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A Five-Step Synthesis of (±)-Tylophorine via a Nitrile-Stabilized Ammonium Ylide

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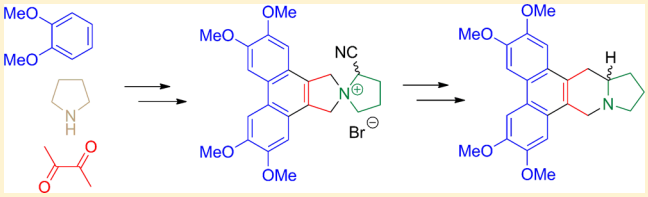
Supporting Information

ABSTRACT: The Stevens rearrangement of a nitrile-stabilized ammonium ylide is the key step of a very short and practical synthesis of the phenanthroindolizine alkaloid (±)-tylophorine. The method requires only five linear steps and is devoid of any protecting group manipulations.

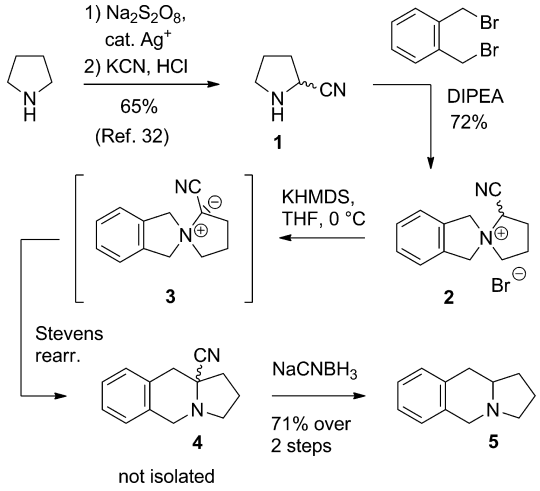


A main goal for the development of new synthetic methods is the increase of efficiency in order to reduce the waste of useful resources. Herein, we describe a very short and efficient synthesis of the phenanthroindolizidine alkaloid (±)-tylophorine (**11**) which only requires five linear steps, two or even three of which can be performed in a one-pot procedure. Veratrol, pyrrolidine, and biacetyl serve as readily available and cheap starting materials.

Tylophorine was first isolated from *Tylophora indica*[1−3] and has been demonstrated to possess a wide range of biological activities such as anti-inflammatory,[4] antiallergic,[5,6] antiasthmatic,[5,6] antibacterial,[7] antifungal,[8] and antiviral.[9] It has been shown to be a potent inhibitor of eukaryotic protein biosynthesis[10] and to inhibit RNA transcription as well as the action of several cyclins regulating the cell cycle.[11] Despite the extensive work on this compound and its congeners, no clear picture for its detailed mode of action and the cellular target has emerged so far.[12] In addition to its effects on living systems, tylophorine is an attractive target molecule for total synthesis and the considerable number of published synthetic approaches comes as no surprise.[6,13−27] Among other methods, Comins' approach using *N*-acyldihydropyridones as building blocks,[27,28] Fürstner's $PtCl_2$-catalyzed cycloisomerization,[29] or the [2 + 2 + 2] cyclotrimerization by Deiters[30] have been used for the construction of the pentacyclic core structure.

In continuation of our studies on the synthesis of highly enantiopure tylophorine by radical cyclization,[31] we became interested in a fast access to the racemic alkaloid. Model studies on 1,2-bis(bromomethyl)benzene showed that its reaction with 2-cyanopyrrolidine (**1**), accessible by silver-catalyzed oxidation of pyrrolidine to the pyrroline trimer and reaction with KCN and HCl,[32,33] furnishes the spirocyclic ammonium bromide **2** in high yield. Treatment of this salt with KHMDS in THF at 0 °C yields the nitrile-stabilized ammonium ylide,[34−37] which readily undergoes a Stevens-rearrangement[37−43] to α-aminonitrile **4**. This material is unstable and eliminates HCN under formation of the conjugated enamine which is prone to side reactions. However, reduction of crude **4** with sodium cyanoborohydride readily furnishes 1,2,3,5,10,10a-hexahydropyrrolo[1,2-b]-isoquinoline (**5**) in 71% yield (Scheme 1).

Scheme 1. Preparation of Model Compound 5 by Stevens Rearrangement of a Spirocyclic Ammonium Ylide



Transfer of this method to the preparation of **11** required dibromide **7**, which could be readily obtained by radical bromination of dimethylphenanthrene **6**. The elegant preparation of the latter material from veratrol and biacetyl in sulphuric acid has been developed by Manson et al. who also discovered the surprising importance of the exact acid concentration on the outcome of the reaction.[44] Reaction of **7** and **1** gave the spirocyclic ammonium salt **8** in 68% yield which could be converted to **11** in 85% yield over two steps without isolation of the intermediate aminonitrile **10** (Scheme 2). Alternatively, **7** could be transformed into **11** in a one-pot procedure over three steps in 49% yield.

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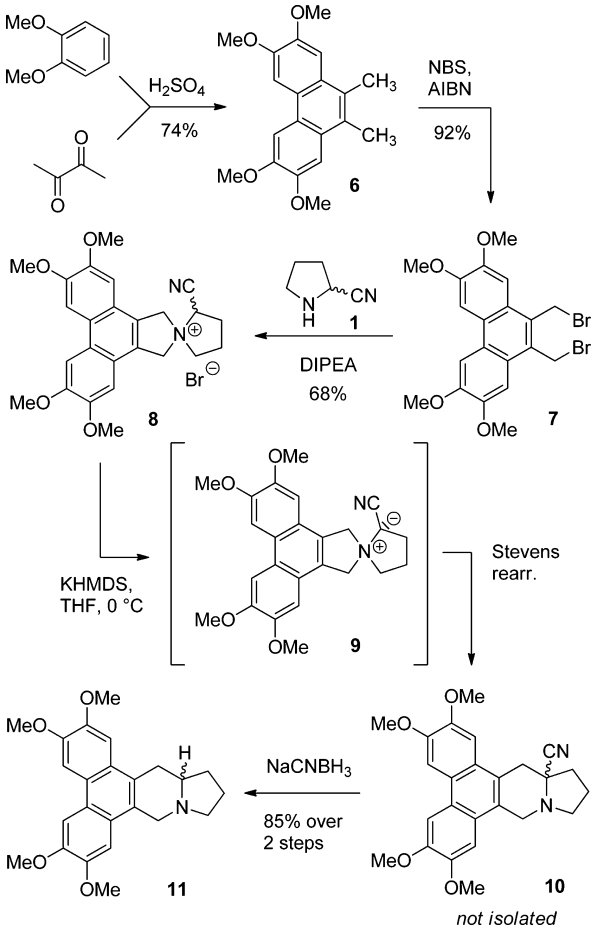
Scheme 2. Synthesis of (±)-Tylophorine in Five Linear Steps



In summary, a protecting group-free synthesis of racemic tylophorine via Stevens rearrangement of a nitrile-stabilized ammonium ylide has been developed. It comprises only five linear steps and thus represents the shortest procedure known so far. Moreover, it requires no chromatographic purifications. While similar rearrangements on ammonium ylides stabilized by carbonyl groups are known,[45−48] the reductive removal of an angular stabilizing group has never been reported to the best of our knowledge.

EXPERIMENTAL SECTION

Pyrrolidine-2-carbonitrile (**1**) was prepared from pyrrolidine according to the method of De Kimpe and Stevens et al.[32]

2′-Cyanospiro[isoindoline-2,1′-pyrrolidin]-1′-ium Bromide (2). A mixture of 1,2-bis(bromomethyl)benzene (2.75 g, 10.4 mmol, 1.0 equiv) and DIPEA (1.80 mL, 10.6 mmol) in ethanol (6 mL) was heated under reflux with stirring while pyrrolidine-2-carbonitrile (**1**: 1.01 g, 10.4 mmol, 1.0 equiv) was added dropwise. After the addition, the mixture was heated under reflux for 12 h. Ethanol was removed under reduced pressure. The residue was partially dissolved in acetone (50 mL) for 30 min under reflux and filtrated while hot to afford the title compound (2.1 g, 72%) as an orange solid. Mp: 178−179 °C dec. ^{1}H NMR, COSY, NOESY (300 MHz, D_2O): δ = 7.53−7.42 (m, 4H, 4 × Ar-*H*), 5.28 (d, ^2J = 14.5 Hz, 1H, H_a-3), 5.26 (mc, 1H, H-2′), 5.14 (s, 2H, H_a-1, H_b-1), 5.06 (d, ^2J = 14.5 Hz, 1H, H_b-3), 4.06−3.85 (m, 2H, H_a-5′, H_b-5′), 2.94−2.81 (m, 1H, H_a-3′), 2.75−2.63 (m, 1H, H_b-3′), 2.51−2.40 (m, 2H, H_a-4′, H_b-4′) ppm. ^{13}C NMR, HMBC, HSQC (151 MHz, D_2O): δ = 131.9 (C3a, C7a), 129.5 (CH), 129.4 (CH), 123.2 (CH), 123.1 (CH), 113.2 (CN), 67.6 (C1), 65.7 (C3), 64.4 (C5′), 62.4 (C1′), 27.2 (C3′), 20.2 (C4′) ppm. IR (ATR): 2941 (m, br), 2876 (m), 1465 (w), 1441 (w), 1356 (w), 1242 (w, sh), 1216 (m), 746 (s) cm^{-1}. ESI-MS (*m*/*z*): 199.13 (100) [M]$^+$. ESI-HRMS: calcd for $[C_{13}H_{15}N_2]^+$ 199.1235, found 199.1229.

1,2,3,5,10,10a-Hexahydropyrrolo[1,2-*b*]isoquinoline (5). To a stirred solution of 2′-cyanospiro[isoindoline-2,1′-pyrrolidin]-1′-ium (**2**: 470 mg, 1.68 mmol) in dry THF (30 mL) was added KHMDS (352 mg, 1.76 mmol, 1.1 equiv) dissolved in dry THF (2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1.5 h. Ethanol (8 mL) and $NaCNBH_3$ (344 mg, 5.47 mmol, 3.3 equiv) were added, and the solution was allowed to warm to room temperature before AcOH (0.6 mL) was added dropwise. The reaction was stirred at room temperature for 10 h, quenched with saturated aq $NaHCO_3$ (30 mL), and extracted with $CHCl_3$ (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was partially dissolved in ice cooled EtOAc (10 mL). The remaining insoluble solid was filtered off by suction. The filtrate was concentrated in vacuo to afford the title compound (207 mg, 71%) as a colorless liquid. R_f = 0.25 ($CHCl_3$/EtOH = 9.5/0.5). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.14−7.05 (m, 4H, 4 × Ar−H), 4.12 (d, ^2J = 14.6 Hz, 1H, H_a-5), 3.43 (d, ^2J = 14.6 Hz, 1H, H_b-5), 3.28 (td, *J* = 8.7, 2.3 Hz, 1H, H_a-4), 2.99 (dd, *J* = 15.9, 3.8 Hz, 1H, H_a-10), 2.75−2.68 (m, 1H, H_b-10), 2.39−2.29 (m, 1H, H-1), 2.26 (pseudo-q, *J* = 9 Hz, 1 H, H_b-4), 2.14−2.04 (m, 1H, H_a-2), 1.99−1.77 (m, 2H, H-3), 1.61−1.51 (m, 1H, H_b-2) ppm. ^{13}C NMR, HMBC, HSQC (75.5 MHz, $CDCl_3$): δ = 135.1, 134.9 (C5a, C9a), 129.6 (CH), 126.7 (CH), 126.6 (CH), 125.8 (CH), 60.8 (C1), 56.0 (C5), 54.9 (C4), 36.1 (C10), 31.1 (C2), 21.6 (C3) ppm. IR (film): 2962 (s), 2782 (s), 1455 (m), 1381 (m), 1158 (m), 999 (m), 743 (s) cm^{-1}. ESI-MS (*m*/*z*): 174.13 (100) [M + H]$^+$. ESI-HRMS: calcd for $[C_{12}H_{16}N]^+$ 174.1283, found 174.1279.

2,3,6,7-Tetramethoxy-9,10-dimethylphenanthrene (6). The title compound was prepared according to the method of Manson and Musgrave.[44] To a solution of veratrole (12.5 g, 90.9 mmol, 2.0 equiv) in 70% aqueous sulfuric acid (150 mL) was added biacetyl (4.00 g, 46.5 mmol) dropwise with stirring during 0.5 h. The mixture was kept at room temperature for 11 days and then filtered and washed with water. The remaining solid was recrystallized from ethanol to afford the title compound (11.2 g, 74%) as a white solid: R_f = 0.43 (cyclohexane/EtOAc = 1/1); mp 224−225 °C dec (lit.[44,49] mp 222−227 °C). ^{1}H NMR, NOESY (400 MHz, $CDCl_3$): δ = 7.74 (s, 2H, H-4, H-5), 7.32 (s, 2H, H-1, H-8), 4.10 (s, 6H, C^3-OCH_3, C^6-OCH_3), 4.03 (s, 6H, C^2-OCH_3, C^7-OCH_3), 2.61 (s, 6H, C^9-CH_3, C^{10}-CH_3) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$): δ = 148.5 (C3,C6), 148.1 (C2, C7), 126.8 (C9, C10), 126.6 (C8a, C10a), 123.4 (C4a, C4b), 105.2 (C4, C5), 103.2 (C8, C1), 56.0 (C^3−OCH_3, C^6-OCH_3), 55.8 (C^2-OCH_3, C^7-OCH_3), 16.2 (C^9-CH_3, C^{10}-CH_3) ppm. IR (film): 3010 (w), 2958 (m, br), 2836 (w), 1620 (m), 1519 (s), 1476 (s), 1422 (s), 1251 (s), 1213 (s), 1195 (s), 1156 (s), 841 (s) cm^{-1}. FD-MS (*m*/*z*): 326.5 (100) [M]$^+$. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.31; H, 7.08.

9,10-Bis(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene (7). To a solution of 2,3,6,7-tetramethoxy-9,10-dimethylphenanthrene (**6**: 500 mg, 1.53 mmol) in CCl_4 (30 mL) were added *N*-bromosuccinimide (550 mg, 3.10 mmol, 2.0 equiv) and a catalytic amount of AIBN (30 mg). The mixture was refluxed for 18 h. It was cooled to room temperature, filtered, and washed thoroughly with water to afford the title compound (682 mg, 92%) as a yellow solid. R_f = 0.40 (cyclohexane/EtOAc = 1/1). Mp: 222−223 °C dec. ^{1}H NMR, NOESY (400 MHz, $CDCl_3$): δ = 7.79 (s, 2H, H-4, H-5), 7.50 (s, 2H, H-1, H-8), 5.10 (s, 4H, 2 × CH_2Br), 4.13 (s, 6H, C^3−OCH_3, C^6−OCH_3), 4.10 (s, 6H, C^2−OCH_3, C^7−OCH_3) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$): δ = 150.0 (C3, C6), 149.2 (C2, C7), 128.7 (C9, C10), 125.6 (C4a, C4b), 124.1 (C8a, C10a), 104.9 (C1, C8), 103.2 (C4, C5), 56.1 (C3, C6), 56.0 (C2, C7), 27.9 (CH_2Br) ppm. IR (film): 2933 (w, br), 2827 (w), 1620 (m), 1514 (s), 1466 (s), 1424 (s), 1252 (s), 1197 (s), 1160 (m), 1042 (s), 837 (s) cm^{-1}. FD-MS (*m*/*z*) 486.2 (100) [M]$^+$, 484.2 (78) [M]$^+$, 482.3 (34) [M]$^+$. Anal. Calcd for $C_{20}H_{20}Br_2O_4$: C, 49.61; H, 4.16. Found: C, 49.37; H, 4.23.

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2′-Cyano-5,6,9,10-tetramethoxy-1,3-dihydrospiro[dibenzo-[*e*,*g*]isoindole-2,1′-pyrrolidin]-1′-ium Bromide (8). A mixture of 9,10-bis(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene (**7**: 223 mg, 0.46 mmol, 1.0 equiv) and DIPEA (80 μL, 0.47 mmol, 1.0 equiv) in dry THF (10 mL) was heated under reflux with stirring while pyrrolidine-2-carbonitrile (**1**: 45 mg, 0.47 mmol, 1.0 equiv) was added dropwise. After the addition, the mixture was heated to reflux for 15 h. THF was removed under reduced pressure and the residue was recrystallized from methanol to afford the title compound (159 mg, 68%) as a beige solid. Mp: 258−260 °C dec. ^{1}H NMR, COSY, NOESY (400 MHz, DMSO-d_6): δ = 8.13 (s, 2H, H-7, H-8), 7.29 (s, 1H, H-4), 7.17 (s, 1H, H-11), 5.73 (d, ^2J = 14.7 Hz, 1H, H$_a$-3), 5.67−5.53 (m, 3H, H$_a$-1, H$_b$-1, H-2′), 5.55 (d, ^2J = 14.7 Hz, 1H, H$_b$-3), 4.18−4.11 (m, 1H, H$_a$-5′), 4.11−4.02 (m, 1H, H$_b$-5′), 4.07 (s, 6H, C^6-OCH_3, C^9-OCH_3), 3.97 (s, 3H, C^5-OCH_3), 3.95 (s, 3H, C^{10}-OCH_3), 2.91−2.80 (m, 1H, H$_a$-3′), 2.77−2.66 (m, 1H, H$_b$-3′), 2.48−2.39 (m, 2H, Ha-4′, Hb-4′) ppm. ^{13}C NMR, HMBC, HSQC (151 MHz DMSO-d_6): δ = 149.7 (C5, C10), 149.2 (C6), 149.1 (C9), 124.9 (C3a), 124.8 (C11b), 124.6 (C3b, C11a), 119.8 (C7a, C7b), 114.4 (CN), 105.4 (C4), 105.3 (C11), 104.7 (C7, C8), 68.3 (C1), 66.9 (C3), 65.2 (C5′), 63.4 (C2′), 56.1 (C^6−OCH_3, C^9−OCH_3), 55.8 (C^{15}−OCH_3), 55.7 (C^{10}-OCH_3), 27.1 (C3′), 20.4 (C4′) ppm. IR (ATR): 3397 (w, br), 2939 (w, br), 2337 (w), 1614 (w), 1520 (m), 1481 (s), 1250 (s), 1213 (w), 1158 (m), 1040 (m, sh), 1021 (m), 857 (m) cm^{-1}. ESI-MS (*m*/*z*): 419.20 (100) [M]$^+$. ESI-HRMS: calcd for [$C_{25}H_{27}N_2O_4$]$^+$ 419.1971, found 419.1969.

***rac*-Tylophorine (11).** (a) To a stirred solution of 2′-cyano-5,6,9,10-tetramethoxy-1,3-dihydrospiro[dibenzo[*e*,*g*]isoindole-2,1′-pyrrolidin]-1′-ium bromide (**8**: 160 mg, 0.32 mmol) in dry THF (10 mL) was added KHMDS (70 mg, 0.35 mmol, 1.1 equiv) dissolved in dry THF (1 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1.5 h. Ethanol (1 mL) and $NaCNBH_3$ (66 mg, 1.05 mmol, 3.3 equiv) were added, and the solution was allowed to warm to room temperature before AcOH (0.12 mL) was added dropwise. The reaction was stirred at room temperature for 13 h, quenched with saturated aq $NaHCO_3$ (15 mL), and extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was washed with EtOAc (50 mL), and the remaining solid was dissolved in $CHCl_3$ (30 mL), cooled to 0 °C, and filtered. The $CHCl_3$ filtrate was concentrated in vacuo to afford the title compound (107 mg, 85%) as a pale yellow solid. R_f = 0.28 (CH_2Cl_2/EtOH = 10/1). Mp: 279−281 °C dec (lit.[50] mp 275−282 °C). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ = 7.83 (s, 1H, Phen-H), 7.82 (s, 1H, Phen-H), 7.31 (s, 1H, Phen-H), 7.16 (s, 1H, Phen-H), 4.62 (d, ^2J = 14.7 Hz, 1H, H-9), 4.11 (s, 6H, 2 × OCH_3), 4.05 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 3.67 (d, ^2J = 14.7 Hz, 1H, H-9), 3.48 (t_{app}., *J* = 8.5 Hz, 1H, H-11), 3.37 (dd, *J* = 15.8 Hz, 2.4 Hz, 1H, H-14), 2.91 (m_c, 1H, H-14), 2.54−2.43 (m, 2H, H-13a, H-11), 2.30−2.20 (m, 1H, H-12), 2.21−1.90 (m, 2H, H-13), 1.84−1.72 (m, 1H, H-12) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$): δ = 148.9 (C_qOMe), 148.9 (C_qOMe), 148.7 (C_qOMe), 148.6 (C_qOMe), 126.5, 126.2, 126.0, 124.5, 123.8, 123.6 (6 × C_q), 104.1, 103.6, 103.5, 103.3 (4 × CH), 60.4 (C13a), 56.2 (OCH_3), 56.2 (OCH_3), 56.1 (OCH_3), 56.0 (OCH_3), 55.3 (C11), 54.2 (C9), 34.0 (C14), 31.4 (C12), 21.8 (C13) ppm. IR (NaCl): 2932 (m, br), 2830 (w), 1618 (m), 1514 (s), 1470 (s), 1426 (m), 1246 (s), 1211 (m), 1045 (m), 1017 (m), 841 (m) cm^{-1}. ESI-MS (*m*/*z*): 394.21 (100) [M + H]$^+$. ESI-HRMS: calcd for [$C_{24}H_{28}NO_4$]$^+$ 394.2018, found 394.2007.

(b) A mixture of 9,10-bis(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene (**7**: 300 mg, 0.62 mmol) and DIPEA (105 μL, 0.62 mmol, 1.0 equiv) in dry THF (15 mL) was heated under reflux with stirring while pyrrolidine-2-carbonitrile (**1**: 60 mg, 0.62 mmol, 1.0 equiv) was added dropwise. After the addition, the mixture was heated under reflux for 12 h. Then the mixture was cooled to 0 °C, and KHMDS (371 mg, 1.86 mmol, 3.0 equiv) dissolved in dry THF (2 mL) was added. The reaction mixture was stirred at this temperature for 5 h. Ethanol (5 mL) and $NaCNBH_3$ (330 mg, 5.25 mmol, 8.5 equiv) were added, and the solution was allowed to warm to room temperature before AcOH (0.6 mL) was added dropwise. The reaction was stirred at room temperature for 15 h, quenched with saturated aq $NaHCO_3$ (25 mL), and extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was washed with EtOAc (50 mL). The remaining solid was dissolved in $CHCl_3$ (30 mL), cooled to 0 °C, and filtered. The $CHCl_3$ filtrate was concentrated in vacuo to afford the title compound (119 mg, 49%) as a pale yellow solid. Mp: 277−280 °C dec (lit.[50] mp 275−282 °C). The spectroscopic data were identical with those of the sample prepared by method a.

■ ASSOCIATED CONTENT

Supporting Information

General methods and spectra for compounds **2**, **5**, **6**−**8**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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