably, trimethylsilyl protection of the tertiary alcohol did not prevent the formation of epoxide **18**. This unanticipated result offered us the opportunity to explore the conversion of the epoxide to the allylic alcohol via organoselenium as reported by Sharpless in 1973.[21] Gratifyingly, we found that the epoxide opening with selenide was high-yielding, and upon treatment of the crude organoselenium product with excess H_2O_2 in acetone, the selenoxide elimination occurred smoothly at 70 °C to provide alkene **3** in 73% yield. PCC oxidation of **3** followed by TBS deprotection furnished (+)-penostatin A in 70% yield. Burgess dehydration of penostatin A completed the synthesis of (+)-penostatin C in 83% yield. The NMR data of our synthetic penostatins A and C were well-consistent with the reported values.[1] Although we noticed that the value of the specific rotation of our synthetic samples was smaller than that of the natural ones, the sign for our samples {**1**, $[\alpha]_D$ +54.4 (*c* 0.16, $CHCl_3$); **2**, $[\alpha]_D$ +79.3 (*c* 0.16, $CHCl_3$)} was the same as that for natural penostatins A and C {A, $[\alpha]_D$ +133.3 (*c* 0.18, $CHCl_3$); C, $[\alpha]_D$ = +120.0 (*c* 1.00, $CHCl_3$)}, which confirmed their absolute configurations. This constitutes the first asymmetric total synthesis of penostatins A and C.

In summary, we have achieved the first asymmetric total syntheses of penostatins A and C and confirmed their absolute configurations. Our synthetic strategy featured a cascade involving an intramolecular Diels–Alder reaction of a 2-pyrone and a retro-hetero-Diels–Alder (decarboxylation) reaction to forge the A and B rings common to penostatins. We believed that this strategy was complementary to the widely used Pauson–Khand reaction for the synthesis of highly functionalized bicyclo[4.3.0]nonanes. In addition, we developed a new method involving Achmatowicz rearrangement,

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epoxidation, Wharton rearrangement, and double oxidation of an α-hydroxy lactol for the synthesis of 6-alkyl-3-hydroxy-2-pyrones, which are difficult to access by prior methods. In light of the versatile utility of 2-pyrones in organic synthesis, our new method addresses the unmet synthetic challenges for 3-hydroxy-2-pyrones and will find wide application in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01649.

Experimental details, procedures, characterization of all compounds, and crystallographic data for compound **13a** (PDF)

Accession Codes

CCDC 1995968 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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