Synthetic Efforts Towards Lannotinidine G Based on an Aziridinium-Mediated Ring Contraction and Dienyne Metathesis

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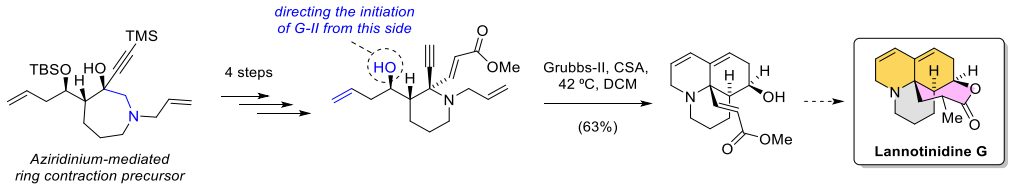
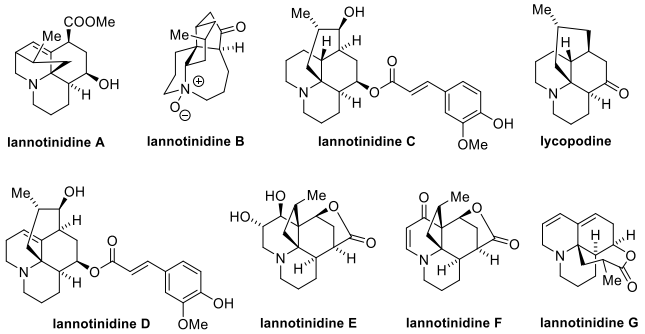
Supporting Information Placeholder



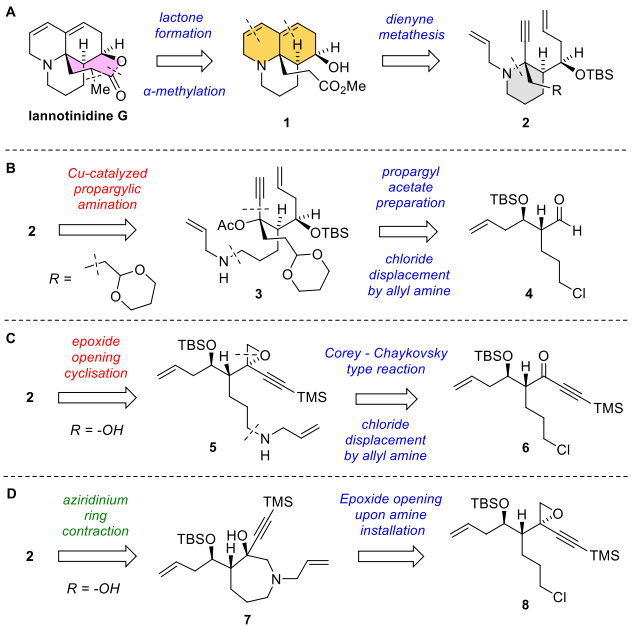
ABSTRACT: Lannotinidine G is a unique Lycopodium alkaloid that features a tricyclic [6/6/6] core with 3 contiguous stereocenters and a 1,3-diene moiety in addition to a 7-membered lactone. Herein, we disclose our efforts towards the synthesis of this natural product which achieved the construction of the aza-tricyclic core with the correct configuration at its three stereocenters. Key features of our strategy include a highly diastereoselective Fráter–Seebach alkylation and Corey-Chaykovsky type epoxide formation, an unusual aziridinium-mediated ring contraction for the formation of the piperidine moiety ,and a regioselective dienyne metathesis.

In 2005, Kobayashi and coworkers isolated seven new *Lycopodium* alkaloids from the club moss of *Lycopodium annotinum*, Lannotinidines A–G (***Scheme 1***).[1] Structurally, they resemble lycopodine, the first ever *Lycopodium* alkaloid reported by Bödeker in 1881,[2] with skeletal variations in their bridging pattern and the oxidation state of their cores. Initial bioactivity screening showed that several members of the group enhance mRNA expression of neurotrophic growth factor (NGF) in 1321N1 human astrocytoma cells.[1] Lannotinidine B, which was synthesized in 2012 by Yao,[3] proved to be most potent of the series. We decided, however, to focus our efforts on Lannotinidine G due to its enticing 1,3-diene moiety that could potentially be utilized to access other *Lycopodium* alkaloids.



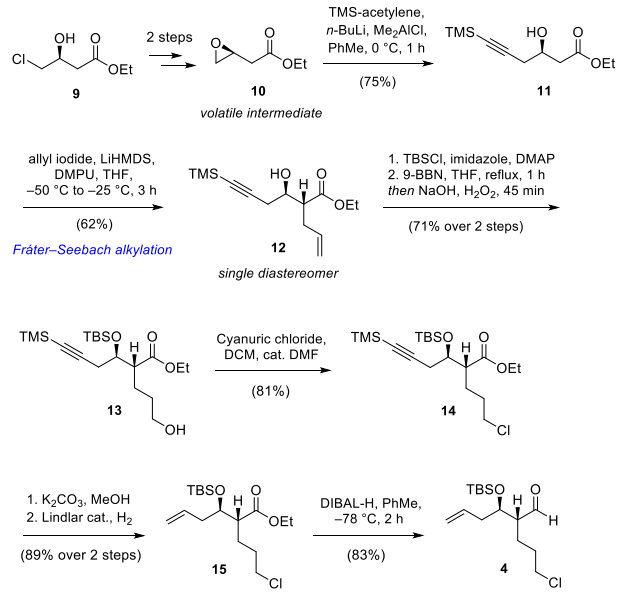
Scheme 1: Lannotinidines A–G and lycopodine structure.

Key structural challenges that needed to be addressed to access Lannotinidine G were the assembly of the 7-membered lactone bearing an α-methyl group, formation of the 1,3-diene moiety, and the installation of an α-tertiary amine stereocenter, which is adjacent to two contiguous stereogenic carbons. From a retrosynthetic aspect, we envisioned a late stage lactonization followed by α-methylation that would complete the synthesis (***Scheme 2A***). Prior to that, we decided to construct the [6/6/6]-tricyclic core via a dienyne ring closing metathesis to install this sensitive moiety at a late stage (***Scheme 2A***). Formation of the α-tertiary amine stereocenter proved more challenging than anticipated. We originally envisioned a copper-catalyzed propargylic amination as a C-N forming step (***Scheme 2B***). This would require substrate **3**, which could be traced back to aldehyde **4**. Since we encountered low diastereoselectivity in the key piperidine forming step, we then devised a strategy based on the cyclization of amino epoxide **5** (***Scheme 2C***). This intermediate in turn could be accessed from the versatile aldehyde **4** via ynone **6**. Upon the failure of this approach, we finally turned toward ring contraction of azepane **7** via an aziridinium intermediate, which correctly installed the piperidine ring to access **2** (***Scheme 2D***). Azepane **7** could be obtained from epoxide **8**, which was derived from ynone **6** and ultimately aldehyde **4**.



Scheme 2: Retrosynthetic analyses for Lannotinidine G.

Our synthetic efforts started from the known epoxide **10**, which could be accessed from ethyl (*S*)-(–)-4-chloro-3-hydroxybutyrate **9** (***Scheme 3***).[4] Nucleophilic opening of the epoxide by an aluminum acetylide afforded **11** in good yield.[5] Subsequent Fráter–Seebach alkylation afforded **12** in good yield and as a single diastereomer.[4a, 6] The use of DMPU and allyl iodide was essential for the success of this transformation. Secondary alcohol **12** was then TBS-protected and hydroboration-oxidation afforded primary alcohol **13**.[7] Conversion of the alcohol to chloride **14** utilizing cyanuric chloride,[8] followed by TMS-methanolysis, and Lindlar reduction gave ester **15**.[9] Finally, our key aldehyde **4** was accessed through chemoselective DIBAL-H reduction of the ester moiety.[10]

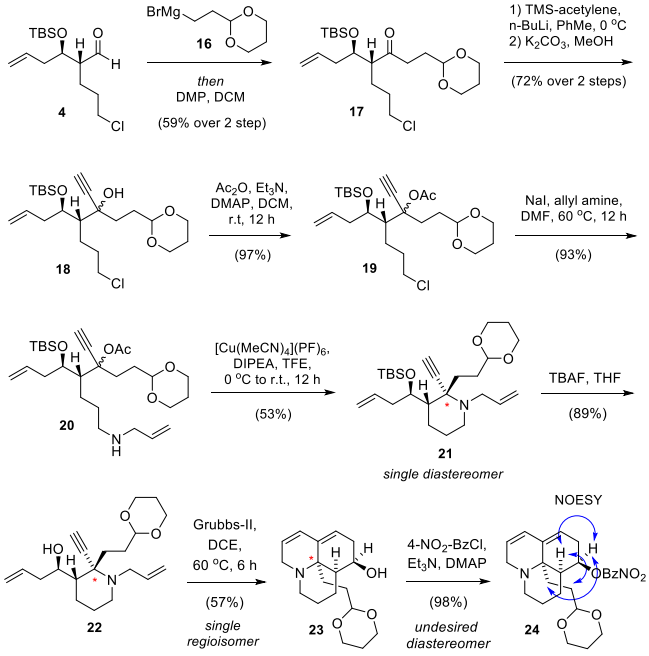


Scheme 3: Synthesis of versatile aldehyde **4** in 10 steps.

Aldehyde **4** was a common starting point of all our efforts towards constructing the piperidine core of **2** in a diastereoselective manner. First, we envisioned a copper-catalyzed propargylic amination. Towards this end, we converted aldehyde **4** into ketone **17** (***Scheme 4***) via Grignard addition using commercially available reagent **16**, followed by Dess-Martin oxidation. Subsequent nucleophilic attack of TMS-acetylide onto the ketone moiety and methanolysis afforded propargylic alcohol **18** as a separable but inconsequential 3:1 mixture of diastereomers.[11] Acetylation of tertiary propargylic alcohol gave **19**, which underwent a one-pot Finkelstein reaction followed by S_N2 displacement to yield secondary allyl amine **20**.

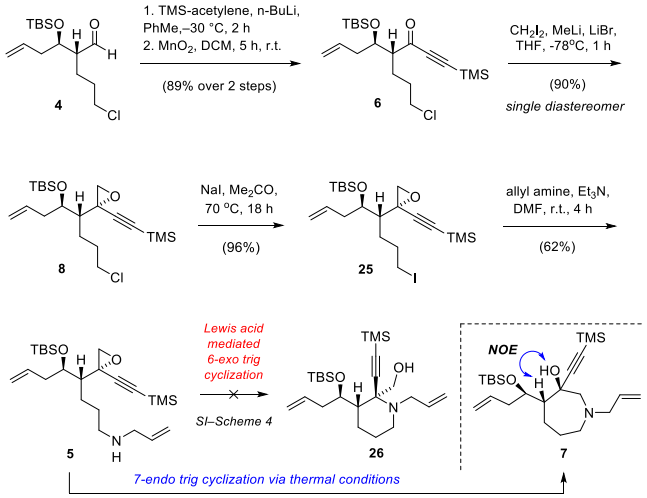
With propargylic acetate **20** in hand, we investigated propargylic aminations[12] to form the piperidine ring. Utilizing $[Cu(MeCN)_4](PF)_6$, as a Cu^I-source and DIPEA in trifluoroethanol,[11] we indeed obtained piperidine **21** as a single diastereomer but in moderate yield. However, at this stage, we were unable to determine the absolute configuration of the newly formed α-tertiary amine stereocenter. Therefore, we decided to carry on with our synthesis and attempt to resolve the stereochemistry of the α-tertiary amine stereocenter from a latter intermediate.

Piperidine **21** was subjected to a TBAF-mediated TBS-deprotection to afford secondary alcohol **22** in good yield. As it was still difficult to determine with confidence the absolute stereochemistry, intermediate **22** was subjected to a regioselective Grubbs-II mediated dienyne metathesis. Since, substrate **22** featured two terminal alkenes, initiation of the catalyst could happen at either, leading to a mixture of [6/6/6]- and [5/6/7]-tricyclic products (***SI–Scheme 1***). The unprotected secondary alcohol, however, could favor the formation of desired [6/6/6]-system by directing the initiation of the catalyst to the homoallylic alkene.[13] Indeed, tricyclic product **23** was isolated as a single regioisomer in moderate yield. Derivatization and examination of the 2D-NMRs due to lack of crystallinity, revealed that the undesired diastereomer **24** was obtained en route to lannotinidine G.



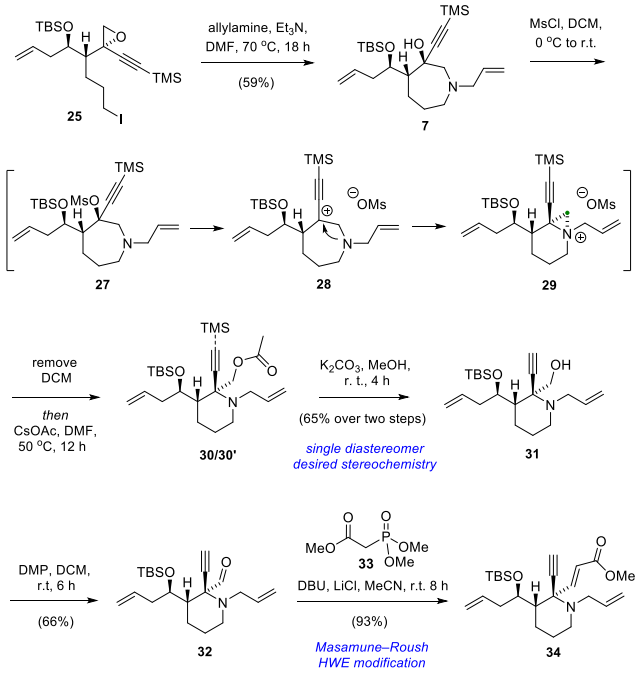
Scheme 4: Synthesis of propargyl acetate intermediate **20** followed by intramolecular Cu-catalyzed propargylic amination and determination of absolute stereochemistry.

Further attempts to reverse the diastereoselectivity (***SI–Scheme 2***) managed to reach a 1/1 ratio of separable diastereomers, but being unable to deprotect the acetal by various conditions (***SI–Scheme 3***) pointed to the need for revision. We next pursued the stereoselective formation of the piperidine ring via an amino epoxide (***Scheme 5***). For this, we converted aldehyde **4** into ynone **6** via lithium acetylide addition and oxidation under mild conditions.[14] Subsequent Corey-Chaykovsky type reaction[15] afforded epoxy-alkyne **8** in high yield and notably as a single diastereomer, the absolute stereochemistry of which was determined at a later stage. Conversion of the chloride **8** into the iodide **25** under Finkelstein conditions set the stage for a chemoselective S_N2 reaction to afford the desired secondary amine **5**. Unfortunately, treatment of **5** with a variety of Lewis acids (e.g. $Sc(OTf)_3$, $Mg(ClO_4)_2$, $Cu(OTf)_2$, Et_2AlCl, $BF_3{\bullet}Et_2O$) failed to provide the desired piperidine **26** via 6-exo trig cyclization. Under thermal conditions, however, we observed the formation of azepane **7** via 7-endo trig cyclization.



Scheme 5: Testing the epoxide opening cyclisation of **5**.

Azepane **7** played an important role in shaping the next iteration of our synthesis (***Scheme 6***). It could be obtained in a single step by reacting iodide **25** with allyl amine at 70 °C (***Scheme 6***). We reasoned that this 7-membered heterocycle could be converted to our desired 6-membered piperidine **25** via ring contraction, followed by intermolecular opening of the intermediate aziridinium ion with the proper nucleophile.[16] Indeed, treatment of **7** with mesyl chloride triggered a sequence of reactions, starting with sulfonylation of the propargylic alcohol, followed by loss of the leaving group, and subsequent trapping of the stabilized tertiary/propargylic cationic intermediate **28** by the neighboring tertiary amine. The aziridinium salt **29** so formed was then treated with CsOAc, which resulted in opening of the ring by nucleophilic attack of the acetate ion on the least substituted carbon. Upon workup, the TMS-alkyne on piperidine **30** was partially deprotected and was obtained as an inseparable mixture with the TMS-product **30'**. After this mixture was subjected to TMS-methanolysis with concomitant deacetylation, alcohol **31** was isolated as a single diastereomer and featuring the desired absolute stereochemistry at the a-tertiary amine center. Oxidation of alcohol **31** with DMP, followed by Masamune-Roush olefination[17] afforded enoate **34**, featuring the ene-yne-ene system needed to complete the tricyclic core and the 3-carbon ester substituent for the final macro-lactonization. Notably, the Masamune–Roush conditions were the only ones that enabled olefination of the hindered aldehyde **32**, whereas classic Horner–Wadsworth–Emmons conditions, Still–Gennari reaction, exposure to a stabilized Wittig reagent, and Wittig-Levine reaction failed.



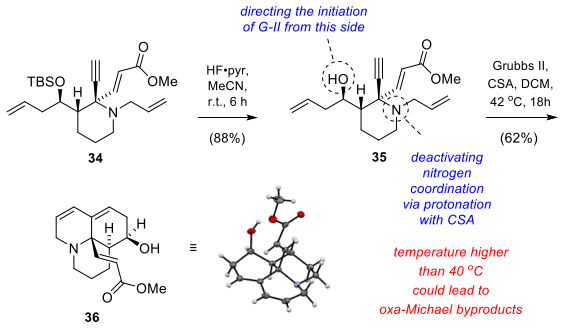
Scheme 6: Synthesis of **34** from azepane intermediate **7**.

Next, we needed to perform a 1,4-reduction of the enoate **34**, remove the TBS protecting group and assemble the tricyclic core bearing the diene system via the planned dienyne metathesis. Unfortunately, reduction of the enoate system using a range of conditions, including commonly used Stryker's reagent[18] or conjugate reductions utilizing Mg/MeOH[19] or SmI_2[20] failed to deliver the reduced product (***SI–Scheme 5 and SI Table 1***). Nucleophilic 1,4-addition to the Michael system by various nucleophiles able to access hindered systems (*e.g.*, EtSH, MeOH, Et_2AlCN) also failed to remove the superfluous double bond. Therefore, we decided to proceed with the metathesis, assuming that the electron-poor enoate system would not interfere.

Removal of the TBS group prior to the metathesis was essential, as proven by test reactions on TBS-protected **34**. Also, as seen earlier, the unprotected secondary alcohol, would favor the formation of desired [6/6/6]-system. To deter coordination to the allyl amine leading to catalyst deactivation, we also employed one equivalent of camphor sulfonic acid (CSA) to protonate the basic nitrogen.[21] We first performed an HF/pyridine mediated TBS deprotection, which afforded product **35** in good yield (***Scheme 7***). It should be noted that the use of TBAF for this transformation resulted exclusively in 1,4-addition of the alcohol to the enoate to afford a tetrahydrofuran (***SI–Scheme 6***).

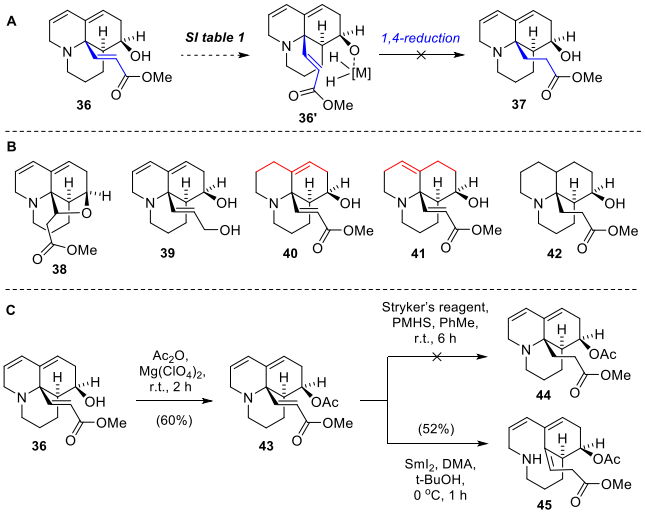
Treatment of ene-yne-ene compound **35** with CSA at 42 °C, followed by addition of Grubbs-II catalyst (30 mol%), afforded the desired product **36** with the desired

regioselectivity in comparatively good yield (***see SI Table 2*** *for metathesis conditions screening*). Its structure was verified by X-ray crystallography, which also confirmed the absolute configuration of the α-tertiary amine stereocenter.



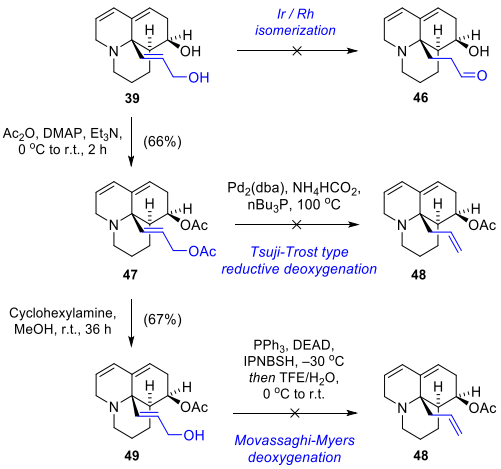
Scheme 7: Formation of key tricyclic product **36** via ene-yne-ene metathesis and its crystal structure.

At this stage, chemoselective reduction of the enoate, lactonization to form the 7-membered heterocycle, and stereoselective α-methylation of the lactone would complete the total synthesis of lannotinidine G. We hypothesized that the reduction of the unsaturated ester would be aided by the nearby secondary alcohol by positioning a metal hydride ***(Scheme 8A)***. Unfortunately, the reduction proved very challenging, with various undesired products formed under different conditions (***Scheme 8B -SI Table 3***). In some cases, the secondary alcohol underwent conjugate addition to the enoate, which is perfectly aligned for such a reaction as seen in the X-ray structure of **36**, affording **38**. The use of LAH and DIBAL-H resulted in 1,2-reduction and afforded the allylic alcohol **39**. Other conditions led to partial or full reduction of the endocyclic diene system to yield **40**, **41**, or **42**. Next, we protected the secondary alcohol as the acetate under carefully controlled conditions to avoid the 1,4-addition. However, conjugate reduction of **43** with Stryker's reagent was also unsuccessful. The use of SmI_2 led to the secondary amine **45** though an unusual fragmentation. (***Scheme 8C***).



Scheme 8: Reduction efforts of intermediate **36**; A) General transformation, B) Reduction products under various conditions, C) Reduction efforts on masked intermediate **43**.

Since reduction of the enoate system could not be achieved, alternatives were explored. Isomerizations of allylic alcohols to saturated aldehydes with various Ir/Rh/Pd catalysts have been reported in literature[22] but allylic alcohol **39** failed to undergo the transformation upon treatment with Crabtree cat., $[Cp^*IrCl_2]_2$ or Wilkinson's cat (***Scheme 9 + SI Table 4***). Diol **39** was then converted to diacetate **47**, which also failed to deliver terminal alkene **48** upon a Pd-catalyzed Tsuji-Trost type reductive deoxygenation.[23] In a final attempt to access **48**, diacetate **47** was selectively deprotected to afford allylic alcohol **49**. An attempted Movassaghi-Myers deoxygenation reaction[24] once again gave only starting material.



Scheme 9: An Ir/Rh-catalyzed isomerization, a reductive Tsuji-Trost type reductive deoxygenation and a Movassaghi-Myers deoxygenation as 1,4-reduction alternatives.

In conclusion, we developed a 20-step synthesis of an advanced intermediate, **36**, that features the [6/6/6]-tricyclic core of lannotinidine G and bears the correct absolute stereochemistry. Highlights of the synthesis include an aziridinium-mediated ring contraction of azepane **7**, which stereoselectively formed a highly substituted piperidine ring, and a hydroxy-directed dienyne metathesis that afforded the tricyclic core of lannotinidine G. Although our most advanced intermediate was a redox manipulation and an α-methylation away from completing the synthesis, 1,4-reduction of the Michael system was an obstacle we could not overcome, whereas efforts to take advantage of other intermediates to achieve our goal proved futile. Revision of our strategy towards lannotinidine G is currently investigated as synthetic studies towards related *Lycopodium* alkaloids are in progress.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx

Figures, Tables, experimental details and characterization data for all new compounds (PDF)

Accession Code CCDC 2314752 contains the supplementary crystallographic data for this paper. These data can be obtained for free at www.ccdc.cam.ac.uk/data_request/cif, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; email: data_request@ccdc.cam.ac.uk.

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Author Contributions

The manuscript was written through contributions of all authors. The authors declare no competing financial interest.

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