Total Synthesis of Thailanstatin A

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S *Supporting Information*

ABSTRACT: The total synthesis of the spliceosome inhibitor thailanstatin A has been achieved in a longest linear sequence of nine steps from readily available starting materials. A key feature of the developed synthetic strategy is the implementation of a unique, biomimetic asymmetric intramolecular oxa-Michael reaction/hydrogenation sequence that allows diastereodivergent access to highly functionalized tetrahydropyrans, which can be used for the synthesis of designed analogues of this bioactive molecule.

Thailanstatin A (**1**, Figure 1A) is a newly discovered natural product with promising biological properties as a potential lead compound for drug discovery and development efforts. Isolated from *Thailandensis burkholderia* MSMB43, thailanstatin A (**1**) and its methyl ester (**2**, Figure 1A) exhibit low nanomolar to subnanomolar cytotoxicities against a number of human cancer cell lines.[1,2] Its mechanism of action, like its natural product congeners FR901464 (**3**, Figure 1A) and spliceostatin A (**4**, Figure 1A),[3] has been shown to involve inhibition of the spliceosome,[4] the cellular machinery responsible for editing mRNA as it emerges from the transcription of DNA through site-specific removal of introns and religation of the remaining exon sequences prior to translation.[5] Given that the spliceosome of cancer cells is more active and displays higher mutation rates than those of normal cells, this cellular component became a validated target for inhibition as a new paradigm for discovery and development of novel anticancer drugs.[6]

The improved stability of **1** vs **3** and **4** (the latter suffering from lactol and glycoside labilities) and its carboxylic acid functionality constitute attractive features for **1** and its analogues as payloads for appropriate drug delivery systems, such as antibody–drug conjugates (ADCs).[7] Indeed, since its isolation, significant advances have been made to produce **1** in larger quantities via optimized fermentation strategies.[8] A chemical synthesis of **1** has the potential to render this molecule readily available and, more importantly, provide a general and expedient entry into a plethora of analogues for biological investigations. In this Communication, we describe a short and efficient total synthesis of thailanstatin A (**1**).

Figure 1B depicts, in retrosynthetic format, the synthetic strategy developed toward thailanstatin A (**1**). Thus, disconnection of **1** through a Suzuki coupling led to advanced intermediates vinyl boronate **5** and vinyl iodide **6**. Further disconnection of **5** at the amide linkage (amide bond formation), the vinyl boronate olefinic bond (cross metathesis), and the tetrahydropyran system (oxa-Michael reaction) as indicated in Figure 1B revealed doubly conjugated hydroxy
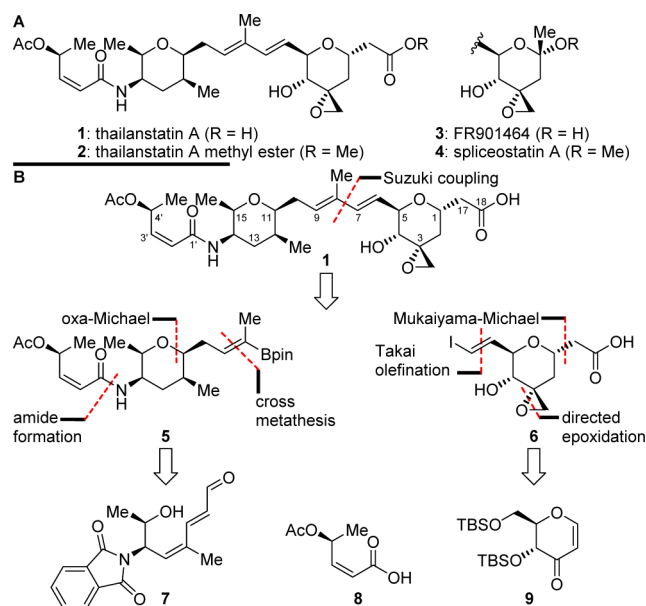

Figure 1. (A) Molecular structures of thailanstatin A (**1**), its methyl ester (**2**), and related natural products FR901464 (**3**) and spliceostatin A (**4**). (B) Retrosynthetic analysis of **1** through intermediates **5** and **6**.

aldehyde **7** and acetoxy carboxylic acid **8** as potential key building blocks. Disassembly of **6** at the vinyl iodide (Takai olefination), epoxide (directed epoxidation), and tetrahydropyran (Mukaiyama–Michael reaction) sites traced this advanced intermediate back to the known and readily available pyranone **9** as a starting material.

For the synthesis of the 2,3,5,6-tetrasubstituted tetrahydropyran ring embedded within intermediate **5**, we were inspired by the proposed biosynthesis of **1** (Figure 2A), which involves an intramolecular oxa-Michael reaction of an acyl carrier protein-bound α,β-unsaturated thioester of a polyketide synthase complex.[1,9] However, in an effort to preserve atom and step economy,[10] and in order to establish a foundation for a diastereodivergent approach to highly functionalized tetrahydropyrans, we sought to explore the asymmetric intramolecular oxa-Michael (AIOM) reaction[11] with an unprecedented substrate possessing an additional degree of unsaturation, i.e., an $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde (**I**, Figure 2B). If successful, this scenario would constitute an entry to 2,6-*syn* or 2,6-*anti* tetrasubstituted dihydropyrans **II** (Figure 2B) in a diastereoselective manner via catalyst control. Furthermore, subsequent substrate-controlled hydrogenation could allow access to
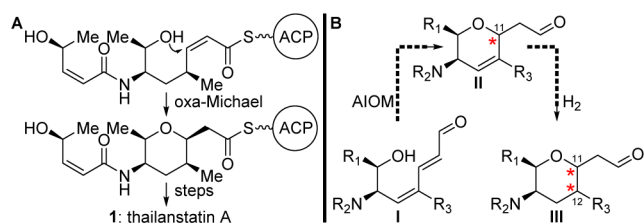
Figure 2. (A) Proposed biosynthetic formation of the tetrasubstituted tetrahydropyran system of thailanstatin A (**1**) through an oxa-Michael reaction. ACP = acyl carrier protein. (B) Proposed diastereodivergent approach to tetrasubstituted dihydropyrans **II** from $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde **I** through asymmetric intramolecular oxa-Michael (AIOM) reaction and tetrasubstituted tetrahydropyrans **III** from **II** via hydrogenation.

tetrasubstituted tetrahydropyrans **III** (Figure 2B) with defined stereochemistry at C11 and C12, respectively.

The synthesis of vinyl boronate **5** from Garner aldehyde **17**[12] is summarized in Scheme 1. Thus, α-methyliodomethylenation of **17** under Stork–Zhao conditions[13] furnished olefinic iodo-Boc derivative **18** (54% yield, Z:E ca. 95:5, chromatographically separated), from which the desired iodo-Phth derivative **19** was generated by protecting group exchange (formic acid; then phthalic anhydride, Et$_3$N, DMAP cat.) in 80% overall yield. Stille coupling of the latter with hydroxystannane **20**[14] [Pd$_2$(dba)$_3$, 73% yield] led to diene **22**, whose MnO$_2$ oxidation afforded the desired (E,Z)-$\alpha,\beta,\gamma,\delta$-unsaturated aldehyde **7** in 90% yield. The same aldehyde (**7**) could also be obtained in one step directly from vinyl iodide **19** and aldehyde stannane **21**[15] through Stille coupling [Pd$_2$(dba)$_3$, 60% yield]. Exposure of **7** to diaryl prolinol catalyst **23**[16] (0.2 equiv) in the presence of benzoic acid (0.2 equiv) in CH$_2$Cl$_2$ induced the desired asymmetric intramolecular oxa-Michael reaction, providing 2,6-*syn*-dihydropyran **24** in 77% yield (dr >20:1). Aldehyde **24** proved to be a challenging substrate for the subsequent hydrogenation reaction. Optimal results were achieved by masking the aldehyde moiety as a diethoxy acetal [**25**, CH(OEt)$_3$, CSA, 91% yield]. It was found that stereoselective hydrogenation from the α-face of the ring system could be achieved with 10% Pd/C in ethanol under a H$_2$ atmosphere at high pressure (80 bar) to afford 2,3,5,6-*syn*-tetrahydropyran **26** (54% yield) after mild aqueous acidic workup. Interestingly, however, and after extensive experimentation, it was discovered that aldehyde **24** could be efficiently hydrogenated directly (H$_2$, 80 bar) in excellent yield with 10% Pd/C in hexafluoro-isopropanol solvent, albeit with modest diastereoselectivity (93%, 7:3 dr, 65% yield for **26**). Methylenation (Tebbe reagent) of saturated aldehyde **26** provided olefin **27** in 76% yield. Rupture of the phthalimide moiety within the latter with methylhydrazine, followed by direct amide coupling with carboxylic acid **8**[17] (EDCI, NMM), led to amide **28** (73% yield), an advanced intermediate reported in the synthesis of FR901464.[3d] Cross metathesis of **28** with commercially available isopropenylboronic acid pinacol ester **29** (Grubbs II cat., ClCH$_2$CH$_2$Cl) afforded vinyl boronate **5** in 71% yield.

During our exploration of the oxa-Michael reaction of aldehyde **7**, it was discovered that the reaction displays an unusually high degree of catalyst control, especially as compared with typical AIOM reactions, in which α,β-unsaturated aldehydes, esters, and amides generally favor the 2,6-*syn*-tetrahydropyran product.[11] Elegant studies by Hong have also shown that olefin geometry (i.e., E or Z α,β-

Scheme 1. Synthesis of Vinyl Boronate 5[a]
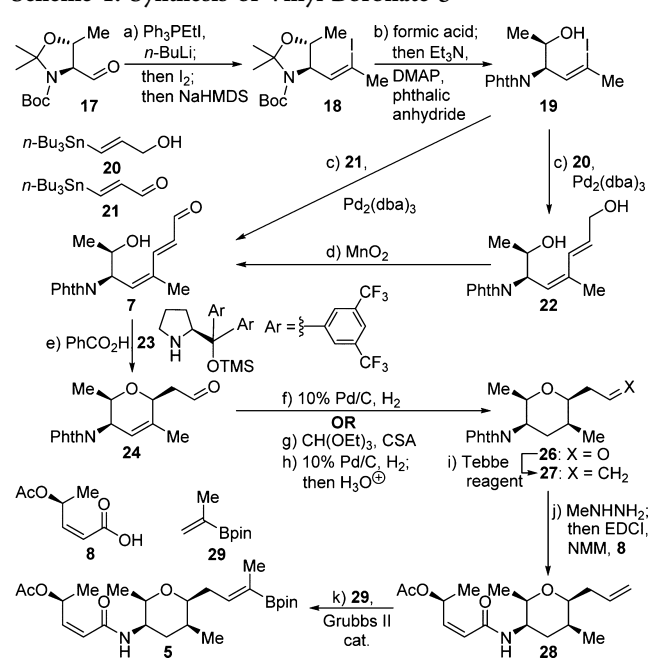
[a]Reagents and conditions: (a) PPh$_3$EtI (2.0 equiv), *n*-BuLi (2.0 equiv), THF, 25 °C, 15 min; then I$_2$ (1.9 equiv); then NaHMDS (1.9 equiv); then **17** (1.0 equiv), THF, −78 → −20 → −78 °C, 1.5 h, 54% (Z:E ca. 95:5); (b) formic acid (neat), 25 °C, 10 min; then phthalic anhydride (1.1 equiv), Et$_3$N (20 equiv), DMAP (0.1 equiv), CHCl$_3$, 70 °C, 48 h, 80% overall; (c) **20** (1.2 equiv), Pd$_2$(dba)$_3$ (0.1 equiv), NMP, 25 °C, 16 h, 73%, or (c) **21** (2.0 equiv), Pd$_2$(dba)$_3$ (0.1 equiv), NMP, 25 °C, 16 h, 60%; (d) MnO$_2$ (20 equiv), CH$_2$Cl$_2$, 25 °C, 1 h, 90%; (e) **23** (0.2 equiv), PhCO$_2$H (0.2 equiv), CH$_2$Cl$_2$, 0 °C, 6.5 h, 77%; (f) 10% Pd/C (50% *w/w*), H$_2$ (80 bar), HFIP, 25 °C, 24 h, 93% (dr 7:3); (g) CH(OEt)$_3$ (10 equiv), CSA (0.1 equiv), EtOH, 25 °C, 2 h, 91%; (h) 10% Pd/C (35% *w/w*), H$_2$ (80 bar), EtOH, 25 °C, 15 h; then 0.1 M aq HCl (3.0 equiv), acetone, 25 °C, 10 min, 54% overall; (i) Tebbe reagent (1.0 equiv), THF, −20 → 0 °C, 1 h, 76%; (j) MeNHNH$_2$ (10 equiv), PhH, 25 °C, 2 h; then EDCI (3.0 equiv), NMM (3.0 equiv), **8** (2.0 equiv), CH$_2$Cl$_2$, 25 °C, 30 min, 73% overall; (k) **29** (5.0 equiv), Grubbs II cat. (0.1 equiv), ClCH$_2$CH$_2$Cl, 80 °C, 1 h, 71%. Abbreviations: Boc = *tert*-butyloxycarbonyl; CSA = camphorsulfonic acid; dba = dibenzylideneacetone; DMAP = N,N-dimethylaminopyridine; EDCI = 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride; HFIP = hexafluoroisopropanol; HMDS = hexamethyl-disilazide; NMM = N-methylmorpholine; NMP = N-methyl-2-pyrrolidinone; Phth = phthaloyl; pin = pinacolato; TMS = trimethylsilyl.

unsaturated aldehydes) can render AIOM reactions stereoselective as a consequence of substrate control, while catalyst control alone is rarely useful for high levels of 2,6-*anti* stereoselectivity.[18] As depicted in Scheme 2A, we found that 2,6-*syn*-dihydropyran **24** or 2,6-*anti*-dihydropyran 11-*epi*-**24** (half-chair structures confirmed by ^{1}H NOE spectroscopy; see Supporting Information (SI) for details) could be accessed in comparable yields with virtually complete stereoselectivity, based solely on catalyst control. In addition, complementary stereoselectivity for the hydrogenation of acetal substrate **25** could be achieved under specific reaction conditions. Thus, as shown in Scheme 2B, treatment of **25** with [Ir(Py)(PCy$_3$)-(COD)BARF] catalyst,[19] a counteranion analogue of Crabtree's catalyst, in CH$_2$Cl$_2$ under 1 atm of H$_2$ cleanly provided 12-*epi*-**26** after workup with dilute acid. Delivery of hydrogen to the β-face of **25** was likely facilitated by the O atom(s) of the

Scheme 2. Diastereodivergent Synthesis of 2,3,5,6-Tetrasubstituted Tetrahydropyrans[a]
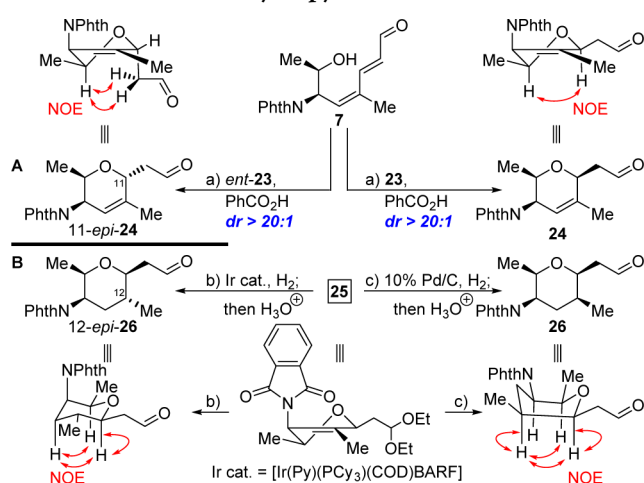
[a]Reagents and conditions: (a) **23** or **ent-23** (0.2 equiv), PhCO$_2$H (0.2 equiv), CH$_2$Cl$_2$, 0 °C, 6.5 h, 77% for **24** (dr >20:1), 64% for **11-epi-24** (dr >20:1); (b) [Ir(Py)(PCy$_3$)(COD)BARF] (0.05 equiv), H$_2$ (1 atm), CH$_2$Cl$_2$, 25 °C, 10 h; then 0.1 M aq HCl (3.0 equiv), acetone, 25 °C, 10 min, 85% overall; (c) 10% Pd/C (35% w/w), H$_2$ (80 bar), EtOH, 25 °C, 24 h; then 0.1 M aq HCl (3.0 equiv), acetone, 25 °C, 10 min, 54% overall. Abbreviations: BARF = tetrakis[3,5-bis-(trifluoromethyl)phenyl] borate; COD = 1,5-cyclooctadiene; Cy = cyclohexyl; Py = pyridine.

acetal and/or the imide carbonyl O atom(s). In contrast, use of heterogeneous conditions led to **26**, the product of H$_2$ delivery from the α-face of **25**, as dictated by the hindered nature of its β-face. The relative configurations of **26** and **12-epi-26** were confirmed by ^{1}H NOE studies, which also revealed a chair conformation for **12-epi-26** and a boat conformation for **26** (due to the large 1,3 diaxial interaction between the bulky N-phthaloyl moiety and the adjacent axial methyl group; see SI for details). This AIOM/hydrogenation approach may prove useful as a general method for the synthesis of highly substituted tetrahydropyrans.

The syntheses of key vinyl iodide building blocks **6** and **6a** are summarized in Scheme 3A. Thus, pyranone derivative **9**[20] was reacted with ketene silyl acetal **10** in the presence of iodine to afford stereoselectively, after treatment with methanolic K$_2$CO$_3$, ketone methyl ester **11** in 98% yield on a 10 g scale.[21] Wittig reaction of the latter with the ylide derived from the phosphonium salt of MeBr and t-BuOK yielded terminal olefin **12** (80% yield), whose conversion to aldehyde **14** was achieved by selective mono-desilylation (PPTS, 98% yield), followed by Swern oxidation [(COCl)$_2$, DMSO; Et$_3$N, 96% yield] of the resulting primary alcohol (i.e., **13**).[12] Takai olefination (CrCl$_2$, CHI$_3$)[22] of aldehyde **14** then led to the desired E-iodo-olefin **15** in 58% yield. Desilylation of the latter (TBAF, 93% yield) furnished allylic alcohol **16**. Saponification of **16** (LiOH) provided acid **16a** as a crystalline solid (mp = 128−136 °C, EtOAc). X-ray crystallographic analysis (see ORTEP in Scheme 3B and SI for details) unambiguously confirmed the 2,6-anti configuration of the tetrahydropyran ring system. Directed epoxidation of **16** with t-BuOOH and VO(acac)$_2$ cat. delivered the targeted hydroxy epoxide methyl ester **6a** (74% yield), whose ^{1}H NOE analysis confirmed its relative stereochemistry (Scheme 3B; see SI for details).[23] Subsequent conversion of

Scheme 3. Synthesis of Vinyl Iodides 6 and 6a[a]
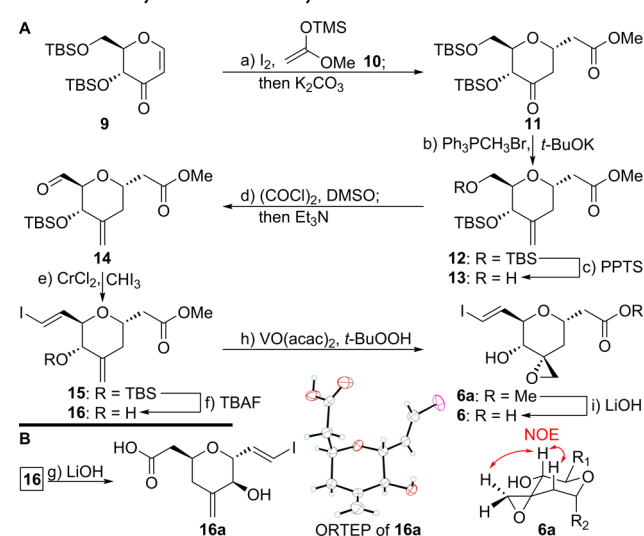
[a]Reagents and conditions: (a) **10** (2.0 equiv), I$_2$ (0.1 equiv), MeCN, −30 → −20 °C, 30 min; then K$_2$CO$_3$ (0.1 equiv), MeOH, 25 °C, 10 min, 98% overall; (b) Ph$_3$PCH$_3$Br (2.5 equiv), t-BuOK (2.0 equiv), THF, 0 °C, 1 h, 72%; (c) PPTS (1.0 equiv), MeOH, 25 °C, 12 h, 98%; (d) (COCl)$_2$ (1.5 equiv), DMSO (3.0 equiv), then Et$_3$N (5.0 equiv), CH$_2$Cl$_2$, −78 → −55 °C, 3 h, 96%; (e) CrCl$_2$ (6.0 equiv), CHI$_3$ (3.0 equiv), THF, 25 °C, 12 h, 58%; (f) TBAF (2.0 equiv), THF, 0 → 25 °C, 30 min, 93%; (g) LiOH (8.0 equiv), 1:1 THF/H$_2$O, 25 °C, 12 h, 98%; (h) VO(acac)$_2$ (0.1 equiv), t-BuOOH (2.1 equiv), CH$_2$Cl$_2$, 0 → 25 °C, 10 h, 74%; (i) LiOH (1.5 equiv), 10:1 THF/H$_2$O, 0 → 25 °C, 12 h, 90%. Abbreviations: DMSO = dimethyl sulfoxide; PPTS = pyridinium p-toluenesulfonate; TBAF = n-tetrabutylammonium fluoride; TBS = tert-butyldimethylsilyl.

methyl ester **6a** to carboxylic acid **6** was accomplished through the action of LiOH (90% yield).

Scheme 4 depicts the final coupling of vinyl iodides **6** and **6a** with vinyl boronate **5** to afford the desired targets **1** and **2**,

Scheme 4. Completion of the Total Synthesis of Thailanstatin A (1) and Its Methyl Ester (2)[a]
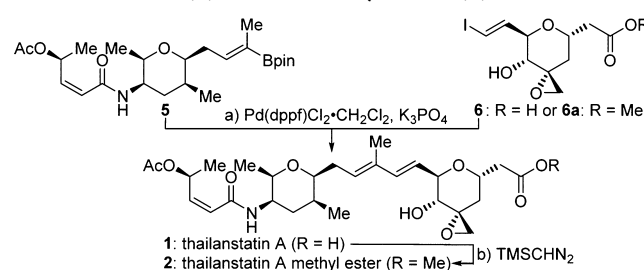
[a]Reagents and conditions: (a) Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (0.02 equiv), K$_3$PO$_4$ (1.0 equiv), **5** (1.1 equiv), **6** or **6a** (1.0 equiv), 1,4-dioxane/MeCN/H$_2$O (3:1:1), 25 °C, 10 min, 52% for **1**, 64% for **2**; (b) TMSCHN$_2$ (3.0 equiv), 3:2 PhMe/MeOH, 0 → 25 °C, 3 h, quant. Abbreviations: dppf = diphenylphosphinoferrocenyl.

respectively. At first, methyl ester **2** was obtained through Suzuki coupling utilizing Pd(PPh$_3$)$_4$ cat. and Tl(OEt) as the base.[24] While the reaction was completed quickly (<15 min, 25 °C), the basic thallium(I) salts caused significant decomposition, presumably due to epoxide and acetate ruptures. To circumvent this problem, the more stable Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ complex was used with K$_3$PO$_4$ as the base in a biphasic system

to deliver thailanstatin A (**1**) and its methyl ester **2** (64% yield), respectively. Despite our efforts to purify **1** by standard chromatographic techniques, we were relegated to employing semipreparative HPLC for its purification (see SI for details). The yield was approximated by treatment of crude **1** with TMSCHN$_2$ to generate chromatographically stable methyl ester **2** (52% overall yield).

The high convergency of the developed synthetic strategy amounts to a rapid and efficient synthesis of thailanstatin A (**1**) and its congeners, while the stereochemical divergency of the method to produce tetrasubstituted tetrahydropyrans bodes well for its application to the construction of a variety of designed analogues within this family of bioactive molecules for biological evaluation. Such studies may lead to the identification of useful biological tools and potential drug candidates to be developed as anticancer drugs or employed as payloads for ADCs or other cancer cell selective delivery systems for the purposes of targeted and personalized cancer therapies.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04781.

> Experimental procedures and characterization data (PDF)
> X-ray crystallographic data for **16a** (CIF)

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Notes

The authors declare no competing financial interest.

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