

Cite this: *Chem. Sci.*, 2025, 16, 8302

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 25th February 2025

Accepted 4th April 2025

DOI: 10.1039/d5sc01508a

rsc.li/chemical-science

Asymmetric total synthesis of penicilfuranone A through an NHC-catalyzed umpolung strategy†

Yiming Ding,^{‡ab} Xianwen Long,^{‡b} Jingwei Zhang,^b Chunlei Qu,^b Peng Wang,^b Xiaodong Yang,^{ib} Pema-Tenzin Puno^{ib} and Jun Deng^{ib}*^a

The first asymmetric total synthesis of penicilfuranone A was accomplished in eight steps through an NHC-catalyzed umpolung strategy. Key features of the synthesis include an Al-Salen catalyzed asymmetric cyanosilylation to install the tertiary alcohol of gregatin A, and an NHC catalyzed Stetter–Aldol cascade reaction. The umpolung strategy of the benzyl aldehyde fragment facilitated a convergent formal [4 + 2] annulation with gregatin A, ultimately leading to the formation of penicilfuranone A.

Introduction

Furancarboxylic acids are a class of naturally occurring phytochemicals isolated from fungi, known for their broad application in polymer synthesis¹ and diverse bioactivities, including phyto-toxic and antibiotic effects.² These compounds have garnered significant attention within the synthetic community due to their complex structures and pharmacological potential.³ In 2016, penicilfuranone A (**1**), a new furancarboxylic acid, was isolated from an endophytic strain of *Penicillium* sp. sh18 by Puno and co-workers.⁴ Structurally, penicilfuranone A (**1**) possesses a tricyclic framework and is classified as an aromatic polyketide (Scheme 1A). It features four stereogenic centers, including three consecutive stereogenic centers and two quaternary chiral centers. Biologically, penicilfuranone A (**1**) exhibited a significant antifibrotic effect in activated hepatic stellate cells, suggesting its potential as a lead compound for the treatment of hepatic fibrosis. In addition to penicilfuranone A (**1**), several structurally divergent gregatin A heterodimers have been discovered,⁵ such as citrifuran A (**2**), asperone A (**3**), and the recently reported penidaleodioid (**4**).

One of the major challenges in the asymmetric synthesis of penicilfuranone A (**1**) lies in the stereo-controlled synthesis of the fully decorated benzocyclohexanone (B ring, highlighted in

red), which is highly oxidized and enriched in stereocenters. The presence of C-19 tertiary alcohol renders this structure prone to aromatization upon exposure to acidic conditions, further complicating its synthesis. The biosynthesis of penicilfuranone A (**1**) is hypothesized to involve gregatin A (**8**) and phenol **9** through an intermolecular Michael addition, an intramolecular aldol addition and subsequent C16 benzylic oxidation (Scheme 1B). Wang and Matsuda showed that gregatin A (**8**) is derived from polyketide **5** through enzyme-catalyzed oxidative cyclization and methylation.⁶ An intriguing aspect of this biosynthetic pathway is the formation of furanone through a vinylogous internal nucleophilic substitution (S_Ni'), where the conjugated double bond migrates to an unconjugated position, forming a quaternary carbon center in an enantioselective manner.

As shown in Scheme 2, in order to make the synthesis convergent and efficient, we conducted a retrosynthetic analysis of penicilfuranone A (**1**) by late-stage formal [4 + 2] annulation to install this stereochemically intricate B ring. The target molecule could be derived from C15 epimerization of **12**, which could be traced back either to gregatin A (**8**) and benzoisofuran (**13**) through an intermolecular Diels–Alder reaction, or to gregatin A (**8**) and benzaldehyde **14** through an intermolecular Stetter/Aldol cascade reaction. The key intermediate, gregatin A (**8**), might be synthesized through linear precursor **15** through a bioinspired vinylogous internal nucleophilic substitution (S_Ni').

Results and discussion

Asymmetric synthesis of key fragments

We initiated our synthesis with the preparation of hemiacetal **20**, benzaldehyde **14a** and gregatin A (**8**) (Scheme 3).

Hemiacetal **20** was synthesized in a three-step sequence. First, commercially available methyl 3,4,5-trimethoxybenzoate **18** was treated with $SnCl_4$ and 1,1-dichlorodimethyl ether,

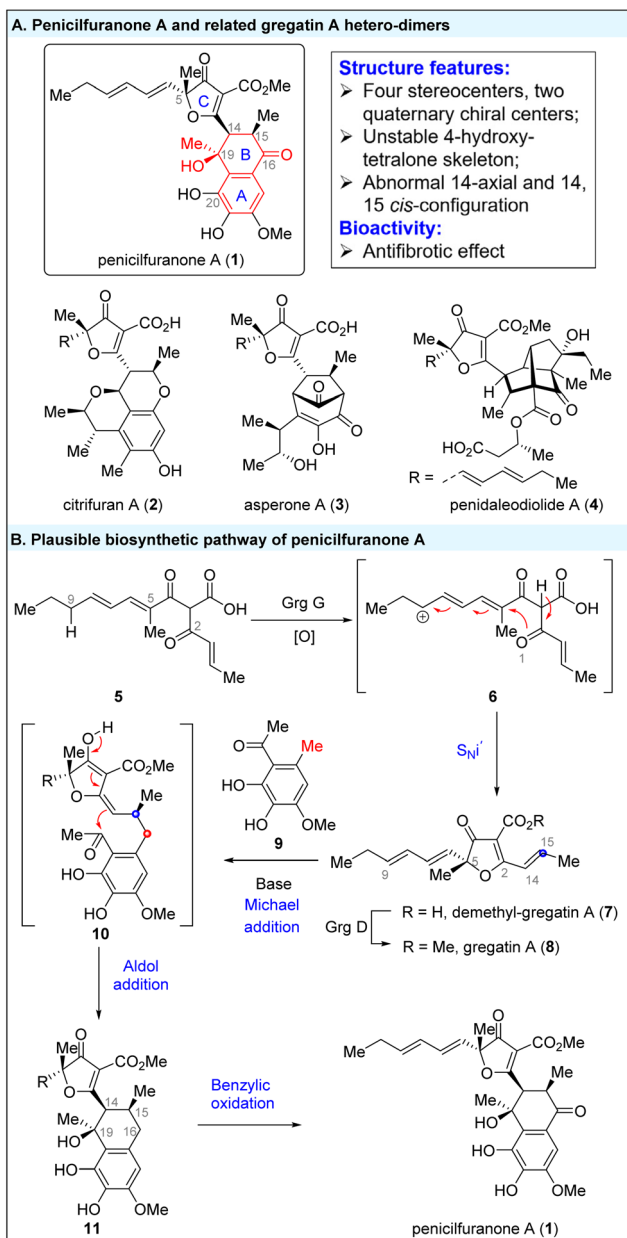
^aKey Laboratory of Medicinal Chemistry for Natural Resources, Ministry of Education, Yunnan Provincial Center for Research & Development of Natural Products, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, China

^bState Key Laboratory and Institute of Elemento-Organic Chemistry, Frontiers Science Center for New Organic Matter, College of Chemistry, Nankai University, Tianjin 300071, China. E-mail: dengjun@nankai.edu.cn

^cState Key Laboratory of Phytochemistry and Natural Medicines, Yunnan Key Laboratory of Natural Medicinal Chemistry, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China

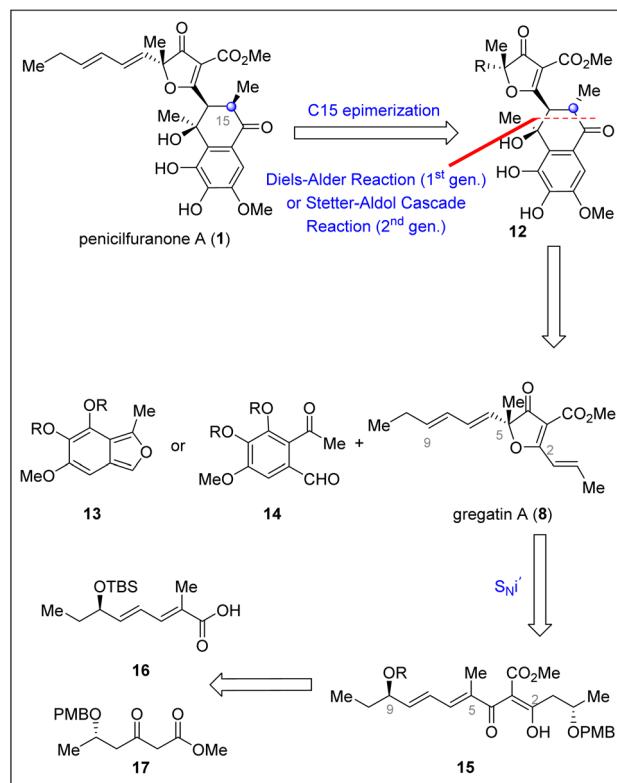
† Electronic supplementary information (ESI) available. CCDC 2424508, 2425647 and 2440564. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5sc01508a>

‡ These authors contributed equally to this work.



Scheme 1 Penicilfuranone A and its proposed biosynthetic pathway.

followed by the addition of methylmagnesium chloride to the resulting aldehyde, leading to the formation of a secondary alcohol. This alcohol was *in situ* trapped by the methyl ester to afford lactone **19** in 76% yield. Reduction of the lactone with DIBAL-H gave hemiacetal **20** in 79% yield. This hemiacetal could then be methylated to provide methyl acetal **21** in 89% yield. Subsequently, diphenol **22** was protected with allyl bromide, and the aldehyde group was reduced, converting aldehyde **22** to benzylic alcohol **23**. After halide-lithium exchange, the resulting aryl lithium was trapped with acetaldehyde to yield diol **24** in 63% yield. The diol was then oxidized using Swern oxidation to give benzaldehyde **14a** in 72% yield. Notably, diol **24** proved unstable under acidic conditions, and treatment with other oxidants (*e.g.*, PIFA or DMP) led to the



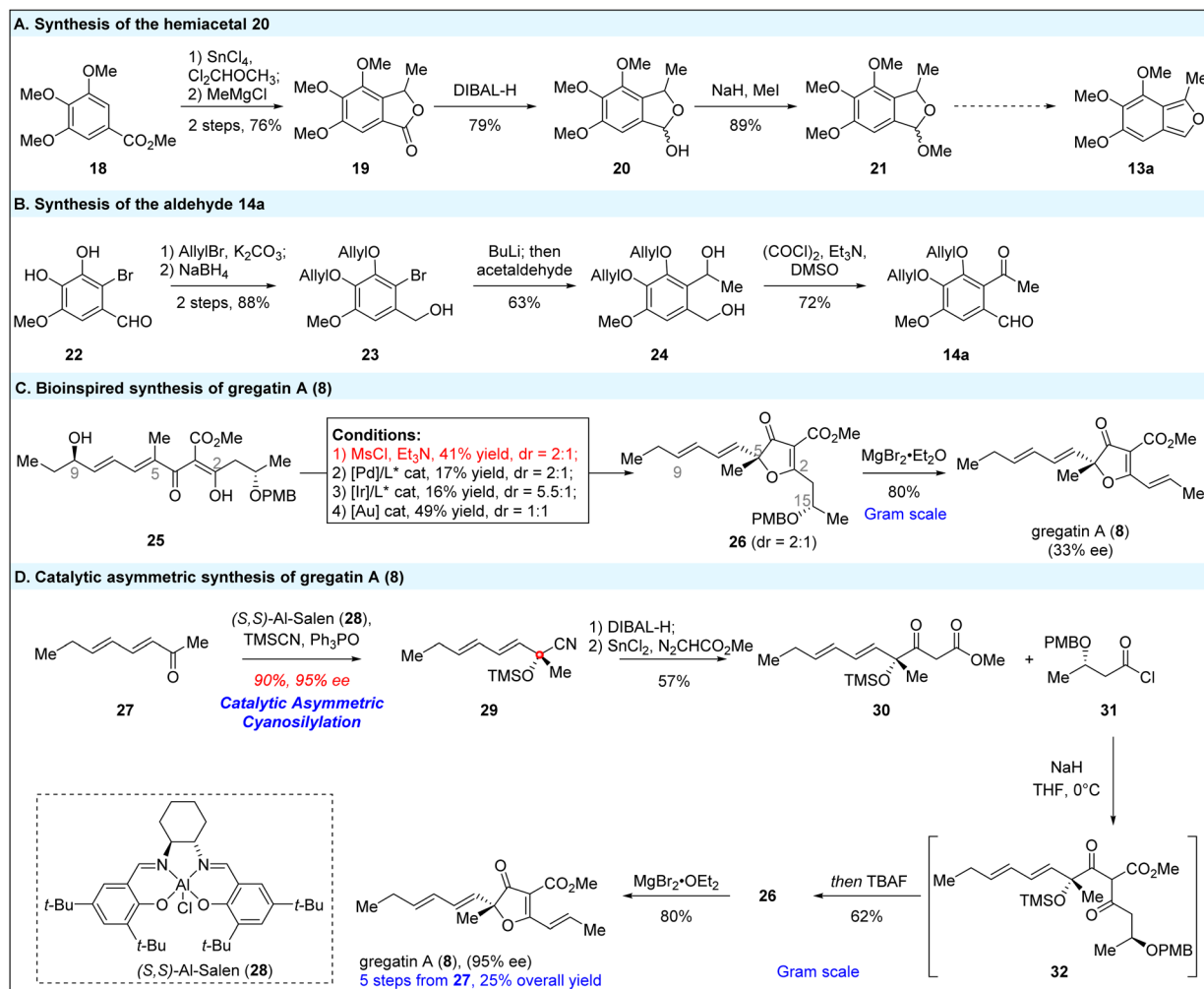
Scheme 2 Retrosynthetic analysis of penicilfuranone A.

formation of undesired isobenzodihydrofuran or styrene by-products.

Next, we turned our attention to the asymmetric synthesis of gregatin A (**8**) (Scheme 3C). In our ongoing efforts to chemically emulate the biosynthetic pathway of natural products,⁷ our initial strategy was to replicate the internal nucleophilic substitution reaction proposed in gregatin A (**8**) biosynthesis (Scheme 1B) and hopefully realize the enantioselective synthesis of gregatin A (**8**) through the C9 → C5 chiral relay strategy. Starting from chiral allylic alcohol,⁸ we synthesized cyclization precursor **25** (90% ee) in five steps (see the ESI†). To our delight, activation of the allylic alcohol with MsCl successfully initiated the vinylogous S_N1' reaction, yielding the desired furanone in 41% yield. However, the 2° → 3° stereocenter chiral relay did not result in sufficient diastereocontrol at the newly formed tertiary C–O bond, leading to a 2 : 1 diastereomeric ratio (dr). Gregatin A (**8**) was obtained in only 33% ee after elimination of the C15 PMBOH with $MgBr_2 \cdot OEt_2$.⁹ The use of $MgBr_2 \cdot OEt_2$ was critical to secure the high yield of gregatin A (**8**), because basic conditions led to side-chain cleavage of gregatin A (**8**) through retro-Aldol addition (see the ESI†). Despite previous success with chiral relay strategies in S_N1' reactions,¹⁰ vinylogous S_N1' reactions remain challenging.¹¹

We were unable to identify conditions that guaranteed both high yield and diastereoselectivity, even with the use of chiral ligands and Pd or Ir catalysts (see ESI Table S1† for details). Since both gregatin A (**8**) and its enantiomer aspertetronin A, are natural products, enantiopure gregatin A (**8**) is essential for





Scheme 3 Asymmetric synthesis of gregatin A (8), hemiacetal 20 and benzaldehyde 14a.

the subsequent formal [4 + 2] annulation to avoid the formation of undesired diastereomers.

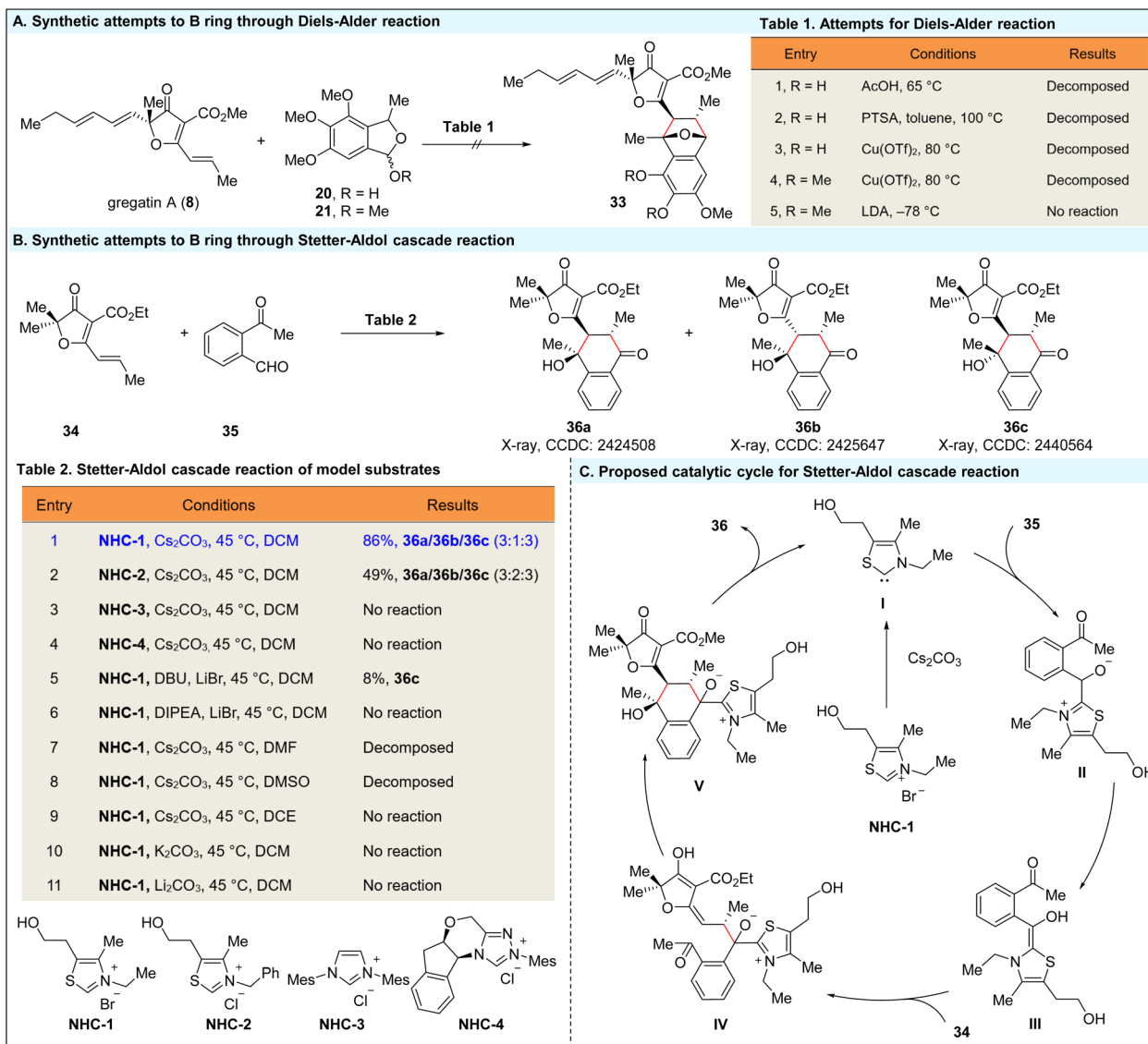
In the asymmetric synthesis of gregatin A (8), the enantioselective installation of the C5 tertiary C–O bond posed a major challenge. Brückner and co-workers achieved the first asymmetric synthesis of gregatin A (8) using the Seebach–Fráter “self-reproduction of stereocenters” methodology, starting from enantiomerically pure lactic esters.^{3h} However, our approach aimed to install this chiral tertiary alcohol *via* the catalytic asymmetric addition of methyl ketone 27. While significant progress has been made in the catalytic asymmetric addition of aryl-substituted ketones,¹² such conditions have not been suitable for alkyl-substituted ketones, such as 27 in this case. After extensive exploration, we were pleased to find that Zhou’s asymmetric cyanosilylation strategy was highly effective for aliphatic ketones.¹³ As shown in Scheme 3D, the catalytic asymmetric cyanosilylation of methyl ketone 27 using Al-Salen as the catalyst proceeded efficiently under standard conditions, delivering an excellent outcome with 90% yield and 95% enantiomeric excess at the decagram scale. Following cyanide reduction with DIBAL-H and formal C–H insertion with methyl

diazooacetate (*via* Roskamp homologation),¹⁴ methyl acetate 30 was obtained in 57% yield over two steps. A subsequent Claisen condensation with acetyl chloride 31, along with desilylation, etherification, and β -elimination of PMBOH, provided gregatin A (8) in an overall yield of 25% from methyl ketone 27. Notably, the use of β -PMBO substituted acetyl chloride 31, rather than a conjugated alkene, was critical for achieving high yield (see ESI Table S2† for more details).

Synthetic attempts to form the B ring of penicilfuranone A (1)

With these three fragments in hand, we focused on constructing the 4-hydroxytetralone skeleton (B ring) of penicilfuranone A (1) *via* a formal [4 + 2] annulation (Scheme 4). Initially, we attempted to construct the B ring through an intermolecular Diels–Alder reaction between gregatin A (8) and benzoisofuran 13a. However, despite exploring various acidic and basic conditions, we were unable to detect the formation of benzoisofuran 13a. Next, we explored trapping the *in situ* generated benzoisofuran 13a with different dienophiles, including gregatin A (8). Unfortunately, this approach also proved unsuccessful, as the conditions required for the formation of isobenzofuran





Scheme 4 Synthetic attempts to form the B ring through the Diels–Alder or Stetter–Aldol cascade reaction.

were incompatible with hemiacetal **20**. Specifically, acidic conditions (*e.g.*, AcOH, PTSA, and Cu(OTf)₂) led to the decomposition of hemiacetal **20**.¹⁵ Additionally, attempts to employ an elimination strategy for methyl acetal **21** with lithium diisopropylamide (LDA) or Cu(OTf)₂ were also unsuccessful (see ESI Table S3† for more details).¹⁶ At this point, we hypothesized that this highly functionalized 4-hydroxytetralone skeleton could be synthesized through an NHC-catalyzed formal [4 + 2] annulation.¹⁷ Stetter reactions, as a well-established type of umpolung reaction,¹⁸ are commonly used to couple benzaldehyde and electron-deficient alkene fragments. We anticipated that the enolate generated from the Stetter reaction could be effectively trapped by the methyl ketone. To quickly verify the feasibility of this approach, we tested model substrates electron-deficient alkene **34** and benzaldehyde **35** for the Stetter–Aldol cascade reaction (Scheme 4B).

We employed an NHC-catalyzed intermolecular Stetter–Aldol cascade reaction to synthesize the 4-hydroxytetralone skeleton.

To prevent homo-benzoin condensation of benzaldehyde **35**, we utilized an activated Michael acceptor, electron-deficient alkene **34** (Table 2). To our delight, treatment of benzaldehyde **35** and alkene **34** with a carbene catalyst, generated by deprotonating the thiazolium salt NHC-1 with Cs₂CO₃, resulted in the desired 4-hydroxytetralone skeleton, which existed as three diastereoisomers—**36a**, **36b**, and **36c** in a 3 : 1 : 3 ratio, achieving an 86% overall yield (entry 1). The structure of **36a**, **36b**, and **36c** was confirmed through X-ray crystallography.¹⁹ NHCs derived from thiazolium salts were effective in promoting the reaction (entry 2),²⁰ while NHCs derived from imidazolium and triazolium salts were ineffective (entries 3 and 4), leading to the homo-benzoin condensation product of benzaldehyde **35**.²¹ Additional screening revealed that Cs₂CO₃ was crucial for the success of the Stetter–Aldol cascade reaction, while other bases, such as K₂CO₃ and Li₂CO₃, and organic bases such as DBU and DIPEA, were ineffective (entries 5–11) or resulted in low yields (entry 5). Furthermore, only DCM was effective in promoting the



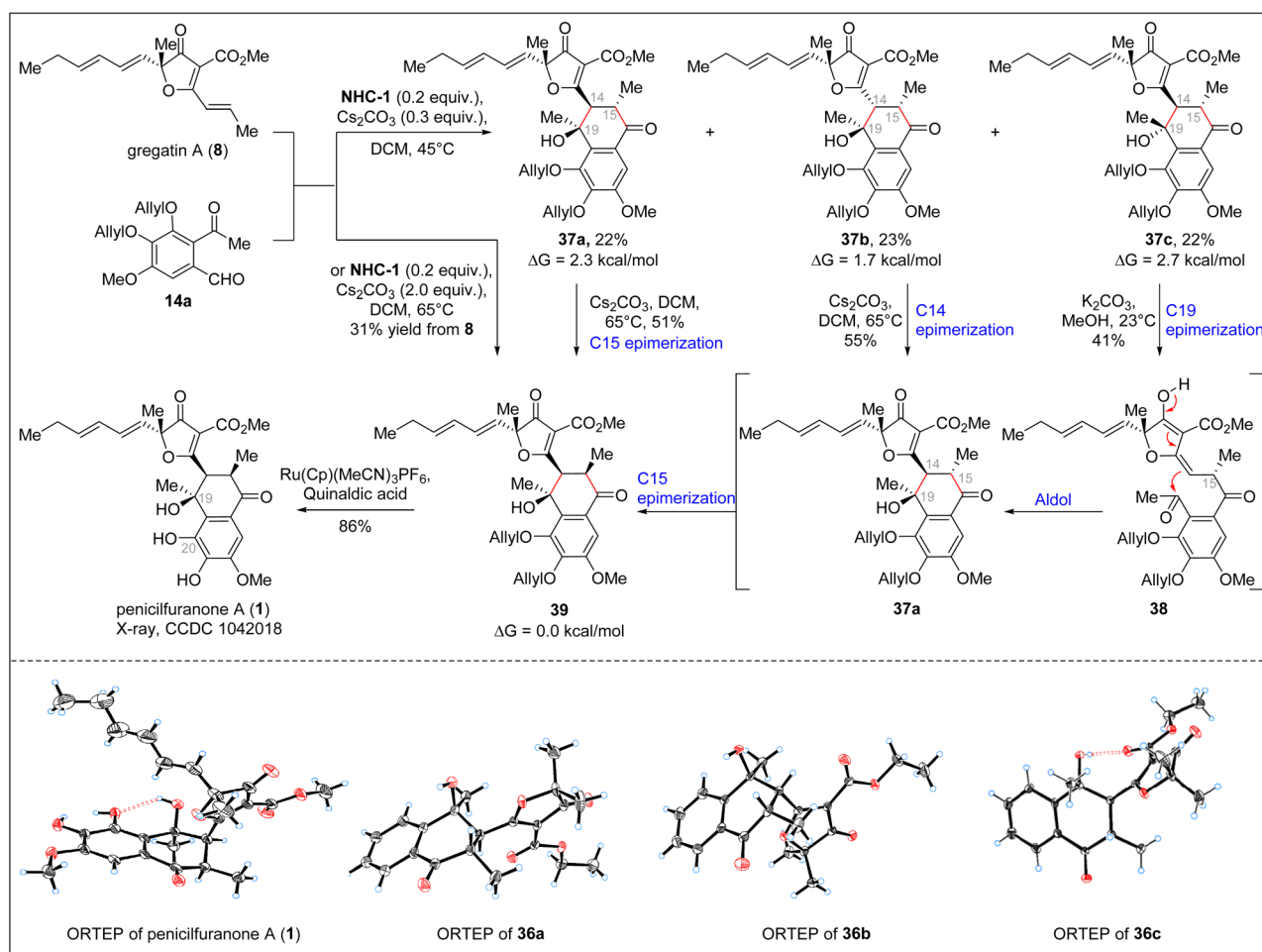
reaction, while other solvents caused decomposition of both alkene **34** and benzaldehyde **35** (entries 7–8). While Ye and other groups have reported intermolecular Stetter–Aldol cascade reactions between benzaldehydes and electron-deficient alkenes,²² to the best of our knowledge, there is no precedent for trapping the enolate with ketones. This represents the first example of an intermolecular Stetter–Aldol cascade reaction with a ketone. As depicted in the proposed catalytic cycle for this Stetter–Aldol cascade reaction (Scheme 4C), NHC catalysis proves to be highly effective in this umpolung formal [4 + 2] annulation, forming two C–C bonds and generating three stereocenters in a single process.

Asymmetric total synthesis of penicilfuranone A (1)

With the optimized conditions in hand, we proceeded with the asymmetric total synthesis of penicilfuranone A (**1**) (Scheme 5). Under the catalysis of NHC-1, benzaldehyde **14a** and gregatin A (**8**) underwent dimerization, yielding three diastereoisomers—**37a**, **37b**, and **37c**—in a 1 : 1 : 1 ratio, with a 67% overall yield. Although three diastereoisomers were formed, all could be converted to the desired compound **39**. For instance, after C15 epimerization with Cs₂CO₃, **37a** could be transformed into **39**;

both **37b** and **37c** could be converted to **39** through a retro-aldol/aldol/C15 epimerization cascade, yielding the precursor to penicilfuranone A (**1**), compound **39**, in a 33% overall yield from gregatin A (**8**). Interestingly, C15 epimerization, which converts the C14/C15 *trans* configuration to the *cis* configuration, initially appeared abnormal. However, preliminary DFT calculation and our experimental results suggested that the *cis* configuration is thermodynamically favored, likely due to the steric repulsion between the C15 methyl group and C14 dihydrofuranone ring fragments (**37b** and **39** versus **37a** and **37c**) (see the ESI† for more details). After identifying these intermediates, we were also able to synthesize compound **39** in one step in a 31% yield from benzaldehyde **14a** and gregatin A (**8**) using excess Cs₂CO₃ (2.0 equiv.).

The crystal structure of penicilfuranone A (**1**) further revealed an intramolecular hydrogen bond between the C19 OH group and the C20 O, which likely plays a crucial role in stabilizing the axial configuration of the dihydrofuranone ring. The final step in the synthesis of penicilfuranone A (**1**) involved deallylation. Under standard conditions (Pd/C, HCO₂NH₄), this step could lead to the formation of penicilfuranone A (**1**) in good yield. However, this condition was not reproducible in some instances. Ultimately, we found that the Ru-catalyzed



Scheme 5 Asymmetric total synthesis of penicilfuranone A (**1**).



deallylation method developed by Kitamura²³ proved robust and efficient for this substrate, yielding penicilfuranone A (**1**) in 86% yield. The synthetic penicilfuranone A (**1**) was fully characterized, and its spectral data were identical to those reported by Puno.⁴

Conclusions

In conclusion, we have successfully achieved the first asymmetric total synthesis of penicilfuranone A (**1**) in the longest linear sequence of eight steps, starting from methyl ketone **27**. Moreover, we have uncovered a novel NHC-catalyzed intermolecular Stetter–Aldol cascade reaction between benzaldehydes and electron-deficient alkenes, enabling the efficient synthesis of the 4-hydroxytetralone skeleton. This new synthetic approach not only facilitates the synthesis of penicilfuranone A (**1**) but also offers opportunities for the synthesis of other 4-hydroxytetralone containing natural products with potential pharmacological activities, such as rishirilide B (**5**)²⁴ and tetracycline (**6**).²⁵

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Y. D., X. L. and J. D. designed the research. Y. D., X. L. and J. Z. performed the synthetic work. J. Z. performed the quantum-molecular calculations. P. W. performed the crystallographic analysis. J. D. wrote the manuscript. X. Y., and P.-T. P. contributed to discussions. J. D. supervised the research.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the National Natural Science Foundation of China (no. 22222105, 22371142, and 22301146), the Frontiers Science Center for New Organic Matter, Nankai University (no. 63181206), a Key project at the central government level: the ability establishment of sustainable use for valuable Chinese medicine resources (no. 2060302), the Fundamental Research Funds for the Central Universities (no. 23JCYBJC01410), and the China Postdoctoral Science Foundation (no. 332608) is gratefully acknowledged.

Notes and references

- J. Iglesias, I. Martínez-Salazar, P. Maireles-Torres, D. M. Alonso, R. Mariscal and M. L. Granados, *Chem. Soc. Rev.*, 2020, **49**, 5704–5771.
- (a) M. Alizadeh, M. Jalal, K. Hamed, A. Saber, S. Kheirouri, F. Pourteymour Fard Tabrizi and N. Kamari, *J. Inflamm.*

- Res.*, 2020, **13**, 451–463; (b) C. Almeida, N. El Aouad, J. Martín, I. Pérez-Victoria, V. González-Menéndez, G. Platas, M. de la Cruz, M. C. Monteiro, N. de Pedro, G. F. Bills, F. Vicente, O. Genilloud and F. Reyes, *J. Antibiot.*, 2014, **67**, 421–423.
- (a) N. G. Clemo and G. Pattenden, *Tetrahedron Lett.*, 1982, **23**, 585–588; (b) K. Takeda, H. Kubo, T. Koizumi and E. Yoshii, *Tetrahedron Lett.*, 1982, **23**, 3175–3178; (c) O. Miyata and R. R. Schmidt, *Tetrahedron Lett.*, 1982, **23**, 1793–1796; (d) A. Takaiwa and K. Yamashita, *Agric. Biol. Chem.*, 1982, **46**, 1721–1722; (e) A. Takaiwa and K. Yamashita, *Agric. Biol. Chem.*, 1984, **48**, 2061–2065; (f) N. G. Clemo and G. Pattenden, *J. Chem. Soc. Perkin Trans. I*, 1985, 2407–2411; (g) H. Burghart-Stoll and R. Brückner, *Org. Lett.*, 2011, **13**, 2730–2733; (h) H. Burghart-Stoll and R. Brückner, *Eur. J. Org. Chem.*, 2012, **2012**, 3978–4017; (i) F. Weber and R. Brückner, *Org. Lett.*, 2014, **16**, 6428–6431; (j) G. Dai, Q. Shen, Y. Zhang and X. Bian, *J. Fungi*, 2022, **8**, 320; (k) Y. Ding, X. Zhao, C. Qu, X. Long, Y. Zhao and J. Deng, *Org. Biomol. Chem.*, 2025, DOI: [10.1039/d4ob02108h](https://doi.org/10.1039/d4ob02108h).
- W.-G. Wang, A. Li, B.-C. Yan, S.-B. Niu, J.-W. Tang, X.-N. Li, X. Du, G. L. Challis, Y. Che, H.-D. Sun and J.-X. Pu, *J. Nat. Prod.*, 2016, **79**, 149–155.
- (a) G.-P. Yin, Y.-R. Wu, M.-H. Yang, T.-X. Li, X.-B. Wang, M.-M. Zhou, J.-L. Lei and L.-Y. Kong, *Org. Lett.*, 2017, **19**, 4058–4061; (b) G.-P. Yin, Y.-R. Wu, C. Han, X.-B. Wang, H.-L. Gao, Y. Yin, L.-Y. Kong and M.-H. Yang, *Org. Chem. Front.*, 2018, **5**, 2432–2436; (c) Q.-Y. Wang, H.-P. Chen, H. Tao, X. Li, Q. Zhao and J.-K. Liu, *Org. Lett.*, 2024, **26**, 7632–7637.
- W.-G. Wang, H. Wang, L.-Q. Du, M. Li, L. Chen, J. Yu, G.-G. Cheng, M.-T. Zhan, Q.-F. Hu, L. Zhang, M. Yao and Y. Matsuda, *J. Am. Chem. Soc.*, 2020, **142**, 8464–8472.
- (a) X. W. Long, Y. M. Ding and J. Deng, *Angew. Chem., Int. Ed.*, 2018, **57**, 14221–14224; (b) Y. Long, Y. M. Ding, H. Wu, C. L. Qu, H. Liang, M. Zhang, X. L. Zhao, X. W. Long, S. Wang, P. T. Puno and J. Deng, *Angew. Chem., Int. Ed.*, 2019, **58**, 17552–17557; (c) X. W. Long, H. Wu, Y. M. Ding, C. L. Qu and J. Deng, *Chem*, 2021, **7**, 212–223; (d) X. Long, J. Li, F. Gao, H. Wu and J. Deng, *J. Am. Chem. Soc.*, 2022, **144**, 16292–16297; (e) X. W. Long, M. Zhang, X. D. Yang and J. Deng, *Org. Lett.*, 2022, **24**, 1303–1307.
- (a) R. M. Moslin and T. F. Jamison, *Org. Lett.*, 2006, **8**, 455–458; (b) R. M. Moslin, K. M. Miller and T. F. Jamison, *Tetrahedron*, 2006, **62**, 7598–7610.
- T. Kikuchi, K. Narita, K. Saijo, C. Ishioka and T. Katoh, *Eur. J. Org. Chem.*, 2016, **34**, 5659–5666.
- For selected examples of S_N1' reaction in natural product synthesis: (a) S. D. Burke and L. Jiang, *Org. Lett.*, 2001, **3**, 1953–1955; (b) S. Tanaka, T. Seki and M. Kitamura, *Angew. Chem., Int. Ed.*, 2009, **48**, 8948–8951; (c) A. Guérinot, A. Serra-Muns, C. Bensoussan, S. Reymond and J. Cossy, *Tetrahedron*, 2011, **67**, 5024–5033; (d) X. Wang, G. Huang, Y. Wang and J. Gui, *J. Am. Chem. Soc.*, 2023, **145**, 9354–9363.
- P.-S. Wang, P. Liu, Y.-J. Zhai, H.-C. Lin, Z.-L. Han and L.-Z. Gong, *J. Am. Chem. Soc.*, 2015, **137**, 12732–12735.



- 12 (a) L.-X. Ruan, B. Sun, J.-M. Liu and S.-L. Shi, *Science*, 2023, **379**, 662–670; (b) M. Cao, H. Wang, F. Hou, Y. Zhu, Q. Liu, C.-H. Tung and L. Liu, *J. Am. Chem. Soc.*, 2024, **146**, 18396–18406; (c) H. An, S. Liu, S.-J. Wang, X. Yu, C. Shi, H. Lin, S. B. Poh, H. Yang, M. W. Wong, Y. Zhao, Z. Tu and S. Lu, *Org. Lett.*, 2024, **26**, 702–707.
- 13 (a) X.-P. Zeng, Z.-Y. Cao, X. Wang, L. Chen, F. Zhou, F. Zhu, C.-H. Wang and J. Zhou, *J. Am. Chem. Soc.*, 2016, **138**, 416–425; (b) X.-P. Zeng and J. Zhou, *J. Am. Chem. Soc.*, 2016, **138**, 8730–8733; (c) W.-B. Wu, X. Yu, J.-S. Yu, X. Wang, W.-G. Wang and J. Zhou, *CCS Chem.*, 2022, **4**, 2140–2152.
- 14 Roskamp Homologation: C. R. Holmquist and E. J. Roskamp, *J. Org. Chem.*, 1989, **54**, 3258–3260.
- 15 Acid-promoted isobenzofuran formation: (a) J. G. Smith, P. W. Dibble and R. E. Sandborn, *J. Org. Chem.*, 1986, **51**, 3762–3768; (b) P. Nandhikonda and M. D. Heagy, *Org. Lett.*, 2010, **12**, 4796–4799.
- 16 Base-promoted isobenzofuran formation: (a) D. Tobia and B. Rickborn, *J. Org. Chem.*, 1986, **51**, 3849–3858; (b) C. Martin, P. Mailliet and J. Maddaluno, *J. Org. Chem.*, 2001, **66**, 3797–3805.
- 17 For selected reviews and examples of NHC catalyzed Umpolung reactions: (a) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606–5655; (b) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167–178; (c) X. Bugaut and F. Glorius, *Chem. Soc. Rev.*, 2012, **41**, 3511–3522; (d) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307–9387; (e) X. Chen, H. Wang, Z. Jin and Y. R. Chi, *Chin. J. Chem.*, 2020, **38**, 1167–1202; (f) X. Fang, K. Jiang, C. Xing, L. Hao and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2011, **50**, 1910–1913; (g) S. Zhuo, T. Zhu, L. Zhou, C. Mou, H. Chai, Y. Lu, L. Pan, Z. Jin and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2019, **58**, 1784–1788; (h) P. Zheng, S. Wu, C. Mou, W. Xue, Z. Jin and Y. R. Chi, *Org. Lett.*, 2019, **21**, 5026–5029; (i) Y. Nakano and D. W. Lupton, *Angew. Chem., Int. Ed.*, 2016, **55**, 3135–3139; (j) M. H. Wang and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2016, **55**, 14912–14922; (k) C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2016, **138**, 7840–7843.
- 18 For reviews of Umpolung reactions: (a) D. Seebach and E. J. Corey, *J. Org. Chem.*, 1975, **40**, 231–237; (b) D. Seebach, *Angew. Chem., Int. Ed.*, 1979, **18**, 239–258; (c) A. B. Smith and C. M. Adams, *Acc. Chem. Res.*, 2004, **37**, 365–377; (d) X.-J. Dai, C.-C. Li and C.-J. Li, *Chem. Soc. Rev.*, 2021, **50**, 10733–10742; (e) B. Shen, D. M. Makley and J. N. Johnston, *Nature*, 2010, **465**, 1027–1032; (f) Y. Wu, L. Hu, Z. Li and L. Deng, *Nature*, 2015, **523**, 445–450; (g) Y. Chen, M. Duan, S. L. Lin, Y. W. Liu, J. Cheng, S.-H. Xiang, P. Yu, K. N. Houk and B. Tan, *Nat. Chem.*, 2024, **16**, 408–416.
- 19 Deposition numbers 2424508 (for **36a**), 2425647 (for **36b**), and 2440564 (for **36c**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
- 20 (a) E. Sánchez-Larios and M. Gravel, *J. Org. Chem.*, 2009, **74**, 7536–7539; (b) E. Sánchez-Larios, J. M. Holmes, C. L. Daschner and M. Gravel, *Org. Lett.*, 2010, **12**, 5772–5775; (c) P. Liu, M. Lei, L. Ma and L. Hu, *Synlett*, 2011, 1133–1136; (d) B.-C. Hong, N. S. Dange, C.-S. Hsu and J.-H. Liao, *Org. Lett.*, 2010, **12**, 4812–4815.
- 21 (a) T. Ema, Y. Oue, K. Akihara, Y. Miyazaki and T. Sakai, *Org. Lett.*, 2009, **11**, 4866–4869; (b) S. Kankala, R. Edulla, S. Modem, R. Vadde and C. S. Vasam, *Tetrahedron Lett.*, 2011, **52**, 3828–3831; (c) T. Ema, K. Akihara, R. Obayashi and T. Sakai, *Adv. Synth. Catal.*, 2012, **354**, 3283–3290; (d) M. Sharique and U. K. Tambar, *Chem. Sci.*, 2020, **11**, 7239–7243.
- 22 For selected examples of NHC catalyzed Stetter–Aldol cascade reaction: (a) F.-G. Sun, X.-L. Huang and S. Ye, *J. Org. Chem.*, 2010, **75**, 273–276; (b) E. Sánchez-Larios, J. M. Holmes, C. L. Daschner and M. Gravel, *Org. Lett.*, 2010, **12**, 5772–5775; (c) D. Barman, T. Ghosh, K. Show, S. Debnath, T. Ghosh and D. K. Maiti, *Org. Lett.*, 2021, **23**, 2178–2182.
- 23 (a) S. Tanaka, H. Saburi, Y. Ishibashi and M. Kitamura, *Org. Lett.*, 2004, **6**, 1873–1875; (b) D. E. Ward and M. M. Zahedi, *Org. Lett.*, 2012, **14**, 6246–6249.
- 24 (a) H. Iwaki, Y. Nakayama, M. Takahashi, S. Uetsuki, M. Kido and Y. Fukuyama, *J. Antibiot.*, 1984, **37**, 1091–1093; (b) J. G. Allen and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2001, **123**, 351–352; (c) M. Odagi, K. Furukori, K. Takayama, K. Noguchi and K. Nagasawa, *Angew. Chem., Int. Ed.*, 2017, **56**, 6609–6612.
- 25 (a) M. G. Charest, C. D. Lerner, J. D. Brubaker, D. R. Siegel and A. G. Myers, *Science*, 2005, **308**, 395–398; (b) C. Sun, Q. Wang, J. D. Brubaker, P. M. Wright, C. D. Lerner, K. Noson, M. Charest, D. R. Siegel, Y. M. Wang and A. G. Myers, *J. Am. Chem. Soc.*, 2008, **130**, 17913–17927.

