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Divergent Access to Histone Deacetylase Inhibitory Cyclopeptides via a Late-Stage Cyclopropane Ring Cleavage Strategy. Short Synthesis of Chlamydocin

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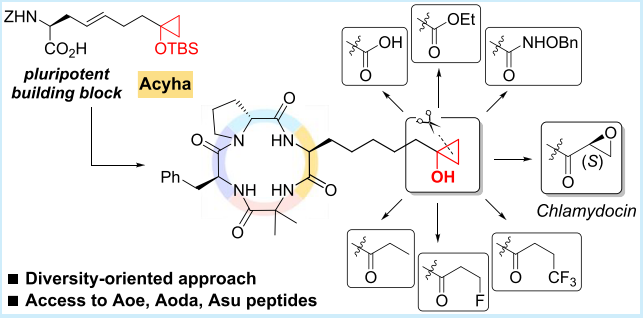
Supporting Information

ABSTRACT: A unified step-economical strategy for accessing histone deacetylase inhibitory peptides is proposed, based on the late-stage installation of multiple zinc-binding functionalities via the cleavage of the strained cyclopropane ring in the common pluripotent cyclopropanol precursor. The efficacy of the proposed diversity-oriented approach has been validated by short stereoselective synthesis of natural product chlamydocin, containing a challenging-to-install fragment of (2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe) and a range of its analogues, derivatives of 2-amino-8-oxodecanoic and 2-aminosuberic acids.



Histone deacetylase (HDAC) enzymes serve as epigenetic gene expression mediators via the regulation of deacetylation/acetylation of histone proteins within eukaryotic cells.[1] Dysfunction of HDAC enzymes is associated with numerous severe physiological processes like cancer, neurodegeneration, and metabolic disorders,[2] thus making them a validated target for therapeutic intervention. Several naturally occurring cyclopeptides with extremely high inhibitory activity against zinc-dependent HDAC enzymes are known.[3] Their structural organization is archetypal and includes a cyclic cap that is responsible for interaction with the peripheral binding site of the enzyme, a hydrophobic spacer, and a zinc-binding group (ZBG) to capture a zinc ion in the catalytic pocket (Figure 1).[1,3] The spacer with ZBG is approximately isosteric with acetylated lysine, suggesting that it mimics an acetylated histone protein.[3] Several natural cyclopeptides [chlamydocin (**1**),[4a] HC-toxin,[4b] trapoxins,[4c] WF-3161,[4d] etc.] contain the epoxy ketone function as a zinc-binding motif in the side chain of (2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe). Zinc-binding ethyl ketone and carboxylate functions are present in apicidines,[4e] in their 2-amino-8-oxodecanoic (Aoda) and 2-aminosuberic acid (Asu) structural units, respectively (Figure 1). The structural principles of such peptides have been translated into HDAC inhibitory drugs approved by the Food and Drug Administration for cancer treatment (e.g., Vorinostat, Belinostat, and Romidepsin).[5] Due to the significance of HDAC inhibitors as therapeutic agents, the clarification of the HDAC enzyme function and design of more selective inhibitors, especially on the level of isoforms, has attracted a great deal of attention.[6] It has been shown that the inhibitory potential and selectivity profile of the peptide HDAC inhibitors can be further diversified by the modification of ZBG or the amino acid sequence.[1,6]

A number of methods have been reported for the synthesis of Aoda[7] and Asu[8] building blocks, compatible with peptide synthesis under the standard Boc/Fmoc/Cbz protocols. In contrast, a vulnerable epoxide functionality, along with an additional chiral center, requires advanced synthetic planning for the Aoe-containing peptides. For example, the first total synthesis of chlamydocin and trapoxin B was implemented by Schmidt[9] and later by Schreiber[10] via multistep sequences from (*R*,*R*)-tartaric acid-derived precursors. The Rich group utilized epoxidation of the corresponding racemic allylic alcohol under Sharpless conditions,[11] while Baldwin exploited free radical homologation of 2-amino-5-iodopentanoic acid.[12] More recently, the Kazmaier group reported the synthesis of several Aoe-containing cyclopeptides via chelate enolate Claisen rearrangement.[13]

Despite these creative contributions, synthesis of similar targets via the distinct multistep protocols from the diverse building blocks hampers access to the realm of HDAC inhibitory peptides. Therefore, the development of a step-economical and general synthetic strategy is highly desired for the preparation of the corresponding molecular libraries.[1,6] Due to the interest of our group in cyclopropanol chemistry,

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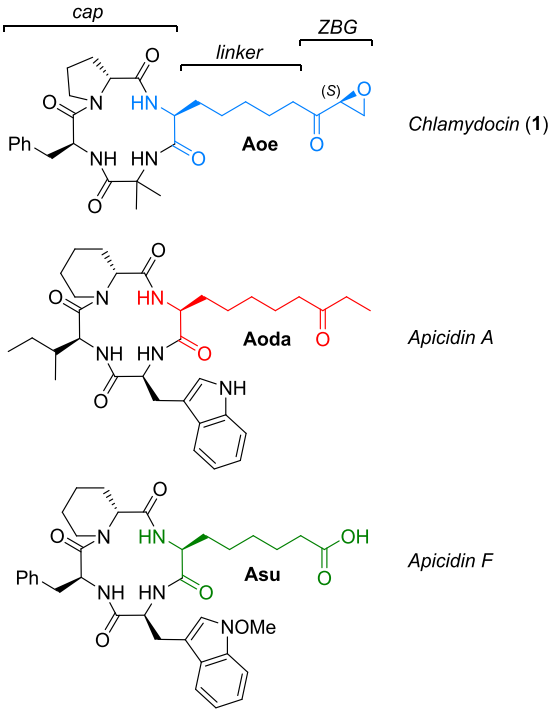

Figure 1. Examples of natural HDAC inhibitors with different zinc-binding groups (ZBGs) in the side chain.

we noticed that all the required zinc-binding motifs [ethyl ketone, carboxylate, and even (*S*)-epoxy ketone] can be straightforwardly generated from the same cyclopropanol moiety, thus offering the required general approach (Figure 2). Cyclopropanols are easily available[14] and versatile synthetic intermediates,[15] with continuously emerging new applications in the synthesis of natural products.[16] The internal ring strain

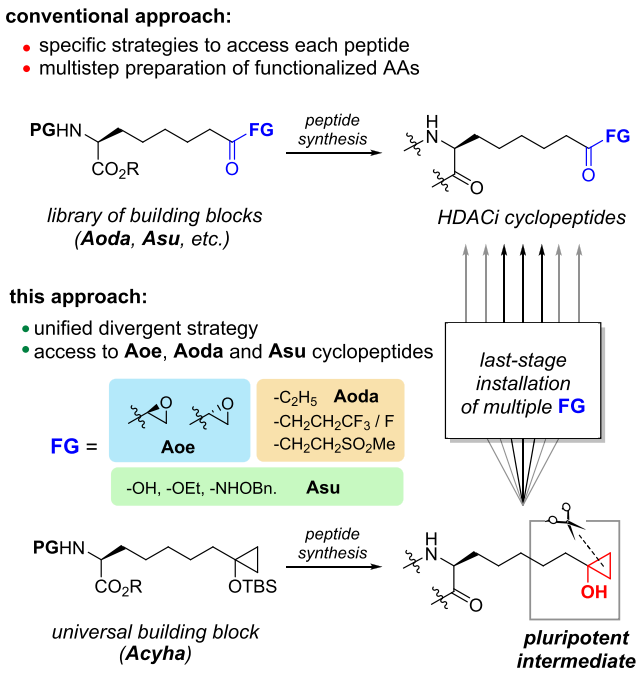

Figure 2. Conventional and proposed strategies for accessing HDAC inhibitory peptides.

of the cyclopropane and the presence of an electron-donating hydroxyl group facilitate ring opening with a range of electrophilic and radical species.[15] These reactions typically occur under mild conditions well tolerated by other functionalities, which makes the cyclopropanol motif suitable for late-stage cleavage. Herein, we demonstrate for the first time the utilization of the cyclopropanol unit as an efficient pluripotent group for diversity-oriented synthesis, which is validated by a concise divergent synthesis of natural product chlamydocin **1** (Figure 1), and a set of its known analogues[1,6] with histone deacetylase inhibitory activity.

Implementation of our approach requires a single universal building block, 2-amino-7-(1-hydroxycyclopropyl)heptanoic acid (Acyha). A carbon skeleton of the latter was assembled by cross-metathesis of two readily available alkene partners, protected (*S*)-allyl glycine **4** and alkene **6** with a masked cyclopropanol functionality (Scheme 1).

Both **4** and **6** can be accessed from commercial starting materials via a short high-yield reaction sequence. The N-terminus of (*S*)-allyl glycine (**3**) was masked with a range of protective groups (Boc, Cbz, and Fmoc) followed by the esterification of the C-terminus to provide amino acid coupling partners **4a**−**c**. TBS-protected cyclopropanol **6** was easily prepared in multigram quantities in three steps and 90% overall yield from ethyl 5-bromovalerate (**5**) via the consequent Kulinkovich cyclopropanation, silylation, and HBr elimination steps.

Because the metathesis of alkene partners **4** and **6** is of type I,[17] its statistical nature and the fast inactivation of the Grubb's catalyst afforded rather low yields of cross-coupling product **7a** in the initial runs. After optimization (see the Supporting Information), we were able to increase the yield of target product **7a** to 75% by using only 1 mol % of the second generation of the Hoveyda−Grubbs catalyst and a 5-fold excess of readily available alkene **6**. Under optimal conditions, cross-coupled products **7a**−**c**, decorated with orthogonal protecting groups at the N- and C-termini, were smoothly prepared in 71−75% yields. The reduction of the double bond and debenzylation of the C-terminus (for Fmoc analogue **7b**) by hydrogenation afforded protected Acyha derivatives **8a** and **8b** in quantitative yields with an intact cyclopropane moiety. It should be noted that the TBS-protected cyclopropanol unit cannot tolerate strong acids, as was evidenced by the fast transformation of **8a** into the corresponding Aoda derivative **9a** under typical Boc removal conditions (TFA/CH_2Cl_2), even prior to the removal of the Boc group itself (see the Supporting Information).

Considering the protecting group compatibility issues, Cbz-carboxylic acid **10c** was selected for the total synthesis of chlamydocin (Scheme 2).

Extensive studies of the synthesis of chlamydocin[9,11−13] and its Aoda/Asu analogues[6c−h] led us to select this macrocycle as the first target to validate our approach. The most efficient strategy for the closure of its macrocyclic ring involved macrolactamization at the C-terminus of D-proline.[9b] Therefore, Aib-Phe-D-Pro-OMe tripeptide **11** was prepared from the corresponding amino acids in 73% total yield over four steps by using standard peptide coupling protocols (see the Supporting Information).[12,13c]

Next, the TBTU-mediated peptide coupling of **11** with Acyha derivative **10c** afforded tetrapeptide **12** in 96% yield. The hydrogenation of the double bond in the latter was conveniently performed in flow mode with the simultaneous

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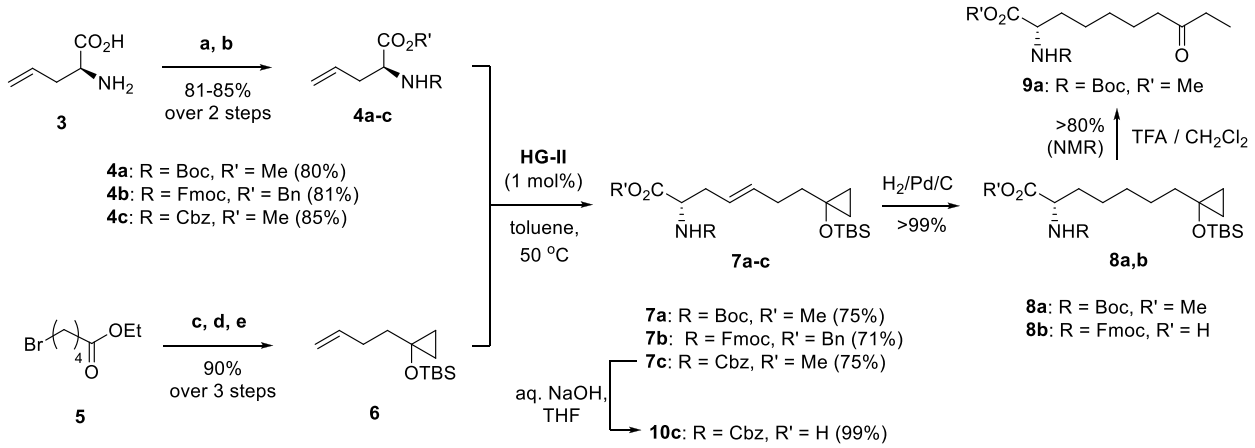
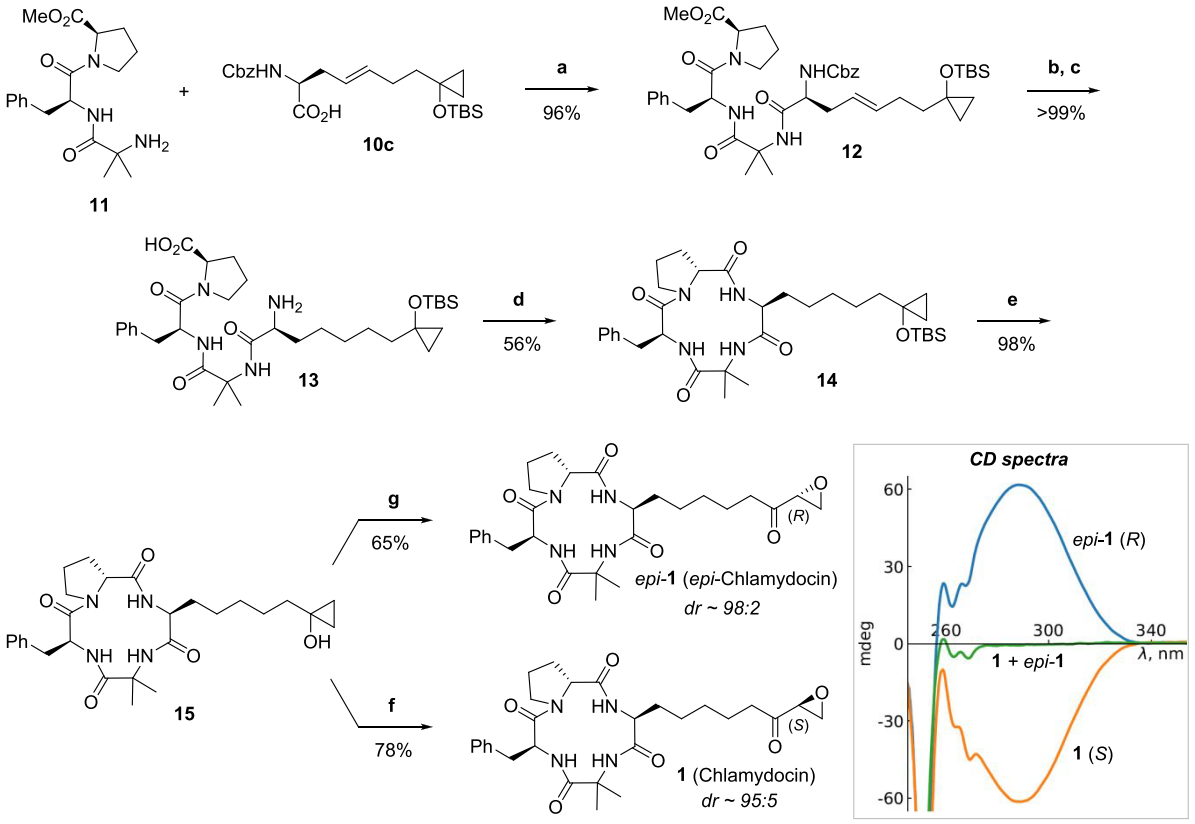
Scheme 1. Synthesis of Protected 2-Amino-7-(1-hydroxycyclopropyl)heptanoic Acid (Acyha) Derivatives[a]



[a]Reagents and conditions for **4a**: (a) Boc_2O, $NaHCO_3$, MeOH, sonification; (b) K_2CO_3, MeI, acetone. Reagents and conditions for **4b**: (a) FmocOSu, K_2CO_3, dioxane/H_2O; (b) BnBr, $NaHCO_3$, DMF. Reagents and conditions for **4c**: (a) CbzCl, $NaHCO_3$, H_2O; (b) K_2CO_3, MeI, acetone. Reagents and conditions for **6**: (c) EtMgBr, Ti(O*i*-Pr)$_4$, Et_2O; (d) TBSCl, imidazole, THF; (e) *t*-BuOK, THF. **HG-II** = Hoveyda−Grubbs catalyst, second generation.

Scheme 2. Stereodivergent Synthesis of Chlamydocin (1) and Its Epimer *epi*-1[a]



[a]Reagents and conditions: (a) TBTU, HOBT, Et_3N in CH_2Cl_2; (b) NaOH in THF/H_2O; (c) 10% Pd/C, H_2 in MeOH, H-Cube (60 °C, 60 bar); (d) HATU, DIEA in DMF; (e) 1 M TBAF in THF; (f) air, 0.5 mol % Mn(acac)$_3$ in THF, 0 °C, 2 h, then poly-D-leucine/SiO_2, DBU, −25 °C, 48 h; (g) air, 0.5 mol % Mn(acac)$_3$ in THF, 0 °C, 2 h, then poly-L-leucine/SiO_2, DBU, −25 °C, 48 h.

removal of the Cbz group, yielding tetrapeptide **13** in quantitative yield after the hydrolytic release of free carboxylate at the D-proline terminus. HATU-enabled macrocyclization afforded macrocyclic tetrapeptide **14** in 56% yield. Finally, the removal of the TBS group in **14** produced the key intermediate **15** with an unmasked cyclopropanol functionality. The latter was transformed into the corresponding (*S*)-epoxy ketone.[18] The aerobic oxidation of **15** catalyzed by 0.5 mol % Mn(acac)$_3$ followed by treatment with DBU in the presence of silica-supported poly-D-leucine afforded chlamydocin **1** in 78% yield. The same transformation performed with poly-L-leucine as a chiral mediator led to the corresponding (*R*)-epoxide epimer

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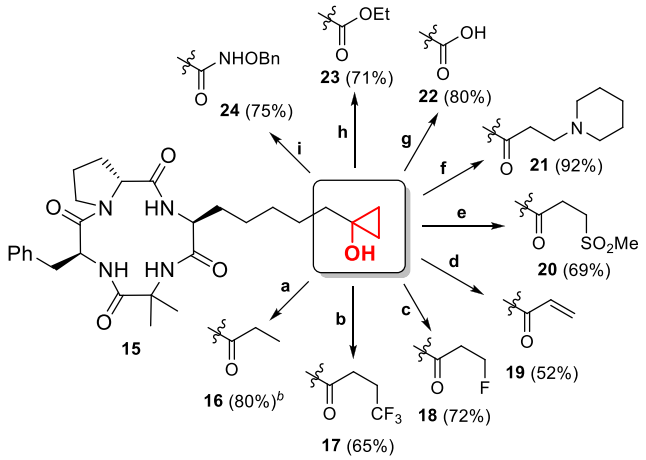
epi-**1**, thus demonstrating stereochemical divergence. Both transformations yielded the corresponding macrocycles as almost pure (*S*)- and (*R*)-diastereoisomers, according to the chiral HPLC analysis [dr >95:5 (see the Supporting Information)]. The measured specific rotation for synthetic **1** ($[\alpha]_D = -140°$) was close to the reported for the natural sample ($[\alpha]_D = -147.5°$).[4a] The (*S*)-configuration of the chiral center in the epoxide moiety of **1** was proven by CD spectroscopy (Scheme 2), showing a negative Cotton effect with a maximum at ∼290 nm for (*S*)-stereoisomer **1**, and an accordingly positive absorption band for its (*R*)-counterpart *epi*-**1**, in full accord with the literature data.[9,11]

Following our method, the natural product chlamydocin was prepared in an affordable 26% overall yield over 10 steps [counted as the longest linear sequence from **3** (see Scheme S1)]. Even more important is the fact that our approach creates a shortcut to a series of chlamydocin analogues by exploiting the pluripotency of the cyclopropanol function in common precursor **15**, as demonstrated by a series of successful cyclopropane cleavage reactions (Scheme 3).

Scheme 3. Divergent Preparation of Aoda- and Asu-Containing Chlamydocin Analogues by Late-Stage Ring Cleavage of the Common Cyclopropane Precursor 15[a]



[a]Reagents and conditions: (a) TFA, CH_2Cl_2, 24 h; (b) Togni reagent, 10 mol % $[Cu(CH_3CN)_4]BF_4$, 20 min; (c) SelectFluor, 20 mol % AgF, C_6H_6/H_2O, reflux, 4 h; (d) air, $Cu(OAc)_2$, MeOH, 3 h; (e) air, $Cu(OAc)_2$, $MeSO_2Na$, MeOH, 3 h; (f) air, $Cu(OAc)_2$, piperidine, MeOH, 45 min; (g) PIFA, acetic acid, 30 min; (h) PIFA, ethanol, 30 min; (i) $PhI(O_2CAr)_2$ (Ar = 2,4,6-trichlorophenyl), CH_2Cl_2, 2 h, then NH_2OBn (10 equiv), 10 h. All reactions were carried out at rt unless noted otherwise. TFA = trifluoroacetic acid, and PIFA = iodosobenzene bis(trifluoroacetate). [b]Compound **16** was prepared directly from TBS-protected cyclopropanol **14**.

Cyclopropanols undergo facile rearrangement to the corresponding carbonyl compounds in the presence of acid or base catalysts.[15c] Therefore, the transformation of TBS-protected cyclopropanol **14** to Aoda-containing cyclopeptide[6c,e] **16** was achieved in 80% yield by treatment with TFA in CH_2Cl_2. In view of the importance of fluorinated compounds in medicinal chemistry,[19] including ^{18}F PET imaging,[20] late-stage trifluoromethylation[21] and fluorination[22] were successfully performed to afford fluorinated Aoda analogues **17** and **18**. A number of functionalized ketones have been prepared via the copper-catalyzed aerobic oxidation of the cyclopropanol moiety,[23] e.g., vinyl ketone **19**, γ-ketosulfone **20**, and β-amino ketone **21**.[24] A side chain of 2-aminosuberic acid (Asu) in compound **22** was installed by the fast and high-yield oxidation of cyclopropanol **15** with bis(trifluoroacetoxy)iodobenzene (PIFA) in acetic acid.[25] Known bioactive Asu derivatives[6,8] have also been prepared. Oxidation of **15** with PIFA in ethanol afforded the corresponding ethyl ester[6c] **23**. We also developed a one-pot protocol for the synthesis of amides (see Scheme S2) via intermediate generation of mixed anhydrides from cyclopropanols in aprotic media.[25d] Thus, oxidation of cyclopropanol **15** with $PhI(O_2CAr)_2$ (Ar = 2,4,6-trichlorophenyl) in CH_2Cl_2 followed by addition of $BnONH_2$ produced benzyl-protected hydroxamic acid **24** in 75% yield. Compound **24** is the immediate precursor of the corresponding free hydroxamic acid,[6d] known as a strong HDAC inhibitor.[6,8]

In conclusion, here we demonstrate the first use of a cyclopropanol functionality as a powerful pluripotent intermediate for diversity-oriented synthesis, on both stereochemical and functional diversity levels. The expedient synthesis of the natural product chlamydocin, its (*R*)-epoxide epimer, and several chlamydocin analogues has verified the efficacy of our approach for accessing Aoe-, Aoda-, and Asu-containing HDAC inhibitory peptides, including their ZBG-modified congeners. Due to the broad spectrum of chemical transformations provided by the rapidly evolving field of cyclopropanol chemistry,[15,16] further advances in the last-stage diversification from the single cyclopropanol precursor can be expected, which are suitable for the generation of bioactive molecular libraries in general and HDAC inhibitory peptides in particular.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03305.

Experimental procedures and characterization data for new compounds and copies of NMR spectra, HPLC chromatograms, and CD spectra (PDF)

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Notes

The authors declare no competing financial interest.

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