Four-Step Total Synthesis of (+)-Yaoshanenolides A and B
Sagar S. Thorat,†‡ Megha N. Palange,†‡ and Ravindar Kontham*†‡

†Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India
‡Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India

Supporting Information

ABSTRACT: A highly concise bioinspired four-step total synthesis of yaoshanenolides A and B possessing tricyclic spirolactone with an unusual 5′H-spiro-[bicyclo[2.2.2]-oct[2]ene-7,2′-furan]-5′-one scaffold is reported. This synthesis features high-yielding aldol-type addition of γ-butyrolactone on to the aldehyde, exocyclic olefination of lactone derivative using Eschenmoser’s salt, and highly facial- and endo-selective [4 + 2]-cycloaddition of fully functionalized 3-methylene-2(SH)-furanone with natural R-(−)-α-phellandrene. The approach allows access to yaoshanenolides A and B in four linear steps in 11 and 13% overall yield.

INTRODUCTION

Natural products have been an exceptional source of small molecules for drug discovery. In the human history, plants and animal-derived natural products have found direct applications in almost all traditional medical preparations. In modern drug discovery, they are continuously entering clinical trials and also have provided leads for new drugs.‡ However, a unique problem associated with the development of natural-product-based drugs are the difficulty to access sufficient quantities of compounds required for comprehensive biochemical investigations and marketing purposes. This is because of the isolation of the natural product in limited quantities and also the stereochemical complexity of their chemical structures that make their synthesis challenging.‡ Hence, there is a need to develop short and high-yielding practical synthetic routes, either with existing or through the development of new chemical technologies.‡ In our journey with the above perspective and inspired by interesting structural features and anticancer activities of yaoshanenolides A (1) and B (2), we have developed the shortest route for their synthesis.

Recently, in the year 2012, Lin and Shi’s group isolated two novel tricyclic spirolactones yaoshanenolides A (1) and B (2) possessing unprecedented 5′H-spiro-[bicyclo[2.2.2]-oct[2]ene-7,2′-furan]-5′-one scaffold and homologous alkyl side chain from the stem bark of Machilus yaoshanensis.§ Several plants of this genus (Lauraceae family) have been known to produce arrays of secondary metabolites with significant biological profiles and have been extensively used as traditional folk medicine in China.§ In addition to this ethnic usage of the plant, compounds 1 and 2 showed significant cytotoxic activities against several human cancer cell lines (A549) with IC_{50} values of 5.1–6.6 μM.§ The relative stereochemistry of yaoshanenolides A and B (8 and 9, proposed structures) was tentatively established based on 2D NMR analysis, and the (S) absolute stereochemistry of the secondary hydroxyl functionality was deduced using the bulkiness rule for the Rh₂(OCOCF₃)₄-induced circular dichroism analysis. In addition, they proposed a biosynthetic pathway, comprising the Diels–Alder reaction of suitable obtusilactones (3–6) and unnatural α-(+)-phellandrene (7) to afford both natural products (8 and 9), among which the structure of the compound 9 was revised recently (vide infra) (Scheme 1).§

Soon after the isolation, Singh research group accomplished the tricyclic spirolactone core of yaoshanenolides in a 10-step linear synthesis, using their in-house protocol of cycloaddition of reactive spiroepoxycyclohexa-2,4-diene with ethyl acrylate.⁵ In 2016, Stratakis’s group reported a highly expedient first total synthesis and structural revision of (+)-yaoshanolide B (2) via the Diels–Alder reaction between R-(−)-α-phellandrene and 5-methylene-2(SH)-furanone derivative in 8 steps and 6.2% overall yield.⁶

RESULTS AND DISCUSSION

As described in the retrosynthetic analysis in Scheme 2, we have designed two unified approaches to access both natural products 1 and 2. In the first approach, we envisioned that 1 and 2 could be accessed from tricyclic spirolactone 10 via Morita–Baylis–Hillman coupling with a suitable commercially available aldehyde. The lactone 10 could be readily prepared through the Diels–Alder reaction between known 5-methylene-2(SH)-furanone (protanemomin) (11) and R-(−)-α-phellandrene (12). The oxidation of 2-methylfuran (13) followed by
dehydration could deliver the desired dienophile 11. In contrast, the second approach uses the fully functionalized 5-methylene-2(5H)-furanone derivative (±)-14 as the dienophile, which would be obtained from commercially available γ-butyrolactone (15) (Scheme 2).

Our first approach to (+)-yaoshanenolide B (2) is outlined in Scheme 3. Oxidation of 2-methylfuran (13) using Pinnick’s conditions (NaClO₂ and NaH₂PO₄) gave 5-hydroxy-5-methyl-2(5H)-one (16), which was immediately subjected to P₂O₅-mediated dehydration reaction to furnish 5-methylene-2(5H)-furanone (11) in 71% yield (for two steps). Next, the Diels–Alder cycloaddition between dienophile 11 and natural R-(−)-α-phellandrene (7) under known reaction conditions of toluene, 110 °C for 12 h, afforded tricyclic spirolactone adducts 10a (endo, less polar) and 10b (exo, more polar) together with negligible quantities of their regio-isomers. Even though this transformation was reported earlier, no clear analytical data were available to establish the structures of 10a and 10b. Hence, we carried out a systematic 2D NMR (COSY, HMBC, HSQC, and NOESY) analysis of these two compounds. The HSQC data established all J₁H⁻⁻¹C connectivities; the remaining skeletal connectivities were confirmed particularly by COSY and HMBC data (Figure 1). The complete stereochemistry of 10a and 10b was established by the examination of their NOESY data and the known absolute configuration of 12. In the case of adduct 10a, strong nuclear Overhauser effect (NOE) correlations of H-6 with H-1/H-9/H₃-10/H₃-12/H-3’ and H-1 with H-3’/H-6 confirmed the endo- and 1R,2R,4R,7R stereochemistry. In the case of adduct 10b, correlations of H-5 with H-4/H₃-12/H-9/H₃-11, H-1 with H-7, and H-3’ with H-8 confirmed its exo- and 1S,2R,4R,8R stereochemistry (Figure 1). After establishing the structures of both adducts 10a and 10b, we turned our attention to executing the final Morita–Baylis–Hillman coupling between endo-adduct 10a and 1-dodecanal (17), which was expected to furnish the desired natural product 2 and its C1″-epimer 2a. Unfortunately, this coupling reaction using several reported procedures (DABCO; TMEDA, MgI₂; TEA; DMAP; LiClO₄, DABCO; imidazole; TiCl₄ or n-Bu₂BOTf) proved to be insurmountable, and in all cases, the starting adduct 10a remained unreactive and fully recovered (Table S1). In addition to this, we planned a roundabout process (Scheme 3), where the α,β-unsaturated double bond in lactone segment of 10a was selectively reduced using Mg–
MeOH\textsuperscript{11} to give the corresponding tricyclic spirolactone, which was subsequently converted into diastereomeric \(\alpha\)-phenylselanyl derivative (18 and 18a). Then, the generation of lithium enolate of lactone 18 or 18a using LDA followed by its addition to the aldehyde 17 was unsuccessful and led to the decomposition. Thus, we have abandoned this strategy and proceeded to the second approach (Scheme 3).

In our second approach, first, the total synthesis of (+)-yaoshanenolide B (2) was planned, which would allow us to compare and confirm the stereochemical outcome with respect to its proposed\textsuperscript{3} and revised\textsuperscript{6} structures. Thus, racemic dienophile 14a was prepared from \(\gamma\)-butyrolactone (15) in three steps (by a modification of Queneau’s procedure\textsuperscript{13}). LiHMDS- and TMSCl-mediated phenylselenation of 15 gave the \(\alpha\)-phenylselanyl intermediate 19 in 79% yield. The addition of lithium enolate of 19 onto the 1-dodecanal (17), followed by immediate oxidative elimination of phenyl selenenic acid using \(\text{H}_2\text{O}_2\), delivered the hydroxy-alkyl tethered \(\alpha\)-\(\beta\)-unsaturated lactone 21 in 81% yield.\textsuperscript{12} Then, exocyclic olefination of 21 using LDA and Eschenmoser’s salt gave the desired dienophile 14a in 52% yield.\textsuperscript{13} On the basis of the earlier report,\textsuperscript{3} the \([4 + 2]\)-cycloaddition reaction between fully functionalized dienophile 14a and \(R\)-(--)-\(\alpha\)-phellandrene (12) was expected to be challenging because of the labile hydroxyl group in 14a (Scheme 4).

Hence, we were inquisitive to verify the feasibility of this transformation. To our delight, this key cycloaddition between 14a and 12 in toluene at 110 °C for 20 h furnished (+)-yaoshanenolide-B (2, more polar) and its \(C_1''\)-epimer 2a (less polar) in 1:1 ratio with high facial and regio-selectivity in a good yield of 75%. To our surprise, respective exo-isomers (2' and 2a') were detected in small amounts (in \(\sim\)93:7 endo/exo ratio), and we did not observe any other products among a total of 16 isomers (from two diastereotopic faces of the \((\pm)-14\) (dienophile) and the unsymmetrical diene (12) each) possible in this reaction (Scheme 4). Utilizing the same strategy (+)-yaoshanenolide A (1, more polar) and its \(C_1''\)-epimer 1a (less polar) in 1:1 ratio was accomplished for the first time using
1-tetradecanal (20) in step 2 (19 → 22 → 14b → 1 and 1a; Schemes 4 and 5). Even after much effort, we were unable to designate exo isomers of yaoshanenolides A and B (2′ and 2a′) through NMR analyses, which could be due to their presence in lower quantities. Hence, we have prepared authentic samples using Stratakis’s protocol of Diels–Alder reaction between acetate-protected dienophile 14a′ and R-(-)-α-phellandrene (12) followed by acetate deprotection and assigned endo/exo ratios based on reported results and analogy (through careful 1H NMR analyses, see the Supporting Information for details).

Even though compounds 1, 1a, 2, and 2a were clearly separable by silica gel column chromatography and the specific rotation data of 1, 2, and 2a are very close to reported values, we were unable to completely assign their structures at this stage because of their indistinguishable 1H and 13C NMR spectral data. Hence, we established structures through 2D NMR analysis (COSY, HSQC, and HMBC). The NOESY analysis of 1, 2, 1a, and 2a showed a similar correlation of H-3′ with H-1/ H-6, H-1 with H-6/H-7/H-9/H-1′, and H-6 with H-12/H-9/H-1′, which confirmed their endo-stereochemistry. In addition, the absolute stereochemistry of the secondary hydroxyl functionality was assigned through the synthesis of corresponding MPA esters using (S)-MPA and compared relative proton chemical shifts with that of reported data. On the basis of the above analysis and known absolute stereochemistry of 12, complete structures of both natural products yaoshanenolide A ((1R,2S,4R,7R,1′S)-1) and B ((1R,2S,4R,7R,1′S)-2) and their C1′-epimers ((1R,2S,4R,7R,1′R)-1a and (1R,2S,4R,7R,1′R)-2a) were established (Figure 2 and Scheme 6).

To understand and rationalize this remarkable face and regioselectivity, we have drawn four most prominent transition states using the (S)-enantiomer of the dienophile 14a that is approaching the less hindered face of the (R)-α-phellandrene (12) among a total of eight possible transition states (Scheme 7). The Re or Si face of the exocyclic double bond of the dienophile (S)-14a approaching the less hindered face of the diene (12) in an endo fashion provides two transition states (TS-A and TS-B); in a similar fashion providing two more exo-transition states is also possible (TS-C and TS-D). In addition to these four transition states, two exo and two endo transition states can arise through the approach of the dienophile (S)-14a toward the more hindered face of the diene 12, these transition states could be highly energetic due to the unfavorable severe steric interactions between isopropyl group of the diene 12 and dienophile (S)-14a; hence, we have excluded those transition states in this discussion. In the case of TS-A, the less hindered face of the (R)-α-phellandrene (12) approaches the Si face of the double bond of the dienophile (S)-14a in an endo fashion, which leads to the formation of corresponding natural product (+)-yaoshanenolide B (2). Another possible endo transition state (TS-B) involving the Re face of the double bond of the dienophile (S)-14a develops significant steric interactions between the vinylic methyl group of diene 12 and the hydroxyl functionality of the dienophile (S)-14a (Scheme 7).

In other possible two exo approaches with any facial orientation of the dienophile (S)-14a (either Si or Re face), molecular models revealed that no significant steric interactions develop between the isopropyl group of the (R)-α-phellandrene (12) and dienophile (S)-14a; this observation is in contrast with that of Stratakis’s report (Scheme 7). In spite of negligible steric...
interactions in the case of exo transition states (TS-C and TS-D), TS-C gave corresponding exo adduct 2′ as a minor product, whereas TS-D failed to furnish the corresponding exo adducts 2c. Among two possible endo adducts 2 and 2b via TS-A and TS-B, respectively, adduct 2 only formed via TS-A and TS-B failed to deliver the adduct 2b because of steric interactions (Scheme 7).

To further understand the observed endo selectivity, we compared the stereochemical outcome of the Diels–Alder reaction of dienophiles 11, 14a′, and 14a with diene 12 through TS-A and TS-C (Scheme 8). The unsubstituted dienophile 11 furnished almost equal amounts of endo and exo adducts 10a and 10b (eq 1), whereas the dienophile 14a′ (possessing acetate derived alkyl chain), which was used in Stratakis’s work, gave endo and exo adducts in 3:1 ratio (eq 2). In contrast to these results, dienophile 14a possessing free hydroxy tethered alkyl chain furnished the endo (2) and exo (2′) adducts in ~93:7 ratio (eq 3). On the basis of these observations, we assume that the endo-rule is governing the stereochemical outcome and also there is an inherent role of the side chain with the free hydroxyl group in stabilizing the endo transition state (TS-A). However, the establishment of the precise reaction pathway requires further mechanistic investigations.

## CONCLUSION

In summary, (+)-yaoshanenolides A and B were prepared in four linear steps from commercially available and affordable starting materials with remarkable face- and endo-selectivity, and an overall yield of 11 and 13%, a marked improvement over existing synthesis. The absolute stereochemistry of (+)-yaoshanenolides A and B and their epimers and the Diels–Alder product of protoanemonin and R-(-)-α-phellandrene were established by extensive NMR analysis. This highly concise and efficient route enables the synthesis of yaoshanenolides and their analogs in good quantities and provides a means to further investigate the biological profile. Our studies in this direction are in progress and will be published in due course.

## EXPERIMENTAL SECTION

### General Information

All reactions were performed under an argon atmosphere with oven (80 °C) or flame-dried glassware with septum seal. Tetrahydrofuran (THF) was distilled from sodium benzenophenone under argon atmosphere immediately prior to use. Anhydrous toluene and dichloromethane were purchased from commercial sources. Reaction temperatures are reported as the temperature of the bath surrounding the reaction vessel. Analytical thin-layer chromatography (TLC) was performed on TLC Silica gel 60 F254. Visualization was accomplished with shortwave UV light, anisaldehyde, or K2MnO4 staining solutions followed by heating. Chromatography was performed on silica gel (100–200 mesh) by standard techniques, and elution with solvents as indicated. 1H and 13C NMR spectra were recorded on Bruker AV 200, 400, and 500 in solvents as indicated. Chemical shifts (δ) are given in ppm. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl3: δ H = 7.27 ppm, δ C = 77.16 ppm), the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; td, triplet of doublet; and br, broad. HRMS data were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. Experimental procedures for all new compounds and known compounds without published experimental procedures are described below. Compounds that are not presented in the main text (manuscript) are numbered starting from S1.

### 5-Methylenefuran-2(5H)-one (11)

To a solution of 2-methylfuran (13) (1 g, 12.18 mmol) in t-BuOH (36 mL) and H2O (6 mL) was added monobasic sodium phosphate monohydrate (2.1 g, 18.27 mmol) followed by sodium chlorite (3.3 g, 36.54 mmol) at 0 °C and allowed it to reach room temperature (rt) slowly. (Caution: After a brief initiation period of 1–2 min, the reaction mixture turned into a bright yellow/orange color and began to be exothermic, hence to be allowed to reach rt very slowly in 2–3 h). The reaction mixture was then transferred to a separatory funnel, and the aqueous layer and salts were drained. The t-BuOH layer was then collected, concentrated under reduced pressure to afford 5-hydroxy-5-

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**Scheme 8. Comparison of the Endo Selectivity in Diels–Alder Reaction of (R)-α-Phellandrene (12) and Differently Substituted Dienophiles (11, 14a, 14a′) through TS-A (Endo, Si-Face)**
methylfuran-2(SH)-one (16) TLC: \( R_f = 0.65 \) (SiO\(_2\), 10% CH\(_2\)Cl\(_2\) / MeOH); the crude product is subjected to next step without further purification. A suspension of crude S-hydroxy-S-methylfuran-2(SH)-one (16) and P\(_2\)O\(_5\) (10.29 g, 36.27 mmol) in benzene (30 mL) was refluxed for 5 h. The mixture was filtered through Celite, and the residue was washed with benzene (2 x 20 mL). The organic layer was concentrated under vacuum and the obtained crude product was purified by silica gel column chromatography (SiO\(_2\), 8% EtOAc / hexanes) afforded S-methylfurfuran-2(SH)-one (11) (0.82 g, 71% for two steps) TLC: \( R_f = 0.8 \) (SiO\(_2\), 70% EtOAc / hexanes); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta = 7.41 \) (d, \( J = 5.7 \) Hz, 1H), 7.36 (benzene), 6.29–6.25 (m, 1H), 5.25 (t, \( J = 2.3 \) Hz, 1H), 4.93 (d, \( J = 2.7 \) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \( \delta = 169.8, 154.9, 143.4, 128.3 \) (benzene), 121.7, 98.2.

Diels–Alder Reaction between 11 and (R)-(-)-\( \alpha \)-Phellandrene (12): Synthesis of 10a and 10b. A mixture of S-methylfurfuran-2(SH)-one (11) (0.4 g, 4.16 mmol) and (R)-(-)-\( \alpha \)-phellandrene (-80%) (12) (1.8 g, 13.72 mmol) in 2 mL toluene was refluxed for 12 h. After complete consumption of 11, the solvent was removed under reduced pressure. The residue was carefully purified by silica gel column chromatography (SiO\(_2\), 2% EtOAc / hexanes) to afford the endo-10a (0.34 g, 35%) and exo-11a (0.34 g, 35%) isomers, along with trace amount of inseparable regio-isomer TLC: \( R_f = 0.3 \) and 0.2 (SiO\(_2\), 10% EtOAc / hexanes).

\(^{19}\)F NMR (CDCl\(_3\), 500 MHz): 6:7.18 (d, \( J = 5.7 \) Hz, 1H), 5.85 (d, \( J = 5.3 \) Hz, 1H), 5.62 (d, \( J = 6.5 \) Hz, 1H), 2.46–2.42 (m, 1H), 2.37 (dd, \( J = 6.5, 1.5 \) Hz, 1H), 2.01–1.94 (m, 1H), 1.87–1.82 (m, 1H), 1.78 (dd, \( J = 1.1 \) Hz, 1H), 1.71–1.6 (2M, 1H), 1.14–1.05 (m, 1H), 1.02–0.95 (m, 1H), 0.78 (d, \( J = 6.9 \) Hz, 3H), 0.76 (d, \( J = 6.9 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \( \delta = 173.2, 162.2, 145.4, 120.4, 118.2, 92.3, 43.3, 39.7, 36.3, 33.6, 32.8, 31.1, 20.9, 20.2, 19.9; IR (CHCl\(_3\), cm\(^{-1}\)): \( \nu = 2957, 2927, 2856, 2361, 2342, 1749\); HRMS (ESI) \( m/z \): calcd for C\(_{11}\)H\(_{12}\)O\(_2\)Na \([\text{M} + \text{Na}]^+\), 255.1356; found, 255.1356.

\(^{15}\)N NMR (CDCl\(_3\), 400 MHz): 6:7.58 (d, \( J = 5.5 \) Hz, 1H), 6.01 (d, \( J = 5.5 \) Hz, 1H), 5.78 (d, \( J = 5.5 \) Hz, 1H), 2.55–2.51 (m, 1H), 2.46–2.43 (m, 1H), 1.84 (s, 3H), 1.82–1.76 (m, 1H), 1.72–1.69 (m, 1H), 1.68–1.64 (m, 1H), 1.40–1.32 (m, 1H), 1.24–1.15 (m, 1H), 1.05–0.97 (m, 1H), 0.84 (d, \( J = 6.7 \) Hz, 3H), 0.82 (d, \( J = 6.7 \) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \( \delta = 172.6, 159.9, 143.2, 121.7, 120.3, 93.3, 43.5, 41.8, 36.9, 35.9, 32.8, 31.0, 21.0, 20.5, 20.0; IR (CHCl\(_3\), cm\(^{-1}\)): \( \nu = 2962, 2930, 2856, 2360, 2340, 1744\); HRMS (ESI) \( m/z \): calcd for C\(_{11}\)H\(_{12}\)O\(_2\)Na \([\text{M} + \text{Na}]^+\), 255.1356; found, 255.1355.

A mixture of (1R,2R,4R,7R)-7-isopropyl-5-methyl-3’-4’-dihydro-5’-H-spiro[bicyclo[2.2.2]octane-2,2’-furan]-5-en-5’-one (S1) was prepared using the reported procedure. \(^{1}H\) NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.68 \) (d, \( J = 7.3 \) Hz, 2H), 7.42–7.29 (m, 3H), 4.26 (td, \( J = 9.1, 4.3 \) Hz, 1H), 4.12 (q, \( J = 8.0 \) Hz, 1H), 3.93 (dd, \( J = 7.9, 4.3 \) Hz, 1H); 2.79–2.64 (m, 1H), 2.35–2.22 (m, 1H); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \( \delta = 172.7, 145.3, 120.5, 90.2, 43.6, 40.2, 39.0, 37.0, 36.7, 32.8, 31.2, 28.8, 21.0, 20.3, 19.8; HRMS (ESI) \( m/z \): calcd for C\(_{21}\)H\(_{27}\)O\(_2\)Se \([\text{M} + \text{H}]^+\), 393.1176; found, 393.1158.

3-(Phenylselanyl)dihydropyrane-2(3H)-one (19). A mixture of (1R,2R,4R,7R)-7-isopropyl-5-methyl-3’-4’-dihydro-5’-H-spiro[bicyclo[2.2.2]octane-2,2’-furan]-5-en-5’-one (10a) (0.41 g, 1.76 mmol) and magnesium turnings (0.42 g, 17.6 mmol, pre-dried in oven at 120 \( ^\circ \)C) in 6 mL of dry methanol, was refluxed for 6 h. The mixture was cooled to 5–10 \( ^\circ \)C, and ice-cold 2 N aqueous HCl was added carefully and diluted with EtOAc. The solution was stirred for 15 min and filtered through sintered funnel to remove solid inorganic waste; organic layer was then separated, dried over anhydrous Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO\(_2\), 4% EtOAc / hexanes) to afford the (1R,2S,4R,7R)-7-isopropyl-5-methyl-3’-4’-dihydro-5’-H-spiro[bicyclo[2.2.2]octane-2,2’-furan]-5-en-5’-one (S1) (0.312 g, 76%) TLC: \( R_f = 0.55 \) (SiO\(_2\), 20% EtOAc / hexanes).
101 MHz): δ 176.2, 135.9, 129.4, 129.2, 128.6, 67.0, 35.9, 30.6. HRMS (ESI) m/z: calcd for C_{10}H_{11}O_{2}Se [M + H]^{+}, 242.9925; found, 242.9923.

3-(1-Hydroxydodecyl)furan-2(5H)-one (21). To a solution of the 3-(phenylselenyl)dihydrofuran-2(3H)-one (19) (1.0 g, 4.15 mmol) in THF (15 mL) was added LHMSD solution (4.57 mL, 1.0 M in THF, 4.57 mmol) dropwise at −78 °C. After the reaction mixture was stirred for 1 h, 1-dodecanal (0.99 g, 5.42 mmol) in THF (5 mL) was added. After 20 min of stirring at −78 °C, the reaction was quenched by the addition of a saturated NH_{4}Cl solution (5 mL). The aqueous layer was washed with brine, dried over Na_{2}SO_{4}, and concentrated under reduced pressure (15 mL). The aqeous layer was extracted with diethyl ether (3 × 15 mL). The combined organic fractions were washed with brine, dried over Na_{2}SO_{4} and concentrated under reduced pressure to afford the crude aldol product, which was used directly for oxidative elimination of phenyl selenenic acid without further purification. To a solution of crude aldol product obtained above in THF/EtOAc (1:1 v/v, 78 ff), 0.88 mmol) in THF (5 mL) was added. After 20 min of stirring at −78 °C, the reaction was quenched by the addition of a saturated NH_{4}Cl solution (15 mL). The aqueous layer was washed with brine, dried over Na_{2}SO_{4}, and concentrated under reduced pressure (15 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic fractions were washed with brine, dried over Na_{2}SO_{4} and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO_{2} 40% EtOAc/hexanes) to give 3-(1-hydroxydodecyl)furan-2(5H)-one (21) (0.89 g, 81%) TLC: R_{f} = 0.6 (SiO_{2} 20% EtOAc/hexanes) and its C1′-epimer (2a) (0.162 g, 36%), TLC: R_{f} = 0.55 (SiO_{2} 20% EtOAc/hexanes).

Diels–Alder Reaction between Dienophile 14a and (R)-(-)-α-Phellandrene (12): Synthesis of 2 and 2a. A mixture of 3-(1-hydroxydodecyl)-5-methylenefuran-2(5H)-one (14a) (0.3 g, 1.07 mmol) and (R)-(-)-α-phellandrene (12) (∼80%, 0.65 g, 4.82 mmol) in 1.5 mL toluene was refluxed for 20 h. After complete consumption of the dienophile 14a, the solvent was removed under reduced pressure. The residue was carefully purified by silica gel column chromatography (SiO_{2} 2% EtOAc/hexanes) to afford (+)-yaoshanenolide B (2) (0.175 g, 39%), TLC: R_{f} = 0.6 (SiO_{2} 20% EtOAc/hexanes) and its C1′-epimer (2a) (0.162 g, 36%), TLC: R_{f} = 0.55 (SiO_{2} 20% EtOAc/hexanes).

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(m, 1H), 1.72−1.66 (m, 1H), 1.53 (dd, J = 13.7, 2.0 Hz, 1H), 1.34−1.2 (m, 19H), 1.09−1.03 (m, 1H), 0.97−0.93 (m, 1H), 0.89 (t, J = 6.8 Hz, 3H), 0.78 (d, J = 3.8 Hz, 3H), 0.77 (d, J = 6.3 Hz, 3H); 13C NMR (CDCl3, 126 MHz): δ 170.9, 169.3, 154.7, 145.0, 136.3, 130.0, 128.8, 128.5, 127.3, 120.2, 90.1, 82.1, 69.5, 57.3, 43.2, 39.7, 39.6, 33.6, 32.8, 32.7, 31.9, 30.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 25.1, 22.7, 20.9, 20.2, 20.1, 14.1; IR (CHCl3, cm−1): ν 2928, 2856, 2361, 2341, 1750; HRMS (ESI) m/z: calc for C39H53O12Na [M + Na]+, 587.3707; found, 587.3709.

(R)-1-(((R,25,4R,7R)-7-Isopropyl-5-methyl-5’-oxo-5’-H-spiro[bicyclo[2.2.2]octane-2,2’-furan]-5-en-4’-ylidene)-5-Methylene[1-((S)-1-Hydroxytetradecyl)-furan-2(5H)-one (22). To the lactone 19 (2.0 g, 8.2 mmol) in anhydrous THF (30 mL) was added LHMDS solution (9.12 mL, 1.0 M in THF, 9.12 mmol) dropwise at −78 °C under argon atmosphere, and then the mixture was continuously stirred for 1 h. Then, 1-tetradecan-14 (2.11 g, 9.95 mmol) in anhydrous THF (10 mL) was added dropwise. After 20 min of stirring at −78 °C, the reaction was quenched by the addition of a saturated aqueous NH4Cl solution (20 mL). Then, extracted with diethyl ether (3 × 15 mL) and the combined organic layers were washed with brine solution, dried over anhydrous Na2SO4, and concentrated to afford the crude lactone product, which was used directly for oxidative elimination step without further purification. To a solution of the above crude lactone product in THF and EtOAc (1:1 v/v, 50 mL) were sequentially added NaHCO3 (6.82 g, 81.2 mmol) and H2O2 (30 wt % in water, 3.2 mL). After 20 min of stirring at rt, the reaction mixture was quenched by the addition of saturated Na2SO4 solution (25 mL). The organic layer was collected, and the aqueous layer was further extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried over Na2SO4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (SiO2, 40% EtOAc/hexanes) afforded 3-(1-Hydroxytetradecyl)furan-2(5H)-one (22) (2.1 g, 78%) TLC: Rf = 0.2 (SiO2, 30% EtOAc/hexanes); 1H NMR (CDCl3, 500 MHz): δ 6.74−6.72 (m, 2H), 2.60−2.55 (m, 1H), 2.49−2.44 (m, 1H), 2.44 (dd, J = 6.7, 1.2 Hz, 2H), 2.08−1.96 (m, 1H), 1.93−1.86 (m, 1H), 1.83 (s, 3H), 1.74−1.66 (m, 4H), 1.30−1.23 (m, 2H), 1.16−1.11 (m, 1H), 1.06−1.0 (m, 1H), 0.89 (t, J = 6.7 Hz, 3H), 0.84 (d, J = 7.3 Hz, 3H), 0.82 (d, J = 7.3 Hz, 3H); 13C NMR (CDCl3, 101 MHz): δ 171.9, 152.3, 145.7, 132.9, 129.3, 97.5, 37.4, 37.3, 36.5, 33.5, 30.9, 29.8, 28.9, 26.5, 24.9, 22.0, 19.8, 19.4, 14.1; IR (CHCl3, cm−1): ν 2928, 2856, 2361, 2341, 1750; HRMS (ESI) m/z: calc for C29H48O3Na [M + Na]+, 467.3496; found, 467.3497.

Diels–Alder Reaction between Dienophile (14b) and (R)-α-Phellandrene (12). A mixture of 3-(1-hydroxytetradecyl)-5-methylenefuran-2(5H)-one (14b) (0.4 g, 1.3 mmol) and (R)-α-phellandrene (12) (~80%, 0.88 g, 6.5 mmol) in 2 mL toluene was refluxed for 20 h. After complete consumption of butenolide (14b), the solvent was removed under reduced pressure. The residue was carefully purified by silica gel column chromatography (SiO2, 2% EtOAc/hexanes) to afford (+)-α-yaochenanolide A (1a) (0.213 g, 37%), TLC: Rf = 0.55 (SiO2, 20% EtOAc/hexanes), and C-1’-epi-(+)-yaochenanolide A (1a) (0.202 g, 35%). TLC: Rf = 0.60 (SiO2, 20% EtOAc/hexanes).

1H NMR (CDCl3, 500 MHz): δ 6.94 (s, 1H), 5.67 (d, J = 6.1 Hz, 1H), 4.48−4.39 (m, 1H), 2.60−2.55 (m, 1H), 2.49−2.44 (m, 1H), 2.41 (dd, J = 6.7, 1.2 Hz, 2H), 2.08−1.96 (m, 1H), 1.93−1.86 (m, 1H), 1.83 (s, 3H), 1.74−1.66 (m, 4H), 1.30−1.23 (m, 2H), 1.16−1.11 (m, 1H), 1.06−1.0 (m, 1H), 0.89 (t, J = 6.7 Hz, 3H), 0.84 (d, J = 7.3 Hz, 3H), 0.82 (d, J = 7.3 Hz, 3H); 13C NMR (CDCl3, 101 MHz): δ 172.9, 152.4, 154.3, 132.9, 120.5, 90.7, 67.1, 43.4, 39.7, 36.4, 35.5, 33.8, 32.9, 31.9, 31.1, 29.67 (2C), 29.65 (2C), 29.58, 29.54, 29.37 (2C), 25.4, 22.7, 20.9, 20.2, 19.9, 14.1; HRMS (ESI) m/z: calc for C39H53O12Na [M + Na]+, 587.3707; found, 587.3709.
Diels–Alder Reaction among 14a and (R)-α-(−)-Phellandrene. A mixture of 1-(5-methylene-2-oxo-2,5-dihydrofuran-3-yl)dodecyl acetate 14a′ (0.04 g, 0.12 mmol) and (R)-α-(−)-phellandrene (12, ~85%) (0.07 g, 0.54 mmol) in 1 mL of toluene was refluxed for 20 h. After complete consumption of the dienophile 14a′, the solvent was removed under reduced pressure. Purification using silica gel column chromatography (SiO2, 2% EtOAc/hexanes) afforded the mixture of compounds (two spots showed on TLC, which are the mixtures with epimers and endo/endo isomers). These two spots were subjected to acetate hydrolysis using Stratagis’s reported method, purified by preparative TLC fractionation, and subjected to 1H NMR analysis, and the obtained data were utilized to identify the endo/endo ratio of this work.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00701.

Physical data; 1H and 13C spectra for all new compounds; and 2D NMR analysis spectral data for selected compounds (PDF).

AUTHOR INFORMATION

Corresponding Author
E-mail: k.ravindar@ncl.res.in (K.R.).

ORCID

Sagar S. Thorat: 0000-0003-1346-7837
Ravindar Komothan: 0000-0002-5837-2777

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are thankful to the SERB (Science and Engineering Research Board), New Delhi, India for the financial support (grant no. YSS/2015/000725). S.S.T. thanks CSIR-India for the award of Junior Research Fellowships (JRF). We thank the reviewers for their thoughtful comments and efforts toward improving our manuscript.

ADDITIONAL NOTE

See Supporting Information for details.

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