Synthetic Studies toward (±)-Furanocembranoid 1: Construction of the Acyclic Carbon Framework

Chada Raji Reddy*†‡ and Siddique Z. Mohammed†‡

*Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India
†Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India
‡Indian Academy of Sciences, Bangalore 560089, India

ABSTRACT: Herein, we report the synthesis of the entire acyclic carbon framework toward (±)-furanocembranoid 1 via the longest linear sequence of 12 steps from commercially available linalool and diethyl 2-isopropylmalonate. Key to the success of this synthetic approach is a silver-catalyzed enyne-annulation reaction for the formation of 2,4-disubstituted furan motif of unique furanocembranoid 1, isolated from Croton oblongifolius. Construction of macrocycle has also been explored using the ring-closing metathesis reaction.

INTRODUCTION

Furanocembranoids are an interesting class of 14-membered macrocycles embedded with a furan and a 5-membered lactone moiety possessing diverse biological activities. In all of these natural products, the macrocyclic framework is linked to C2 and C5 positions of the furan ring with C3 substitution. In 2007, a unique class of novel furanocembranoids 1−3 (Figure 1) was isolated from the stem bark of Croton oblongifolius, which contains the macrocyclic skeleton connected to C2 and C4 positions of furan without five-membered lactone. Their structures were determined on the basis of the NMR spectroscopy and mass spectrometry (MS) analyses. Furanocembranoid 1 (1a) and 3 (1c) displayed good cytotoxicity against human tumor cell lines such as BT474 (human breast ductal carcinoma), CHAGO (human undifferentiated lung carcinoma), Hep-G2 (human liver hepatocellular carcinoma), KATO-3 (human gastric carcinoma), and SW-620 (human colon adenocarcinoma). The distinctive feature of 1a, having C2–C4 linked bicyclic furan, provoked us to explore the synthesis of this molecule. To the best of our knowledge, the synthesis of furanocembranoid 1 remains unexplored to date.

Alkyne-assisted annulation reactions to deliver furan skeletons have been regarded as a powerful tool for the synthesis of natural products. Recently, we have also successfully explored the cycloisomerization of enynols for the synthesis of substituted furans. On this basis, we considered that cyclodehydration of enynediol could be a key step in the late-stage construction of the 2,4-disubstituted furan core of furanocembranoid 1. Scheme 1 outlines our retrosynthetic analysis of 1a. (±)-Furanocembranoid 1 might be derived by the ring-closing metathesis (RCM) reaction of furanyl diene 2. This was believed to result from the addition of alkene fragment 3 onto protected hydroxy ketone subunit 4. This alkene 3 might, in turn, be accessed from one of the most widely occurring natural products, (±)-linalool, and ketone 4 was planned to be obtained from the commercially available diethyl 2-isopropylmalonate.

RESULTS AND DISCUSSION

Our synthesis commenced with the protection of hydroxyl group of the natural linalool (5) to prepare tert-butyldimethylsilyl (TBDM) ether 7 (Scheme 2). In the presence of tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine, TBS-ether 7 was obtained in 95% yield. The thus formed 7 was subjected to allylic oxidation using SeO2 and tert-butylhydroperoxide in CH2Cl2 at room temperature (rt), which provided a mixture of aldehyde and alcohol. The mixture was reduced using LiAlH4 in tetrahydrofuran (THF) at 0 °C to afford the allylic alcohol in 67% yield in two steps. The alcohol 8 was then converted to iodide by treatment with I2 in the presence of N-BuLi to afford diene 9 in 87% yield. Liberation of the terminal acetylene using K2CO3 in MeOH then led to the key intermediate 3 in 85% yield.

The synthesis of ketone subunit 4 starting from the commercially available diethyl 2-isopropylmalonate (6) is described in Scheme 3. Compound 6 underwent sequential LiAlH4-mediated reduction, followed by selective silylation to generate monosilylated alcohol in 82% in two steps. Oxidation of this material using Dess-Martin periodinane (DMP) followed by one-carbon Wittig olefination (CH3PhP′Br−/BuOK) afforded terminal alkene 11 in 76% overall yield.
desilylation of 11 provided the homoallylic alcohol (volatile in nature), which was subsequently oxidized to aldehyde (volatile aldehyde was not isolated) using DMP in CH$_2$Cl$_2$, followed by treatment with $\beta$-ketophosphonate 13 in the presence of Ba(OH)$_2$·8H$_2$O in THF/H$_2$O to give enone 12 in 65% yield in three steps. Selective reduction of conjugated olefin using Stryker’s reagent to lutein offered the desired ketone fragment 4 in 95% yield. After acquiring both the fragments 3 and 4 in gram scale, we proceeded further toward the total synthesis of furanocembranoid 1. Thus, the alkynyl lithium anion, generated from alkyn 3 in the presence of $n$-BuLi, was added to ketone 4 to afford the propargylic alcohol 14 in 96% yield. Selective deprotection of primary tert-butylidemethylsilyl (TBDMS) group of 14 using TBAF in THF furnished the diol 15 in 90% yield. Much to our delight, AgNO$_3$-mediated enyne-assisted cyclization of the enyne diol 15 in CH$_2$Cl$_2$ at room temperature provided the desired dienyl-furan $E$-16a in 90% yield. With substantial amounts of $E$-16a in hand, we were in a position to test the crucial ring-closing metathesis (RCM) reaction. Disappointingly, all of the RCM reactions tried on $E$-16a using different catalysts, Grubb’s first-generation (G-I) and second-generation (G-II) catalysts and the Hoveyda–Grubbs catalysts, failed to give the product (starting material recovered). Herein, we reasoned that the failure of the RCM reaction might be due to steric hindrance posed by the TBDMS group of allylic tert-hydroxyl functionality and predicted that the free tert-hydroxyl group might allow the RCM reaction. Therefore, furan 16a was transformed to 2 using TBAF in THF at 60 °C. Unfortunately, 2 is also futile to provide the desired product (formation of a nonpolar unidentified mixture of products observed) under all of the
tested ring-closing metathesis reaction conditions with various catalysts (see Table S1). Disappointingly, the acetate precursor E-16b, prepared by acetylation of 2 by the action of Ac2O in pyridine, did not provide the corresponding macrocyclic derivative under the same conditions used for 2 (Scheme 4).

**CONCLUSIONS**

In summary, we have achieved the chemical synthesis of the complete acyclic carbon framework toward structurally intriguing (±)-furanocembranoid 1 in the longest linear sequence of 12 steps. The synthesis featured silver-catalyzed enyne-annulation reaction, which enabled rapid construction of 2,4-disubstituted furan skeleton. An extensive synthetic exploration directed toward the completion of the total synthesis based on ring-closing metathesis was ineffective to access the macrocycle, which represents synthetic challenges for future work. Notably, multigram quantities of 3, 4, and 16 are readily prepared through this approach, which is envisioned to serve as the foundation for the synthesis of furanocembranoid 1.

**General Information.** Reactions were monitored by thin-layer chromatography (TLC) on silica plates using UV light, anisaldehyde, and β-napthol for visualization. Column chromatography was performed on silica gel (60–120 mesh) using petroleum ether and ethyl acetate as eluents. 1H and 13C NMR spectra were recorded in CDCl3 solvent on 400 and 500 MHz spectrometers. Chemical shifts δ and coupling constants J are given in parts per million (ppm) and hertz (Hz), respectively. Chemical shifts are reported relative to residual solvent as an internal standard for 1H and 13C (CDCl3: δ 7.26 ppm for 1H, and 77.0 ppm). IR spectra were recorded as neat compound. Mass spectra were recorded on a micromass VG 70−70H or a liquid chromatography/mass selective detector trap SL spectrometer operating at 70 eV using direct inlet system. High-resolution mass spectrometry (HRMS) data were recorded by electrospray ionization (ESI) with a quad time-of-flight mass analyzer.

**Experimental Section.** tert-Butyl(3,7-dimethylocta-1,6-dien-3-yloxy)dimethylsilane (7). To a solution of linalool 5 (10 g, 64.9 mmol) in anhydrous dichloromethane (DCM, 100 mL), 2,6-lutidine (11.3 mL, 97.4 mmol) and TBSOTf (15.7 mL, 78 mmol) were added at 0 °C. The reaction mixture was stirred at the same temperature for 15 min and quenched by the addition of water (50 mL). The organic layer was separated, washed with water (20 mL) and brine (20 mL), and dried over Na2SO4. The solvent was evaporated under reduced pressure.

**Scheme 3. Synthesis of Ketone Subunit 4**

**Scheme 4. Synthesis of Furan Segment of 1a**
pressure to afford the crude product, which was purified by column chromatography using 0.5% ethyl acetate/hexane (v/v) to give pure silyl ether 7 (16.5 g) in 95% yield as a colorless oil. \( R_t = 0.9 \) (hexane/ethyl acetate = 9:5.0:5); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 5.77 (dd, \( J = 17.3, 10.7 \) Hz, 1H), 5.10–4.98 (m, 2H), 4.93–4.88 (m, 1H), 2.03–1.80 (m, 2H), 1.60 (d, \( J = 1.1 \) Hz, 3H), 1.52 (s, 3H), 1.43–1.36 (m, 2H), 1.22 (s, 3H), 0.83–0.80 (m, 9H), 0.01 to –0.03 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 147.7, 131.1, 128.6, 113.6, 77.5, 71.1, 45.5, 29.5, 28.0, 27.8, 24.9, 20.4, 19.6, 0.0; IR (KBr): \( \nu_{\text{max}} = 2930, 2858, 1463, 1372, 1043, 774 \) cm\(^{-1}\).

(E)-6-(tert-Butyldimethylsilyloxy)-2,6-dimethylocta-2,7-dien-1-ol (8). To a solution of TBDMS-silyl ether 7 (11 g, 41.00 mmol) in \( \text{CH}_2\text{Cl}_2 \) (100 mL) at room temperature, t-BuO\( \text{O} \) (9.07 mL, 5 M in decane, 45.1 mmol) was added and stirred vigorously. Then, SeO\(_2\) (1.82 g, 16.42 mmol) was added portion-wise at 0 \( ^{\circ} \)C until all of the solids dissolved. The mixture was again brought to room temperature. The mixture was stirred for 5 h and then for 20 min at -10 \( ^{\circ} \)C. Then, the reaction mixture was quenched with saturated aq sodium thiosulfate (3 \( \times 15 \) mL) and then with \( \text{EtOAc} \) (75 mL) and the separated organic layer was dried over Na\(_2\)SO\(_4\) and concentrated. To this crude product, which was filtered through a pad of celite and the solvent was removed by evaporation under reduced pressure. The residue was extracted with pentane (40 mL), washed with \( \text{NaOH} \) (20 mL), and the organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography \((\text{EtOAc/hexane } = 4:1)\) to give allylic alcohol 8 as a colorless liquid. \( R_t = 0.2 \) (hexane/ethyl acetate = 9:1) \((7.8 \) g, 38.02 mmol, 2 equiv) was added in four equal portions over 30 min. Then, 

isopropylmalonate \((10 \) g, 49.5 mmol) in dry THF (50 mL) was added dropwise, and the mixture was stirred at 0 \( ^{\circ} \)C until all of the solids dissolved to give a clear colorless solution \((-5 \) min). Then, iodine \((9.65 \) g, 38.02 mmol, 2 equiv) was added in four equal portions over 20 min. The resulting dark orange mixture was stirred at 0 \( ^{\circ} \)C for 15 min. The reaction mixture was diluted with pentane (30 mL), and the organic layer was washed with three portions of saturated aq sodium thiosulfate \((3 \times 15 \) mL) and then with two 15 mL portions of saturated aq copper (II) sulfate. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford crude iodide as yellow oil. To the solution of trimethylsilylacetylene \((3.1 \) g, 31.68 mmol) in THF \((5 \) mL) at \(-40^{\circ} \)C, n-BuLi \((2.5 \) M in \( \text{n-hexane} \), 12.67 mL, 31.68 mmol) was added and the reaction mixture was stirred at the same temperature for 15 min and then for 20 min at \(-10^{\circ} \)C. Then, the reaction mixture was again brought to \(-40^{\circ} \)C and the above-prepared iodide was added to the reaction mixture, gradually warmed to rt, and stirred for 12 h. After completion of the reaction (monitored by TLC), saturated aq NH\(_4\)Cl was added and the mixture was extracted with pentane. The organic extract was evaporated under reduced pressure to give crude product, which was purified by SiO\(_2\) column chromatography \((\text{pentane/} \text{Et}_2\text{O } = 10:1)\) to give tetraremethyloxiane-alkyne \(9 \) (5.70 g, 16.5 mmol) in methanol \((40 \) mL), potassium carbonate \((5.4 \) g, 39.15 mmol) was added and the resulting mixture was stirred for 5 h at room temperature. After completion of the reaction, the reaction mixture was filtered through a pad of celite and the solvent was removed by evaporation under reduced pressure. The residue was extracted with pentane \((40 \) mL), washed with \( \text{water} \) \((20 \) mL), and the organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by column chromatography \((\text{silica gel, Et}_2\text{O/} \text{hexane } = 1:1)\) to afford compound 3 as a colorless oil \((3.87 \) g, 85% yield). \( R_t = 0.9 \) (hexane/ethyl acetate = 9:5.0:5); \(^1\)H NMR \((400 \) MHz, CDCl\(_3\)): \( \delta \) 5.77 (dd, \( J = 17.3, 10.7 \) Hz, 1H), 5.15 (s, 3H), 5.04–4.93 (m, 1H), 2.90 (s, 2H), 2.15–1.93 (m, 2H), 1.66 (d, \( J = 6.9 \) Hz, 3H), 1.53–1.46 (m, 2H), 1.30 (d, \( J = 3.3 \) Hz, 3H), 0.94–0.84 (m, 9H), 0.17–0.15 (m, 9H), 0.07 (d, \( J = 5.2 \) Hz, 6H); \(^{13}\)C NMR \((100 \) MHz, CDCl\(_3\)): \( \delta \) 145.5, 129.2, 126.1, 111.5, 104.6, 86.5, 75.3, 43.3, 29.8, 27.4, 25.8, 22.6, 18.2, 15.8, 0.0, -2.2; IR (KBr): \( \nu_{\text{max}} = 2928, 2857, 1463, 1372, 1042, 872, 682 \) \text{cm}\(^{-1}\).
1-(tert-Butyldimethylsilyloxy)-5-isopropyleth-6-en-2-one (4). A solution of enone 12 (2.6 g, 9.22 mmol) in dry degassed toluene (30 mL) was transferred via a syringe to a flask containing Stryker’s reagent (5.42 g, 2.78 mmol; transferred into the flask inside a glovebox). The resulting orange-brown solution was stirred for 1 h at room temperature. The reaction mixture was exposed to air, few drops of water were added, and stirring was continued for 1 h. The crude mixture was filtered through a pad of celite utilizing Et2O as eluent. The solvent was removed under reduced pressure, followed by purification via flash column chromatography (SiO2, hexane/EtOAc = 95:5) to afford ketone 4 (2.49 g, 95%) as a clear oil. Rf = 0.5 (hexane/EtOAc = 9:1); 1H NMR (400 MHz, CDCl3); δ 5.42 (d, J = 17.1, 10.2, 9.4 Hz, 1H), 5.00–4.79 (m, 2H), 4.14 (s, 2H), 2.51–2.22 (m, 2H), 1.78–1.59 (m, 2H), 1.52–1.33 (m, 2H), 0.91–0.72 (m, 15H), 0.17 (s, 6H); 13C NMR (100 MHz, CDCl3); δ 211.4, 140.2, 116.1, 69.4, 50.6, 36.7, 31.8, 25.8, 25.2, 20.6, 19.1, 18.3, −5.5; IR (KBr): υ max = 2954, 2863, 1726, 1436, 1105, 1012, 844, 699 cm−1; MS (ESI): m/z calcd for C16H30O2SiNa (M + Na)+: 307.2069, found: 307.2071.

Dimethyl 3-(tert-Butyldimethylsilyloxy)-2-oxopropylphosphonate (13).10 n-BuLi (9.41 mL of a 2.5 M solution in hexane, 23.52 mmol) was added to a solution of methyl dimethylphosphonate (2.92 g, 23.52 mmol) in anhydrous THF (30 mL) at −78 °C and stirring was continued for 30 min. Methyl glycolate TBS ether (4.00 g, 19.6 mmol) in THF (10 mL) was added to the above reaction mixture. After 1 h, the reaction mixture was quenched with aq NH4Cl (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na2SO4), partially concentrated in vacuo, and the crude residue was purified by flash chromatography on silica gel (EtOAc/hexane = 1:1) to give ketophosphonate 13 colorless oil (3.84 g, 66.19%). Rf = 0.5 (EtOAc/hexane = 2:1); 1H NMR (400 MHz, CDCl3); δ 4.17 (s, 2H), 3.72 (m, 2H), 2.51 (dd, J = 15.8, 8.1 Hz, 1H), 1.82 (m, 15H), 0.04 to 0.03 (m, 6H); MS (ESI): m/z calcd for C16H32O2SiNa (M + Na)+: 297.2092, found: 297.2092.

(1) 1H NMR (500 MHz, CDCl3): δ 7.89 (s, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 5.42 (d, J = 10.7, 5.0 Hz, 1H), 5.39 (dd, J = 10.7, 10.3 Hz, 1H), 5.00 (d, J = 10.7 Hz, 1H), 4.97 (d, J = 10.7 Hz, 1H), 4.33–4.30 (m, 8H), 3.70 (t, J = 8.1 Hz, 2H), 3.04 (d, J = 8.1 Hz, 2H), 2.88–2.74 (m, 2H), 2.67 (t, J = 10.7 Hz, 1H), 2.14–2.02 (m, 15H), 0.04 to 0.03 (m, 6H); MS (ESI): m/z calcd for C16H32O2SiNa (M + Na)+: 307.2069, found: 307.2071.

(2) 1H NMR (400 MHz, CDCl3): δ 7.59 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 5.44 (d, J = 8.1 Hz, 2H), 5.36 (dd, J = 10.7, 10.3 Hz, 1H), 5.00 (d, J = 10.7 Hz, 1H), 4.97 (d, J = 10.7 Hz, 1H), 4.33–4.30 (m, 8H), 3.70 (t, J = 8.1 Hz, 2H), 3.57 (t, J = 8.1 Hz, 2H), 3.04 (d, J = 8.1 Hz, 2H), 2.88–2.74 (m, 2H), 2.67 (t, J = 10.7 Hz, 1H), 2.14–2.02 (m, 15H), 0.04 to 0.03 (m, 6H); MS (ESI): m/z calcd for C16H32O2SiNa (M + Na)+: 307.2069, found: 307.2071.
ACS Omega

Article

2H), 1.72−1.51 (m, 7H), 1.45−1.32 (m, 4H), 1.26−1.18 (m, 3H), 0.84−0.76 (m, 24H), 0.06 to −0.10 (m, 12H). 13C NMR (100 MHz, CDCl3): δ 145.5, 140.7, 129.6, 126.0, 115.5, 111.7, 83.3, 82.4, 75.4, 71.4, 71.2, 70.1, 50.9, 43.5, 36.5, 36.4, 31.7, 31.6, 28.8, 27.3, 26.4, 26.3, 25.9, 25.8, 22.7, 20.6, 18.9, 18.3, 15.9, −2.0, −5.3, −5.4; IR (KBr): vmax = 2956, 2863, 1467, 1255, 1117, 1046, 842, 777 cm−1; MS (ESI): m/z 599 (M + Na)+; HRMS (ESI): m/z calcd for C34H64O3SiNa (M + Na)+: 599.4292, found: 599.4287.

(E)-10-(tert-Butyldimethylsiloxy)-2-(3-isopropylpent-4-enyl)-6,10-dimethyldodeca-6,11-dien-3-yn-1,2-diol (15). To a solution of 14 (4.3 g, 7.25 mmol) in THF (40 mL), TBAF (1.0 M in THF, 8.94 mL, 8.94 mmol) was added and stirred for 2.5 h. The reaction mixture was quenched withaq NH4Cl solution (20 mL) and extracted with EtOAc (3 × 10 mL). The solvent was evaporated under reduced pressure and purified by SiO2 column (EtOAc/hexane = 1:9) to give 15 (3.09 g, 90%) as a colorless oil. Rf = 0.5 (hexane/ethyl acetate = 2:1); 1H NMR (500 MHz, CDCl3): δ 5.76 (dd, J = 15.5, 10.7, 9.3 Hz, 1H), 5.47 (dddd, J = 17.1, 10.2, 9.3, 4.6 Hz, 1H), 5.27 (td, J = 7.3, 1.3 Hz, 1H), 5.07 (dd, J = 17.3, 1.6 Hz, 1H), 4.97−4.84 (m, 3H), 3.55 (dd, J = 11.0, 1.0 Hz, 1H), 3.41 (s, 1H), 2.81 (s, 2H), 2.43 (d, J = 9.3 Hz, 1H), 2.06−1.85 (m, 3H), 1.73−1.48 (m, 7H), 1.43−1.35 (m, 4H), 1.23 (s, 3H), 0.83−0.80 (m, 12H), 0.77 (dd, J = 6.8, 1.4 Hz, 3H), 0.02 to −0.04 (m, 4H, 6H); 13C NMR (100 MHz, CDCl3): δ 145.5, 140.47, 129.3, 126.3, 115.8, 111.7, 83.9, 82.7, 82.7, 75.4, 72.1, 72.0, 70.1, 70.0, 50.7, 43.5, 36.2, 36.1, 31.7, 28.7, 27.4, 26.3, 25.9, 22.7, 20.6, 18.9, 18.8, 18.3, 15.9, −2.1 (IR, KBr) (vmax = 3480, 2928, 2860, 1732, 1464, 1255, 1046, 775 cm−1; MS (ESI): m/z 485 (M + Na)+; HRMS (ESI): m/z calcd for C38H64O3SiNa (M + Na)+: 485.3427, found: 485.3427.

(E)-8-(4-(3-Isopropylpent-4-enyl)furan-2-yl)-3,7-dimethyl-octa-1,6-dien-3-yl acetate (16b). To a solution of alcohol 2 (30 mg, 0.09 mmol) in pyridine (1 mL), 4-dimethylaminopyridine (13 mg, 0.11 mmol) and acetic anhydride (11 μL, 0.11 mmol) were added and stirring was continued for 48 h at 60 °C. The mixture was poured into water. The aqueous mixture was extracted with EtOAc, and the combined organic layers were washed with saturated aqueous CuSO4 solution, water, and brine. The organic layer was dried with Na2SO4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with EtOAc/hexane (9:5) to give acetate (24 mg, 72%). Rf = 0.6 (hexane/ethyl acetate = 9:1); 1H NMR (500 MHz, CDCl3): δ 6.99 (d, J = 0.9 Hz, 1H), 5.91 (dt, J = 17.5, 7.3 Hz, 1H), 5.81 (s, 1H), 5.50 (dd, J = 17.1, 10.2, 9.4 Hz, 1H), 5.18−5.10 (m, 10H), 5.10−5.02 (m, 2H), 4.98 (dd, J = 10.2, 2.3 Hz, 1H), 4.88 (ddd, J = 17.1, 2.2, 0.6 Hz, 1H), 3.16 (d, J = 11.8 Hz, 2H), 2.37−2.27 (m, 1H), 2.20−2.10 (m, 1H), 1.99−1.90 (m, 1H), 1.86−1.77 (m, 1H), 1.78−1.66 (m, 2H), 1.61−1.51 (m, 5H, 14H), 1.43−1.32 (m, 1H, 0.81 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H); 13C NMR (100 MHz, CDCl3): δ 169.9, 154.1, 141.7, 140.5, 137.1, 132.3, 126.0, 125.9, 115.7, 113.7, 107.7, 82.8, 50.2, 39.6, 38.5, 32.0, 31.6, 23.5, 22.9, 22.4, 22.2, 20.6, 18.9, 15.8; IR (KBr): vmax = 2962, 2876, 1769, 1737, 1457, 1249, 1106, 906, 924 cm−1; MS (ESI): m/z 395 (M + Na)+; HRMS (ESI): m/z calcd for C22H34O2SiNa (M + Na)+: 395.2562, found: 395.2572.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02328.

Copies of 1H and 13C NMR spectra of all new compounds and explored RCN conditions (Table S1) (PDF)

AUTHOR INFORMATION

Corresponding Author

E-mail: raijreddy@iict.res.in.

ORCID

Chada Raji Reddy: 0000-0003-1491-7381

Notes

The authors declare no competing financial interest.
**ACKNOWLEDGMENTS**

S.Z.M. and C.R.R. acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi, for research fellowship and financial support as part of the 12th Five Year Plan Project under title ORIGIN (CSC-108) (IICT/Pubs./2018/044).

**REFERENCES**

(1) (a) Craig, R. A., II; Stoltz, B. M. Polycyclic furanobutenolide-derived cembranoid and norcembranoid natural products: Biosynthetic connections and synthetic efforts. *Chem. Rev.* 2017, 117, 7878–7909. (b) Li, Y.; Pattenden, G. Perspectives on the structural and biosynthetic interrelationships between oxygenated furanocembranoids and their polycyclic congeners found in corals. *Nat. Prod. Rep.* 2011, 28, 1269–1310. (2) Pudhom, K.; Vilaivan, T.; Ngamrojanavanich, N.; Dechangipart, S.; Sommit, D.; Petsom, A.; Roengsumran, S. Furanocembranoids from the Stem Bark of *Croton oblongifolius*. *J. Nat. Prod.* 2007, 70, 659–661. (3) (a) Li, Y.; Palframan, M. J.; Pattenden, G.; Winne, J. M. A strategy towards the synthesis of plumarellide based on biosynthesis speculation, featuring a transannular 4 + 2 type cyclisation from a cembranoid furanoxenonan ion intermediate. *Tetrahedron* 2014, 70, 7229–7240. (b) Persich, P.; Llaveria, J.; Ihermet, R.; Hao, T. D.; Stade, R.; Kondoh, A.; Fursten, A. Increasing the structural span of alkyl ketones. *Chem. – Eur. J.* 2013, 19, 13047–13058. (c) Toró, A.; Deslongchamps, P. Furano transeanulate Diels-Alder approach to (+)-chatancin: An asymmetric total synthesis of (+)-anhydrochatancin. *J. Org. Chem.* 2003, 68, 6847–6852. (4) Guo, Y.; Quan, T.; Lu, Y.; Luo, T. Enantioselective total synthesis of (-)-wortmannin. *J. Am. Chem. Soc.* 2017, 139, 6815–6818. (5) For representative references for the enyne-assisted furan formation, see: (a) Hashmi, A. S. K.; Haffner, T.; Rudolph, M.; Rominger, F. Cyclization of 2-alkynylallyl alcohols to highly disubstituted furans via gold(I)-catalyzed double hydroamination or tandem heterocyclodehydration and tandem heterocyclodehydration—hydration of 3-ynes-1,2-diols and 1-amino-3-yn-2-ol derivatives. *J. Org. Chem.* 2013, 78, 4919–4928. (f) Egi, M.; Azechi, K.; Akai, S. Cationic gold(I)-mediated intramolecular cyclization of 3-alkyne-1,2-diols and 1-amino-3-alkyn-2-ols: A practical route to furans and pyrroles. *Org. Lett.* 2009, 11, 5002–5005. (9) Zhang, F.; Peng, L.; Zhang, T.; Mei, T.; Liu, H.; Li, Y. Total synthesis of (12)-isocembrine: A tactic for both diene construction and macrocycle formation. *Synth. Commun.* 2003, 33, 3761–3770. (10) Bates, R. W.; Lek, T. G. A synthesis of cyanidine A by intramolecular oxo-Michael addition. *Synthesis* 2014, 46, 1731–1738. (11) Fukui, Y.; Brückner, A. M.; Shin, Y.; Balachandran, R.; Day, B. W.; Curran, D. P. Fluorous mixture synthesis of (−)-dicyostatin and three stereoisomers. *Org. Lett.* 2006, 8, 301–304. (12) For selected references, see: (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. A general model for selectivity in olefin cross metathesis. *J. Am. Chem. Soc.* 2003, 125, 11360–11370. (b) Grela, K. *Olef in Metathesis: Theory and Practice*, 1st ed.; John Wiley and Sons, Inc., 2014.

resolution of pyranones. *Angew. Chem., Int. Ed.* 2016, 55, 1820–1824. (b) Kalaizakis, D.; Noutsias, D.; Vassilikogiannakis, G. First total synthesis of pandamamine. *Org. Lett.* 2015, 17, 3596–3599. (c) Gryparis, C.; Lykakis, I. N.; Efè, C.; Zaravinos, L. P.; Vidalı, Y.; Kladou, E.; Stratakis, M. Functionalized 3(2H)-furanes via photooxygenation of (β-keto)-2-substituted furans: Application to the biosynthetic synthesis of *Metrekenetrene*. *Org. Biomol. Chem.* 2014, 12, 5655–5658. (d) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. A highly efficient access to spiroketals, monos-unsaturated spiroketal, and furans: Hg(II)-catalyzed cyclization of alkyl diols and triols. *Org. Lett.* 2011, 13, 3178–3181. (e) Yoshimura, F.; Sasaki, M.; Hattori, I.; Komatsu, K.; Sakai, M.; Tanino, K.; Miyashita, M. Synthetic studies of the zoanthamid alkaloids: The total syntheses of norzoanthamine and zozanthamine. *Chem.– Eur. J.* 2009, 15, 6626–6644. (f) For cyclization using other metals, see: (a) Gu, H.; Sun, X.; Wang, Y.; Wu, H.; Wu, P. Highly efficient mesoporous polymer supported phosphate-gold(I) complex catalysts for amination of allylic alcohols and intramolecular cyclization reactions. *RSC Adv.* 2018, 8, 1737–1743. (b) Paitoi, P. H.; Abboud, S. K. A.; Aponick, N. Incorporation of axial chirality into phosphino-imidazoline ligands for enantioselective catalysis. *ACS Catal.* 2017, 7, 2133–2138. (c) Iqbal, A.; Sahraoui, E. H.;eeper, F. J. Gold(I)-catalysed synthesis of a furan analogue of thiamine pyrophosphate. *Beilstein J. Org. Chem.* 2014, 10, 2580–2585. (d) Spina, R.; Colacino, E.; Martinez, J.; Lamaty, F. Poly(ethylene glycol) as a reaction matrix in platinum- or gold-catalyzed cycloisomerization: A mechanistic investigation. *Chem.– Eur. J.* 2013, 19, 3817–3821. (e) Gabriele, B.; Velti, L.; Plastina, P.; Mancuso, R.; Vetere, M. V.; Maltese, V. Copper-catalyzed synthesis of substituted furans and pyrroles by heterocyclodehydration and tandem heterocyclodehydration—hydration of 3-ynes-1,2-diols and 1-amino-3-yn-2-ol derivatives. *J. Org. Chem.* 2013, 78, 4919–4928.