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Asymmetric Total Syntheses of (−)-Penicipyrone and (−)-Tenuipyrone via Biomimetic Cascade Intermolecular Michael Addition/Cycloketalization

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ABSTRACT

The first total syntheses of (−)-penicipyrone and (−)-tenuipyrone were accomplished enantioselectively in 12 steps with an 11% yield and 6 steps with a 28% yield from the known 4-((*tert*-butyldimethylsilyl)oxy)-cyclopent-2-enone, respectively, by developing a biomimetic bimolecular cascade cyclization featuring an intermolecular Michael addition/cyclo-(spiro-)ketalization sequence. The relative, absolute stereochemistry and carbon connectivity of penicipyrone was further confirmed by X-ray crystallographic analysis and comparison of optical rotations.

Recently, two newly isolated polycyclic 4-hydroxy-2-pyrones (Figure 1) penicipyrone (**1**)[1] and tenuipyrone (**2**)[2] have attracted our attention because of their unprecedented polycyclic skeletons and unexplored biological activities, which might be due to the inadequate supply from natural sources. Penicipyrone (**1**), a novel *cis*-fused tricyclic 6,6,5-pyrone with three contiguous chiral centers, was isolated in 2009 with only 1.2 mg out of 15 L of culture broth of Fungus *Penicillium sp.* PSU-F44, which exhibited antibacterial activity. Tenuipyrone (**2**) was isolated by Asai and Oshima in 2012 with 1.2 mg from 6.9 L of culture medium of entomopathogenic fungus, *Isaria tenuipes*, in the presence of the epigenetic modifying agents histone deacetylase inhibitor and DNA methyltransferase inhibitor. Structurally, tenuipyrone represents a rare tetracyclic 6,6,5,5-pyrone bearing a spiroketal moiety with four contiguous stereocenters.[2] The biogenesis of tenuipyrone was proposed to involve intermolecular Michael addition of 4-hydroxy-6-methyl-2-pyrone (**3**) to cephalosporolide B (**4**), followed by Dieckmann condensation and spiroketalization (Figure 1). To the best of our knowledge, neither total syntheses nor synthetic studies of penicipyrone and tenuipyrone have been reported. Herein, we report the first, asymmetric total syntheses of (−)-penicipyrone (*ent*-**1**) and (−)-tenuipyrone (**2**) by developing a novel biomimetic cascade cyclization featuring an

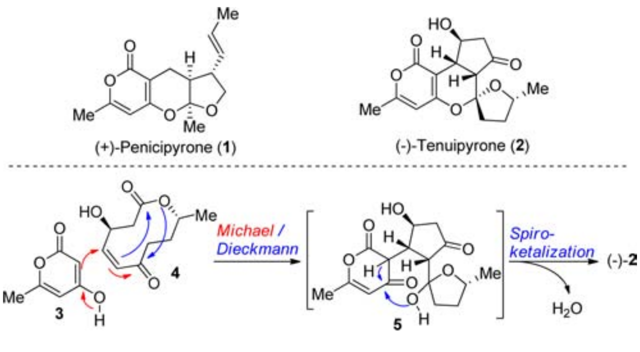

Figure 1. Tenuipyrone and penicipyrone and biosynthetic hypothesis of tenuipyrone.

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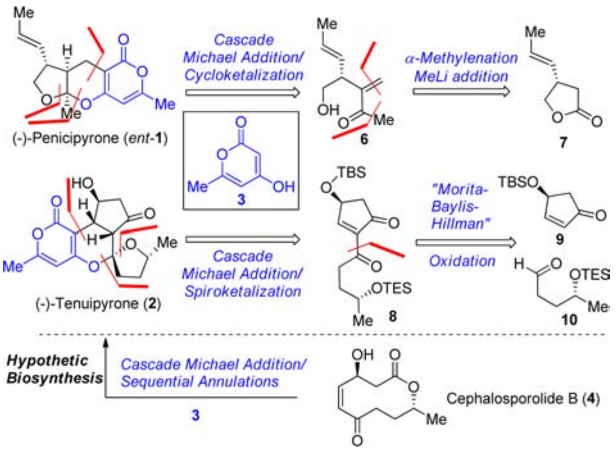
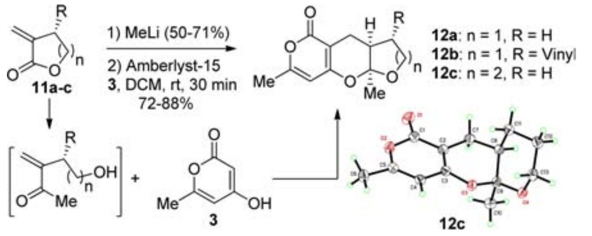
intermolecular Michael addition/cycloketalization.[3] This cascade cyclization may also provide quick and efficient access to other *cis*-fused polycyclic pyrones for potential medicinal applications.

Our synthetic strategy (Scheme 1) was primarily inspired by the biosynthetic hypothesis of tenuipyrone. Although the corresponding biosynthesis of penicipyrone (**1**) has not been proposed yet, we believe that a similar cascade intermolecular Michael addition/cycloketalization could be applied to build up the tricyclic pyrone. Therefore, as outlined in Scheme 1, we envisioned that cascade intermolecular Michael addition of 4-hydroxy-6-methyl-2-pyrone (**3**),[4] followed by cycloketalization (or spiroketalization),[5] would provide the tricyclic and tetracyclic pyrones found in penicipyrone and tenuipyrone, respectively, when α,*β*-unsaturated ketones **6** and **8** were employed as the corresponding Michael acceptors. The relative stereochemistry of the newly formed chiral centers in penicipyrone might arise by stereoinduction from ketone **6** through formation of thermodynamically more stable *cis*-fused tricyclic 6,6,5-ketal with the central pyran ring forming *anti*- to the propenyl side chain to minimize the steric hindrance. A similar stereoinduction might operate for the new chiral centers in the cascade intermolecular Michael addition/spiroketalization for the total synthesis of tenuipyrone (**2**), with addition of 4-hydroxy-2-pyrone *anti*- to the silyloxy substituent. Ketone **6** could be readily synthesized via α-methylenation and methyllithium opening of *γ*-butyrolactone **7**.[6] The 1,3-diketone **8** could be prepared by oxidation of Morita–Baylis–Hillman[7] adducts of 4-((*tert*-butyldimethylsilyl)oxy)-cyclopent-2-enone (**9**)[8] and optically pure aldehyde **10**. At the outset of our synthetic studies, it is not clear whether 4-hydroxy-6-methyl-2-pyrone would undergo 1,4-addition to α,*β*-unsaturated *ketones* since it has been well established that it readily reacts with α,*β*-unsaturated aldehyde in a 1,2-addition fashion in the presence of secondary amine or other catalysts.[9] Therefore, we wished to determine if 1,4-addition of 4-hydroxy-6-methyl-2-pyrone to α,*β*-unsaturated *ketones* would occur followed by cycloketalization. To this end, three racemic α-methylene lactones (**11a**–**11c**) were prepared as model compounds for the cascade intermolecular Michael addition/cycloketalization processes (Scheme 2).

Scheme 1. Retrosynthetic Analyses



Scheme 2. Amberlyst-15 Promoted Cascade Intermolecular Michael Addition/Cycloketalization



As shown in Scheme 2, treatment of the α-methylene lactone with methyllithium afforded the cascade cyclization precursors: *γ*-(or *δ*-) hydroxyl-α,*β*-unsaturated ketones, in good yields (50–71%), which were unconsequentially in equilibrium with the less favored lactol as indicated by ^{1}H NMR. The key cascade intermolecular Michael addition/cycloketalization process was then explored by addition of the individual ketone to the 4-hydroxy-6-methyl-2-pyrone (**3**) in the presence of Amberlyst-15. To our delight, the cascade cyclization proceeded smoothly to give *cis*-fused tricyclic ketals (**12a**–**12c**), corresponding to the penicipyrone core structure, in excellent yields (72–88%) with exclusive regioselectivity. The relative

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(3) For recent advances in the biomimetic total synthesis of natural products, see: (a) *Biomimetic Organic Synthesis*; Poupon, E., Nay, B., Eds.; Wiley-VCH Verlag & Co. KGaA: Weinheim, Germany, 2011. (b) De la Torre, M. C.; Sierra, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 160. (c) Bulger, P. G.; Bagal, S. K.; Marquez, R. *Nat. Prod. Rep.* **2008**, *25*, 254. For cascade reactions involving Michael addition in the total synthesis of natural products, see selected reviews: (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (e) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

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(6) Parsons, P. J.; Lacrouts, P.; Buss, A. D. *J. Chem. Soc., Chem. Commun.* **1995**, 437.

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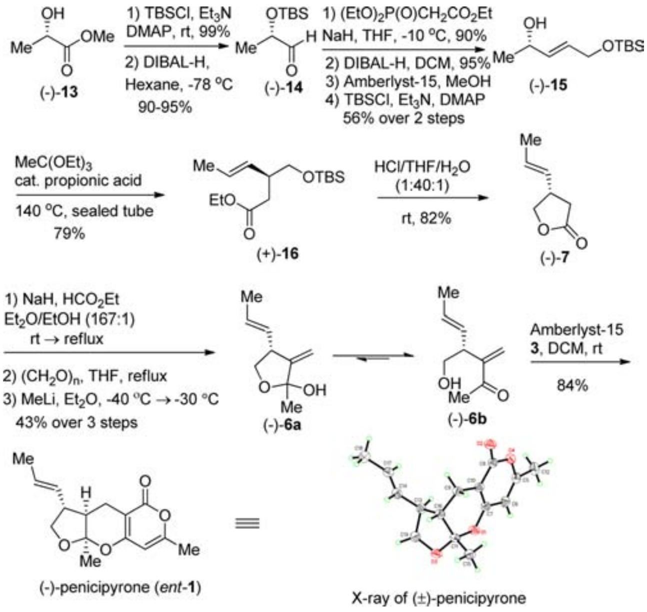
stereochemistry and carbon skeleton of **12c** were further verified by X-ray diffraction analysis.[10]

Encouraged by this newly established bimolecular cascade cyclization process, we set out to undertake the asymmetric total synthesis of penicipyrone. As depicted in Scheme 3, the commercially available chiral building block (−)-methyl lactate (**13**), which was expected to give the enantiomer of natural penicipyrone, was protected as the *tert*-butyldimethylsilyl (TBS) ether and then reduced to aldehyde **14**. A two-carbon extension was achieved by Horner−Wadsworth−Emmons (HWE)[11] olefination of **14**. Reduction of HWE adducts with DIBAL-H and protective group adjustments afforded the enantiomerically pure allylic alcohol **15**. Note that the racemic **15** was initially obtained in high yield at large scale from *cis*-2-butene-1,4-diol in three steps (> 80% yield, TBS monoprotection, Parikh−Doering oxidation, and MeMgCl addition). The optically active alcohol **15** was subjected to Johnson−Claisen rearrangement[12] to afford *trans*-alkene **16** in 79% yield with excellent stereochemistry transfer. Acid-mediated lactonization of **16** cleanly delivered the γ-butyrolactone **7**,[6] which was converted to γ-hydroxyl-α,β-unsaturated ketone **6**, the precursor for the cascade cyclization, through a three-step reaction sequence: Claisen condensation with ethyl formate, aldol addition with paraformaldehyde,[13] and γ-butyrolactone opening by methyllithium. With a reliable supply of ketone **6** in hand, we reached the key cascade intermolecuar Michael addition/cycloketalization. Gratifyingly, treatment of ketone **6** and 4-hydroxy-6-methyl-2-pyrone (**3**) with Amberlyst-15 in DCM promoted the cascade cyclization efficiently and completed the first, asymmetric total synthesis of (−)-penicipyrone (*ent*-**1**) in 84% yield with exclusive diastereoselectivity (for spectra comparison, see Supporting Information).[10] All aspects of spectroscopic data were in good agreement with those of the natural product,[14] except the optical rotation. The optical rotation of our synthetic penicipyrone has an opposite sign (synthetic: $[\alpha]_D$ −52.8, lit. +51),[1,10] verifying the empirical assignment of the absolute stereochemistry of natural penicipyrone. Moreover, a single crystal of racemic synthetic penicipyrone was obtained for the first time for X-ray diffraction analysis, which further confirmed the constitutional structure and its relative stereochemistry of the synthetic penicipyrone.

Scheme 3. Total Synthesis of (−)-Penicipyrone



Next, our attention turned to the total synthesis of the more complex tenuipyrone (**2**). As outlined in Scheme 4, our synthetic venture commenced with the synthesis of the known nonracemic 4-((*tert*-butyldimethylsilyl)oxy)-cyclopent-2-enone (**9a**),[8] a widely used chiral building block in prostaglandin synthesis,[15] which can be prepared in gram scales in five steps from furfuryl alcohol.[10] The other coupling partner, aldehyde **10**, was readily obtained in two steps with excellent yield.[10] The union of these two fragments **9a** and **10** was very challenging. Considerable efforts to unite enone **9a** with aldehyde **10** through the obvious Morita−Baylis−Hillman coupling proved fruitless. Alternatively, Nozaki−Hiyama−Kishi[16] coupling of **9b** and **10** gave the desired β-keto alcohol **19** but with poor reproducibility in 0−20% yields. Finally, it was found that the coupling of organoselenium **18** derived from **9a** with aldehyde **10** could be achieved efficiently in 48−65% yields as a single diastereomer using the method developed by Toru.[17] Mechanistically, it involved 1,4-addition of tributylstannyllithium to enone **18** to generate enolate, followed by aldol reaction of enolate with aldehyde **10** and spontaneous destannylselenenylation. Dess-Martin periodinane[18] oxidation of the alcohol **19** gave the β-keto-enone **8** (95% yield) for the key cascade cyclization. To our delight, under the identical cascade cyclization conditions for the syntheses of penicipyrone and tricyclic pyrrones **12a**−**c**, β-keto-enone **8** underwent Amberlyst-15 promoted cascade

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(10) See Supporting Information for details.

(11) For a selected review, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

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(14) Personal email communication and discussion with professor Rukachaisirikul: the 165.2 ppm signal in the ^{13}C NMR was barely observed in the original spectrum due to weak signals, and 160.6 ppm might be misassigned for the carbon with a resonance of 165.2 ppm. As for ^1H NMR, the only difference between the synthetic (2.12 ppm) and natural (2.18 ppm) product may arise from use of a combination of $CDCl_3$ and CD_3OD (minor) solvents for recording the ^1H NMR spectrum of the natural penicipyrone. See Supporting Information for more details.

(15) For a selected review, see: Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed.* **1984**, *23*, 847.

(16) (a) Namba, K.; Cui, S.; Wang, J.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5417. (b) Namba, K.; Wang, J.; Cui, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5421. For a representative review, see: (c) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.

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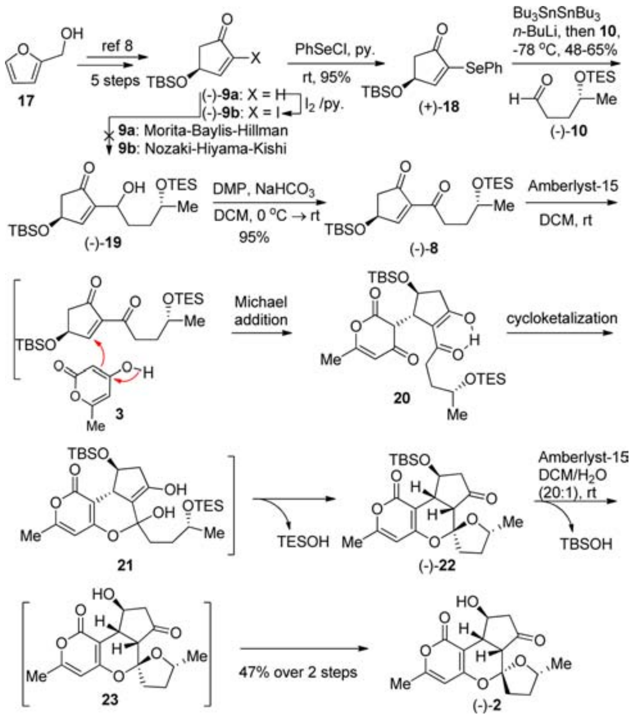
(18) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

intermolecular Michael addition/spiroketalization with 4-hydroxy-6-methyl-2-pyrone (**3**) to afford the (−)-teunipyrone (**2**) although it was obtained as a minor component of the product mixture with the major component tentatively assigned as a potential diastereomer **22**, possibly a kinetically favored product. Noteworthy was the unexpected removal of both TES and TBS during the cascade reactions.

Scheme 4. Total Synthesis of (−)-Tenuipyrone (**2**)



Further efforts to improve the yield of the desired tenuipyrone in the cascade cyclization revealed that (1) tenuipyrone may not be stable under strong acid/base conditions because it decomposed when treated with tetrabutylammonium fluoride or in $CDCl_3$ solution in the NMR tube over 7 h while recording ^{13}C NMR spectra and (2) the diastereomer **22** was initially formed as the only product based on TLC and then converted slowly into the tenuipyrone by Amberlyst-15. Based on these findings and extensive experimentation, we could improve the cascade cyclization by employing the two-step sequence: (a) Amberlyst-15 in dry DCM triggering the cascade cyclization of 4-hydroxy-6-methyl-2-pyrone (**3**) and **8** within 30 min to afford the tetracyclic tenuipyrone (**2**, 16% yield) and its TBS ether diastereomer **22** (60% yield) and (b) subjecting **22** to isomerization mediated by Amberlyst-15 in wet DCM with concomitant removal of the TBS protecting group to provide (−)-tenuipyrone (**2**) in 47% combined yield over two steps. Mechanistically, this novel cascade intermolecular Michael addition/spiroketalization is different from the well established formal [3 + 3] cycloaddition of α,β-unsaturated aldehyde and 4-hydroxy-6-methyl-2-pyrone involving Knoevenagel condensation and 6π-electron electrocyclization.[9] We proposed that intermolecular Michael addition of **3** to **8** was initiated by a Brønsted acid, followed by enolization of β-ketolactone **20** and spiroketalization to provide the kinetically favored spiroketal **22**, which was further isomerized under acidic conditions to afford the thermodynamically favored spiroketal of (−)-tenuipyrone (**2**). All spectroscopic data of our synthetic sample were identical to the reported data of natural (−)-tenuipyrone (**2**).[2,10]

In summary, we have accomplished the first, concise asymmetric total syntheses of (−)-penicipyrone (*ent*-**1**) and (−)-tenuipyrone (**2**) in 12 steps with an 11% yield from (−)-methyl-lactate (**13**) and 6 steps with a 28% yield from the known 4-((*tert*-butyldimethylsilyl)oxy)-cyclopent-2-enone (**9a**) (11 steps with 3.5% yield from furfuryl alcohol), respectively, by developing a biomimetic cascade cyclization featuring an intermolecular Michael addition/cycloketalization (spiroketalization). We have further confirmed the relative and absolute configuration of penicipyrone with X-ray diffraction analysis and comparison of optical rotations. The new biomimetic cascade polycyclization has provided chemical evidence for the potential biosynthetic pathway of tenuipyrone and has demonstrated its viability and efficiency for different γ-(or δ-) hydroxy-α,β-unsaturated ketone substrates. Further explorations and exploitations of the cascade intermolecular Michael addition/cycloketalization are ongoing in our laboratory.

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Supporting Information Available. Detailed experimental procedures, characterizations, and copies of ^{1}H and ^{13}C NMR spectra of new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.