Proceedings of CONF-MCEE 2026 Symposium: Advances in Sustainable Aviation and Aerospace Vehicle Automation
DOI: 10.54254/2755-2721/2026.KA28307

Retrosynthetic and Total Synthesis Analysis of Penidaleodiolide A

Haoming Li[1*†], Bowen Gu[2†]

[1]*Shenzhen College of International Education, Shenzhen, China*
[2]*Dulwich College, London, United Kingdom*
**Corresponding Author. Email: erichaomingli@gmail.com*
[†]*These authors contributed equally to this work and should be considered co-first authors.*

Abstract. Penidaleodiolide A, a natural product with unique structural motifs and potential biological activity, possesses a complex molecular framework that presents a highly challenging target for the field of organic synthesis. In this work, we systematically analyze the retrosynthetic and total synthesis strategies for Penidaleodiolide A. First, the research background and scientific value of this natural product are outlined. Next, the molecular structure is deconstructed via retrosynthetic analysis to identify key synthetic intermediates and strategic bond disconnection points. Finally, incorporating current advances in organic synthetic methodology, we discuss the core reactions and strategic choices in the total synthesis, offering theoretical insights and practical guidance for the synthesis of related natural products.

Keywords: Retrosynthesis, Penidaleodiolide, reaction strategies

1. Introduction

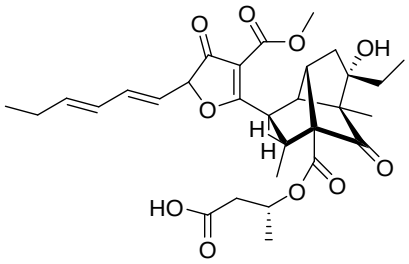
Natural products, owing to their diverse molecular structures and rich biological activities, have long been important sources for drug discovery and organic synthesis [1,2]. For example, Cordycicadins A–D, isolated from the entomopathogenic fungus Cordyceps cicadae, are a class of anorectic polyketides featuring an unusual exocyclic enol ether bridge [3]. Tricrilactones A–H, oligomeric macrocyclic lactones isolated from Trichocladium crispatum (an alpine moss-associated fungus), exhibit potent anti-osteoporosis activity [4]. In 2016, Puno and co-workers isolated a novel furanoic acid compound, penicilfuranone A, from an endophytic Penicillium sp. (strain sh18) [5].

Penidaleodiolide A is a polyketide natural product isolated from Penicillium daleae L3SO (a strain from the rhizosphere of Monarda uniflora). As shown in Figure 1, its structure contains multiple stereogenic centers, oxygenated heterocycles, and a unique bridged ring system [6]. Not only does it exhibit a high degree of structural complexity, but preliminary bioactivity screening has also revealed potential neuro-transmission regulatory activity [6]. These features have made Penidaleodiolide A a recent research focus in natural product chemistry and synthetic chemistry. As a result of these characteristics, Penidaleodiolide A has recently become a focal point of research in both natural product chemistry and synthetic chemistry.

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2755-2721/2026.KA28307

From a scientific standpoint, studying the synthesis of Penidaleodiolide A is important for three main reasons. First, its complex molecular structure makes it an excellent “molecular probe” for testing novel synthetic methodologies [7], meaning that efforts to construct it could help advance key techniques like asymmetric catalysis, macrocyclization, and heterocycle formation. Second, given its potential biological activity, Penidaleodiolide A provides a valuable scaffold for drug discovery; completing its total synthesis in sufficient quantities allows detailed pharmacological evaluation that could ultimately guide the development of new therapeutic agents [8]. Third, the approaches developed in the synthesis of Penidaleodiolide A can yield general strategies and technical insights for constructing related natural products with similar structural motifs, thereby promoting broader progress in the field of natural product synthesis. Therefore, conducting a retrosynthetic and total synthetic analysis of Penidaleodiolide A has significant theoretical and practical value.



Penidaleodiolide A

Figure 1. Stereostructure of Penidaleodiolide A

2. Retrosynthetic analysis of Penidaleodiolide A

Retrosynthetic analysis, a core strategy in synthetic design, deconstructs the target molecule into simpler precursors or commercially available starting materials according to rational bond-disconnection rules, thereby enabling the construction of a complete synthetic pathway [9]. The molecular structure of Penidaleodiolide A includes a complex bridged ring system, a furan ring, and multiple stereogenic centers. In particular, a carboxylate ester is attached externally to a three-atom bridged ring. These features imply that any retrosynthetic analysis must address three primary challenges: efficient macrocyclization, precise control of the stereochemistry at all chiral centers, and construction of the furan-2-carboxylate ring system. A detailed discussion of these issues follows.

2.1. Structural features of the target molecule

For the initial retrosynthetic step, the core structural features of Penidaleodiolide A are identified. Its molecular formula is C_30H_38O_10, and it contains an oxygenated furan-2-carboxylate methyl ester moiety. The furan ring is fused to a bridged bicyclic framework, and the molecule contains six stereogenic centers; notably, one carboxylate ester is connected externally on a three-atom bridge. These characteristics mean that the retrosynthetic plan must tackle three main issues: forming the macrocycle effectively, controlling the stereochemistry of all chiral centers, and constructing the furan-2-carboxylate ring system.

DOI: 10.54254/2755-2721/2026.KA28307

2.2. Key bond disconnections and intermediate design

In the preparation of furan-2-carboxylate derivatives, a [4+2] cycloaddition is a commonly used strategy to construct complex heterocyclic frameworks [10]. Figure 2 explicitly demonstrates the strategy engaged for bond selections and corresponding breaking down. First, for synthetic simplicity, Penidaleodiolide A is conceptually cleaved into two fragments that can engage in a Diels–Alder (DA) reaction. Specifically, the complex bridged heterocycle of Penidaleodiolide A is disconnected by an aldol condensation to yield an intermediate (compound D). The tautomerization of D produces compound D1, in which the bridged ring can be further disassembled to yield a planar Diels–Alder precursor. Specifically, a Michael addition is proposed to open the bridged ring of D1, yielding compound C. In this way, the two substrates A and B for the Diels–Alder reaction are obtained.

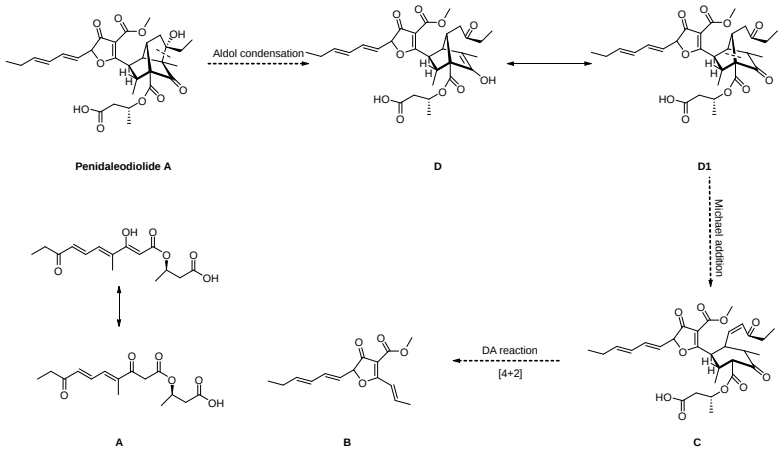


Figure 2. Retrosynthetic analysis of Penidaleodiolide A

2.3. Retrosynthetic analysis of fragment A

Manifested in Figure 3, fragment A is further deconstructed as follows. Via an esterification/transesterification reaction, the fragment can be broken down into the commercially available compounds A5 and A4. Compound A4 is then transformed into A3 through a Riley oxidation [11]. Compound A3 can be constructed by an aldol condensation, which in retrosynthesis corresponds to disconnecting it into compound A2 and methyl formate ($HCOOCH_3$). Finally, compound A2 can be further broken down by an aldol condensation into the commercially available compound A1 and methyl propionate.

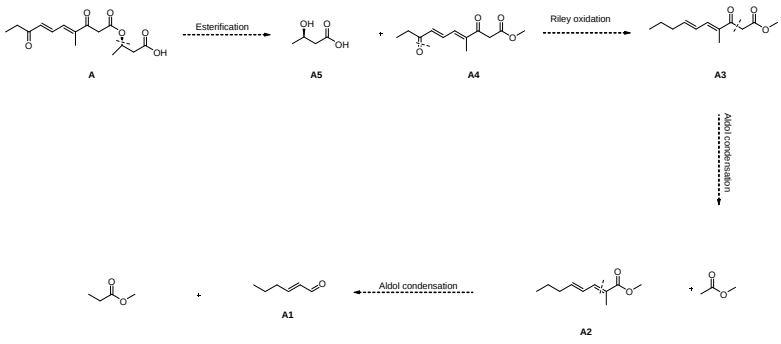


Figure 3. Retrosynthetic analysis of fragment A in Penidaleodiolide A

DOI: 10.54254/2755-2721/2026.KA28307

2.4. Retrosynthetic analysis of fragment B

As shown in Figure 4, fragment B is further deconstructed as follows. In fragment B, the allyl group can be introduced by elimination of a hydroxyl group; protection of this hydroxyl with a para-methoxybenzyl (PMB) group yields compound B5. The ether bond in compound B5 can be traced back via an $MgBr_2 \cdot OEt_2$-catalyzed intramolecular dehydration to give compound B4 [12]. Compound B4, in turn, can be obtained by C-alkylation to yield compound B3. Compound B3 can be generated via the Buchner–Curtius–Schlotterbeck reaction, which involves the reaction of an aliphatic diazo compound with a carbonyl compound to form a cyclopropyl ketone [13]. Finally, compound B2 is obtained by the reaction of the starting material B1 with trimethylsilyl cyanide (TMSCN), where B1 is the initial feedstock.

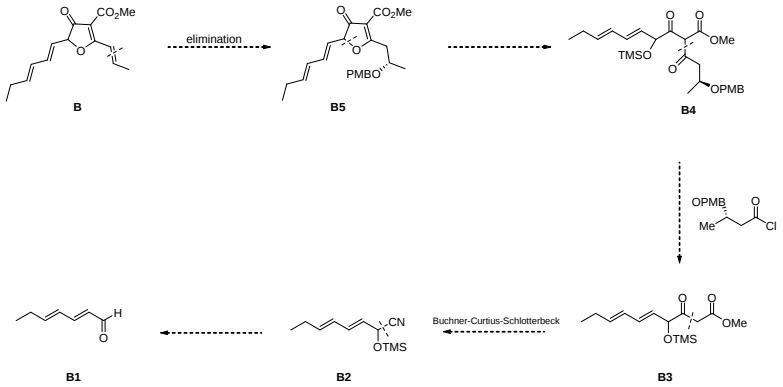


Figure 4. Retrosynthetic analysis of fragment B in Penidaleodiolide A

2.5. Summary of the retrosynthetic route

Based on the above disconnections, the retrosynthetic route of Penidaleodiolide A can be summarized as: Penidaleodiolide A (target) → bridged-ring precursor D (cleavage of the triatomic bridge) → planar precursor C (cleavage of the oxa-bridge) → fragment A + fragment B → commercially available starting materials. This retrosynthetic sequence systematically deconstructs the complex target into simpler fragments, each of which can be prepared by established synthetic methods, providing a clear framework for designing a total synthesis route.

3. Total synthesis of Penidaleodiolide A

In view of the above retrosynthetic analysis and leveraging current organic synthesis techniques (such as functional group protection and macrocyclization), the total synthesis of Penidaleodiolide A should proceed via the sequence: fragment assembly → macrocyclization → late-stage modifications. The synthesis will need to address three key challenges: stereochemical control of the multiple chiral centers, enhancement of reaction efficiency, and functional group compatibility. The detailed synthetic strategies are discussed below, indicated by Figure 5.

3.1. Synthesis of fragment A

To prepare fragment A, an aldol condensation between A1 and methyl propionate (mediated by LDA in THF) generates compound A2. A2 then undergoes a second aldol condensation with methyl formate (using sodium methoxide in methanol) to yield A3. The terminal alkene of A3 is oxidized

DOI: 10.54254/2755-2721/2026.KA28307

(for example, with SeO_2) to produce A4. Finally, A4 and A5 undergo transesterification under basic conditions to yield fragment A (one of the Diels–Alder substrates). This sequence forms the ester linkage via transesterification while preserving the stereocenter, and because the conditions are relatively mild, a reasonable degree of stereochemical control is maintained in the final product.

3.2. Synthesis of fragment B

For fragment B, the synthetic route is designed to build the furan ring and introduce an alkene for the Diels–Alder reaction with fragment A. Initially, B1 is treated with trimethylsilyl cyanide (TMSCN) under basic conditions, resulting in B2 via nucleophilic addition. Next, B2 is reduced with DIBAL-H to generate an aldehyde intermediate, which subsequently undergoes a Buchner–Curtius–Schlotterbeck reaction with methyl diazoacetate to yield B3. Next, compound B3 is subjected to C-acylation under basic conditions (NaH/THF) to yield compound B4. Treatment of B4 with TBAF removes the TMS protecting group, effecting an intramolecular dehydration and ring closure to form compound B5. Compound B5 is then deprotected by acid (removal of the PMB group) and undergoes a second dehydration to form fragment B, the other Diels–Alder substrate. This route exploits intramolecular dehydration to construct the furan ring and introduce the conjugated double bond; the mild conditions result in relatively high yields.

3.3. Synthesis of Penidaleodiolide

With fragments A and B in hand, the final assembly proceeds as follows. The enolic form of compound A undergoes a Diels–Alder [4+2] reaction with compound B under acidic conditions, yielding the adduct C. Compound C is then subjected to a base-induced 1,4-Michael addition to produce compound D. Finally, an intramolecular aldol condensation of compound D under basic conditions furnishes the target Penidaleodiolide A (Figure 5). The structure and stereochemistry of the synthesized product are verified by ^1H NMR, ^13C NMR, high-resolution mass spectrometry (HRMS), and X-ray single-crystal diffraction, confirming that the synthetic product is identical to natural Penidaleodiolide A.

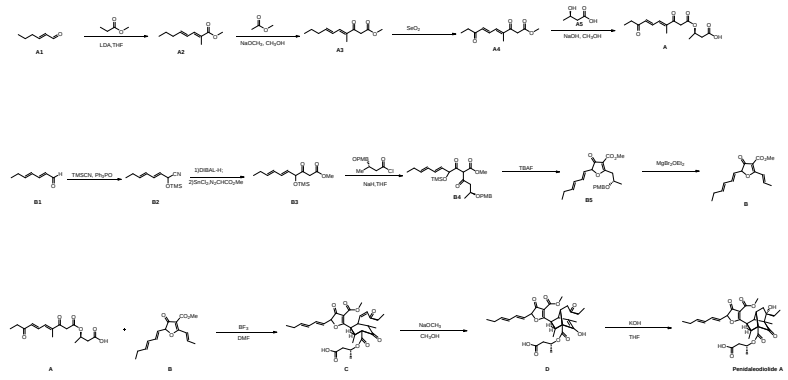


Figure 5. Total synthesis analysis of Penidaleodiolide A

4. Conclusion and outlook

In this work, retrosynthetic analysis of Penidaleodiolide A revealed a synthetic strategy centered on disconnection of the bridged ring and decomposition into two key fragments, thus overcoming the challenge of deconstructing the complex target molecule. Based on this analysis and utilizing key techniques such as fragment coupling and macrocyclization, a complete total synthesis route was

DOI: 10.54254/2755-2721/2026.KA28307

devised. The route addresses the major challenges of stereochemical control of the chiral centers and efficiency of macrocyclization, providing a viable plan for the laboratory synthesis of Penidaleodiolide A.

For future research, the synthesis of Penidaleodiolide A could proceed in three directions:

1. Optimization of the synthetic route: Develop novel methodologies (e.g., photocatalysis, biocatalysis) to reduce the number of steps and improve the overall yield, enabling scalable production.

2. Structure–activity relationship studies: Using the synthetic Penidaleodiolide A and its derivatives, conduct in-depth SAR studies to identify the core pharmacophores of bioactivity, thereby providing precise guidance for drug design.

3. Extension to related natural products: Apply the synthetic strategies developed for Penidaleodiolide A to the synthesis of other family members (such as Penidaleodiolide B/C and other macrocyclic lactones), establishing a general synthetic platform and advancing the field of natural product synthesis.

Acknowledgement

Haoming Li and Bowen Gu contributed equally to this work and should be considered co-first authors.

References

[1] Atanas G. Atanasov, Claudiu T. Supuran, et al. Natural products in drug discovery: advances and opportunities. Nat. Rev. Drug Discov., 2011, 20, 200–216.
[2] Gao S.-S., Li X.-M., et al. Two new diterpenes of cyclopiane class from a marine-derived endophytic fungus Penicillium chrysogenum QEN-24S. Chem. Biodivers., 2011, 8, 1748–1753.
[3] Wang Q. Y., Chen H. P., Liu J. K. Isopimarane diterpenes from the rice fermentation of the fungicolous fungus Xylaria longipes HFG1018. Phytochem. Lett., 2021, 45, 100–104.
[4] Han W. B., Zhai Y. J., et al. Tricrilactones A–H, potent anti-osteoporosis macrolides with distinctive ring skeletons from Trichocladium crispatum, an alpine moss-associated fungus. Angew. Chem. Int. Ed., 2023, 62 (15), e202300773.
[5] Iglesias J., Martínez-Salazar I., Maireles-Torres P., Alonso D. M., Mariscal R., Granados M. L. Recent advances in the synthesis of furanones and furandiones. Chem. Soc. Rev., 2020, 49, 5704–5771.
[6] Wang Q.-Y., Chen H.-P., et al. Penidaleodiolides A and B, cage-like polyketides with neurotransmission-regulating activity from the soil fungus Penicillium daleae L3SO. Org. Lett., 2024, 26, 7632–7637.
[7] Moore R. E., Scheuer P. J. Palytoxin: a new marine toxin from a coelenterate. Science, 1971, 172, 495–498.
[8] Lei X., Li Y., et al. Strain-driven dyotropic rearrangement: a unified ring-expansion approach to α-methylene-γ-butyrolactones. Angew. Chem. Int. Ed., 2021, 60 (8), 4221–4230.
[9] Corey E. J., Erickson B. W. Oxidative hydrolysis of 1, 3-dithiane derivatives to carbonyl compounds using N-halosuccinimide reagents. J. Org. Chem., 1971, 36 (23), 3553–3560.
[10] Ding Y., Deng J. Asymmetric total synthesis of penicilfuranone A through an NHC-catalyzed umpolung strategy. Chem. Sci., 2025, 16, 8302.
[11] Wang P., Lindsey J. S. Riley oxidation of heterocyclic intermediates on paths to hydroporphyrins—a review. Molecules, 2020, 25 (8), 1858.
[12] Kikuchi T., Narita K., Saijo K., Ishioka C., Katoh T. Synthesis of methoxy-substituted phenols via intramolecular coupling reactions. Eur. J. Org. Chem., 2016, 2016, 5659–5666.
[13] Holmquist C. R., Roskamp J. R. A homologation of carbonyl compounds via diazoacetate chemistry: formation of α-chloroketones and β-hydroxyesters. J. Org. Chem., 1989, 54, 3258–3260.