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π^4s + π^2s Cycloaddition of Spiroepoxycyclohexa-2,4-dienone, Radical Cyclization, and Oxidation−Aldol−Oxidation Cascade: Synthesis of BCDE Ring of Atropurpuran

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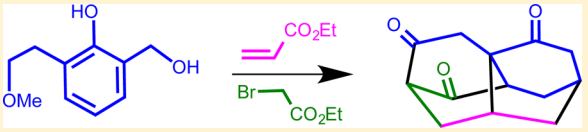
Supporting Information

ABSTRACT: Synthesis of a tetracyclic ring system (BCDE) of atropurpuran is described. Oxidative dearomatization, cycloaddition of spiroepoxycyclohexa-2,4-dienone, radical cyclization, and a tandem oxidation−aldol−oxidation are the key features of our methodology.



INTRODUCTION

Efficient creation of molecular entities endowed with structural, functional, and stereochemical complexity is an important aspect of the design and development of new methodology for organic synthesis.[1] Tandem or cascade reactions are often employed for rapid generation of molecular complexity.[1,2] Recently, cycloaddition of the reactive species such as *o*-quinols, masked *o*-quinones, and 6,6-spiroepoxycyclohexa-2,4-dienones generated by oxidative dearomatization of phenols has proved to be a powerful concept for efficient synthesis of a diverse array of molecular architecture.[3−5]

Recently, a unique C_{20} diterpenoid atropupuran **1** (Figure 1) was isolated from *Aconitum hemsleyanum* var. *atropupureum* by

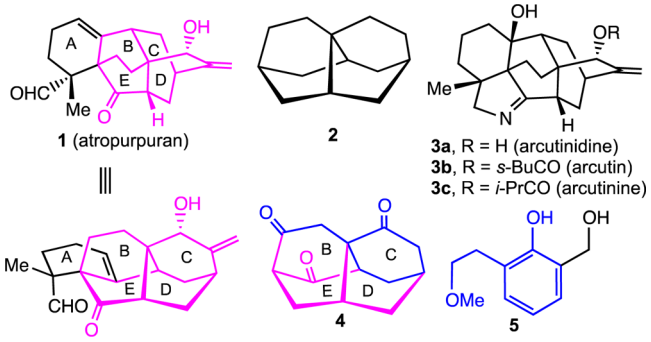


Figure 1. Atropurpuran **1**, diterpene alkaloids **3a−c**, related structures, and aromatic precursor.

Wang and co-workers.[6] The structure of atropurpuran was deduced by detailed NMR studies and further confirmed by a single-crystal X-ray structure determination. Remarkably, the pentacyclic architecture of atropurpuran **1** consists of five six-membered rings out of which four rings (BCDE) are present in boat form. Interestingly, rings B, C, D, and E of atropurpuran constitute a tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]tridecane framework of type **2** that has two bicyclo[2.2.2]octane rings fused together. The pentacyclic ring system of atropurpuran is also present in the structure of a few rare diterpene alkaloids such as arcutinidine **3a**, arcutin **3b**, and arcutinine **3c** that were isolated from *Aconitum arcuatum*.[7] The structural similarity between atropurpuran and acrutines presumably provides a biosynthetic link among these natural products.[8]

The complex molecular structure of atropurpuran appears to pose a high order of synthetic challenge. While synthesis of atropurpuran has not been achieved so far, there are only a few studies describing efforts toward synthesis of its molecular framework or parts thereof.

Recently, an elegant synthesis of pentacyclic framework of atropurpuran was reported by Kobayashi and his research group employing intramolecular cycloaddition of an embellished masked *o*-quinone as a key feature.[9a] A tandem sigmatropic shift, electrocyclic reaction, and Diels−Alder reaction was utilized by Hsung and co-workers for the synthesis of tricyclic ring system (BCD) of atropurpuran,[9b] whereas synthesis of ring A of atropurpuran by intramolecular Michael addition was presented by Zhang and associates.[9c] Most recently, Qin and co-workers reported a synthesis of tricyclic ring system (ABC) of atropurpuran.[9d] It appears that synthesis of the tetracyclic core **2** of atropurpuran that contains two fused bicyclo[2.2.2]octane rings (rings BCDE) is one of the most difficult tasks.

In view of the structural intricacy of atropurpuran, its biosynthetic significance and our continuing interest in creating molecular complexity from aromatics,[5] we wish to report herein a synthesis of functionalized tetracyclic framework **4** (ring BCDE) (Figure 1) of atropurpuran from a simple aromatic precursor **5**. Cycloaddition between electron deficient π-partners, radical cyclization, and aldol reaction are the key features of our design.

Our approach toward synthesis of the tetracyclic compound **4** is shown in Scheme 1. The strategy hinges upon recognition of structural and functional features of **4** with that of the

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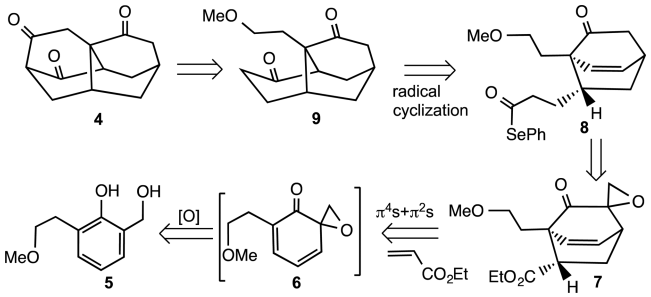
bridged bicyclic compound **7** via the intermediates **8** and **9** (Scheme 1).

Scheme 1. Retrosynthetic Plan



We conceptualized that the trione **4** would be derived from the tricyclic precursor **9** via demethylation followed by oxidation, aldol, and further oxidation. The precursor **9** would be prepared from the bridged bicyclic compound **8** endowed with olefinic moiety and appropriately disposed seleno ester moiety via acyl radical cyclization. The enone **8** would be easily derived from the keto ester **7** via manipulation of the oxirane ring and carbethoxy function and the compound **7**, in turn, would be assembled from *o*-hydroxymethyl phenol **5** via oxidative dearomatization to the spiroepoxycyclohexa-2,4-dienone **6** and subsequent cycloaddition with ethyl acrylate (Scheme 1).

There are several interesting features of our strategy. For example, the key precursor **8** contains all the carbons required for its elaboration to tetracyclic trione **4** including the *endo*-seleno ester moiety so as to permit the acyl radical cyclization. Further, the precursor **8** would be derived from the keto epoxide **7** that is endowed with appendage at the bridgehead (required for creation of ring B and E) and *endo*-carbethoxy group that would readily permit its transformation into the carbon chain bearing seleno-ester group. Remarkably, the precursor **7** having ring C and D of atropurpuran would be readily assembled from a simple aromatic precursor **5**, in the very beginning of the synthetic route.

RESULTS AND DISCUSSION

Conceptually, the key precursor **8** may be prepared by the cycloaddition of cyclohexa-2,4-dienone of type **I** (Figure 2)

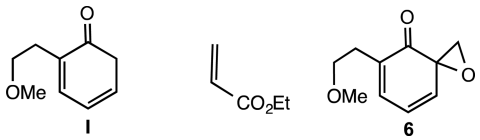
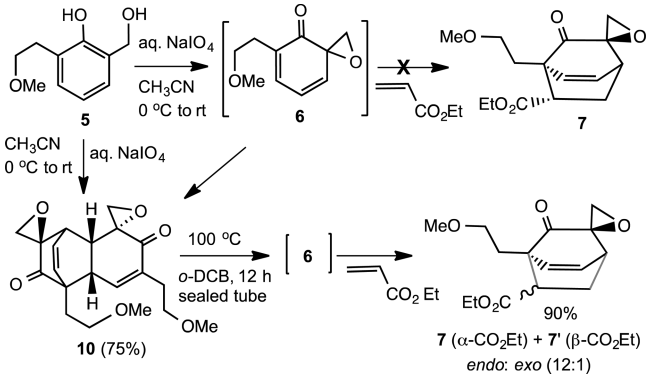


Figure 2. Potential precursors.

with ethyl acrylate followed by manipulation of the ester group. However, the dienone **I** is the keto-tautomer of the corresponding phenol and there are no obvious routes for its preparation. Hence, we considered employing the spiroepoxycyclohexadienone **6** as an equivalent of dienone **I**. At the outset, however, we were aware that spiroepoxycyclohexa-2,4-dienones have fleeting existence and instantaneously undergo dimerization in the absence of reactive dienophiles.[5d,e,10]

Thus, the *o*-hydroxymethylphenol **5** was subjected to oxidative dearomatization in the presence of ethyl acrylate following a procedure developed in our laboratory.[11] However, it did not give the desired adduct **7**; instead, the dimer **10** was obtained as a result of cycloaddition between 2 mol of the spiroepoxycyclohexa-2,4-dienone **6** (Scheme 2). The structure

Scheme 2. Dearomatization and Retro-Diels–Alder/Diels–Alder cascade



of the dimer **10** was thoroughly established with the help of spectral data and confirmed through single-crystal X-ray structure determination (see the Supporting Information).

It appears that the energy of activation required for the cycloaddition of **6** with ethyl acrylate is not available under ambient conditions. Therefore, we considered generating cyclohexadienone **6** via a thermal retro-Diels–Alder reaction of the dimer **10** in the presence of ethyl acrylate with a hope that the cycloaddition may occur to give the desired adduct.

Therefore, the dimer **10** was prepared by oxidation of **5** and heated in the presence of ethyl acrylate in a sealed tube at 100 °C. Indeed, chromatography of the reaction mixture furnished the desired adduct (**7** + **7′**) in excellent yield (90%) as a inseparable mixture of *endo*/*exo* isomer (12:1) containing the *endo* isomer as a major product (Scheme 2). The *endo*/*exo* ratio was determined by ^{1}H NMR spectroscopy. It is interesting to note the efficiency of the retro-Diels–Alder/Diels–Alder cascade. The structure of adduct was deduced from its spectral features and further confirmed through subsequent chemical transformation (vide infra). The mixture of adducts was then transformed into the desired precursor **8** as follows.

Thus, the mixture of adduct (**7** + **7′**) was treated with Zn–NH_4Cl in aq methanol at ambient temperature to give the *α*-hydroxymethyl ketone **12** as a major product (83%) along with a minor product **11** formed as a result of deoxygenation of oxirane ring (Scheme 3). Oxidation of **12** with Jones' reagent followed by decarboxylation gave a stereoisomeric mixture of keto ester from which the desired *endo*-stereoisomer **13** was obtained (Scheme 3). The CO group of the keto ester **13** was protected as ketal **14** that upon reduction with lithium aluminum hydride furnished the alcohol **15** in excellent yield. Oxidation of **15** with TPAP–NMO gave the aldehyde **16** that upon Wittig reaction furnished the homologated ester **17** (Scheme 3).

Regioselective reduction of the conjugated double bond in **17** by treatment with $NaBH_4$–CuCl gave the ketal ester **18**. Interestingly, treatment of **18** with aq KOH in refluxing methanol and subsequent acidic workup led to hydrolysis of the ester and ketal moiety to give the keto acid **19**, which was treated with *N*-(phenylseleno)phthalimide and tributylphosphine[12] to furnish the required selenoester **8** (Scheme 4). After the key precursor **8** was prepared, it was subjected to radical

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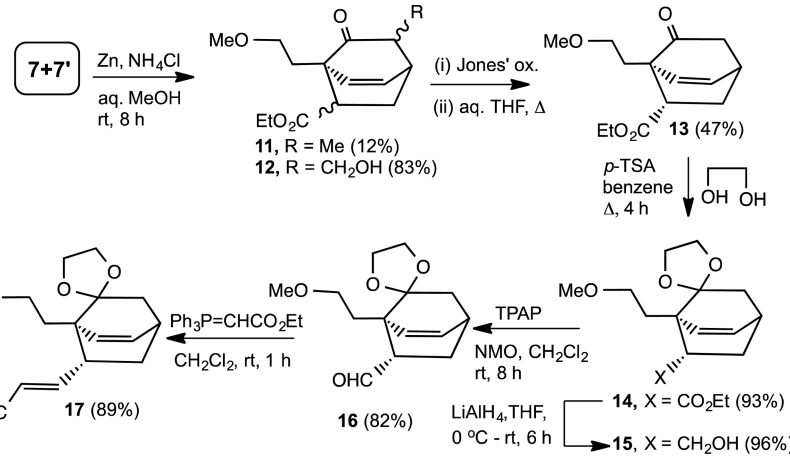
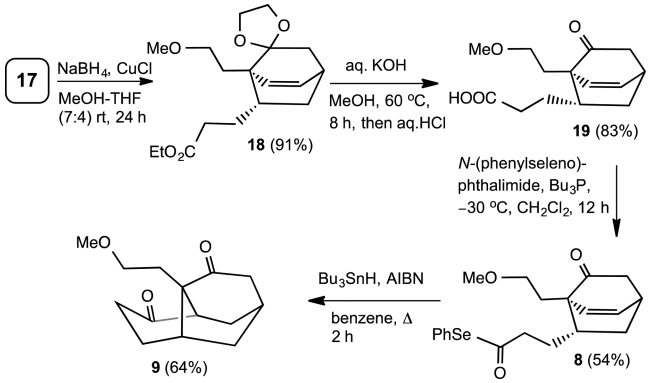
Scheme 3. Preparation of Precursor 17



Scheme 4. Synthesis of Tricyclic Intermediate 9



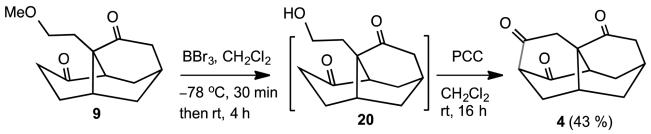
cyclization. Thus, a solution of selenoester **8** in benzene containing AIBN was treated with Bu_3SnH, and the reaction mixture was refluxed for 2 h. Removal of solvent followed by chromatography gave the tricyclic dione **9** in good yield (Scheme 4).

The structure of the cyclized product **9** was deduced from the following spectral features and comparison with the spectral characteristic of its progenitor. Thus, compound **9** exhibited IR absorption at 1715 cm^{-1} for the CO groups. The ^1H NMR spectrum (400 MHz) of **9** did not show signals due to olefinic protons, which strongly suggested that the double bond of bicyclo[2.2.2]octane framework had participated in the radical cyclization. The ^{13}C NMR spectrum (100 MHz) of the product **9** was more revealing as it exhibited two characteristic signals at δ 212.6 and 211.3 for the CO groups present in the six-membered rings. Further, the cyclized compound **9** showed signals at δ 68.7, 58.6, 50.2, 48.4, 45.1, 31.8, 31.2, 29.9, 29.6, 28.3, 27.5, and 26.7 due to other carbons. The high-resolution mass spectrum of compound **9** gave a peak at m/z 259.1311 $(M + Na)^+$ (required 259.1305) corresponding to its molecular formula.

A comparison of the above signals, in particular the signals due to CO groups of cyclized product **9** with CO signals of the precursor **8** that appeared at δ 212.6 and 200.1, clearly suggested that cyclization had occurred. Thus, the transformation of selenoester **8** into the tricyclic dione **9** also proved the structure and stereochemical orientation of the ester group in compound **13** and other precursors derived from ketoester **13**.

Toward the synthesis of tetracyclic trione **4**, the tricyclic dione **9** was treated with BBr_3 to give the demethylated product **20**, which was directly subjected to oxidation with PCC. Remarkably, chromatography of the crude product furnished the tetracyclic trione **4** (Scheme 5) formed as consequence of the oxidation–aldol–oxidation cascade. The structure of tetracyclic trione **4** was deduced from the following spectral features.

Scheme 5. Demethylation and Oxidation–Aldol–Oxidation Cascade



Thus, the IR spectrum of **4** showed an absorption band at 1713 cm^{-1} for the carbonyl groups. The ^1H NMR (400 MHz) spectrum of **4** displayed signals at δ 3.32 (dd, J_1 = 3.5 Hz, J_2 = 2.2 Hz, 1H), 2.65 (AB system partially merged with another signal, J_{AB} = 19.9 Hz, 2H), 2.60–2.53 (m, 1H), 2.42–2.35 (m, 3H), 2.34–2.18 (m, 4H), 2.12–2.00 (m, 2H), 1.49–1.42 (m, 1H), corresponding to 14 protons present in compound **4**. The ^{13}C NMR spectrum of **4** was more revealing and showed three distinct signals at δ 210.5, 208.8, and 204.5, which clearly suggested the presence of three carbonyl groups in its molecular structure. Further, it exhibited signals at δ 64.7, 46.3, 29.3, and 28.1 due to four methine carbons. In addition, signals were observed at δ 43.8, 41.2, 36.3, 36.0, 30.5, and 47.9 due to the presence of five- methylene carbons and one quaternary carbon, respectively. The presence of three CO groups, four methine carbons, five methylene carbons, and one quaternary carbon clearly revealed its tetracyclic structure. The high-resolution mass spectrum of compound **4** gave a peak at m/z 241.0843 $(M + Na)^+$ (required 241.0835) corresponding to its molecular formula.

In summary, we have described a novel stereoselective synthesis of functionalized tetracyclic ring system of atropurpuran comprising rings BCDE from a simple aromatic precursor. Oxidative dearomatization of a *o*-hydroxymethylphenol, and a retro-Diels–Alder/intermolecular Diels–Alder cascade led to appropriately appended and functionalized adduct. Further manipulation of the oxirane ring and the

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carbethoxy group gave a key precursor that upon acyl radical cyclization furnished the tricyclic dione containing a methoxyethyl chain at the bridgehead. Demethylation of the methoxy group resulted in a tricyclic compound having a hydroxyethyl chain at the bridgehead that upon treatment with PCC underwent a highly remarkable tandem oxidation−aldol−oxidation reaction to finally give the tetracyclic trione bearing the tetracyclic framework of atropurpuran.

EXPERIMENTAL SECTION

General Remarks. IR spectra were recorded on an FT-IR instrument. ^{1}H (400 MHz/500 MHz) and ^{13}C (100 MHz/125 MHz) spectra were recorded using an NMR spectrometer. Samples were dissolved in $CDCl_3$ as a solvent and TMS as an internal standard. Chemical shifts were reported in parts per million (ppm) relative to either a tetramethylsilane (TMS) internal standard or the signals due to the solvent. The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets. Coupling constants are reported in hertz (Hz). High-resolution mass spectra were recorded on a Q-TOF micro mass spectrometer with ESI mode of analysis. Melting points were recorded in capillary tubes and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) using silica gel, and spots were visualized with iodine vapor. Column chromatography was performed on silica gel for chromatography (100−200 mesh).

Oxidation of *o*-(Hydroxymethyl)phenol 5: Preparation of Epoxy Dimer 10. To a solution of compound **5** (6.5 g, 35 mmol) in acetonitrile (120 mL) was added a solution of $NaIO_4$ (19.1 g, 89 mmol) in water (150 mL) dropwise at 5 °C. The reaction mixture was stirred for 5 h at ambient temperature. It was filtered on a Celite bed to remove inorganic salts. The organic layer was separated from the filtrate, and the aqueous layer was extracted with ethyl acetate (4 × 30 mL). The organic extracts were combined, washed with brine (30 mL), and dried on sodium sulfate. The solvent was removed in vacuo, and product was chromatographed on silica gel. Elution with petroleum ether−ethyl acetate (50:50) afforded compound **10** (4.81 g, 75%) as a colorless solid. R_f = 0.4 petroleum ether/ethyl acetate (60:40). Mp: 132−133 °C. IR (film) ν_{max}: 2926, 1731, 1693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, J = 4.5 Hz, 1H), 6.57 (merged dd, $J_1 = J_2$ = 8.1 Hz, 1H), 5.88 (d, J = 8.1 Hz, 1H), 3.78−3.70 (m, 1H), 3.60−3.52 (m, 1H), 3.50−3.43 (m, 1H), 3.42−3.36 (m, 2H), 3.34 (s, 3H), 3.30 (s, 3H), 3.15 (part of an AB system, J_{AB} = 6.2 Hz, 1H), 2.92 (part of an AB system, J_{AB} = 6.2 Hz, 1H), 2.90−2.86 (m, 1H), 2.83 (s, 2H), 2.71 (dd, J_1 = 8.9 Hz, J_2 = 1.9 Hz, 1H), 2.58−2.43 (m, 2H), 2.18 (merged dd, $J_1 = J_2$ = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.3, 193.1, 142.0, 140.5, 134.3, 133.2, 70.5, 69.5, 59.1, 58.8, 58.7, 58.5, 58.1, 57.8, 54.0, 41.02, 41.0, 39.8, 30.6, 29.5. HRMS (ESI) (m/z): found 383.1471 (M + Na)$^+$, calcd for $C_{20}H_{24}NaO_6$ 383.1465.

Ethyl 4-(2-Methoxyethyl)-3-oxospiro[bicyclo[2.2.2]oct[5]-ene-2,2′-oxirane]-8-carboxylate (7 + 7′). A mixture of epoxy dimer **10** (1.2 g, 3.33 mmol) and ethyl acrylate (1.5 mL, 13.3 mmol) in *o*-dichlorobenzene (2 mL) was heated in sealed tube at 100 °C for 12 h. The reaction mixture was brought to room temperature and charged on a column of silica gel. Elution with petroleum ether first gave *o*-dichlorobenzene, and further elution with petroleum ether−ethyl acetate (97:03) gave the residual ethyl acrylate. Continued elution with petroleum ether−ethyl acetate (90:10) furnished the mixture of adduct 7 + 7′ as a colorless liquid (0.84 g, 90%). R_f = 0.6 petroleum ether/ethyl acetate (80:20). IR (film) ν_{max}: 2981, 1732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 and 6.44 (merged dd, $J_1 = J_2$ = 8.2 Hz, total 1H), 6.26 and 6.13 (d, J = 8.2 Hz, total 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.60−3.44 (m, 2H), 3.31 and 3.27 (s, total 3H), 3.14 (part of an AB system, J_{AB} = 6.1 Hz, 1H), 2.88 (dd partly merged with part of an AB system, J_1 = 10.1 Hz, J_2 = 5.4 Hz, 1H), 2.85 (part of an AB system, J_{AB} = 6.1 Hz, 1H), 2.63−2.57 (m, 1H), 2.47 (merged dd, $J_1 = J_2$ = 10.4 Hz, 1H), 2.22−2.13 (m, 1H), 2.04−1.95 (m, 1H), 1.86−1.77 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 172.9, 133.7, 131.7, 69.3, 61.0, 58.5, 57.8, 53.8, 53.6, 53.5, 43.6, 37.9, 29.2, 14.3. HRMS (ESI) (m/z): found 303.1202 (M + Na)$^+$, calcd for $C_{15}H_{20}NaO_5$ 303.1203.

Ethyl 1-(2-Methoxyethyl)-8-methyl-7-oxobicyclo[2.2.2]oct-5-ene-2-carboxylate (11) and Ethyl-8-(Hydroxymethyl)-1-(2-methoxyethyl)-7-oxobicyclo[2.2.2]oct-5-ene-2-carboxylate (12). To a mixture of keto epoxide 7 + 7′ (7.0 g, 25 mmol) in methanol−water (185 mL, 6:1) were added activated zinc (36 g, excess) and ammonium chloride (6.68 g, excess). The reaction mixture was stirred for 8 h at room temperature, after which it was filtered on a Celite bed to remove zinc and washed with ethyl acetate (25 mL). The filtrate was concentrated in vacuum so as to remove most of the solvent, and the residue was diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the product was chromatographed on silica gel. Elution with petroleum ether−ethyl acetate (95:05) furnished the deoxygenated compound **11** as a colorless liquid (0.85 g, 12%). R_f = 0.7 petroleum ether/ethyl acetate (80:20). IR (film) ν_{max}: 2925, 1723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 and 6.48 (merged dd, $J_1 = J_2$ = 8.0 Hz, total 1H), 6.01 and 5.92 (d, J = 8.0 Hz, total 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.62−3.54 (m, 1H), 3.50−3.43 (m, 1H), 3.29 (s, 3H), 2.80−2.74 (m, 1H), 2.58 (dd, J_1 = 10.0 Hz, J_2 = 6.2 Hz, 1H), 2.32−2.23 (m, 1H), 2.16−2.03 (m, 2H), 1.94−1.84 (m, 1H), 1.64−1.56 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.11 (d, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 213.4, 173.3, 137.7, 129.7, 69.7, 60.9, 58.5, 53.4, 43.9, 42.3, 37.6, 29.6, 27.2, 15.1, 14.3 (signals due to major isomer). HRMS (ESI) (m/z): found 289.1411 (M + Na)$^+$, calcd for $C_{15}H_{22}NaO_4$ 289.1410.

Continued elution with petroleum ether−ethyl acetate (70:30) furnished the mixture of keto alcohol **12** as a colorless liquid (5.85 g, 83%). R_f = 0.3 petroleum ether/ethyl acetate (80:20). IR (film) ν_{max}: 3439, 2928, 1715 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 and 6.48 (merged dd, $J_1 = J_2$ = 8.0 Hz, total 1H), 6.06 and 5.93 (d, J = 8.0 Hz, total 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.80 (dd, J_1 = 10.9 Hz, J_2 = 7.0 Hz, 1H), 3.62−3.51 (m, 2H), 3.50−3.42 (m, 1H), 3.29 and 3.28 (s, total 3H), 3.04−2.97 and 2.96−2.90 (m, total 1H), 2.82 and 2.62 (dd, J_1 = 10.0 Hz, J_2 = 6.2 Hz, total 1H), 2.59−2.48 (br s, 1H), 2.30−2.20 (m 2H), 2.19−2.05 (m, 1H), 1.95−1.85 (m, 1H), 1.67−1.57 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.7, 173.0, 137.4, 129.7, 69.5, 62.4, 60.9, 58.5, 53.7, 49.6, 43.9, 34.2, 29.3, 27.9, 14.2 (signals due to major isomer). HRMS (ESI) (m/z): found 305.1361 (M + Na)$^+$, calcd for $C_{15}H_{22}NaO_5$ 305.1359.

Ethyl 1-(2-Methoxyethyl)-7-oxobicyclo[2.2.2]oct-5-ene-2-carboxylate (13). To a solution of the keto alcohol **12** (1.18 g, 4.18 mmol) in acetone (60 mL) was added freshly prepared Jones' reagent dropwise at ∼5 °C. After the reaction was complete (TLC, 1 h), 2-propanol (10 mL) was added slowly to quenched excess Jones' reagent. Solvent was removed in vacuo, and the residue was diluted with water and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (1 × 20 mL) and dried over anhydrous sodium sulfate. Removal of the solvent gave a β-keto acid that was directly subjected to decarboxylation as follows.

The β-keto acid thus obtained was taken up in a THF−water mixture (70 mL, 1:1), and the reaction mixture was refluxed for 15 h (TLC). THF was removed in vacuo, and the aqueous layer was extracted with ethyl acetate and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was chromatographed on silica gel. Elution with petroleum ether−ethyl acetate (90:10) gave the compound **13** as a colorless liquid (0.493 g, 47%). R_f = 0.5 petroleum ether/ethyl acetate (90:10). IR (film)ν_{max}: 2933, 1728, 1451 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.53 (merged dd, $J_1 = J_2$ = 8.1 Hz, 1H), 6.00 (d, J = 8.1 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.61−3.53 (m, 1H), 3.51−3.43 (m, 1H), 3.28 (s, 3H), 3.03−2.96 (m, 1H), 2.75 (dd, J_1 = 10.1 Hz, J_2 = 5.9 Hz, 1H), 2.18−2.06 (m, 4H), 2.02−1.92 (m, 1H), 1.81−1.68 (m merged with signal due to H_2O in $CDCl_3$, 1H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.4, 173.3, 136.4, 130.0, 69.6, 60.8, 58.5, 53.4, 42.8, 39.9, 32.8, 31.8, 29.5, 14.3. HRMS (ESI) (m/z): found 275.1254 (M + Na)$^+$, calcd for $C_{14}H_{20}NaO_4$: 275.1254.

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Ethyl 1-(2-Methoxyethyl)spiro[bicyclo[2.2.2]oct[5]ene-2,2′-[1,3]dioxolane]-7-carboxylate (14). To a mixture of ethylene glycol (4 mL), *p*-toluenesulfonic acid (0.05 g), and benzene (75 mL) dried in a Dean−Stark apparatus was added a solution of compound **13** (1.6 g, 6.34 mmol) in dry benzene under nitrogen atmosphere. The reaction mixture was refluxed for 4 h, after which it was cooled and poured into a saturated solution of sodium bicarbonate (25 mL) and stirred vigorously. The benzene layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed with brine (10 mL) and dried over anhydrous sodium sulfate. Removal of solvent followed by chromatography on silica gel [petroleum ether/ethyl acetate (80:20)] gave the compound **14** as a colorless liquid (1.74 g, 93%). R_f = 0.5 petroleum ether/ethyl acetate (85:15). IR (film) ν_{max}: 2923, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.42 (dd, J_1 = 8.2 Hz, J_2 = 6.6 Hz, 1H), 6.05 (d, J = 8.2 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.96−3.85 (m, 4H), 3.62−3.48 (m, 2H), 3.32 (s, 3H), 3.10 (dd, J_1 = 9.8 Hz, J_2 = 5.5 Hz, 1H), 2.76−2.68 (m, 1H), 2.07−1.95 (m, 3H), 1.75−1.69 (m, 1H), 1.68−1.62 (m merged with signal due to H_2O in $CDCl_3$, 1H) 1.59−1.51 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 136.1, 132.7, 113.8, 70.4, 64.3, 64.1, 60.4, 58.5, 45.7, 42.3, 42.2, 32.8, 30.8, 30.3, 14.3. HRMS (ESI) (m/z): found 319.1511 $(M + Na)^+$, calcd for $C_{16}H_{24}NaO_5$ 319.1516.

1-(2-Methoxyethyl)spiro[bicyclo[2.2.2]oct[5]ene-2,2′-[1,3]-dioxolan]-7-yl)methan-ol (15). A solution of ketal ester **14** (0.9 g, 3.04 mmol) in dry THF (25 mL) was slowly added to a stirred suspension of lithium aluminum hydride (0.17 g, 4.56 mmol) in THF (40 mL) at ∼5 °C under nitrogen atmosphere. After completion of the reaction (6 h), the reaction mixture was cooled in an ice bath and then quenched by dropwise addition of cold water. The reaction mixture was filtered through a Celite bed and washed with ethyl acetate (20 mL). Solvent was removed in vacuo, and the residue was diluted with water (10 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvent followed by chromatography on silica gel [petroleum ether/ethyl acetate (60:40)] furnished an alcohol **15** (0.74 g, 96%) as a colorless liquid. R_f = 0.3 petroleum ether/ethyl acetate (70:30). IR (film) ν_{max}: 3417, 2932 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.34 (dd, J_1 = 8.2 Hz, J_2 = 6.5 Hz, 1H), 5.91 (d, J = 8.2 Hz, 1H), 3.95−3.83 (m, 4H), 3.66−3.52 (m, 3H), 3.39−3.28 (m merged with s, 4H), 2.68−2.58 (m, 1H), 2.40−2.30 (m, 1H), 2.19−2.09 (m, 2H), 1.98−1.82 (m, 2H), 1.70−1.55 (m, 2H), 1.25−1.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 133.1, 114.6, 70.6, 65.4, 64.0, 63.9, 58.7, 45.6, 42.3, 38.4, 31.4, 30.7, 29.8. HRMS (ESI) (m/z): found 255.1589 $(M + H)^+$, calcd for $C_{14}H_{23}O_4$: 255.1591.

1-(2-Methoxyethyl)spiro[bicyclo[2.2.2]oct[5]ene-2,2′-[1,3]-dioxolane]-7-carbaldehyde (16). To a mixture of alcohol **15** (0.8 g, 3.14 mmol), NMO (0.55 g, 4.72 mmol), and powdered molecular sieves (4 Å, 1 g) in dry CH_2Cl_2 (75 mL) was added tetrapropylammonium perruthenate, TPAP (0.11 g, 0.31 mmol), at room temperature under nitrogen atmosphere. After completion of the reaction (TLC, ∼8 h), the reaction mixture was filtered through a Celite bed and washed with CH_2Cl_2 (30 mL). The filtrate was concentrated, and the product was chromatographed on silica gel. Elution with petroleum ether/ethyl acetate (90:10) gave the aldehyde **16** as a colorless liquid (0.65 g, 82%). R_f = 0.6 petroleum ether/ethyl acetate (90:10). IR (film) ν_{max}: 2928, 1716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.41 (d, J = 4.2 Hz, 1H), 6.46 (dd, J_1 = 8.3 Hz, J_2 = 6.6 Hz, 1H), 6.09 (d, J = 8.3 Hz, 1H), 3.99−3.85 (m, 4H), 3.58 (t, J = 7.5 Hz, 2H), 3.31 (s, 3H), 3.01−2.94 (m, 1H), 2.82−2.74 (m, 1H), 2.07 (merged dd, J_1 = J_2 = 7.2 Hz, 2H), 1.93−1.84 (m, 1H), 1.78−1.58 (m merged with signal due to H_2O in $CDCl_3$, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.6, 136.3, 132.8, 113.4, 70.0, 64.4, 58.5, 50.0, 45.3, 42.9, 30.7, 30.3, 28.1. HRMS (ESI) (m/z): found 275.1255 $(M + Na)^+$, calcd for $C_{14}H_{20}NaO_4$ 275.1254.

***(E)*-Ethyl 3-(1-(2-Methoxyethyl)spiro[bicyclo[2.2.2]oct[5]ene-2,2′-[1,3]dioxolan]-7-yl)acrylate (17).** To a stirred solution of ethyl (triphenylphosphoranylidene) acetate (4.77 g, 13.6 mmol) in dry CH_2Cl_2 (80 mL) was added a solution of aldehyde **16** (1.72 g, 6.82 mmol) in dichloromethane (20 mL) at ∼5 °C. The reaction mixture was stirred for 1 h at room temperature. Removal of solvent followed by chromatography on silica gel [petroleum ether−ethyl acetate (80:20)] furnished the Wittig product **17** (1.95 g, 89%) as a colorless liquid. R_f = 0.5 petroleum ether/ethyl acetate (80:20). IR (film) ν_{max}: 2923, 1717 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.55 (dd, J_1 = 15.4 Hz, J_2 = 10.7 Hz, 1H), 6.45 (merged dd, J_1 = J_2 = 8.2 Hz, 1H), 6.04 (d, J = 8.2 Hz, 1H), 5.76 (d, J = 15.4 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.98−3.85 (m, 4H), 3.59−3.46 (m, 2H), 3.31 (s, 3H), 2.92−2.84 (m, 1H), 2.68−2.63 (br s, 1H), 2.00−1.91 (m, 1H), 1.90−1.79 (m, 2H), 1.74−1.60 (m merged with signal due to H_2O in $CDCl_3$, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.20−1.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 151.8, 135.8, 132.3, 121.1, 113.9, 70.4, 64.3, 63.9, 60.3, 58.6, 46.3, 42.6, 41.3, 33.6, 30.8, 30.7, 14.4. HRMS (ESI) (m/z): found 345.1677 $(M + Na)^+$, calcd for $C_{18}H_{26}NaO_5$ 345.1672.

Ethyl 3-(1-(2-Methoxyethyl)spiro[bicyclo[2.2.2]oct[5]ene-2,2′-[1,3]dioxolan]-7-yl)propanoate (18). To a solution of compound **17** (1.2 g, 3.72 mmol) and CuCl (0.33 g, 3.35 mmol, excess) in MeOH/THF (7:4, 60 mL) at 0 °C was added $NaBH_4$ (1.4 g, 37.2 mmol). The reaction mixture was stirred at ambient temperature for 24 h, after which it was filtered on a Celite bed to remove inorganic material and washed with ethyl acetate (30 mL). The filtrate was concentrated in vacuo, and the residue was diluted with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (1 × 20 mL) and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was chromatographed on silica gel. Elution with petroleum ether−ethyl acetate (80:20) furnished the compound **18** as a colorless liquid (1.1 g, 91%). R_f = 0.5 petroleum ether/ethyl acetate (80:20). IR (film) ν_{max}: 2934, 1734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.30 (merged dd, J_1 = J_2 = 8.2 Hz, 1H), 5.82 (d, J = 8.2 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.92−3.80 (m, 4H), 3.60−3.49 (m, 2H), 3.33 (s, 3H), 2.63−2.55 (m, 1H), 2.34−2.24 (m, 1H), 2.20−2.10 (m, 2H), 2.08−1.93 (m, 2H), 1.92−1.76 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H), 1.14−1.02 (m, 1H), 1.00−0.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 134.6, 133.6, 114.5, 70.3, 63.9, 63.8, 60.4, 58.6, 46.7, 42.5, 34.6, 32.8, 32.0, 30.7, 30.1, 28.0, 14.4. HRMS (ESI) (m/z): found 347.1830 $(M + Na)^+$, calcd for $C_{18}H_{28}NaO_5$ 347.1829.

3-(1-(2-Methoxyethyl)-7-oxobicyclo[2.2.2]oct-5-en-2-yl) propanoic Acid (19). To a solution of ester **18** (0.85 g, 2.62 mmol) in methanol (30 mL) was added potassium hydroxide (0.44 g, 7.87 mmol) in water (15 mL). The reaction mixture was heated at 60 °C for 8 h. The reaction mixture was cooled and quenched by dropwise addition of dilute hydrochloric acid, after which it was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of solvent afforded the acid **19** (0.55g, 83%) as a colorless liquid. R_f = 0.3 petroleum ether/ethyl acetate (30:70). IR (film) ν_{max}: 3431, 2926, 1716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.49 (merged dd, J_1 = J_2 = 8.1 Hz, 1H), 5.86 (d, J = 8.1 Hz, 1H), 3.67−3.58 (m, 1H), 3.55−3.46 (m, 1H), 3.34 (s, 3H), 2.94−2.87 (m, 1H), 2.44−2.33 (m, 1H), 2.29−2.18 (m, 1H), 2.14−2.02 (m, 3H), 2.01−1.92 (m, 3H), 1.85−1.75 (m, 1H), 1.30−1.15 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.2, 178.8, 136.9, 130.0, 69.4, 58.5, 55.0, 40.1, 36.7, 32.7, 31.4, 29.2, 27.2. HRMS (ESI) (m/z): found 275.1253 $(M + Na)^+$, calcd for $C_{14}H_{20}NaO_4$: 275.1254.

***Se*-Phenyl-3-(1-(2-methoxyethyl)-7-oxobicyclo[2.2.2]oct-5-en-2-yl)propaneselenoate (8).** Tributylphosphine (0.4 mL, 1.60 mmol) was added dropwise to a stirred solution of acid **19** (0.27 g, 1.07 mmol) in dichloromethane (45 mL) at −30 °C. After 5 min, *N*-(phenylseleno)phthalimide (0.485 g, 1.60 mmol) was added in a single portion, and the reaction mixture was stirred at −30 °C for 12 h. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layer was washed with brine (15 mL) and dried over anhydrous sodium sulfate. Removal of solvent followed by chromatography on silica gel [petroleum ether−ethyl acetate, (85:15)] furnished the seleno ester **8** as a colorless liquid (0.23 g, 54%). R_f = 0.6 petroleum ether/ethyl acetate (80:20). IR (film) ν_{max}: 2925, 1719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.53−7.46 (m, 2H), 7.43−7.33 (m, 3H), 6.48 (merged dd,

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$J_1 = J_2$ = 8.1 Hz, 1H), 5.87 (d, J = 8.1 Hz, 1H), 3.65−3.56 (m, 1H), 3.53−3.44 (m, 1H), 3.34 (s, 3H), 2.95−2.87 (m, 1H), 2.77−2.67 (m, 1H), 2.66−2.57 (m, 1H), 2.11−2.00 (m, 4H), 1.99−1.90 (m, 2H), 1.87−1.77 (m, 1H), 1.35−1.23 (m, 1H), 1.22−1.14 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.6, 200.1, 136.9, 135.9, 130.2, 129.5, 129.1, 126.4, 69.6, 58.7, 55.2, 44.9, 40.2, 36.8, 32.9, 31.4, 29.4, 28.0. HRMS (ESI) (m/z): found 415.0783 $(M + Na)^+$, calcd for $C_{20}H_{24}NaO_3Se$ 415.0784.

8a-(2-Methoxyethyl)octahydro-1,6-methanonaphthalene-2,8-dione (9). To a stirred solution of seleno ester **8** (0.128 g, 0.32 mmol) and AIBN (0.05 g, 0.32 mmol) in dry degassed benzene (40 mL) was added tributyltin hydride (TBTH) (0.13 mL, 0.49 mmol), and the reaction mixture was refluxed for 2 h. The solvent was evaporated, and the residue was chromatographed on silica gel. Elution with petroleum ether first gave some tin impurities. Continued elution with petroleum ether−ethyl acetate (50:50) gave the cyclized compound **9** (0.049 g, 64%) as a colorless liquid. R_f = 0.4 petroleum ether−ethyl acetate (70:30). IR (film) ν_{max}: 2927, 1715 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.49−3.42 (m, 1H), 3.40−3.33 (m, 1H), 3.28 (s, 3H), 2.97−2.86 (m, 1H), 2.43−2.36 (m, 1H), 2.35−2.17 (m, 5H), 2.16−2.08 (m, 2H), 2.01−1.92 (m, 1H), 1.91−1.78 (m, 3H), 1.73−1.65 (m, 1H), 1.57−1.48 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.6, 211.3, 68.7, 58.6, 50.2, 48.4, 45.1, 31.8, 31.2, 29.9, 29.6, 28.3, 27.5, 26.7. HRMS (ESI) (m/z): found 259.1311 $(M + Na)^+$, calcd for $C_{14}H_{20}NaO_3$ 259.1305.

Hexahydro-1*H*-2,4a-ethano-4,7-methanonaphthalene-1,5,11(2*H*)-trione (4). To a solution of compound **9** (0.07g, 0.29 mmol) in dichloromethane (35 mL) was added boron tribromide (0.6 mL, 0.59 mmol) dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and then at ambient temperature for 4 h. After completion of reaction (TLC), the reaction mixture was cooled in an ice bath and quenched by dropwise addition of cold water. The reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic extract was washed with brine (10 mL) and dried over sodium sulfate. Removal of the solvent gave demethylated compound **20** (0.057 g), which was directly subjected to oxidation as follows.

To a solution of demethylated compound **20** (0.057 g, 0.25 mmol) in dichloromethane (30 mL) was added PCC (0.276 g, 1.28 mmol), and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was diluted with dichloromethane (50 mL) and filtered through a Celite bed. The Celite bed washed with CH_2Cl_2 (3 × 20 mL). The filtrate was concentrated under reduced pressure, and the residue was chromatographed over silica gel. Elution with petroleum ether−ethyl acetate (40:60) furnished the trione **4** (0.027 g, 43%) as a colorless solid. R_f = 0.5 petroleum ether/ethyl acetate (50:50). Mp: 191−192 °C. IR (film) ν_{max}: 2927, 1713 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.32 (dd, J_1 = 3.5 Hz, J_2 = 2.2 Hz, 1H), 2.65 (AB system partly merged with another signal, J_{AB} = 19.9 Hz, 2H), 2.60−2.53 (m, 1H), 2.42−2.35 (m, 3H), 2.34−2.18 (m, 4H), 2.12−2.00 (m, 2H), 1.49−1.42 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.5, 208.8, 204.5, 64.7, 47.9, 46.3, 43.8, 41.2, 36.3, 36.0, 30.5, 29.2, 28.0. HRMS (ESI) (m/z): found 241.0843 $(M + Na)^+$, calcd for $C_{13}H_{14}NaO_3$ 241.0835.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00728.

^{1}H, ^{13}C NMR spectra of all compounds and crystal structure and data of compound **10** (PDF)

X-ray crystallographic data for **10** (CIF)

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Notes

The authors declare no competing financial interest.

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