

Enantioselective Total Synthesis of (−)-Novofumigatonin

Vincent A. P. Ruf,[‡] Lukas J. Sprenger,[‡] Kirill Volynskiy, Vanessa M. Kandler, Nima Nasiri, and Erick M. Carreira^{*}



Cite This: *J. Am. Chem. Soc.* 2025, 147, 31456–31462



Read Online

ACCESS |

Metrics & More

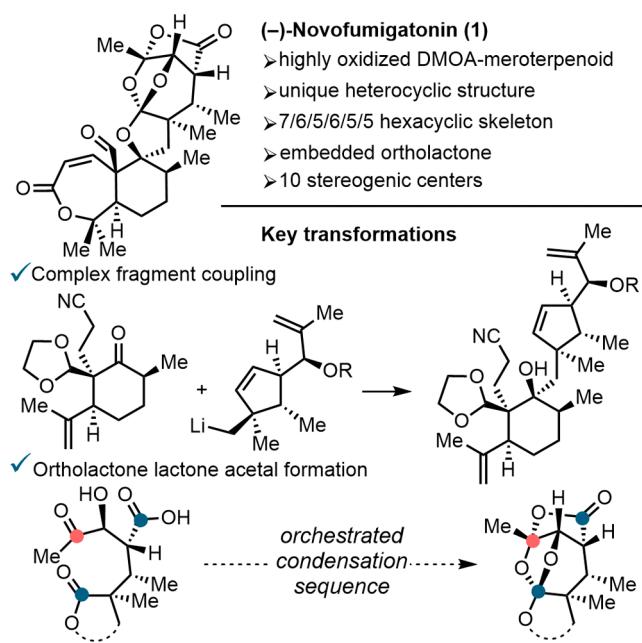
Article Recommendations

Supporting Information

ABSTRACT: We disclose the first and enantioselective synthesis of novofumigatonin, an ortholactone meroterpenoid natural product featuring an unprecedented 7/6/5/6/5/5 hexacyclic skeleton. On a strategic level, this was addressed by a highly convergent strategy that hinges on coupling of a complex neopentylic organolithium reagent and a highly hindered ketone. A unique approach to the ortholactone–acetal was required as it is not peripheral but embedded within the complex carbocyclic framework. This key challenge was addressed by orchestration of a condensation cascade triggered by the selective generation of an oxocarbenium ion. Tempering reactivity in the face of the densely functionalized skeleton proved key and culminated in the total synthesis of novofumigatonin. Of note, this represents the first study on the construction of such an embedded ortholactone, potentially useful for preparation of such motifs in the context of complex molecule synthesis.

In 2008, novofumigatonin (**1**) (Scheme 1) was isolated by Rank¹ from cultures of *Aspergillus novofumigatus*, a fungus

Scheme 1. Novofumigatonin and Key Transformations



found in the Galápagos Islands.^{2,3} Novofumigatonin is one of the most structurally complex and heavily oxygenated members of the 3,5-dimethylorsenilic acid (DMOA)-meroterpenoid class of secondary metabolites.^{4–6} The biosynthesis of **1** was elucidated through a series of CRISPR-Cas9 gene deletion and isolation experiments, leading to identification of an oxidative biosynthetic pathway to the unusual heterocyclic structure.^{7,8} The 7/6/5/6/5/5 hexacyclic skeleton of **1**, with its unique embedded ortholactone and

lactone–acetal cage, sparked our interest. Orthoesters and ortholactones are uncommon structural motifs in natural products^{9,10} and, other than ortho-formates and -acetates, rare in small-molecules. They are typically not considered robust, and they are rather acid labile.^{11,12} Other potentially reactive groups in **1** include an α,β -unsaturated ϵ -lactone and an aldehyde. Herein, we report the first and enantioselective total synthesis of novofumigatonin (**1**). The approach includes convergent coupling of two fragments, involving the addition of a neopentylic organolithium reagent to a highly hindered ketone (Scheme 1). A second salient feature of the strategy is the orchestration of steps that proceed from a highly functional-group-dense hydroxy-keto-lactone–acid precursor to the dioxabicyclo[3.2.1]octane ortholactone–acetal tetracyclic core of the target.

Retrosynthetic analysis of **1** (Scheme 2, top) commenced with dissection of the ortholactone and lactone–acetal to give hydroxy-keto-acid– γ -lactone **2**. In this respect, **1** and **2** differ synthetically by merely one equivalent of water: **2** \rightarrow **1** + H₂O. This simplistic analysis, however, masks the complexity involving the network of pathways and intermediates from **IV** to **V** (Scheme 2, bottom) that are possible from hydroxy-keto-acid– γ -lactone **2** to the dioxabicyclo[3.2.1]octane, incorporating ortholactone and lactone–acetal motifs. The assortment of functional groups, namely hydroxyl, ketone, acid and lactone, that participate in sequential condensation reactions requires a route that navigates the myriad of reactive intermediates (Scheme 2, bottom). Executing a successful strategy to the natural product requires judicious timing for the introduction

Received: June 20, 2025

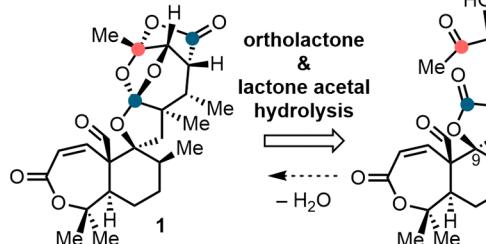
Revised: July 24, 2025

Accepted: July 25, 2025

Published: August 20, 2025



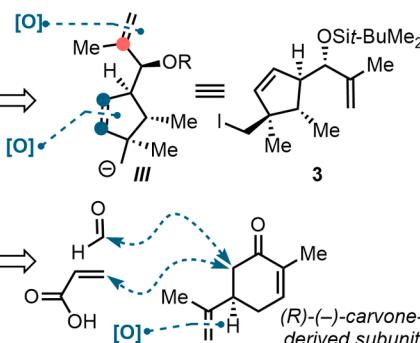
Scheme 2. Retrosynthesis and Key Challenges

1st Key Challenge2nd Key Challenge

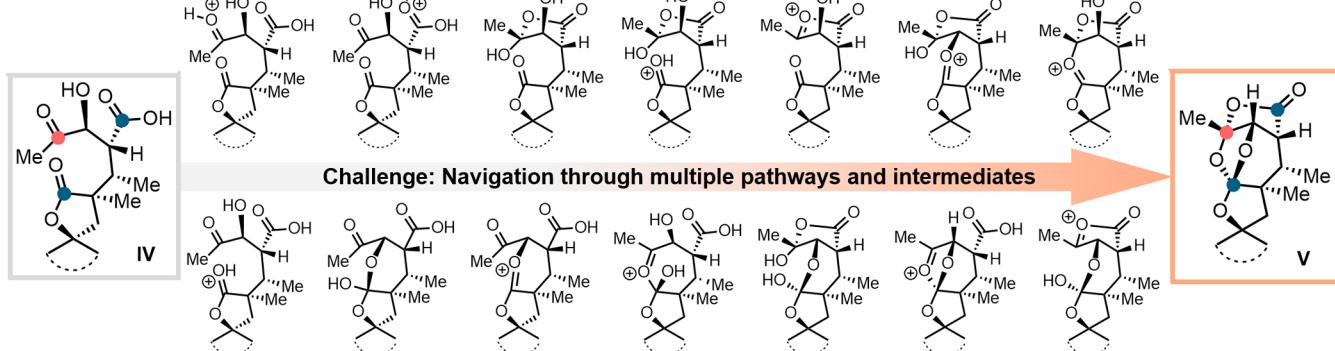
convergent fragment coupling

II

I



selected plausible intermediates in the dioxabicyclo[3.2.1]octane ortholactone-acetal formation



of the ortholactone–acetal, as subsequent steps would need to be compatible with the labile ensemble of functionalities.

An additional retrosynthetic consideration was the disconnection of **2** along the C9/C11-bond, leading to **I** and synthon **II**. This would be beneficial in the synthesis as it would entail convergent coupling of two approximately equally sized fragments (Scheme 2).¹³ In parallel, carrying the hydroxy, keto and acid groups through the synthetic sequence prior to condensation was another critical challenge posed by **II**. These considerations led to selection of the olefins in **III**, which would be oxidatively unmasked to the requisite functional group pattern. Accordingly, the synthesis of iodide **3** as a precursor to a neopentylic organometal species and its coupling to a carvone-derived ketone were envisioned.

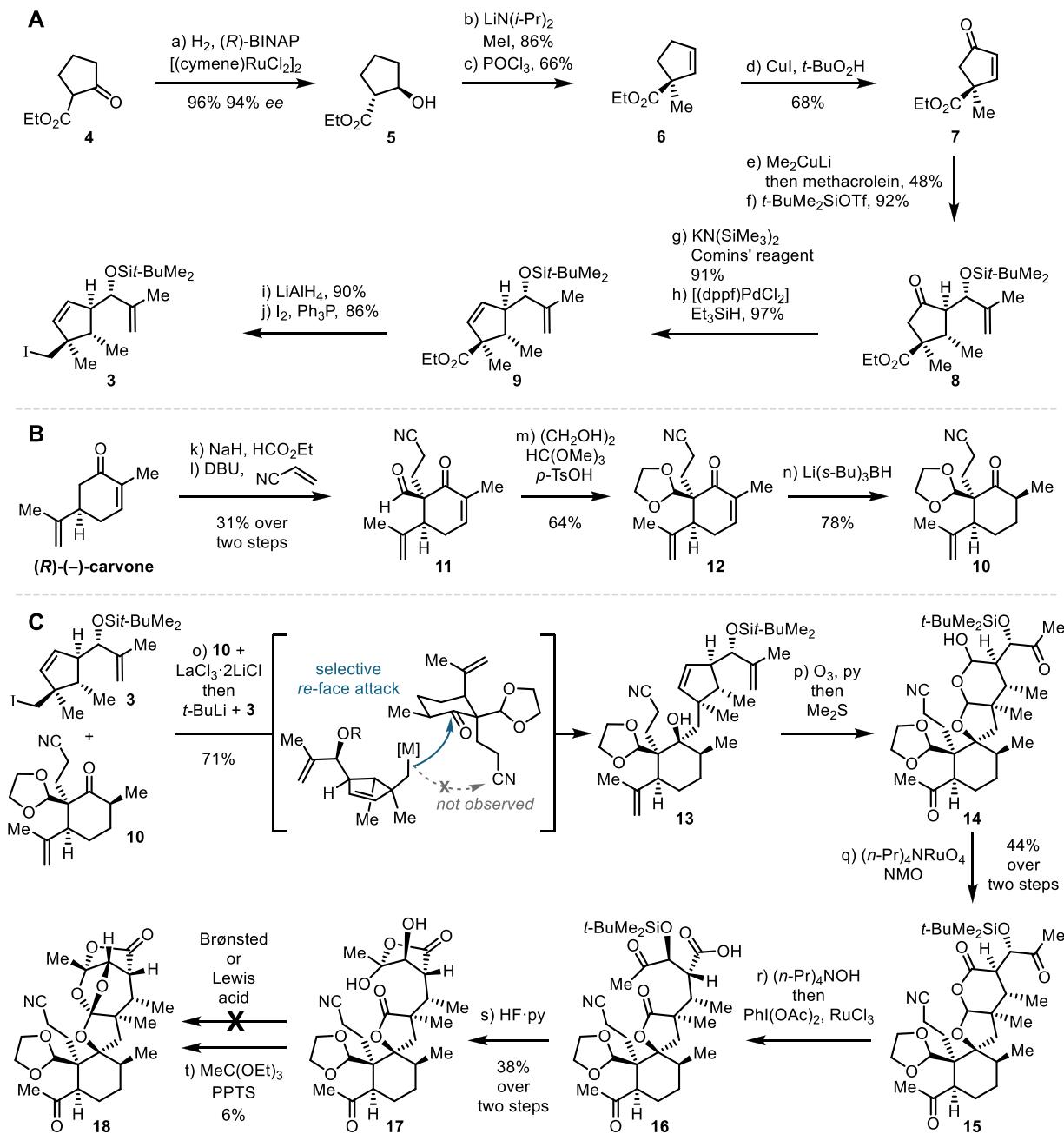
The synthesis of iodide **3** (Scheme 3, A) commenced with enantioselective Noyori reduction of ethyl 2-oxocyclopentane-1-carboxylate (**4**) to give secondary alcohol **5** in 96% yield and 94% ee.¹⁴ Fráter–Seebach alkylation followed by elimination furnished olefin **6**.¹⁵ Allylic oxidation was achieved by treatment of **6** with catalytic CuI/t-BuO₂H, resulting in enone **7** (68% yield).¹⁶ Determination of the enantiopurity of **7** indicated some erosion (79% ee by HPLC vs 94% ee for **5**), which likely occurs during the Fráter–Seebach alkylation step.¹⁷ Enone **7** was subjected to a sequence of reactions, consisting of conjugate addition of Me₂CuLi followed by subsequent trapping with methacrolein, giving rise to the aldol product in 48% isolated yield alongside 30% of its diastereomer (see SI). Subsequent silylation of the secondary alcohol furnished **8** in 92% yield. Vinyl triflate formation (KN(SiMe₃)₂ followed by Comins' reagent) and subsequent reduction with 3 mol% [(dppf)PdCl₂] and Et₃SiH delivered olefin **9** in 91% and 97% yield, respectively. Finally, LiAlH₄

reduction and Appel iodination gave rise to iodide **3** in 77% yield over two steps.

Preparation of **10** started with condensation between (R)-(-)-carvone and HCO₂Et (Scheme 3, B).¹⁸ Subsequent Michael addition of the unpurified 1,3-dicarbonyl compound with acrylonitrile furnished nitrile **11** in 31% yield (two steps). After aldehyde protection as the corresponding dioxolane, enone **12** was reduced by treatment with Li(s-Bu)₃BH. Diastereoselective protonation of the ensuing enolate provided the ketone product as a 4:1 mixture of C_α-epimers (NMR), which were separable by silica-gel chromatography to give **10** in 78% yield as a single isomer.

We next turned our attention to the coupling of the two highly sterically hindered fragments (Scheme 3, C). Iodide **3** was subjected to metal–halogen exchange (2.2 equiv *t*-BuLi, Et₂O–pentane), and the intermediate organolithium was treated with **10**. This resulted in addition of the organolithium to the nitrile as a minor product and recovery of **10** as a mixture of epimers at C_α (d.r. 2:1). We next employed lanthanide salts, which are known to preclude enolization.^{19–21} Therefore, ketone **10** was pretreated with LaCl₃·2LiCl in THF and stirred at r.t. for 1 h. Subsequently, a solution of the organolithium (2.0 equiv) was added to the ketone/LaCl₃·2LiCl mixture at -40 °C. Under these conditions, clean addition to ketone **10** was effected, furnishing 3°-alcohol **13** (71% yield, single diastereomer).

Ozonolysis of **13** followed by reductive workup gave rise to hemiacetal **14** as a mixture of diastereomers. Ley–Griffith oxidation furnished lactone–acetal **15** in 44% yield over two steps as a single diastereomer. Further oxidation of the acyloxyacetal **15** was necessary to match the oxidation pattern found in **1**. Conditions were required to effect saponification of the δ-lactone followed by oxidation. We found that

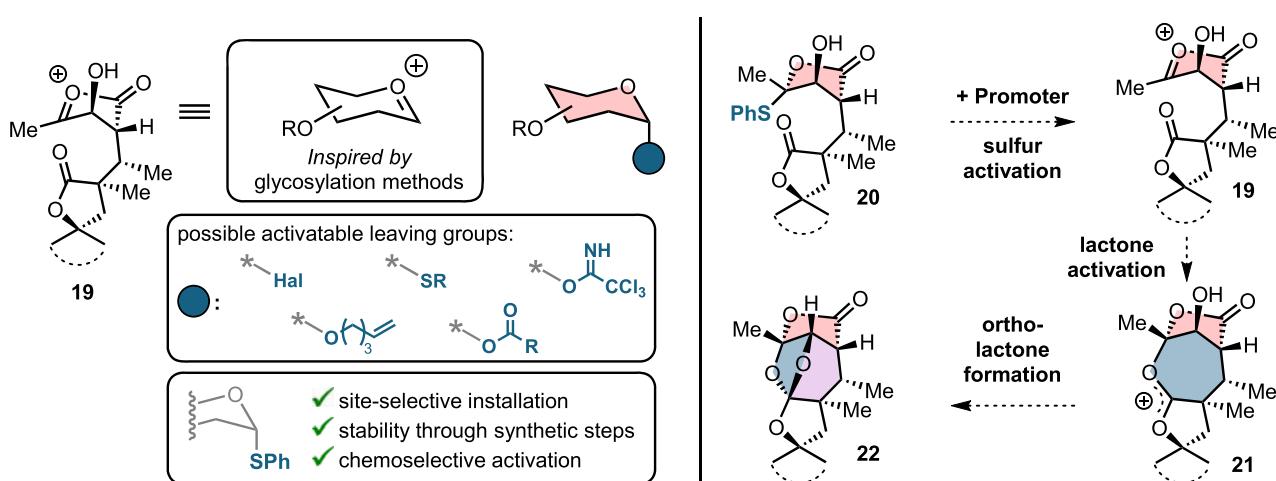
Scheme 3. Building Block Synthesis, Fragment Coupling, and Initial Ortholactone Formation Reaction^a

^aReagents and conditions: (a) H_2 (100 atm), $[(\text{cymene})\text{RuCl}_2]_2$ (0.25 mol%), (R)-BINAP (0.6 mol%), CH_2Cl_2 , 60°C , 96%, 94% ee; (b) $\text{LiN}(i\text{-Pr})$, THF, -50 to -10°C , then MeI , THF, -78 to -10°C , 86%; (c) POCl_3 , py, 0 to 50°C , 66%; (d) CuI (10 mol%), $t\text{-BuO}_2\text{H}$, NaHCO_3 , MeCN , 40°C , 68%, 79% ee; (e) CuI , MeLi , Et_2O , 0°C , then 7, 0°C , then methacrolein, THF, -78 to -50°C , 48%; (f) $t\text{-BuMe}_2\text{SiOTf}$, 2,6-lutidine, CH_2Cl_2 , 0°C , 92%; (g) $\text{KN}(\text{SiMe}_3)_2$, THF, -78°C , then Comins' reagent, -78°C , 91%; (h) $[(\text{dpdpf})\text{PdCl}_2]$ (3.0 mol%), Et_3SiH , DMF, 60°C , 97%; (i) LiAlH_4 , Et_2O , 0°C , 90%; (j) Ph_3P , imidazole, I_2 , THF, 0°C to r.t., 86%; (k) NaH , HCO_2Et , EtOH (10 mol%), Et_2O ; (l) acrylonitrile, DBU (20 mol%), DMF, 60°C , 31% over two steps; (m) $(\text{CH}_2\text{OH})_2$, $\text{HC}(\text{OMe})_3$, $p\text{-TsOH}\cdot\text{H}_2\text{O}$ (10 mol%), PhMe, 50°C , 64%; (n) $\text{Li}(s\text{-Bu})_3\text{BH}$, THF, -78°C , **10** (78%), *epi*-**10** (20%); (o) $t\text{-BuLi}$, 3 (2.0 equiv), Et_2O -pentane (4:3), -78°C to r.t., then **10**, $\text{LaCl}_3\cdot 2\text{LiCl}$, THF -40°C , 71%; (p) O_3 , $\text{CH}_2\text{Cl}_2\text{-MeOH-py}$ (3:3:1), -78°C , then Me_2S , -78°C to r.t.; (q) $(n\text{-Pr})_4\text{NRuO}_4$ (20 mol%), NMO, $\text{CH}_2\text{Cl}_2\text{-MeCN}$ (2:1), 44% over two steps; (r) $(n\text{-Pr})_4\text{NOH}$, $\text{MeCN-H}_2\text{O}$ (7:1), then $\text{PhI}(\text{OAc})_2$, $\text{RuCl}_3\cdot x\text{H}_2\text{O}$ (20 mol%); (s) $\text{HF}\cdot\text{py}$, $\text{THF-py-H}_2\text{O}$ (10:2:1), 50°C , then SiO_2 , 38% over two steps; (t) PPTS, $\text{MeC}(\text{OEt})_3$, 6%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. NMO = *N*-methyl morpholine-*N*-oxide. PPTS = pyridinium *p*-toluenesulfonate.

treatment of **15** with 2 equiv of a 1 M solution of $(n\text{-Pr})_4\text{NOH}$ in water followed by $\text{PhI}(\text{OAc})_2$ and $\text{RuCl}_3\cdot\text{hydrate}$ afforded **16**, which was used without purification.²² Desilylation with $\text{HF}\cdot\text{pyridine}$ gave hemiacetal **17** (38%, two steps).

We initially examined the simplest approach to the dioxabicyclo[3.2.1]octane cage, namely, treatment of **17** with various acids (e.g., $p\text{-TsOH}$, PPTS, $\text{Sc}(\text{OTf})_3$, HCO_2H) to promote condensation with formation of ortholactone **18**. Despite considerable experimentation, we were unable to

Scheme 4. Revised Ortholactone Formation



detect its formation, instead reisolating starting material or a complex mixture of multiple unidentified products (see SI). In a leading experiment, treatment of **17** with $\text{MeC(OEt)}_3/\text{PPTS}$ led to the formation of **18**, albeit in 6% yield. The generation of a large number of reactive intermediates from **17** by uncontrolled protonation may promote decomposition or unproductive pathways.²³

As an alternative to uncontrolled activation modes by Brønsted or Lewis acids, we pursued strategies achieving site- and chemoselective activation. Analyzing the various potential cationic intermediates and the network of pathways interconnecting them, we focused on oxocarbenium ion **19** (Scheme 4). Cation **19** bears analogy to oxocarbenium ions generated in glycosylation methods, which prescribe activatable leaving groups.^{24,25} Utilization of such groups in our setting would need to meet three criteria: site-selective installation, stability through subsequent synthetic steps, and chemoselective activation. With these considerations, we chose to incorporate a thioacetal, as shown for **20**.^{26–28} Thioacetal activation would enable a sequence of steps: **20** → **19** → **21** → **22**. The initially formed cation **19** would be poised to undergo capture by the spiro-fused lactone, ultimately resulting in attack by the 2°-alcohol to give **22**.

Subjecting carboxylic acid **16** to $\text{Ph}_2\text{S}_2/\text{Me}_3\text{P}$ resulted in thioester **23** in 68% yield over two steps from **15** (Scheme 5). After considerable experimentation, we found that treatment of **23** with $\text{KN}(\text{SiMe}_3)_2$ (10 equiv)/ PhSH (20 equiv) in THF over 40 h led to formation of thioacetal **24** as an inconsequential mixture of diastereomers (44%, d.r. 1.5:1) alongside recovered **23** (17%). We noted that reaction time, base, and stoichiometry of the latter and PhSH were crucial for formation of **24** and minimization of side products (see SI).^{29,30} Next, addition of MeLi to **24** mediated by $\text{LaCl}_3 \cdot 2\text{LiCl}$ gave the corresponding 3°-alcohol in 88% yield.¹⁹ Deprotection of the 2°-alcohol with $(n\text{-Bu})_4\text{NF}$ provided diol **25** (86% yield), setting the stage for the sulfur-mediated ortholactone formation cascade.

In initial experiments, a variety of thiophilic activators (*N*-bromosuccinimide, Br_2 , Selectfluor, PhSCl , dimethyl-(methylthio)sulfonium trifluoromethanesulfonate, AgPF_6 and AgBF_4 , see SI) were screened. Under optimized conditions, the use of *N*-bromosuccinimide with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) converted **25** to ortholactone **26**

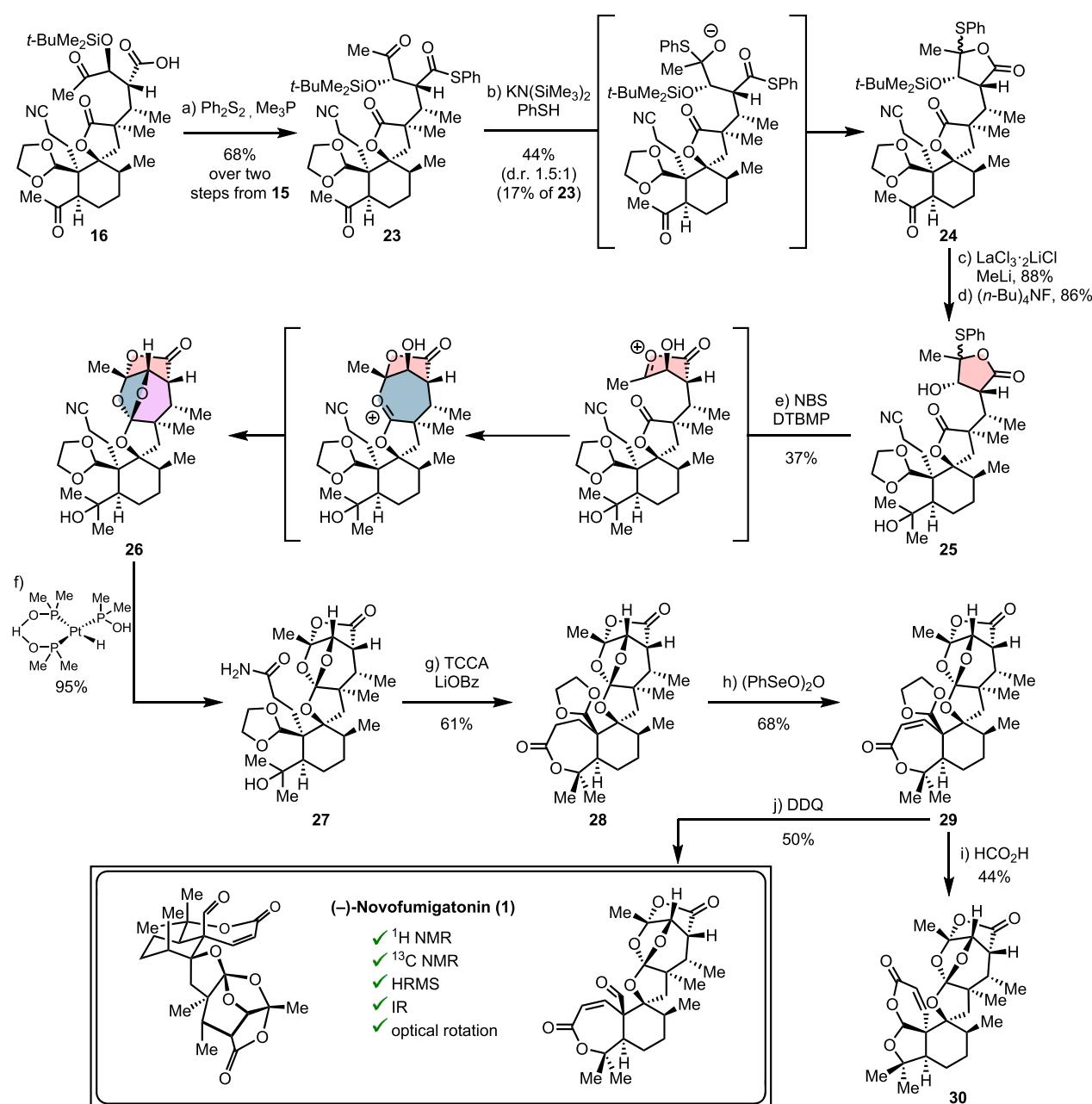
in 37% yield. With the critical ortholactone/lactone-acetal cage assembled, we proceeded to complete the synthesis of **1**.

The sequence involving the final steps commenced with manipulation of the nitrile in **26**. Heating of **26** with Ghaffar-Parkins catalyst ($[\text{PtH}(\text{Me}_2\text{POH})((\text{Me}_2\text{PO})_2\text{H})]$) in aqueous EtOH led to amide **27** in 95% yield.^{31,32} It was of some concern to us that the conditions typically employed for amide activation would not be compatible with the ortholactone (H^+) or bicyclic γ-lactone (alkaline).³³ As such, we turned our attention to oxidations. Recently, Bao and Wan reported the formation of esters from primary amides, involving the use of 2 equiv alcohol, trichloroisocyanuric acid (TCCA) and LiOBz in cyclohexane.³⁴ Under modified conditions, we found that treatment of **27** with TCCA in toluene (r.t. to 60 °C) afforded lactone **28** in 61% yield. Desaturation of **28** using $(\text{PhSeO})_2\text{O}$ afforded α,β -unsaturated ε-lactone **29** (68%).³⁵

In the original isolation procedure, novofumigatonin (**1**) was extracted with an $\text{EtOAc}/\text{HCO}_2\text{H}$ mixture.¹ This suggested to us that **1** might be sufficiently stable to acid to effect selective dioxolane deprotection. Treatment of **29** with HCO_2H led to formation of **30** accompanied by traces of **1**. This leading result compelled us to investigate other conditions that are known to effect chemoselective acetal deprotection in the presence of other acid-labile functional groups and thereby minimize formation of **30** (see SI). Under optimized conditions, treatment of **29** with DDQ in wet MeCN furnished novofumigatonin (**1**) in 50% yield, thus completing the first total synthesis of the natural product.^{36,37} The analytical data (¹H NMR, ¹³C NMR, HRMS, IR, $[\alpha]_D$) of synthetic **1** are in agreement with data reported for the isolated material.^{1,7}

In conclusion, we have achieved the first and enantioselective total synthesis of novofumigatonin (**1**). A powerful anionic fragment coupling followed by a series of oxidative transformations led to the rapid construction of the highly oxygenated backbone of **1**. Access to the uniquely complex heterocyclic cage of the natural product was enabled by a cascade of reactions hinging on a novel, sulfur-mediated ortholactone formation. We present a synthetic strategy to this class of oxygenated DMOA-meroterpenoids, exemplified by the synthesis of one of its most highly oxidized members isolated to date. This study serves as an entry point for the

Scheme 5. Completion of the Synthesis



^aReagents and conditions: (a) Ph_2S_2 , Me_3P , py, then **16**, 68% over two steps from **15**; (b) $\text{KN}(\text{SiMe}_3)_2$, PhSH , THF, then **23**, THF, 44% (d.r. 1.5:1), 17% recovered **23**; (c) $\text{LaCl}_3 \cdot 2\text{LiCl}$, THF, r.t., then MeLi , -78°C , 88%; (d) $(n\text{-Bu})_4\text{NF}$, EtOAc , -78 to -6°C , 86%; (e) N -bromosuccinimide (NBS), DTBMP, 4 Å MS, CH_2Cl_2 , 37%; (f) Ghaffar–Parkins catalyst (40 mol%), $\text{EtOH-H}_2\text{O}$ (4:1), 60°C , 95%; (g) trichloroisocyanuric acid (TCCA), LiOBz , PhMe , r.t. to 50 to 60°C , 61%; (h) $(\text{PhSeO})_2\text{O}$, 4 Å MS, PhCl , 140°C , 68%; (i) $\text{HCO}_2\text{H-H}_2\text{O}$ (3:1), 44%; (j) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), $\text{MeCN-H}_2\text{O}$ (10:1), 35°C , 50%.

synthesis of other complex natural products bearing embedded ortholactones.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.Sc10466>.

Experimental procedures and characterization data for all new compounds and X-ray crystallographic data ([PDF](#))

Accession Codes

Deposition Numbers 2452287, 2452289, and 2463553 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe [Access Structures service](#).

AUTHOR INFORMATION

Corresponding Author

Erick M. Carreira — ETH Zürich, Department of Chemistry and Applied Biosciences, Laboratory of Organic Chemistry,

8093 Zürich, Switzerland; orcid.org/0000-0003-1472-490X; Email: carreira@ethz.ch

Authors

Vincent A. P. Ruf – ETH Zürich, Department of Chemistry and Applied Biosciences, Laboratory of Organic Chemistry, 8093 Zürich, Switzerland; orcid.org/0009-0004-6417-5085

Lukas J. Sprenger – ETH Zürich, Department of Chemistry and Applied Biosciences, Laboratory of Organic Chemistry, 8093 Zürich, Switzerland; orcid.org/0000-0001-7932-8065

Kirill Volynskiy – ETH Zürich, Department of Chemistry and Applied Biosciences, Laboratory of Organic Chemistry, 8093 Zürich, Switzerland; orcid.org/0009-0002-8069-1819

Vanessa M. Kandler – ETH Zürich, Department of Chemistry and Applied Biosciences, Laboratory of Organic Chemistry, 8093 Zürich, Switzerland

Nima Nasiri – ETH Zürich, Department of Chemistry and Applied Biosciences, Laboratory of Organic Chemistry, 8093 Zürich, Switzerland; orcid.org/0000-0002-4719-7811

Complete contact information is available at:

<https://pubs.acs.org/10.1021/jacs.Sc10466>

Author Contributions

[‡]V.A.P.R. and L.J.S. contributed equally to this work.

Funding

We thank ETH Zürich for funding of this work. L.J.S. is an awardee of the Scholarship Fund of the Swiss Chemical Industry (SSCI).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to Dr. Marc-Olivier Ebert, René Arnold, Rainer Frankenstein, and Stephan Burkhardt for NMR measurements and to Dr. Nils Trapp and Michael Solar for X-ray crystallographic analysis.

REFERENCES

- (1) Rank, C.; Phipps, R. K.; Harris, P.; Fistrup, P.; Larsen, T. O.; Gotfredsen, C. H. Novofumigatonin, a New Orthoester Meroterpenoid from *Aspergillus novofumigatus*. *Org. Lett.* **2008**, *10* (3), 401–404.
- (2) Hong, S.-B.; Seung-Joo, G.; Hyeyon-Dong, S.; C, F. J.; Samson, R. A. Polyphasic taxonomy of *Aspergillus fumigatus* and related species. *Mycologia* **2005**, *97* (6), 1316–1329.
- (3) Samson, R. A.; Hong, S.; Peterson, S. W.; Frisvad, J. C.; Varga, J. Polyphasic taxonomy of *Aspergillus* section *Fumigati* and its teleomorph *Neosartorya*. *Stud. Mycol.* **2007**, *59*, 147–203.
- (4) Geris, R.; Simpson, T. J. Meroterpenoids produced by fungi. *Nat. Prod. Rep.* **2009**, *26* (8), 1063–1094.
- (5) Jiang, M.; Wu, Z.; Liu, L.; Chen, S. The chemistry and biology of fungal meroterpenoids (2009–2019). *Org. Biomol. Chem.* **2021**, *19* (8), 1644–1704.
- (6) For selected examples of total syntheses of DMOA-meroterpenoids, see: (a) Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. Annulative Methods Enable a Total Synthesis of the Complex Meroterpene Berkeleyone A. *J. Am. Chem. Soc.* **2016**, *138* (45), 14868–14871. (b) Elkin, M.; Szewczyk, S. M.; Scruse, A. C.; Newhouse, T. R. Total Synthesis of (\pm)-Berkeleyone A. *J. Am. Chem. Soc.* **2017**, *139* (5), 1790–1793. (c) Xu, G.; Elkin, M.; Tantillo, D. J.; Newhouse, T. R.; Maimone, T. J. Traversing Biosynthetic Carbocation Landscapes in the Total Synthesis of Andrin and Terretonin Meroterpenes. *Angew. Chem., Int. Ed.* **2017**, *56* (41), 12498–12502. (d) Powers, Z.; Scharf, A.; Cheng, A.; Yang, F.; Himmelbauer, M.; Mitsuhashi, T.; Barra, L.; Taniguchi, Y.; Kikuchi, T.; Fujita, M.; Abe, I.; Porco, J. A., Jr. Biomimetic Synthesis of Meroterpenoids by Dearomatization-Driven Polycyclization. *Angew. Chem., Int. Ed.* **2019**, *58* (45), 16141–16146. (e) Zhang, Y.; Ji, Y.; Franzoni, I.; Guo, C.; Jia, H.; Hong, B.; Li, H. Enantioselective Total Synthesis of Berkeleyone A and Preaustinoids. *Angew. Chem., Int. Ed.* **2021**, *60* (27), 14869–14874. (f) Yang, F.; Porco, J. A., Jr. Unified, Asymmetric Total Synthesis of the Asnovolins and Related Spiromeroterpenoids: A Fragment Coupling Approach. *J. Am. Chem. Soc.* **2022**, *144* (28), 12970–12978. (g) Yang, F.; Oladokun, A.; Porco, J. A., Jr. Evolution of a Strategy for the Unified, Asymmetric Total Syntheses of DMOA-Derived Spiromeroterpenoids. *J. Org. Chem.* **2024**, *89* (17), 11891–11908. (h) Li, X.; Chang, Z.; Duan, S.; Xie, Z. Total Synthesis of Berkeleyone A and Preaustinoid A through Epoxypolyene Cyclization. *Angew. Chem., Int. Ed.* **2025**, *64* (4), No. e202416211. (i) Tang, F.; Zhang, Z.-C.; Song, Z.-L.; Li, Y.-H.; Zhou, Z.-H.; Chen, J.-J.; Yang, Z. Asymmetric Total Synthesis of Janthinoid A. *J. Am. Chem. Soc.* **2025**, *147* (6), 4731–4735. (j) Zhang, J.; Luo, X.; Zhang, J.; Li, C. Total Synthesis of DMOA-Derived Meroterpenoids: Achieving Selectivity in the Synthesis of (+)-Berkeleyacetal D and (+)-Peniciacetal I. *J. Am. Chem. Soc.* **2025**, *147* (7), 5933–5942.
- (7) Matsuda, Y.; Bai, T.; Phippen, C. B. W.; Nødvig, C. S.; Kjærboelling, I.; Vesth, T. C.; Andersen, M. R.; Mortensen, U. H.; Gotfredsen, C. H.; Abe, I.; Larsen, T. O. Novofumigatonin biosynthesis involves a non-heme iron-dependent endoperoxide isomerase for orthoester formation. *Nat. Commun.* **2018**, *9* (1), 2587.
- (8) Mori, T.; Zhai, R.; Ushimaru, R.; Matsuda, Y.; Abe, I. Molecular insights into the endoperoxide formation by Fe(II)/ α -KG-dependent oxygenase NvfI. *Nat. Commun.* **2021**, *12* (1), 4417.
- (9) Liao, S.-G.; Chen, H.-D.; Yue, J.-M. Plant Orthoesters. *Chem. Rev.* **2009**, *109* (3), 1092–1140.
- (10) For selected examples of total syntheses of orthoester- and ortholactone-containing natural products, see: (a) Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. Enantioselective synthesis of natural (-)-australide B, an unusual ortho ester metabolite produced by toxigenic cultures of *Aspergillus ustus*. *J. Am. Chem. Soc.* **1994**, *116* (6), 2665–2666. (b) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. The First Synthesis of a Daphnane Diterpene: The Enantiocontrolled Total Synthesis of (+)-Resiniferatoxin. *J. Am. Chem. Soc.* **1997**, *119* (52), 12976–12977. (c) Nicolaou, K. C.; Mitchell, H. J.; Suzuki, H.; Rodríguez, R. M.; Baudoin, O.; Fylaktakidou, K. C. Total Synthesis of Everninomicin 13,384–1—Part 1: Synthesis of the A1B(A)C Fragment. *Angew. Chem., Int. Ed.* **1999**, *38* (22), 3334–3339. (d) Nicolaou, K. C.; Rodríguez, R. M.; Fylaktakidou, K. C.; Suzuki, H.; Mitchell, H. J. Total Synthesis of Everninomicin 13,384–1—Part 2: Synthesis of the FGHA2 Fragment. *Angew. Chem., Int. Ed.* **1999**, *38* (22), 3340–3345. (e) Nicolaou, K. C.; Mitchell, H. J.; Rodríguez, R. M.; Fylaktakidou, K. C.; Suzuki, H. Total Synthesis of Everninomicin 13,384–1—Part 3: Synthesis of the DE Fragment and Completion of the Total Synthesis. *Angew. Chem., Int. Ed.* **1999**, *38* (22), 3345–3350.
- (11) Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. Ortho ester hydrolysis. The complete reaction mechanism. *J. Am. Chem. Soc.* **1977**, *99* (14), 4827–4829.
- (12) Chiang, Y.; Kresge, A. J.; Lahti, M. O.; Weeks, D. P. Hydrolysis of ortho esters: further investigation of the factors that control the rate-determining step. *J. Am. Chem. Soc.* **1983**, *105* (23), 6852–6855.
- (13) For a review on fragment coupling in total synthesis, see: Tomanik, M.; Hsu, I. T.; Herzon, S. B. Fragment Coupling Reactions in Total Synthesis That Form Carbon–Carbon Bonds via Carbanionic or Free Radical Intermediates. *Angew. Chem., Int. Ed.* **2021**, *60* (3), 1116–1150.

- (14) Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. Dynamic kinetic resolution in BINAP—ruthenium(II) catalyzed hydrogenation of 2-substituted 3-oxo carboxylic esters. *Tetrahedron: Asymmetry* **1990**, *1* (1), 1–4.
- (15) Kuwata, K.; Hanaya, K.; Sugai, T.; Shoji, M. Chemo-enzymatic synthesis of (R)-5-hydroxymethyl-2-isopropyl-5-methylcyclopent-1-en-1-yl trifluoromethylsulfonate, a potential chiral building block for multicyclic terpenoids. *Tetrahedron: Asymmetry* **2017**, *28* (7), 964–968.
- (16) Salvador, J. A. R.; Sáe Melo, M. L.; Campos Neves, A. S. Copper-catalysed allylic oxidation of Δ^5 -steroids by t-butyl hydroperoxide. *Tetrahedron Lett.* **1997**, *38* (1), 119–122.
- (17) We hypothesize that two pathways may lead to epimerization: (i) retro-aldol/aldol reaction during the Fráter–Seebach alkylation; and (ii) because the diastereomers (d.r. 20:1) were not separated following the Fráter–Seebach alkylation, the minor diastereomer leads to the enantiomer of **6** in the subsequent elimination step.
- (18) Jansen, B. J. M.; Hendrikx, C. C. J.; Masalov, N.; Stork, G. A.; Meulemans, T. M.; Macaev, F. Z.; de Groot, A. Enantioselective Synthesis of Functionalised Decalone by Robinson Annulation of Substituted Cyclohexanones, Derived from R-(−)-Carvone. *Tetrahedron* **2000**, *56* (14), 2075–2094.
- (19) Krasovskiy, A.; Kopp, F.; Knochel, P. Soluble Lanthanide Salts ($\text{LnCl}_3 \cdot 2 \text{ LiCl}$) for the Improved Addition of Organomagnesium Reagents to Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2006**, *45* (3), 497–500.
- (20) Imamoto, T.; Sugiura, Y.; Takiyama, N. Organocerium reagents. Nucleophilic addition to easily enolizable ketones. *Tetrahedron Lett.* **1984**, *25* (38), 4233–4236.
- (21) Dimitrov, V.; Kostova, K.; Genov, M. Anhydrous cerium(III) chloride — Effect of the drying process on activity and efficiency. *Tetrahedron Lett.* **1996**, *37* (37), 6787–6790.
- (22) Nannini, L. J. Total Synthesis of Sarcophytin and Studies Towards Pavidolide B and Related Cembranoids. Doctoral Dissertation No. 25429, ETH Zurich, 2018.
- (23) Examples may include elimination, retro-aldol reaction, translactonization or epimerization:
-
- (24) Das, R.; Mukhopadhyay, B. Chemical O-Glycosylations: An Overview. *ChemistryOpen* **2016**, *5* (5), 401–433.
- (25) For selected examples of orthoester formation from glycoside onium ions, see: (a) Zuurmond, H. M.; van der Laan, S. C.; van der Marel, G. A.; van Boom, J. H. Iodonium ion-assisted glycosylation of alkyl (aryl) 1-thio-glycosides: regulation of stereoselectivity and reactivity. *Carbohydr. Res.* **1991**, *215* (2), C1–C3. (b) Crich, D.; Hu, T.; Cai, F. Does Neighboring Group Participation by Non-Vicinal Esters Play a Role in Glycosylation Reactions? Effective Probes for the Detection of Bridging Intermediates. *J. Org. Chem.* **2008**, *73* (22), 8942–8953. (c) Muru, K.; Cloutier, M.; Provost-Savard, A.; Di Cintio, S.; Burton, O.; Cordeil, J.; Groleau, M.-C.; Legault, J.; Déziel, E.; Gauthier, C. Total Synthesis of a Chimeric Glycolipid Bearing the Partially Acetylated Backbone of Sponge-Derived Agminoside E. *J. Org. Chem.* **2021**, *86* (21), 15357–15375.
- (26) Zhong, W.; Boons, G.-J.; Crich, D.; Bowers, A. A. Glycoside Synthesis from 1-Sulfur/Selenium-Substituted Derivatives: Sections 4.1 and 4.2. *Handbook of Chemical Glycosylation* **2008**, 261–329.
- (27) Lian, G.; Zhang, X.; Yu, B. Thioglycosides in Carbohydrate Research. *Carbohydr. Res.* **2015**, *403*, 13–22.
- (28) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. A mild and general method for the synthesis of O-glycosides. *J. Am. Chem. Soc.* **1983**, *105* (8), 2430–2434.
- (29) The reaction was performed on at least 20-mg scale as the transformation was found to be capricious on smaller scale.
- (30) For related transformations, see: (a) Wheeler, D. D.; Young, D. C.; Erley, D. S. Reactions of Phthalaldehydic Acid. *J. Org. Chem.* **1957**, *22* (5), 547–556. (b) Ito, K.; Miyajima, S. (Z)- and (E)-4,4-Dimethyl-5-oxo-2-pentenoic Acids and Their Derivatives. *Bull. Chem. Soc. Jpn.* **1986**, *59* (3), 815–818. (c) Takahashi, M.; Sekine, N.; Fujita, T.; Watanabe, S.; Yamaguchi, K.; Sakamoto, M. Solid-State Photochemistry of O-Aroylbenzothioates: Absolute Asymmetric Phthalide Formation Involving 1,4-Aryl Migration. *J. Am. Chem. Soc.* **1998**, *120* (49), 12770–12776. (d) Sakulsombat, M.; Angelin, M.; Ramström, O. Tandem reversible addition-intramolecular lactonization for the synthesis of 3-functionalized phthalides. *Tetrahedron Lett.* **2010**, *51* (1), 75–78. (e) Kanishchev, O. S.; Lavoignat, A.; Picot, S.; Médebielle, M.; Bouillon, J.-P. New route to the 5-((aryltio- and heteroaryltio)methylene)-3-(2,2,2-trifluoroethyl)-furan-2(5H)-ones—Key intermediates in the synthesis of 4-aminoquinoline γ -lactams as potent antimalarial compounds. *Bioorg. Med. Chem. Lett.* **2013**, *23* (22), 6167–6171.
- (31) Ghaffar, T.; Parkins, A. W. A new homogeneous platinum containing catalyst for the hydrolysis of nitriles. *Tetrahedron Lett.* **1995**, *36* (47), 8657–8660.
- (32) Ghaffar, T.; Parkins, A. W. The catalytic hydration of nitriles to amides using a homogeneous platinum phosphinito catalyst. *J. Mol. Catal. A: Chem.* **2000**, *160* (2), 249–261.
- (33) O'Connor, C. Acidic and basic amide hydrolysis. *Q. Rev. Chem. Soc.* **1970**, *24* (4), 553–564.
- (34) Wan, X.; Lin, J.; Bai, J.; Li, J.; Wang, K.; Cao, Z.; Li, M.; Bao, X.; Wan, X. Interception of RCONCl_2 : late-stage hydrolysis and esterification of primary amides. *Org. Chem. Front.* **2024**, *11* (1), 183–193.
- (35) Barton, D. H. R.; Lester, D. J.; Ley, S. V. Dehydrogenation of steroid ketones using benzeneseleninic anhydride. *J. Chem. Soc., Chem. Commun.* **1978**, *3*, 130–131.
- (36) Tanemura, K.; Suzuki, T.; Horaguchi, T. 2,3-Dichloro-5,6-dicyano-p-benzoquinone as a mild and efficient catalyst for the deprotection of acetals. *J. Chem. Soc., Chem. Commun.* **1992**, *14*, 979–980.
- (37) For a discussion on the mechanism of the DDQ-mediated acetal deprotection, see: Oku, A.; Kinugasa, M.; Kamada, T. Deprotection of Acetals and Silyl Ethers by DDQ. Is DDQ a Neutral Catalyst? *Chem. Lett.* **1993**, *22* (1), 165–168.

■ NOTE ADDED AFTER ASAP PUBLICATION

This Communication published ASAP on August 20, 2025. Scheme 3 has been updated and the corrected version reposted on August 21, 2025.