Total synthesis of (-)-penicimutan a and related congeners
Total synthesis of (−)-penicimutanin a and related congeners†‡

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The first total synthesis of penicimutanin A (1) was achieved within 10 steps (LLS). Key innovations in this synthesis consist of (1) a highly efficient electro-oxidative dearomatization; (2) an unprecedented bisoxirane-directed intermolecular aldol reaction from the sterically hindered face of the ketone and (3) the diastereoselective one-step Meerwein–Eschenmoser–Claisen rearrangement enabling the construction of vicinal quaternary stereocenters. Related family members e.g. penicimutanolone (3) and penicimutatin (5) have also been synthesized alongside, elucidating their absolute configurations, hence the absolute configuration of 1.

Introduction

Fungi have been exploited as rich sources to generate structurally appealing molecules featuring synthetically challenging motifs and consecutive stereocenters, which often display promising bioactivities towards life-threatening diseases.1 In particular, for deep sea-derived fungal strains, chemical mutagenesis is commonly used to activate “muted genes” for the discovery of new natural products.2 Penicimutanin A (1) and B (2) are two representative secondary metabolites reported by Cui and coworkers in 2014 (Fig. 1), isolated from a marine-derived fungal strain identified as Penicillium purpurogenum G59 through chemical mutagenesis.3 An interesting observation is that, in addition to 1, penicimutanolone (3) and penicimutatin (5) together with vicinal quaternary center-bearing pyrroloindoline-containing4–6 fructigenine A (4)4a,b were also isolated alongside, indicating their biosynthetic interrelationship. More importantly, it implied that chemical mutagenesis may have activated a “linchpin gene” of the marine-derived fungus which endogenously joined penicimutanolone (3) and fructigenine A (4) together, in contrast to the terrestrial-derived fungal strain where only analogues of 3 were isolated.5,6 These secondary metabolites and their congeners were found to possess a range of biological activities from anti-fungal as a histidine kinase inhibitor to anti-inflammatory as well as anti-tumor effects.3–5 However, the scarcity of these compounds from natural sources greatly hampered their further biological profiling. What’s more, the absolute configuration of penicimutanin A (1) and penicimutanolone (3) remained undetermined.

It is clear that to address the aforementioned structural uncertainty issues, practical and reliable chemical synthesis of these natural products would be necessary. However, to the best of our knowledge, total synthesis of penicimutanin A and its congeners (e.g. 2, 3 and 5) has not been reported.

The challenge for their synthesis could be three-fold. First, these natural products are characterized by a fully oxygenated cyclohexane ring which contains an acid/base-sensitive cis-

Fig. 1 Penicimutanin A and the related congeners.
bisoxirane moiety, and is part of a spirocyclic ring skeleton (Fig. 1). Second, the trans relationship between the C8 hydroxyl group and the bisoxirane represents a unique feature which indicated a non-directed expodiation. Third, controlling the stereochemistry for forming the labile C2 hemi-aminal ether is not trivial. On the other hand, the south fragment 4’ contains a diketopiperazine fused hexapyrroloindoline, which possessed a C3 1,1-dimethylpropenyl (reverse prenyl) group generating a vicinal all-carbon quaternary stereocenter. The highly oxidized hydrophilic core skeletons, together with the lipophilic aliphatic side chain of penicimutanin, were postulated to account for their observed biological activities.

In this article, we describe our detailed development of an efficient and scalable approach for the asymmetric total synthesis of penicimutanin A (1), penicimutanolone (3) and penicimutatin (5).

Results and discussion

Biosynthetically, it was hypothesized that penicimutanin A (1) could be disconnected into deAc-fructigenine A (4’) and penicimutanolone (3) through the hemi-aminal ether formation (“linchpin” step). The south fragment 4’ could be accessed through a biomimetic aza-Claisen rearrangement followed by indoline formation from the natural congener 5, which itself was an N-prenylated diketopiperazine compound and could be reached from commercially available (S)-tryptophan ester 6. On the other hand, the northern fragment 3 could be easily accessed through a side chain attaching after a diastereoselective aldol reaction from bisoxirane 7, which might be obtained through an oxidative dearomatization from the commercially available (S)-Cbz-tyrosine 8. This design features a biomimetic, convergent strategy, in the hope of obtaining four natural products from common starting materials (Scheme 1).

Our synthesis of deacetyl fructigenine A (4’) started with selective prenylation of commercially available tryptophan ester 6 in 86% yield with isoprenyl bromide 9. The desired prenylation product 10 was condensed with Fmoc-L-tyrosine after Boc removal, affording compound 11 in 76% overall yield. Upon Fmoc deprotection under standard conditions, the diketopiperazine-containing penicimutanin 5 was achieved with 65% yield (Scheme 2A). The intended biomimetic aza-Claisen was proved unviable after extensive condition screening (see the ESI, ‡ for details). Our rationale is that the intrinsic sp² hybridized nitrogen atom of the indole framework inhibited the formation of the chair transition state TS-5, in which the N-atom was twisted into a transient sp³ hybridized form (TS-5 in Scheme 2A).

Given the above results, a one-pot diastereoselective Meerwein–Eschenmoser–Claisen (MEC) rearrangement was developed to construct C3 reverse prenylated oxindoles from non-protected C3-ester indole and isoprenyl alcohol through an AlCl₃ catalytic protocol. The L-tryptophan derivative 13 was subjected to our AlCl₃-mediated conditions. To our delight, the oxindole 16 was achieved in a satisfactory 54% yield with

Scheme 1 Retro-synthesis.

Scheme 2 Synthesis of fructigenine A (4’) and penicimutanin (5).
synthetically acceptable stereocontrol (d.r. = 2.5 : 1). Compound 16 possessed the key reversely prenylated vicinal quaternary oxindole motif, which was cyclized through reductive amination conditions under Bn-deprotection (66% yield) and Boc protection (69% yield) to achieve hexahydropropyroloindoline 18 in 46% yield. Compound 18 was coupled with L-Fmoc-phenylalanine and cyclized upon Fmoc removal, achieving the deAc-fructigenine 4 in 72% overall yield. The known natural product fructigenine 4 (reported as [α]_20^D = −129.3° (c 0.30, MeOH)) was also successfully obtained through acylation in 55% yield and spectroscopic data of 4 ([α]_20^D = −128.0° (c 0.35, MeOH)) were in good agreement with those previously reported (see the ESI‡ for other spectroscopic data).

Our synthesis of the penicimutanolone (3) started with oxidative dearomatization of the commercially available (S)-Cbz-tyrosine (8). The recent development and innate sustainability of electrochemistry prompted us to develop the electro-oxidative dearomatization of 8 (Table 1) in a synthetically useful fashion. The idea is to use an in situ formed milder hypervalent iodine oxidant ii from PhI (i) (Table 1).² We first tried the electro-oxidation with 1 equivalent of LiClO₄ at a constant electrical current of 2.1 mA in TFE. Gratifyingly, the desired spirocycle 19 was isolated in 38% yield. We further investigated the electrical current (entries 2 and 3, Table 1), electrolyte (entries 2–5) and loading of i (entry 2–5) and concluded that the reaction can be optimized to 65% isolated yield when using optimal amounts of the aforementioned factors. Serendipitously, an electrical power cut happened during another trial, which left the reaction standing still overnight after only several hours of electrical oxidation. However the reaction yield was improved to 82% (entry 6, Table 1). A careful adjustment of other co-factors and stirring time enabled us to obtain the oxidative dearomatization reaction in a satisfactory 85% isolated yield.

With enough amounts of 19 in hand, we set off to install the key bisoxirane moiety (Scheme 3). Due to 19’s instability, a selective NaBH₄ reduction followed by TES protection were carried out to release the strain of spirocyclic lactone, yielding dienone 20 in 45% yield over two steps. A diastereoselective Luche-reduction was performed, providing β-OH alcohol (d.r. = 3 : 1) which allowed the mCPBA mediated...
epoxidation to proceed smoothly affording 22 as a single diastereoisomer in 51% overall yield. The key reaction precursor 23 was obtained in 80% yield upon DMP oxidation. Crystallographic analysis showed unambiguous structural evidence of compound 23.  

It was hypothesized that introduction of an acetylonyl group at the C8 position could be delivered from the more sterically hindered β-face of 23, thus affording the desired stereoisomer by utilizing the bisoxirane moiety as a directing group (Scheme 3). With this assumption, the proposed bisoxirane-directed 1,2-addition was attempted by in situ generation of the oxophilic cerium-enolate instead of its traditional lithium counterpart. Gratifyingly, the transformation was realized in a 72% yield, with a resultant diastereoselective (d.r. = 10 : 1) formation of the desired α-OH isomer 24. The efficacy of this challenging diastereoselective 1,2-addition step was attributed to a better chelation effect of the cerium-enolate as well as its reduced basicity. With the core skeleton in hand, side chain 25 (see the ESI‡ for preparation and characterization of 25) was coupled with compound 24 over a three-step sequence, affording penicimutanolone 3 in an overall 47% yield. The spectroscopic data of synthetic C4′,C6′-(R,R)-penicimutanolone ([α]D25 = −91.1° (c 0.25, MeOH)) correspond to the natural sample of penicimutanolone ([α]D25 = −99.7° (c 0.5, MeOH)) very well thus confirming its absolute configuration (see Table S1 in the ESI‡ for a full comparison of NMR data).

Conclusion

In summary, we have completed the first total synthesis and determined the absolute configurations of penicimutanol A (1) and its related congeners penicimutanolone (3), fructigenine A (4) and penicimutan (5) in a highly convergent and biomimetic fashion from the commercially available (S)-tryptophan and (S)-tyrosine derivatives for the first time. The highly concise total synthesis of 3 (10 step LLS) was enabled by an improved and highly efficient electro-oxidative deamination as well as an unprecedented diastereoselective 1,2-addition directed by the bisoxirane moiety. A modified one-pot diastereoselective MEC rearrangement was developed to reach fructigenine A (4) in only 6 steps. Further investigation of this methodology in natural product synthesis and biological profiling of penicimutans is currently on-going in our group.

Conflicts of interest

There are no conflicts to declare.
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