Natural Product Synthesis

DOI: 10.1002/anie.201207307

Total Synthesis of (−)-Acetylaranotin**

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Epidithiodiketopiperazines are an important class of natural products because of their unique structural and biological properties.[1] Among them, acetylaranotin (**1**),[2] SCH64874 (**2**),[3] compound **3**,[4] emethallicin A (**4**),[5] MPC1001 (**5**),[6] and emestrin (**6**)[7] feature a dihydrooxepine moiety fused to a pyrrolidine/epidithiodiketopiperazine (Figure 1). They also

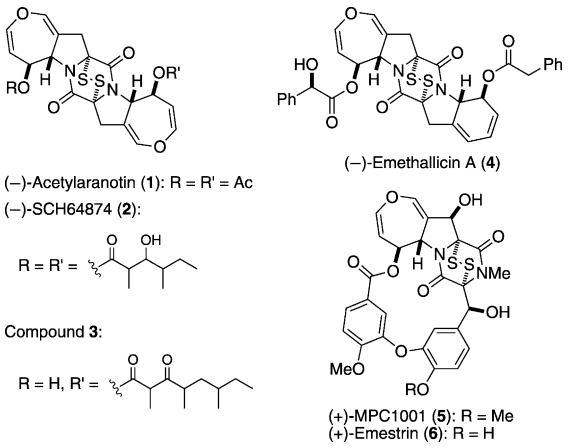
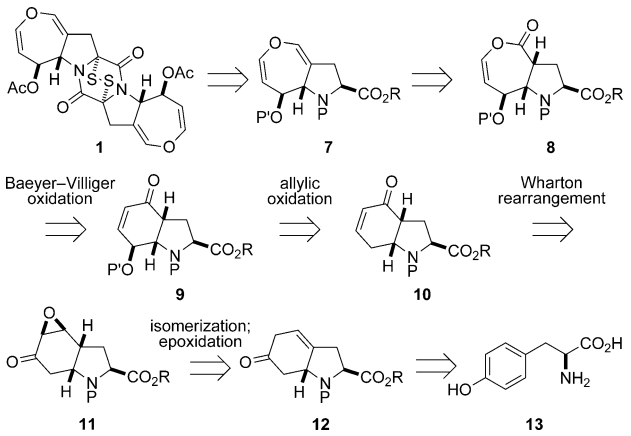


Figure 1. Natural products containing dihydrooxepine moiety.

display a range of intriguing biological activities, such as: inhibitory activity against viral RNA polymerase,[2] antagonistic activity of epidermal growth factor receptor,[3] potent antituberculous activity,[4] inhibitory activity against histamine release,[5] antiproliferative activity against DU145 human prostate cancer cell line,[6a] and antagonistic activity of chemokine receptor (CCR2).[7c] While numerous synthetic approaches were investigated, only a limited number of successful preparations of the characteristic dihydrooxepine ring have been reported.[8,9] During the synthetic studies on MPC1001, Peng and Clive established a synthetic method for a pyrrolidinone-fused dihydrooxepine through tetrahydrooxepine formation followed by selenoxide elimination.[10] Recently, Reisman and co-workers accomplished the first total synthesis of (−)-acetylaranotin (**1**), using a rhodium-catalyzed formation of tetrahydrooxepine and subsequent elimination of hydrogen chloride, providing the dihydrooxepine.[11] Herein, we report the total synthesis of (−)-acetylaranotin (**1**) through the efficient formation of the proline-fused dihydrooxepine ring by unusual vinylogous Rubottom oxidation and regioselective Baeyer–Villiger oxidation.

Our retrosynthetic analysis is shown in Scheme 1. We planned to introduce the base- and reduction-labile epidisulfide moiety, which is bridged to the diketopiperadine, at the final stage of the synthesis. Disconnection of the two amide



Scheme 1. Retrosynthetic analysis of acetylaranotin (**1**). P/P′ = protecting group. R = alkyl group.

bonds divides the C_2-symmetric acetylaranotin (**1**) to monomer **7** with a dihydrooxepine ring fused to a proline moiety. The dihydrooxepine skeleton would be formed by Baeyer–Villiger oxidation[12] of cyclohexenone **9** followed by the reduction of enol lactone **8** via the enol triflate. If the oxygen functionality at the γ position of α,β-cyclohexenone **9** is introduced by an allylic oxidation of **10**, compound **9** would be synthesized from β,γ-unsaturated ketone **12** by isomerization of the double bond, epoxidation of the resultant enone, and Wharton rearrangement.[13] Thus, we set known compound **12** as a starting material, which is prepared from L-tyrosine (**13**) according to the method reported by Wipf et al.[14]

The synthesis of enone **16** commenced with the preparation of the known β,γ-unsaturated ketone **14** through oxidative cyclization of L-Cbz-tyrosine[14] (Scheme 2). Treatment of **14** with catalytic DBU provided α,β-unsaturated ketone, which was then subjected to basic H_2O_2 to give α,β-epoxyketone **15** almost quantitatively. Subsequent Wharton

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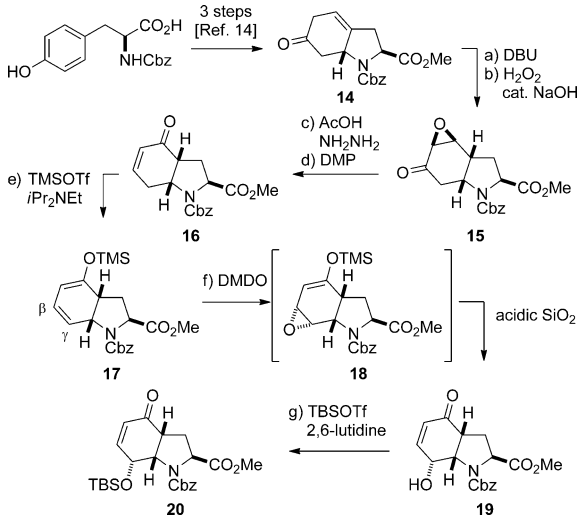
[**] This work was financially supported by the Funding Program for Next Generation World-Leading Researchers (LS008), the KAKENHI, and Grant-in-Aid for Scientific Research (B) (20390003). We thank Dr. M. Isaka (BIOTEC, NSTDA, Thailand) for providing a sample of the natural product and valuable discussion. We appreciate Prof. Y. Iwabuchi (Tohoku University) for the generous gift of 9-azanoradamantane *N*-oxyl (nor-AZADO).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201207307.



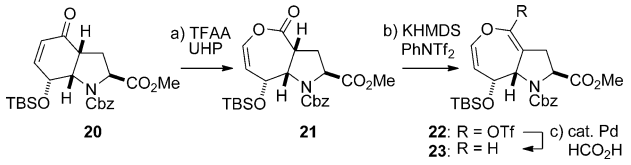
Scheme 2. Synthesis of substrate **20** for Baeyer–Villiger oxidation. Reagents and conditions: a) cat. DBU, CH_2Cl_2, RT, quant.; b) H_2O_2, cat. NaOH, MeOH, 0 °C, 97%; c) $NH_2NH_2{\cdot}H_2O$, AcOH, CH_2Cl_2, 0 °C→RT, 55%; d) DMP, CH_2Cl_2, 0 °C, 97%; e) TMSOTf, iPr_2NEt, CH_2Cl_2, RT; f) DMDO, CH_2Cl_2/acetone, −78 °C; evaporation; acidic silica gel, 56% (over 2 steps); g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 75%. Ac = acetyl, Cbz = benzyloxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMDO = dimethyldioxirane, DMP = Dess–Martin periodinane, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

rearrangement and Dess–Martin oxidation of the resulting allyl alcohol proceeded smoothly to afford enone **16**.

At this point, we investigated the oxidation of the allylic position. Since the conventional oxidation reactions using SeO_2 or brominating agent[15] resulted in a complex mixture, we devised an alternative method for this transformation. To this end, we have successfully established a stepwise protocol, including regioselective dienol silyl ether formation and vinylogous Rubottom oxidation. Thus, treatment of **16** with TMSOTf and Hünig's base gave dienol silyl ether **17** as an exclusive product. Subsequent DMDO oxidation followed by acidic workup with silica gel gave the desired γ-hydroxyenone **19** as a sole product,[16] which was then protected as its TBS ether **20**. In contrast to the conventional Rubottom oxidation that gives α-hydroxyketones, the result indicated that the epoxidation occurred at the β,γ-double bond to generate epoxide **18**.

Surprisingly, the protected hydroxy group of compound **20** is located on the concave face, as determined by X-ray crystallographic analysis for the advanced intermediate **27**.[17] Since further experiments showed unsuccessful condensation of monomer units possessing the same configurations as natural product **1**,[18] we decided to invert the stereochemistry of the hydroxy-bearing carbon center after dimerization and continued further transformations using **20**.

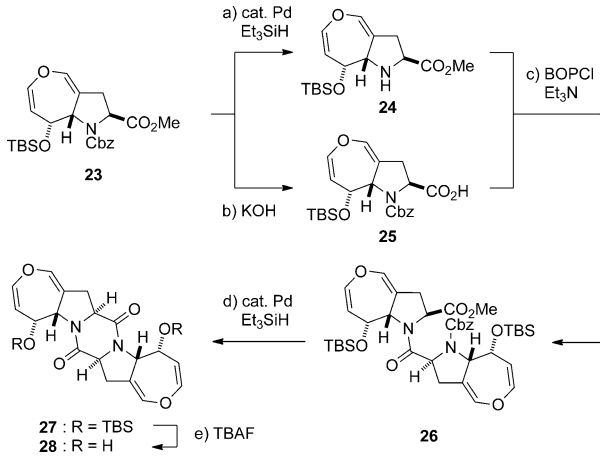
We then focused on the construction of the dihydrooxepine skeleton using a Baeyer–Villiger oxidation[12] to form enol lactone (Scheme 3). Thus, we examined a variety of oxidants and found that a combination of TFAA/UHP systems[12c] gave the best results. Gratifyingly, the expected Baeyer–Villiger oxidation proceeded to give enol lactone **21**



Scheme 3. Synthesis of dihydrooxepine **23**. Reagents and conditions: a) TFAA, UHP, CH_2Cl_2, −20 °C, 53% total yield after 4 reaction cycles (19% of **20** recovered; after a single reaction cycle: 23% yield, 65% yield based on recovered starting material); b) KHMDS, $PhNTf_2$, THF, −78 °C, 77%; c) cat. $Pd(OAc)_2$, PPh_3, HCO_2H, nBu_3N, DMF, 65 °C, 94%. DMF = *N*,*N*-dimethylformamide, KHMDS = potassium hexamethyldisilazide, TFAA = trifluoroacetic anhydride, UHP = urea hydrogen peroxide.

exclusively as a single isomer. After conversion to enol triflate **22**, subjection to the palladium-catalyzed reduction conditions gave dihydrooxepine **23** in excellent yield with the Cbz group intact.

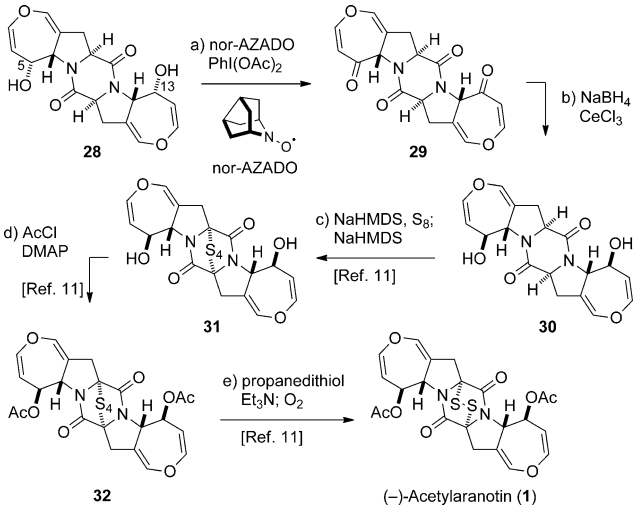
The stage was now set for dimerization of monomer **23** (Scheme 4). First, the Cbz group was removed by the palladium-catalyzed hydrogenolysis to give secondary amine



Scheme 4. Dimerization of monomer. Reagents and conditions: a) Et_3SiH, cat. $Pd(OAc)_2$, cat. Et_3N, CH_2Cl_2, 45 °C, 91%; b) KOH, THF/MeOH/H_2O, RT, quant.; c) BOPCl, Et_3N, CH_2Cl_2, RT, 83%; d) Et_3SiH, cat. $Pd(OAc)_2$, cat. Et_3N, CH_2Cl_2, 45 °C, 78%; e) TBAF, THF, RT, 74%. BOPCl = bis(2-oxo-3-oxazolidinyl)phosphonyl chloride, TBAF = tetrabutylammonium fluoride.

24, and the methyl ester was hydrolyzed to provide carboxylic acid **25**. The crucial condensation of **24** and **25** was then carried out using BOPCl to afford amide **26** in high yield. The diketopiperazine ring was then formed by removal of the Cbz group and subsequent reaction of the generated amine with the ester to give the corresponding amide. Finally, two TBS groups were removed to give unprotected diol **28**.

The remaining tasks for the total synthesis of acetylaranotin (**1**) were stereochemical inversion of the hydroxy-bearing carbon centers at positions 5 and 13, and introduction of the disulfide moiety (Scheme 5). Since the Mitsunobu conditions provided a complex mixture of products, we examined an oxidation–reduction sequence. Among a variety



Scheme 5. Total synthesis of (−)-acetylaranotin (**1**). Reagents and conditions: a) nor-AZADO, $PhI(OAc)_2$, CH_2Cl_2, RT, 93%; b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, CH_2Cl_2–EtOH, −78 °C, 69%; c) NaHMDS, S_8, THF, RT, 31%; d) AcCl, DMAP, CH_2Cl_2, RT, 44%; e) propanedithiol, Et_3N, MeCN, then O_2, RT, 40%. nor-AZADO = 9-azanoradamantane *N*-oxyl, DMAP = *N*,*N*-dimethyl-4-aminopyridine, NaHMDS = sodium hexamethyldisilazide.

of conditions tested, oxidation of diol **28** with nor-AZADO[19] proceeded smoothly to provide vinylogous lactone **29**. Subsequent reduction was best effected by a combination of $NaBH_4$ and $CeCl_3$ at −78 °C to provide known diol **30**[11] as a sole isomer. This facial selectivity was consistent with the result of the Rubottom oxidation; the oxidant approached on the opposite side to the adjacent bridgehead hydrogen. Finally, following the synthetic route developed by Reisman and co-workers,[11] introduction of the tetrasulfide moiety to the diketopiperazine skeleton using the protocol reported by Nicolaou and co-workers,[20] and subsequent acetylation provided **32**, the tetrasulfide moiety of which was reduced to a disulfide moiety to give (−)-acetylaranotin (**1**).

In conclusion, we have accomplished the total synthesis of (−)-acetylaranotin (**1**) in 22 steps (0.06% overall yield) from commercially available L-Cbz-tyrosine (Reisman: 19 steps (0.5% overall yield) from commercially available *trans*-cinnamaldehyde). The approach features the efficient formation of the proline-fused dihydrooxepine ring through unusual vinylogous Rubottom oxidation, and successful dimerization of the monomer unit, which possesses an unnatural stereochemistry.

Received: September 10, 2012
Published online: November 19, 2012

Keywords: aranotin · diketopiperazine · oxidation · rearrangement · total synthesis

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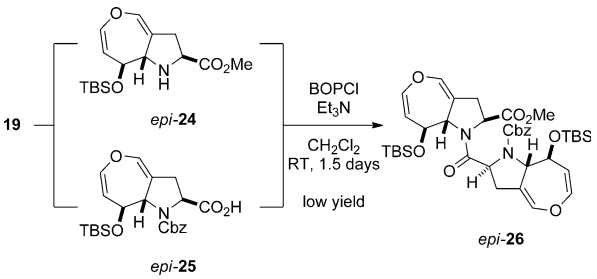
[17] For details, see the Supporting Information.

[18] Interestingly, the stereochemistry of the hydroxy-bearing carbon center was found to be important for the condensation. Thus, *epi*-**24** and *epi*-**25**, the stereochemistry of which corresponds with that of natural acetylaranotin (**1**), were subjected to the same condensation conditions as described in Scheme 4, providing *epi*-**26** in low yield, even after prolonged reaction time.



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