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Total synthesis of isoroquefortine E and phenylahistin

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ABSTRACT

Isoroquefortine E and phenylahistin were synthesized using the Horner–Wadsworth–Emmons reaction as the key step to build the dehydroamino acid moiety. The syntheses provided the materials for the biological studies of the roquefortine–phenylahistin molecules.

Roquefortine E (**1**), a natural product isolated from an Australian strain of *Gymnoascus reessii* Baranetzki, by Capon and co-workers in 2005, is the first roquefortine to be isolated from a fungus other than *Penicillium*.[1] It combines the main structural features of two classes of natural products: the cyclized isoprenylated tryptophan of the roquefortine C (**2**) and the isoprenylated dehydrohistidine of the phenylahistin (**3**).[2,3] Both roquefortine C and phenylahistin were reported to have potent biological activities; phenylahistin showed strong binding affinity toward microtubules and potent growth inhibition of various cancer cell lines.[3b] Roquefortine E (**1**), however, only showed weak cytotoxic activity to mammalian cells.[1] The structure and biological activity relationship among these compounds is still unknown. Phenylahistin has a *Z* dehydroamino acid moiety, while roquefortine C contains an *E* structure. Isoroquefortine C, the *Z* isomer of roquefortine C, does not show any significant biological activity. Roquefortine C (**2**) and phenylahistin (**3**) have already been synthesized but no total synthesis of roquefortine E (**1**) has been reported yet[4] (Fig. 1).

Capon reported that roquefortine E should have the *E* configuration by comparing the ^{1}H and ^{13}C NMR data of roquefortine E to that of roquefortine C and isoroquefortine C. However, the authors failed to convert roquefortine E to isoroquefortine E by the treatment with UV light, under the conditions used for the conversion of roquefortine C to isoroquefortine C. A synthesis of roquefortine E and isoroquefortine E should confirm the *E/Z* configuration of roquefortine E and also provide enough material for further biological studies. Therefore, we began the syntheses of both **1** and **3**. The synthesis of aldehyde **9** started from the conversion of amino acid (−)-serine (**4**) to TBS-protected methyl ester **5**. Following Baran's protocol, a controlled prenyl magnesium chloride addition, thiourea **7** formation, oxidation–elimination, and TBS deprotection converted **6** to imidazole **8**.[5] Aldehyde **9** was obtained by the oxidation of alcohol **8** with manganese dioxide (Scheme 1).

Due to the instabilities of Boc, mesyl, and tosyl-protecting groups on the free nitrogen of imidazole **9**, we chose *ortho*-nitrobenzyl (ONB) as the protecting group.[6] After LDA treatment of

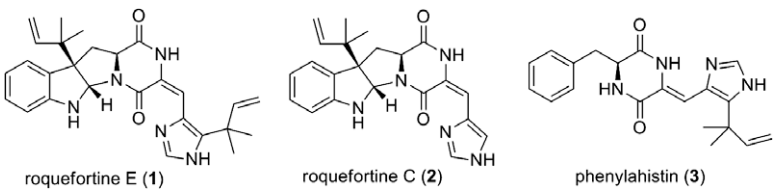

Figure 1. Roquefortine E, roquefortine C and phenylahistin.

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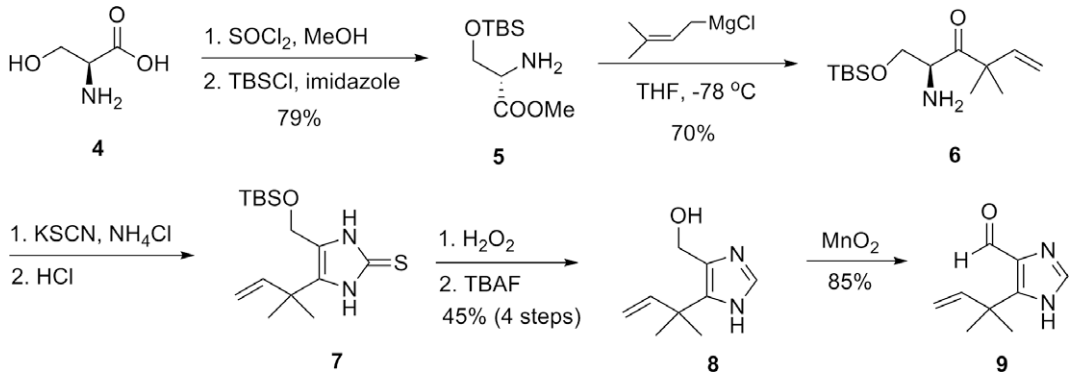
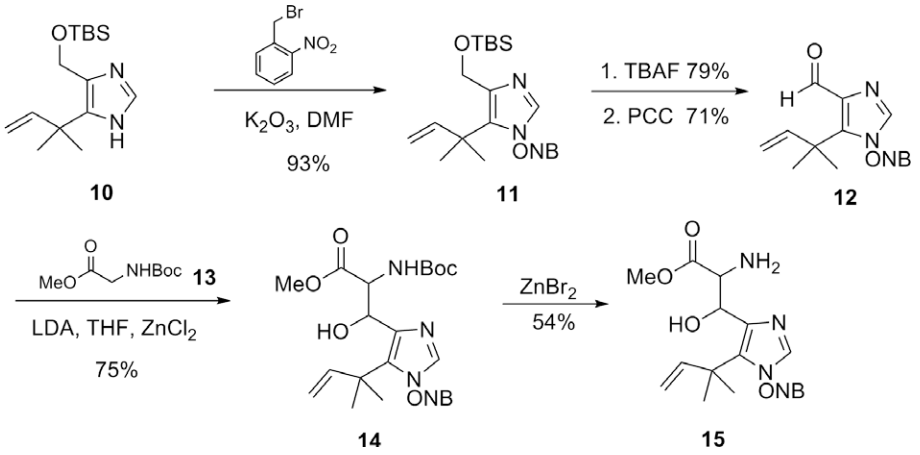
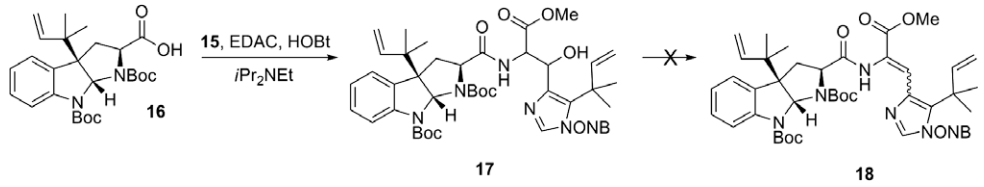


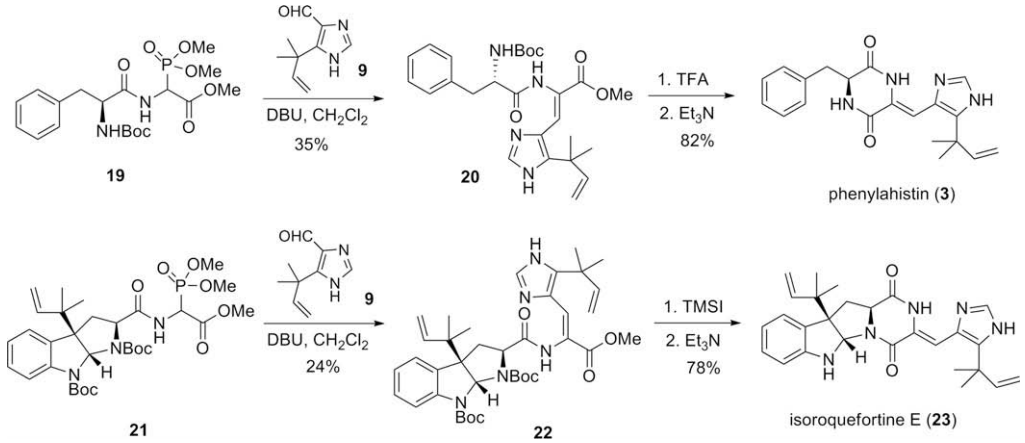
Scheme 1. Synthesis of aldehyde **9**.



Scheme 2. Synthesis of amine **15**.



Scheme 3. The elimination approach.



Scheme 4. Synthesis of phenylahistin and isoroquefortine E.

Boc-protected glycine methyl ester, the resulting enolate was added to aldehyde **12** to afford a mixture of diastereomeric aldol addition products (**14**). Zinc chloride addition was necessary to make the polar dianion enolate of **13** soluble in THF. Subsequent zinc bromide treatment removed the Boc group to afford amine **15**[7] (Scheme 2).

Acid **16**[8] was coupled with amine **15** under standard conditions to form compound **17**, the precursor for the elimination reaction. Unfortunately, all efforts to dehydrate compound **17** were unsuccessful (Scheme 3).

The Horner–Wadsworth–Emmons (HWE) reaction is an established method to construct the carbon–carbon double bond of the dehydroamino acid moiety.[9] The known phosphonate **19**[4c] was coupled with aldehyde **9** to give compound **20**, which was deprotected and cyclized to give (−)-phenylahistin. Aldehyde **12** and other protected imidazoyl aldehydes failed to give good yields in this HWE reaction. Phosphonate **21**[6] was coupled with aldehyde **9** under standard HWE conditions to give product **22**. Subsequent treatment with TMSI and triethyl amine afforded isoroquefortine E (**23**) as the final product[10] (Scheme 4).

In conclusion, a concise total synthesis of isoroquefortine E and phenylahistin was completed and will allow the structure–activity relationship of roquefortines and phenylahistin to be investigated. The synthesis and evaluation of the biological activities of the analogs of roquefortines and phenylahistin will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.074.

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10. *Selected data. Compound* **22**: ^{1}H NMR ($CDCl_3$): δ 11.19 (1H, br), 8.02 (1H, s), 7.54 (1H, s), 7.39 (1H, d, J = 7.9 Hz), 7.26 (1H, t, J = 7.4 Hz), 7.21 (1H, d, J = 7.5 Hz), 7.10 (1H, d, J = 7.5 Hz), 6.92 (1H, s), 6.19 (1H, s), 6.13 (1H, dd, J = 17.5, 10.6 Hz), 5.87 (1H, dd, J = 17.4, 10.8 Hz), 5.09 (4H, m), 3.80 (3H, s), 1.54 (9H, s), 1.50 (9H, s), 1.48 (3H, s), 1.45 (3H, s), 1.06 (3H, s), 0.98 (3H, s); ^{13}C NMR ($CDCl_3$): δ 171.5, 165.8, 155.3, 154.0, 152.4, 147.4, 142.9, 142.8, 137.0, 133.8, 128.6, 125.6, 124.9, 123.7, 120.2, 118.8, 115.2, 114.6, 110.9, 82.7, 81.8, 79.1, 61.9, 61.8, 52.4, 40.4, 39.5, 28.6, 28.5, 28.4, 27.9, 22.9, 22.3; HRMS (ESI) m/z calcd for $C_{20}H_{23}N_4O_2$ $(M+H)^+$: 690.3796, found $(M+H)^+$: 690.3867; IR (cm^{-1}): 3282 (w, br), 2978 (m), 1716 (s), 1480 (m), 1368 (m), 1164 (m), 734 (w); $[\alpha]_D^{22}$ +49 (c 0.65, $CHCl_3$). *Isoroquefortine E* (**23**): ^{1}H NMR ($CDCl_3$): δ 11.85 (1H, br), 9.18 (1H, br), 7.51 (1H, s), 7.16 (1H, J = 7.5 Hz), 7.08 (1H, t, J = 7.6 Hz), 6.93 (1H, s), 6.74 (1H, t, J = 7.5 Hz), 6.57 (1H, d, J = 7.7 Hz), 6.02 (1H, dd, J = 17.5, 10.5 Hz), 5.99 (1H, dd, J = 17.4, 10.8 Hz), 5.65 (1H, s), 5.21 (1H, dd, J = 10.5, 0.7 Hz), 5.17 (1H, dd, J = 17.4, 0.6 Hz), 5.12 (1H, dd, J = 10.8, 1.1 Hz), 5.09 (1H, dd, J = 17.4, 1.1 Hz), 4.94 (1H, s), 4.10 (1H, dd, J = 11.5, 5.8 Hz), 2.60 (1H, dd, J = 12.3, 5.8 Hz), 2.47 (1H, dd, J = 11.6, 12.0 Hz), 1.50 (6H, s), 1.14 (3H, s), 1.03 (3H, s); ^{13}C NMR ($CDCl_3$): δ 165.5, 158.7, 150.4, 144.6, 143.6, 136.6, 132.4, 132.3, 128.9, 128.9, 125.6, 125.2, 118.8, 114.4, 113.3, 108.9, 105.4, 78.1, 61.6, 59.1, 40.9, 37.5, 37.2, 28.0, 27.9, 23.0, 22.5; HRMS (ESI) m/z calcd for $C_{27}H_{32}N_5O_2$ $(M+H)^+$: 458.2485, found $(M+H)^+$: 458.2556; IR (cm^{-1}): 3234 (w, br), 2971 (m), 1661 (s), 1436 (s), 1215 (m), 918 (w), 733 (w); $[\alpha]_D^{24}$ −233 (c 0.50, $CHCl_3$).