JOC The Journal of Organic Chemistry

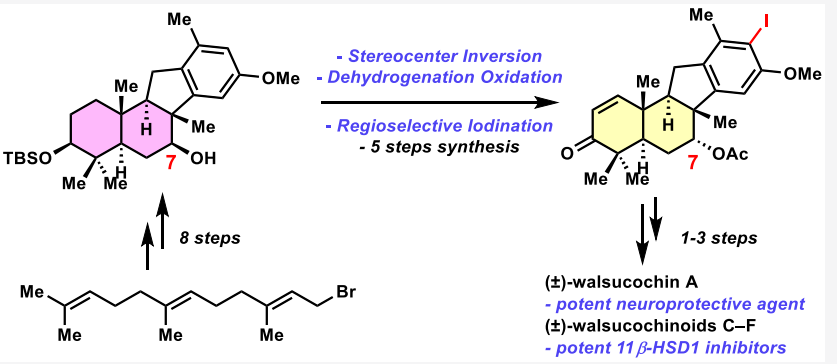
pubs.acs.org/joc Note

Divergent Entry to Walsucochin Nortriterpenoids: Total Syntheses of (±)-Walsucochin A and (±)-Walsucochinoids C−F

Danyang Zhang,‖ Dan Xu,‖ Xinyue Chen, Huan Zhou, and Gong Xu*

Cite This: https://doi.org/10.1021/acs.joc.1c00401 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Nortriterpenoids isolated from *Walsura cochinchinensis* have attracted much attention from both synthetic and medicinal chemists, yet only recently have efficient synthetic approaches to any members appeared. Shown here is that the common intermediate with a 6/6/5/6-fused tetracyclic ring nucleus can be converted to walsucochin family members. The first total syntheses of (±)-walsucochin A, (±)-walsucochinoids C−F, and their analogues were achieved in this work.

Nortriterpenoids are structurally and biologically important natural products, which have been isolated and shown various biological activities such as anti-HIV, antitumor, anti-inflammation, and antifeedant properties.[1−5] The *Walsura* genus (family Meliaceae), in particular has provided chemists with an abundance of structurally interesting and biologically attractive nortriterpenoids (Figure 1).[6−10] In 2008, Yue and co-workers reported two novel C_{24} nortriterpenoids, walsucochins A (**1**) and B (**2**), with significant neuroprotective activities from *Walsura cochinchinensis*.[10] In the search for inhibitors of 11β-HSD1, the same group further isolated walsucochinoids C−N (**3**−**14**) as novel limonoids with a rearranged skeleton from this genus. Of these compounds, walsucochinoids D (**4**) and E (**5**) displayed mild inhibitory activity against mouse and human 11β-HSD1 with IC_{50} values of 13.4 ± 1.7 μM and 8.25 ± 0.69 μM, respectively.[7] 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1), an enzyme responsible for the regulation of intracellular cortisol levels, has become an attractive therapeutic target for the treatment of a number of metabolic diseases like obesity, type 2 diabetes, and metabolic syndromes.[11−15]

Structurally, walsucochin nortriterpenoids possess a complex 6/6/5/6-fused tetracyclic ring skeleton, which has been found in other secondary metabolites, such as SHIP1-activating pelorol,[16−19] akaols,[20] and the antifungal dasyscyphins D and E.[21] Walsucochin nortriterpenoids feature a phenylacetylene or phenylfuran motif fused into the five-membered C ring, and different oxidation states in ring A/B. Typically, walsucochin A (**1**), walsucochinoids C, E−H (**3**, **5**−**8**) have a conjugated carbonyl moiety in ring A, and an equatorial H-7 in ring B (Figure 1).

Because of their significant biological properties and interesting structural features, walsucochin nortriterpenoids have attracted much attention from chemists, including our group. In 2014, the total synthesis of (−)-walsucochin B was accomplished by She and co-workers.[22] Their synthesis relies on a cationic polyolefin cyclization to construct the core framework and the stereocenters in the natural product, a late-stage free-radical halogenation, and Seyferth−Gilbert homologation to install the acetylene moiety (Scheme 1a). Very recently, we reported a concise total synthesis of nortriterpenoids including (±)-walsucochin B (**2**) and (±)-walsucochinoids M and N (**13**, **14**) via the intermediate **22**.[23] Key steps of our synthetic route are the radical cyclization and benzannulation for rapid construction of the 6/6/5/6-fused tetracyclic skeleton, a Cu-mediated C-H hydroxylation

Received: February 18, 2021

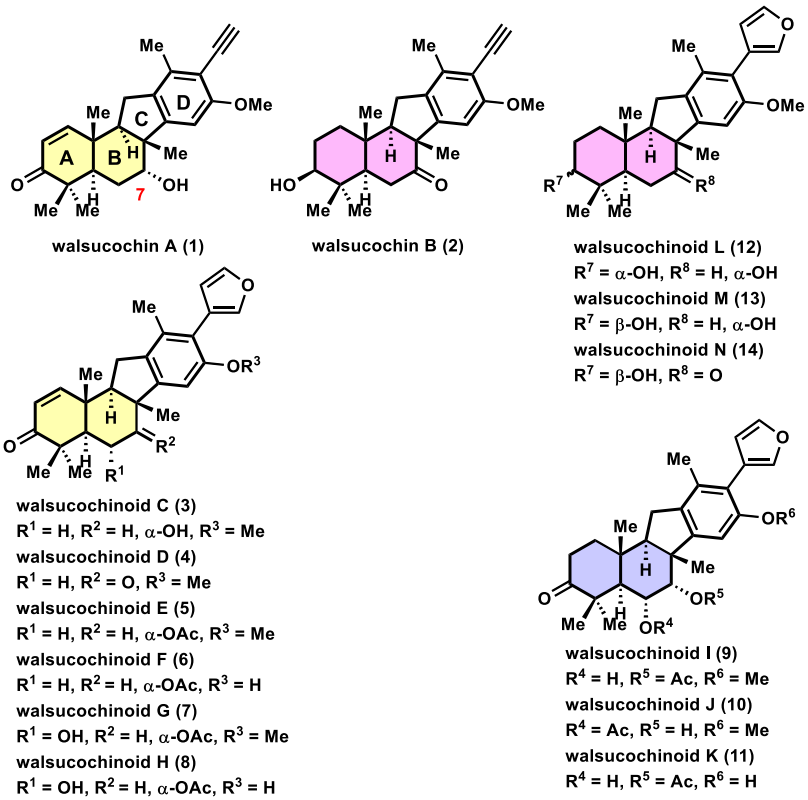


Figure 1. Walsucochin A and the related natural products from *Walsura cochinchinensis*.

reaction to site-selectively install the oxygen function at the C-7 position of the target molecules (Scheme 1b). We were keen to extend the reach of this chemistry and in particular to establish its application to other walsucochin nortriterpenoids. Here, we report the application of this strategy to the first total syntheses of (±)-walsucochin A (**1**) and (±)-walsucochinoids C−F (**3**−**6**) and their analogues.

Our synthetic route started from the known product **22**, which was prepared on a muti-gram scale in 8 steps for the syntheses of (±)-walsucochin B (**2**) and (±)-walsucochinoids M and N (**13**, **14**) (Scheme 1b−c).[23] The iodide **23** was proposed to be the key intermediate, from which walsucochin A (**1**) and walsucochinoids C−F (**3**−**6**) could be approached through cross-coupling reactions. To realize the conversion of **22** to **23**, because the benzylic position in compound **22** is sensitive to oxidation conditions, a selective oxidation reaction needs to be utilized to install the conjugated carbonyl moiety in the ring A. Several oxidation methods to furnish the desired *α*,*β*-unsaturated system have been developed, in which *o*-iodoxybenzoic acid (IBX) mediated oxidation seems to be a general method for mild and direct conversion of alcohols to *α*,*β*-unsaturated carbonyl compounds.[24−26] In our case, the hydroxy group at the C-7 position of the **22** needs to be inverted and protected before the oxidative transformation.

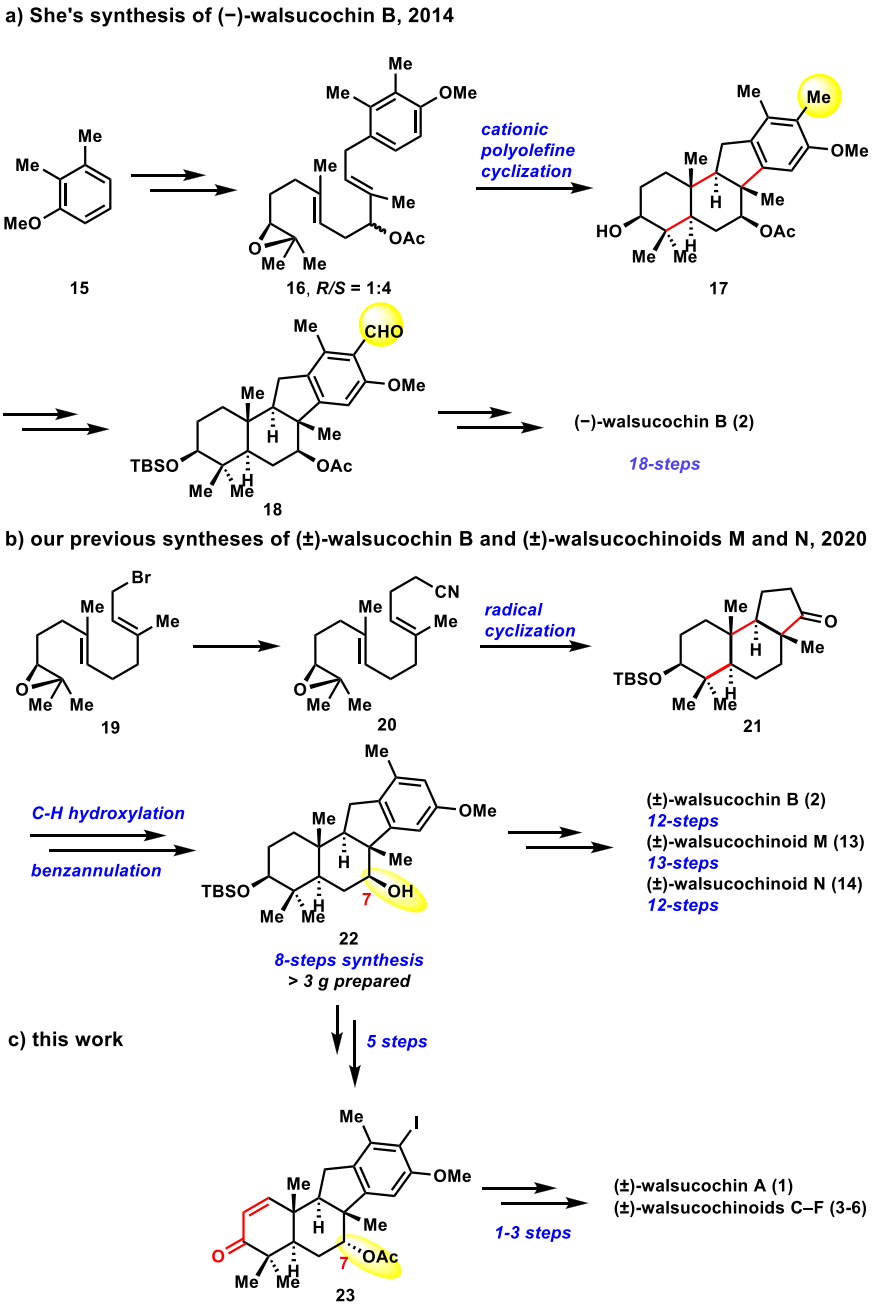
With this concern in mind, we first focused our attention on the inversion of the secondary alcohol **22** (Scheme 2). The Mitsunobu reaction and the SN_2 reaction of the sulfonates with oxygen nucleophiles are two principal methods used for alcohol inversion.[27−29] However, neither conditions gave any desired products, which may be due to severe steric hindrance. When mesylate **25** was treated with CsOAc and 4-dimethylaminopyridine (DMAP) in toluene,[30] only a trace amount of elimination byproduct was observed.

We then focused on the stereoselective reduction strategy. As shown in Scheme 3, oxidation of alcohol **22** to ketone **27** was conducted smoothly using Dess−Martin periodinane (DMP). Then various reducing conditions were tested for the optimal stereoselectivity (see the Supporting Information). Gratifyingly, the reduction with lithium tri-*sec*-butylborohydride (L-selectride),[31] a sterically hindered hydride attacking predominantly (≥95% stereoselectivity) from the equatorial side, gave the 7*α*-hydroxy epimer **28** in 77% yield as the major diastereomer, which can be easily purified by silica gel column chromatography. Next, regioselective iodination with *N*-iodosuccinimide (NIS) in hexafluoroisopropanol (HFIP) and DCM successfully generated the expected iodide **29** in 98% yield. Acetylation of alcohol **29** with Ac_2O and subsequent desilylation with tetrabutylammonium fluoride (TBAF) gave the desired alcohol **31**.

With the successful synthesis of **31**, we turned our attention to the modification of the A ring (Scheme 3). According to Nicolaou's method,[25] the oxidation was conducted by treatment of **31** with IBX (5.0 equiv) in DMSO at 85 °C. However, this reaction was found to be sluggish, furnishing the expected *α*,*β*-unsaturated ketone **23** as a mixture, which is due to the incomplete dehydrogenation. The methoxy-substituted substrate **31** was supposed to coordinate with the hypervalent iodine reagent via the lone pair of electrons on the ethereal oxygen, and therefore, the desired reaction course was distorted. The similar observation has also been noted by Nicolaou and co-workers.[24] When *p*-toluenesulfonic acid monohydrate ($PTSA·H_2O$) was introduced to accelerate the reaction,[24] the process works better to give the desired product **23** but in low yield (<30%). Knowing the TBS group can also be removed under acid conditions,[32] we assumed that the product **23** could be obtained from **30** in a one-pot reaction.

https://doi.org/10.1021/acs.joc.1c00401
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Synthetic Approaches to Walsucochin Nortriterpenoids



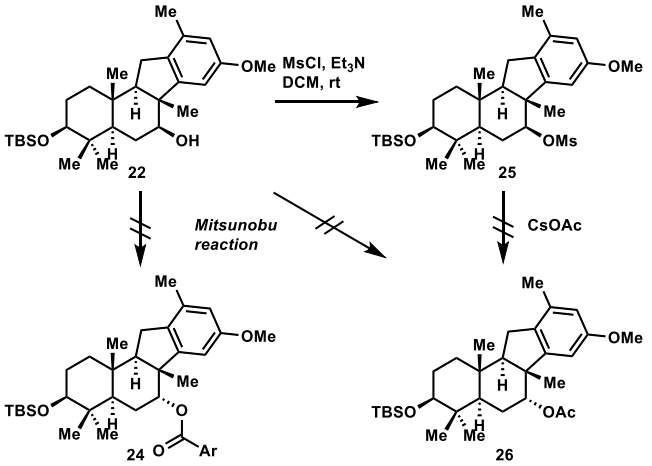
Surprisingly, subsequent treatment of **30** with PTSA·H_2O and IBX in DMSO at 85 °C in one pot successfully afforded the iodide **23** in an excellent yield (80%). Its relative configuration was confirmed by X-ray crystallography (Scheme 3). Notably, this dehydrogenation oxidation process can be performed selectively, and benzylic oxidation was not observed in such case. This result is consistent with the Nicolaou's finding that a free *o*-position is required for the IBX-mediated benzylic oxidation. In addition, the acceleration of the reaction rate may be due to the ready formation of the tosylate derivative of IBX (IBX-OTs), which has been proven to be an efficient reagent for the oxidative dehydrogenation of steroidal alcohols to the corresponding enones.[33]

With the key intermediate iodide **23** in hand, only an acetylene or furan motif installation is required for the syntheses of walsucochin A (**1**) and walsucochinoid E (**5**). The iodide **23** was first reacted with TMSCCH by direct Sonogashira coupling (CuI, $PdCl_2(PPh_3)_4$, Et_3N), and the acetate **32** with a trimethylsilylethynyl group was obtained in 82% yield. Ultimately, saponification (K_2CO_3, MeOH, 60 °C) of the acetate **32**, accompanied by desilylation, finished the synthesis of (±)-walsucochin A (**1**). Overall, only 7 steps were needed to access this complex C_{24} nortriterpenoid from the readily available intermediate **22**, which can be prepared on a gram scale. The structure of (±)-walsucochin A (**1**) was determined as previously reported.[10]

Subsequently, we focused on the syntheses of novel limonoids walsucochinoids C−F (**3**−**6**) by following the strategy depicted in Scheme 3. The installation of the furan ring was realized by a Suzuki−Miyaura cross-coupling reaction ($Pd(PPh_3)_4$, 3-furanylboronic acid), furnishing (±)-walsucochinoid E (**5**), for the first time, in 87% yield. Cleavage of the

https://doi.org/10.1021/acs.joc.1c00401
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Attempted Approaches for Alcohol Inversion

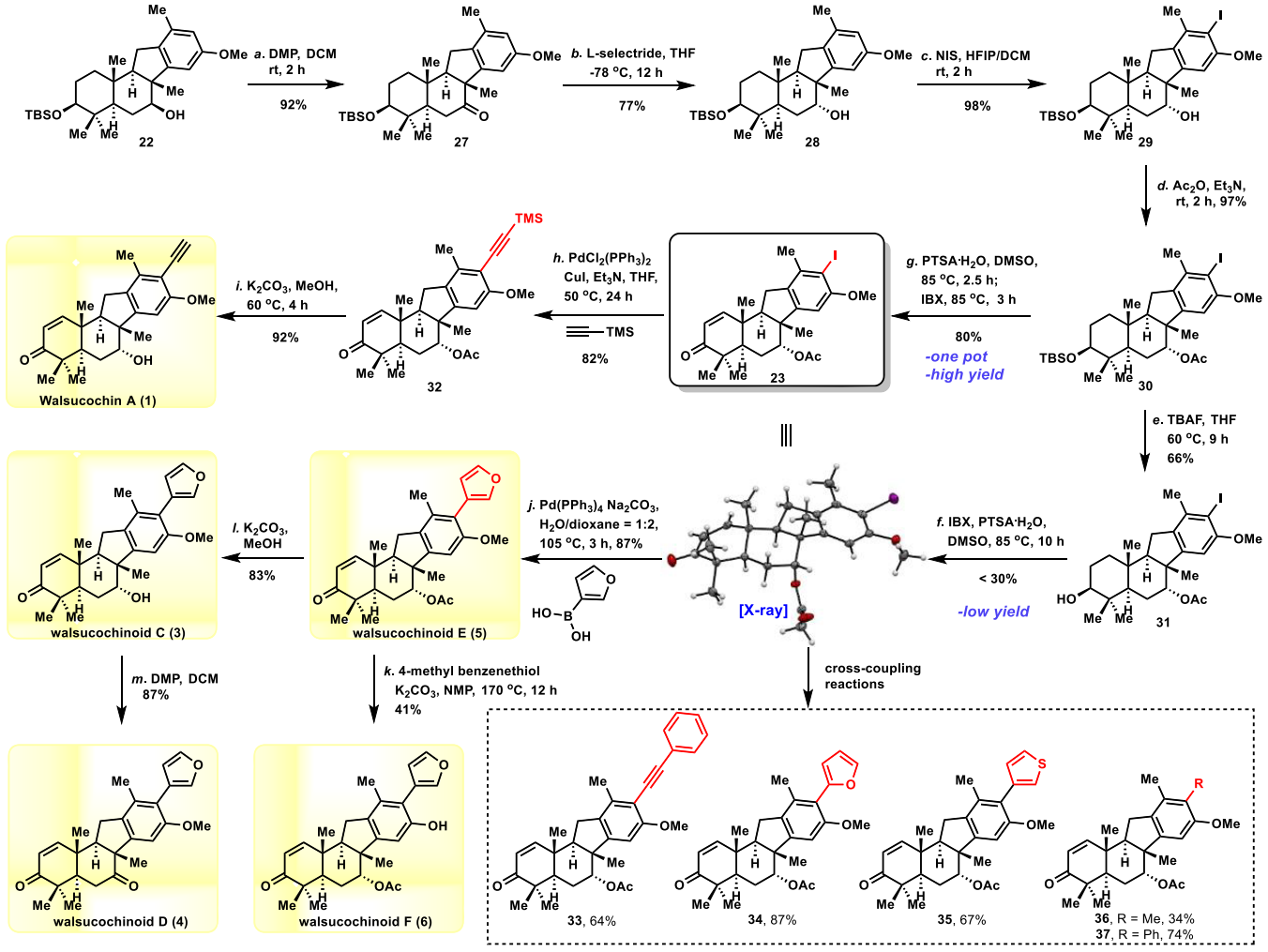


methyl ether in (±)-walsucochinoid E (**5**) with 4-methyl thiophenol and K_2CO_3 then achieved the total synthesis of (±)-walsucochinoid F (**6**) in a moderate yield. Finally, saponification (K_2CO_3, MeOH) of the (±)-walsucochinoid E (**5**) resulted in the formation of the (±)-walsucochinoid C (**3**), which was oxidized with DMP, giving the (±)-walsucochinoid D (**4**) in 87% yield. The NMR spectral data of the synthetic material were in full agreement with those reported for the natural products (see the Supporting Information).[7]

After completing the syntheses of (±)-walsucochin A (**1**) and (±)-walsucochinoids C−F (**3**−**6**), a series of walsucochin analogues (**33**−**37**) were synthesized through cross-coupling reactions (Scheme 3). Given the decent 11β-HSD1 inhibitory activities of walsucochinoids D and E (**4**, **5**), the syntheses, which add to the growing list of walsucochin nortriterpenoids, will accelerate structure−activity relationship studies for the identification of effective 11β-HSD1 inhibitors of walsucochin nortriterpenoids.

In summary, a concise synthetic approach has been developed for the first syntheses of (±)-walsucochin A (**2**) and (±)-walsucochinoids C−F (**3**−**6**) in overall yields of 41%, 39%, 34%, 47%, and 19%, respectively, over 6−8 steps from the key intermediate **22**. The key features of our synthesis involve the stereoselective reduction and an efficient one-pot IBX-mediated oxidation of TBS ether to furnish the desired

Scheme 3. Synthesis of (±)-Walsucochin A (1) and (±)-Walsucochinoids C−F (3−6) and Their Analogues[a]



[a]Notes: TBS = *t*-butyldimethylsilyl, DMP = Dess−Martin periodinane, DCM = dichloromethane, L-selectride = tri-*sec*-butylborohydride, THF = tetrahydrofuran, NIS = *N*-iodosuccinimide, HFIP = hexafluoroisopropanol, TBAF = tetrabutylammonium fluoride, IBX = *o*-iodoxybenzoic acid, PTSA·H_2O = *p*-toluenesulfonic acid monohydrate, TMS = trimethylsilyl, NMP = *N*-methyl pyrrolidone.

https://doi.org/10.1021/acs.joc.1c00401
J. Org. Chem. XXXX, XXX, XXX−XXX

ring A/B. Importantly, this synthesis serves as a general platform to concisely access the walsucochin nortriterpenoids from the key intermediate iodide **23**. Further analogue synthesis and biological evaluation is currently ongoing in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless stated otherwise, all reactions were carried out in flame-dried glassware under a nitrogen atmosphere with dry solvents. For reactions that require heating, an oil bath was used as the heat source. Anhydrous tetrahydrofuran (THF) and dichloromethane (DCM) were obtained by passing these previously degassed solvents through activated alumina columns. All other reagents and solvents were purchased from commercial sources (Sigma-Aldrich, Energy Chemical, Adamas) and used as obtained. Solvents for chromatography were used as received from Titan chemical. All reactions were monitored by thin-layer chromatography (TLC) on GF_{254} precoated silica gel plates and visualized by UV irradiation and staining with *p*-anisaldehyde or potassium permanganate developing agents. A rotary evaporator was used to remove volatile solvents under reduced pressure. All flash column chromatography was performed using silica gel (200−300 mesh). ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded with a Bruker AVANCE III 400 or 500 MHz for ^{1}H (101 or 126 MHz for ^{13}C{^{1}H}) in $CDCl_3$. Chemical shifts are reported relative to the residual solvent signal or trimethylsilane (TMS) as internal standard (^{1}H NMR: δ = 7.26 ($CDCl_3$); ^{13}C{^{1}H} NMR: δ = 77.16 ($CDCl_3$)). Melting points (mp) were recorded on an SGWX-4B apparatus and are uncorrected. IR spectra were taken on a Thermo Nicolet, Avatar 330 FT-IR spectrometer as thin films and are reported in frequency of absorption (cm^{-1}). Only selected resonances are reported. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q Exactive mass spectrometer or a Bruker Maxis System equipped with an electrospray ionization source. X-ray crystallographic analyses were performed on a Bruker APEX-II CCD diffractometer using single crystals.

Synthesis of (±)-Walsucochin A (1) and (±)-Walsucochinoids C−F (3−6). *rac-3-((tert-Butyldimethylsilyl)oxy)-8-methoxy-4,4,6a,10,11b-pentamethyl-1,2,3,4,4a,5,6a,11,11a,11b-decahydro-6H-benzo[a]fluoren-6-one ((±)-**27**).* To a stirred solution of alcohol **22** (802.9 mg, 1.70 mmol, 1.0 equiv) in dichloromethane (20.0 mL) at 0 °C were sequentially added sodium bicarbonate (1.43 g, 17.0 mmol, 10.0 equiv) and the Dess−Martin periodinane (DMP, 1.44 g, 3.40 mmol, 2.0 equiv). After 0.5 h, the resulting mixture was warmed to room temperature and stirred for 2.0 h. Then the reaction was quenched with sat. aq. $Na_2S_2O_3$ solution (20.0 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 15.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give the crude residue which was purified by silica gel flash chromatography (ethyl acetate:petroleum ether = 1:30) to afford ketone **27** (737.3 mg, 92%) as a white solid: mp = 153.2−153.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ 7.14 (d, J = 2.4 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 3.80 (s, 3H), 3.21 (dd, J = 11.3, 4.6 Hz, 1H), 2.82 (t, J = 14.2 Hz, 1H), 2.58−2.53 (m, 2H), 2.38 (dd, J = 14.1, 2.8 Hz, 1H), 2.21 (s, 3H), 1.92 (dd, J = 10.6, 7.7 Hz, 1H), 1.81−1.58 (m, 3H), 1.36−1.29 (m, 1H), 1.30 (s, 3H), 1.24 (s, 3H), 1.15 (td, J = 13.4, 3.6 Hz, 1H), 0.90 (s, 12H), 0.85 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$/TMS) δ 211.9, 158.9, 148.8, 134.9, 131.6, 113.7, 107.0, 79.3, 63.2, 58.4, 57.0, 55.6, 40.0, 37.8, 37.0, 36.3, 28.2, 27.6, 26.0 (3C), 25.5, 23.4, 19.3, 18.2, 16.0, 15.4, −3.6, −4.8; IR (KBr): 2954, 2932, 2855, 1710, 1597, 1473, 1281, 1256, 1140, 1101, 1049 cm^{-1}; HRMS (ESI-ion trap) m/z: [M + Na]$^+$ Calcd for $C_{29}H_{46}O_3SiNa$ 493.3108; Found 493.3111.

*rac-3-((tert-Butyldimethylsilyl)oxy)-8-methoxy-4,4,6a,10,11b-pentamethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]-fluoren-6-ol ((±)-**28**).* To a solution of ketone **27** (124.0 mg, 0.263 mmol, 1.0 equiv) in THF (7.0 mL) at −78 °C was added a solution of L-selectride (1.3 mL, 1.30 mmol, 4.9 equiv, 1.0 M in THF) dropwise. The resulting solution was stirred at the same temperature for 12 h and then quenched with water (4.0 mL) at −78 °C. The resulting mixture was warmed to room temperature and extracted with ethyl acetate (3 × 5.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude material was then purified by silica gel flash chromatography (ethyl ether:petroleum ether = 1:7) to afford alcohol **28** (95.5 mg, 77%) as a white solid: mp = 175.9−176.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ 6.51 (d, J = 2.3 Hz, 1H), 6.48 (d, J = 2.3 Hz, 1H), 4.28 (d, J = 2.9 Hz, 1H), 3.78 (s, 3H), 3.26 (dd, J = 11.3, 4.4 Hz, 1H), 2.55−2.40 (m, 2H), 2.23 (s, 3H), 2.13 (dd, J = 12.2, 6.7 Hz, 1H), 1.91−1.85 (m, 2H), 1.76−1.64 (m, 1H), 1.61−1.52 (m, 3H), 1.44 (t, J = 7.9 Hz, 1H), 1.24−1.14 (m, 1H), 1.04 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H), 0.90 (s, 9H), 0.81 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$/TMS) δ 159.0, 151.2, 136.1, 134.3, 112.5, 104.2, 79.7, 71.1, 56.2, 55.6, 52.2, 48.1, 39.2, 38.5, 36.9, 28.4, 27.7, 26.1 (3C), 25.84, 25.78, 23.6, 19.5, 18.3, 16.2, 15.9, −3.6, −4.8; IR (KBr): 3456, 2933, 2855, 1607, 1474, 1382, 1360, 1312, 1253, 1203, 1104, 1144, 1053, 1026, 1005 cm^{-1}; HRMS (ESI-ion trap) m/z: [M + Na]$^+$ Calcd for $C_{29}H_{48}O_3SiNa$ 495.3265; Found 495.3270.

*rac-3-((tert-Butyldimethylsilyl)oxy)-9-iodo-8-methoxy-4,4,6a,10,-11b-pentamethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo-[a]fluoren-6-ol ((±)-**29**).* To a solution of alcohol **28** (175.5 mg, 0.371 mmol, 1.0 equiv) in HFIP/DCM (7.2 mL, 3:1, v/v) was added *N*-iodosuccinimide (NIS, 89.4 mg, 0.397 mmol, 1.07 equiv) at room temperature. The reaction was complete after stirring for 2 h. Most of the HFIP was removed under reduced pressure to give the crude material which was purified by silica gel flash chromatography (ethyl acetate:petroleum ether = 1:15) to afford iodide **29** (217.7 mg, 98%) as a white solid: mp = 195.1−196.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ 6.44 (s, 1H), 4.30 (s, 1H), 3.87 (s, 3H), 3.25 (dd, J = 11.5, 4.2 Hz, 1H), 2.64−2.51 (m, 2H), 2.39 (s, 3H), 2.12 (dd, J = 12.1, 6.7 Hz, 1H), 1.93−1.84 (m, 2H), 1.76−1.65 (m, 1H), 1.61−1.50 (m, 3H), 1.42 (dd, J = 11.2, 4.6 Hz, 1H), 1.24−1.14 (m, 1H), 1.05 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H), 0.90 (s, 9H), 0.81 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$/TMS) δ 157.4, 150.9, 139.9, 135.3, 101.5, 91.2, 79.6, 71.0, 56.9, 56.0, 52.2, 48.1, 39.2, 38.4, 36.9, 28.4, 27.7, 27.6, 26.1 (4C), 25.6, 23.7, 18.3, 16.1, 15.9, −3.6, −4.8; IR (KBr): 3464, 2954, 2934, 2855, 1588, 1461, 1315, 1253, 1216, 1106, 1059, 1003 cm^{-1}; HRMS (ESI-ion trap) m/z: [M + Na]$^+$ Calcd for $C_{29}H_{47}IO_3SiNa$ 621.2231; Found 621.2238.

*rac-3-((tert-Butyldimethylsilyl)oxy)-9-iodo-8-methoxy-4,4,6a,10,-11b-pentamethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo-[a]fluoren-6-yl Acetate ((±)-**30**).* To a stirred solution of iodide **29** (81.7 mg, 0.136 mmol) in CH_2Cl_2 (2.5 mL) at room temperature were sequentially added DMAP (5.0 mg, 0.0409 mmol, 0.3 equiv), Et_3N (0.15 mL, 1.08 mmol, 7.9 equiv), and Ac_2O (0.10 mL, 1.06 mmol, 7.8 equiv). The resulting mixture was stirred at room temperature for 2 h before it was quenched with sat. aq. $NaHCO_3$ (2.0 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 2.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel flash column chromatography (ethyl ether:petroleum ether = 1:10) afforded acetate **30** (84.8 mg, 97%) as a white solid: mp = 183.3−183.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ 6.36 (s, 1H), 5.54 (s, 1H), 3.79 (s, 3H), 3.24 (dd, J = 11.4, 4.4 Hz, 1H), 2.64−2.50 (m, 2H), 2.38 (s, 3H), 2.09 (dd, J = 11.9, 6.9 Hz, 1H), 1.98−1.81 (m, 2H), 1.91 (s, 3H), 1.76−1.66 (m, 1H), 1.64−1.53 (m, 2H), 1.30 (dd, J = 12.9, 2.7 Hz, 1H), 1.24−1.14 (m, 1H), 1.08 (s, 3H), 1.05 (s, 3H), 0.90 (s, 9H), 0.85 (s, 3H), 0.79 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$/TMS) δ 171.1, 157.1, 151.5, 139.2, 133.9, 101.8, 90.4, 79.5, 72.6, 57.4, 56.8, 50.7, 49.4, 39.1, 38.3, 36.6, 28.4, 27.6, 27.5, 26.0 (3C), 25.5, 24.7, 23.4, 21.5, 18.3, 16.0, 15.7, −3.6, −4.7; IR (KBr): 2928, 2851, 1731, 1585, 1463, 1378, 1359, 1317, 1257, 1222, 1102, 1065, 1043, 1006 cm^{-1}; HRMS (ESI-ion trap) m/z: [M + Na]$^+$ Calcd for $C_{31}H_{49}IO_4SiNa$ 663.2337; Found 663.2342.

*rac-3-Hydroxy-9-iodo-8-methoxy-4,4,6a,10,11b-pentamethyl-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-1H-benzo[a]fluoren-6-yl Acetate ((±)-**31**).* To the solution of acetate **30** (100.0 mg, 0.156 mmol,

https://doi.org/10.1021/acs.joc.1c00401
J. Org. Chem. XXXX, XXX, XXX−XXX

1.0 equiv) in THF (3.7 mL) was added tetrabutylammonium fluoride solution (0.78 mL, 1.0 M in THF, 0.780 mmol, 5.0 equiv) at room temperature. The reaction mixture was heated to 60 °C and stirred for 9 h at the same temperature. Then the reaction was cooled to room temperature, quenched with sat. aq. NH_4Cl solution (3.0 mL), and extracted with ethyl acetate (3 × 5.0 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After filtration, the extract was concentrated and the residue was purified by silica gel flash chromatography (ethyl acetate:petroleum ether = 1:4) to afford alcohol **31** (53.8 mg, 66%) as a white solid: mp = 219.7−221.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 6.36 (s, 1H), 5.55 (s, 1H), 3.79 (s, 3H), 3.28 (dd, J = 9.7, 4.6 Hz, 1H), 2.68−2.50 (m, 2H), 2.38 (s, 3H), 2.16−2.06 (m, 1H), 2.03−1.82 (m, 2H), 1.91 (s, 3H), 1.79−1.60 (m, 3H), 1.39−1.27 (m, 2H), 1.09 (s, 3H), 1.05 (s, 3H), 0.94 (s, 3H), 0.83 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$/TMS) δ 171.0, 157.2, 151.3, 139.2, 133.8, 101.8, 90.5, 79.0, 72.4, 57.3, 56.8, 50.7, 49.3, 38.5, 38.3, 36.7, 28.0, 27.4, 27.2, 25.5, 24.5, 23.4, 21.5, 16.0, 15.2; IR (KBr): 3498, 2921, 2855, 1733, 1462, 1377, 1315, 1251, 1081, 1039, 1026 cm^{-1}; HRMS (ESI-ion trap) m/z: [M + Na]$^+$ Calcd for $C_{25}H_{35}IO_4Na$ 549.1472; Found 549.1472.

*rac-9-Iodo-8-methoxy-4,4,6a,10,11b-pentamethyl-3-oxo-4,4a,5,6,6a,11,11a,11b-octahydro-3H-benzo[a]fluoren-6-yl Acetate ((±)-**23**).* To the solution of acetate **30** (100.0 mg, 0.156 mmol, 1.0 equiv) in DMSO (2.6 mL, 0.3 M with respect to IBX) was added *p*-toluenesulfonic acid monohydrate (38.6 mg, 0.203 mmol, 1.3 equiv). The reaction mixture was heated to 85 °C and stirred for 2.5 h at the same temperature. Then, IBX (218.6 mg, 0.780 mmol, 5.0 equiv) was added to the solution, which was stirred at 85 °C until consumption of starting material was complete (monitored by TLC plates; reaction is normally ca. 3 h). The reaction was cooled to room temperature, diluted with water (5.0 mL), and extracted with Et_2O (5 × 3.0 mL). The combined organic layers were washed with 5% $NaHCO_3$ (5.0 mL), H_2O (2 × 5.0 mL), and brine (2 × 5.0 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (dichloromethane:petroleum ether = 3:1), affording ketone **23** (65.5 mg, 80%) as a white solid: mp = 233.4−235.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ 7.13 (d, J = 10.0 Hz, 1H), 6.38 (s, 1H), 5.91 (d, J = 10.0 Hz, 1H), 5.61 (s, 1H), 3.80 (s, 3H), 2.88 (dd, J = 13.8, 6.3 Hz, 1H), 2.74 (t, J = 13.1 Hz, 1H), 2.42 (s, 3H), 2.42−2.38 (m, 1H), 2.26 (dd, J = 13.4, 2.7 Hz, 1H), 2.16−2.07 (m, 1H), 1.90 (s, 3H), 1.90−1.84 (m, 1H), 1.33 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H), 1.13 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$/TMS) δ 204.8, 170.9, 158.2, 157.4, 150.8, 139.4, 132.8, 125.9, 101.5, 90.8, 71.5, 56.8, 51.9, 51.3, 47.7, 44.6, 39.5, 27.3, 27.1, 25.6, 25.1, 23.4, 21.4, 21.1, 19.0; IR (KBr): 2961, 2928, 2852, 1722, 1665, 1588, 1459, 1378, 1316, 1249, 1214, 1080, 1030 cm^{-1}; HRMS (ESI-ion trap) m/z: [M + Na]$^+$ Calcd for $C_{25}H_{31}IO_4Na$ 545.1159; Found 545.1163.

*rac-8-Methoxy-4,4,6a,10,11b-pentamethyl-3-oxo-9-((trimethylsilyl)ethynyl)-4,4a,5,6,6a,11,11a,11b-octahydro-3H-benzo[a]fluoren-6-yl Acetate ((±)-**32**).* To a flame-dried, nitrogen-flushed tube were added ketone **23** (60.4 mg, 0.116 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (8.1 mg, 0.0116 mmol, 0.1 equiv), PPh_3 (6.1 mg, 0.0231 mmol, 0.2 equiv), and CuI (6.6 mg, 0.0347 mmol, 0.3 equiv). The tube was immediately sealed and flushed with nitrogen. Then deoxygenated Et_3N (2.0 mL) was added. After 10 min, trimethylsilylacetylene (TMSA, 59.4 mg, 0.605 mmol, 5.2 equiv) was added and the reaction mixture was stirred at 50 °C for 24 h. Then the mixture was filtered through a pad of Celite. Removal of solvent under reduced pressure afforded a crude residue which was purified by preparative thin layer chromatography on silica gel (diethyl ether:petroleum ether = 1:2) to afford alkyne **32** (46.7 mg, 82%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 10.0 Hz, 1H), 6.38 (s, 1H), 5.90 (d, J = 10.0 Hz, 1H), 5.59 (s, 1H), 3.78 (s, 3H), 2.80 (dd, J = 13.8, 6.3 Hz, 1H), 2.64 (t, J = 13.0 Hz, 1H), 2.43−2.32 (m, 1H), 2.34 (s, 3H), 2.25 (dd, J = 13.3, 2.5 Hz, 1H), 2.16−2.04 (m, 1H), 1.93−1.82 (m, 1H), 1.86 (s, 3H), 1.31 (s, 3H), 1.13 (s, 3H), 1.12 (s, 6H), 0.25 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.8, 170.8, 160.3, 158.3, 151.1, 138.8, 131.7, 125.8, 110.1, 102.5, 101.0, 100.6, 71.5, 56.2, 51.8, 51.6, 47.7, 44.6, 39.5, 27.3, 25.9, 25.0, 23.2, 21.2, 21.1, 19.0, 17.7, 0.4; IR (KBr): 2958, 2148, 1737, 1671, 1601, 1463, 1376, 1320, 1246, 1213, 1146, 1100, 1030 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{30}H_{40}O_4SiNa$ 515.2588; Found 515.2585.

*(±)-Walsucochin A (**1**).* To a solution of alkyne **32** (23.6 mg, 0.0479 mmol, 1.0 equiv) in MeOH/THF (2.4 mL, 5:1, v/v) was added potassium carbonate (66.2 mg, 0.479 mmol, 10.0 equiv) at room temperature. The reaction was stirred at 60 °C for 4 h, and the solvents were then removed. After addition of sat. aq. NH_4Cl solution (2.0 mL), the mixture was extracted with ethyl acetate (3 × 3.0 mL). The combined organic layers were washed with brine (3.0 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by preparative thin layer chromatography on silica gel (ethyl acetate:petroleum ether = 1:3) to afford (±)-walsucochin A (**1**, 16.7 mg, 92%) as a white solid: mp = 218.5−220.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 10.0 Hz, 1H), 6.50 (s, 1H), 5.88 (d, J = 10.0 Hz, 1H), 4.38 (s, 1H), 3.89 (s, 3H), 3.50 (s, 1H), 2.82 (dd, J = 13.9, 6.3 Hz, 1H), 2.65 (t, J = 13.1 Hz, 1H), 2.48−2.34 (m, 2H), 2.38 (s, 3H), 2.05 (t, J = 13.7 Hz, 1H), 1.88 (d, J = 14.4 Hz, 1H), 1.29 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 205.3, 161.0, 158.6, 151.0, 139.6, 133.2, 125.8, 109.6, 100.6, 84.9, 79.3, 70.1, 56.3, 53.1, 50.4, 46.3, 44.7, 39.7, 27.4, 26.5, 26.0, 23.5, 21.3, 19.2, 17.8; IR (KBr): 3442, 2939, 2098, 1660, 1602, 1575, 1463, 1380, 1318, 1216, 1145, 1091, 1045 cm^{-1}; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{25}H_{30}O_3Na$ 401.2087; Found 401.2086.

*(±)-Walsucochinoid E (**5**).* To a flame-dried, nitrogen-flushed tube were added ketone **23** (150.0 mg, 0.287 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (33.2 mg, 0.0287 mmol, 0.1 equiv), Na_2CO_3 (304.3 mg, 2.871 mmol, 10.0 equiv), and 3-furanylboronic acid (160.6 mg, 1.436 mmol, 5.0 equiv). The tube was immediately sealed and flushed with nitrogen. Then deoxygenated water/dioxane (12.0 mL, 1:2, v/v) was added. The reaction mixture was heated at 105 °C for 3 h, then allowed to gradually reach the room temperature. The mixture was neutralized with HCl solution (1 M) and extracted with ethyl acetate (3 × 7.0 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum to give the crude material, which was purified by column chromatography (dichloromethane:petroleum ether = 3:1) to yield the pure (±)-walsucochinoid E (**5**, 115.6 mg, 87%) as a white solid: mp = 186.2−187.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ 7.49 (s, 1H), 7.39 (s, 1H), 7.16 (d, J = 10.0 Hz, 1H), 6.48 (s, 1H), 6.44 (s, 1H), 5.91 (d, J = 10.0 Hz, 1H), 5.64 (s, 1H), 3.68 (s, 3H), 2.84 (dd, J = 13.8, 6.3 Hz, 1H), 2.70 (t, J = 13.0 Hz, 1H), 2.44 (dd, J = 12.2, 6.3 Hz, 1H), 2.27 (dd, J = 13.3, 2.6 Hz, 1H), 2.17 (s, 3H), 2.13 (dd, J = 13.4, 2.3 Hz, 1H), 1.93 (s, 3H), 193−1.87 (m, 1H), 1.34 (s, 3H), 1.20 (s, 3H), 1.14 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$/TMS) δ 204.9, 170.9, 158.4, 156.9, 149.6, 142.1, 141.3, 134.7, 132.1, 125.8, 120.1, 119.3, 113.0, 101.4, 71.6, 56.1, 52.0, 51.4, 47.7, 44.6, 39.5, 27.3, 26.3, 25.1, 23.5, 21.4, 21.1, 19.0, 17.7; IR (KBr): 2933, 2854, 1734, 1670, 1592, 1461, 1376, 1316, 1245, 1211, 1156, 1090, 1030 cm^{-1}; HRMS (ESI-ion trap) m/z: [M + Na]$^+$ Calcd for $C_{29}H_{34}O_5Na$ 485.2299; Found 485.2303.

*(±)-Walsucochinoid F (**6**).* To a flame-dried, nitrogen-flushed tube were added (±)-walsucochinoid E (30.0 mg, 0.065 mmol, 1.0 equiv), 4-methylbenzenethiol (16.1 mg, 0.13 mmol, 2.0 equiv), and potassium carbonate (9.0 mg, 0.065 mmol, 1.0 equiv). The tube was immediately sealed and flushed with nitrogen. Then *N*-methyl pyrrolidone (NMP, 1.0 mL) was added. The reaction mixture was heated at 170 °C for 12 h, then allowed to gradually reach the room temperature. The reaction mixture was quenched with water (1.0 mL) and extracted with ethyl acetate (3 × 3.0 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum to give the crude material, which was purified by preparative thin layer chromatography on silica gel (ethyl acetate:petroleum ether = 1:3) to afford the (±)-walsucochinoid F (**6**, 11.9 mg, 41%) as a yellowish solid: mp = 253.2−254.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.61 (t, J = 1.6 Hz, 1H), 7.47 (s, 1H), 7.15 (d, J = 10.0 Hz, 1H), 6.47 (s, 1H), 6.42 (s, 1H), 5.90 (d, J = 10.0 Hz, 1H), 5.53 (s, 1H), 5.06 (s, 1H), 2.82 (dd, J = 13.9, 6.4 Hz, 1H), 2.68 (t, J = 13.0 Hz, 1H), 2.43 (dd, J = 12.2, 6.4 Hz, 1H), 2.23 (dd, J

https://doi.org/10.1021/acs.joc.1c00401
J. Org. Chem. XXXX, XXX, XXX−XXX

= 13.3, 2.6 Hz, 1H), 2.16−2.06 (m, 1H), 2.11 (s, 3H), 1.98−1.90 (m, 1H), 1.95 (s, 3H), 1.33 (s, 3H), 1.18 (s, 3H), 1.131 (s, 3H), 1.125 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$/TMS) δ 205.0, 170.8, 158.4, 152.9, 150.8, 144.4, 141.3, 134.4, 131.6, 125.8, 119.0, 116.2, 112.5, 105.0, 71.8, 52.0, 51.0, 47.7, 44.6, 39.5, 27.3, 26.1, 24.8, 23.6, 21.4, 21.2, 19.0, 17.5; IR (KBr): 3444, 2970, 2938, 1732, 1667, 1436, 1378, 1317, 1248, 1212, 1159, 1032 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{32}O_5Na$ 471.2142; Found 471.2139.

*(±)-Walsucochinoid C (**3**).* To a solution of (±)-walsucochinoid E (47.6 mg, 0.103 mmol, 1.0 equiv) in MeOH/THF (3.0 mL, 2:1, v/v) was added potassium carbonate (149.0 mg, 1.08 mmol, 10.5 equiv) at 0 °C. The reaction was stirred at room temperature overnight, and the solvents were then removed. After addition of sat. aq. NH_4Cl solution (2.0 mL), the mixture was extracted with ethyl acetate (3 × 3.0 mL). The combined organic layers were washed with brine (3.0 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography on silica gel (ethyl acetate:dichloromethane = 1:10) to afford (±)-walsucochinoid C (**3**, 35.8 mg, 83%) as a white solid: mp = 207.2−208.5 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.50 (s, 1H), 7.39 (s, 1H), 7.16 (d, J = 10.0 Hz, 1H), 6.58 (s, 1H), 6.43 (s, 1H), 5.89 (d, J = 10.0 Hz, 1H), 4.42 (s, 1H), 3.76 (s, 3H), 2.85 (dd, J = 13.8, 6.3 Hz, 1H), 2.70 (t, J = 13.0 Hz, 1H), 2.53−2.38 (m, 2H), 2.17 (s, 3H), 2.08 (t, J = 13.7 Hz, 1H), 1.91 (dt, J = 14.5, 3.1 Hz, 1H), 1.32 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$/TMS) δ 205.4, 158.8, 157.1, 149.0, 142.2, 141.2, 135.5, 133.7, 125.5, 120.1, 119.9, 113.0, 101.0, 70.2, 56.2, 53.0, 50.5, 46.4, 44.8, 39.7, 27.4, 26.40, 26.35, 23.7, 21.3, 19.2, 17.7; IR (KBr): 3439, 2938, 1657, 1462, 1382, 1315, 1213, 1154, 1090, 1071, 1043 cm^{-1}; HRMS (ESI-ion trap) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{32}O_4Na$ 443.2193; Found 443.2189.

*(±)-Walsucochinoid D (**4**).* To a stirred solution of (±)-walsucochinoid C (10.7 mg, 0.0254 mmol, 1.0 equiv) in dichloromethane (1.0 mL) were successively added sodium bicarbonate (21.0 mg, 0.250 mmol, 9.84 equiv) and Dess−Martin periodinane (DMP, 21.5 mg, 0.0507 mmol, 2.0 equiv) at 0 °C. After 0.5 h, the resulting mixture was warmed to room temperature and stirred for 2 h. Then the reaction was quenched with sat. aq. $Na_2S_2O_3$ solution (2.0 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 2.0 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a crude residue which was purified by preparative thin layer chromatography on silica gel (dichloromethane) to afford (±)-walsucochinoid D (**4**, 9.3 mg, 87%) as a white solid: mp = 154.6−156.2 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.50 (s, 1H), 7.39 (s, 1H), 7.25 (s, 1H), 7.19 (d, J = 10.0 Hz, 1H), 6.43 (s, 1H), 5.96 (d, J = 9.8 Hz, 1H), 3.80 (s, 3H), 3.02 (t, J = 14.3 Hz, 1H), 2.91−2.79 (m, 2H), 2.43 (d, J = 14.4 Hz, 1H), 2.33−2.22 (m, 2H), 2.17 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 1.19 (s, 3H), 1.19 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$/TMS) δ 209.9, 203.9, 157.0, 156.8, 146.9, 142.2, 141.3, 134.3, 131.0, 126.5, 120.1, 120.0, 113.0, 104.7, 58.8, 57.9, 56.2, 54.8, 45.3, 39.1, 36.9, 27.3, 26.2, 23.6, 20.9, 19.0, 17.6; IR (KBr): 2935, 1713, 1670, 1583, 1461, 1424, 1376, 1326, 1273, 1090, 1061 cm^{-1}; HRMS (ESI-ion trap) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{30}O_4Na$ 441.2036; Found 441.2035.

Syntheses of Walsucochin Analogues 33−37. *rac-8-Methoxy-4,4,6a,10,11b-pentamethyl-3-oxo-9-(phenylethynyl)-4,4a,5,6,6a,11,11a,11b-octahydro-3H-benzo[a]fluoren-6-yl Acetate ((±)-**33**).* To a flame-dried, nitrogen-flushed tube were added ketone **23** (20.0 mg, 0.0383 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (2.7 mg, 0.00385 mmol, 0.1 equiv), PPh_3 (2.0 mg, 0.00762 mmol, 0.2 equiv), and CuI (2.2 mg, 0.0116 mmol, 0.3 equiv). The tube was immediately sealed and flushed with nitrogen. Then deoxygenated Et_3N (1.0 mL) was added. After 10 min, phenylacetylene (24.0 mg, 0.235 mmol, 6.1 equiv) was added and the reaction mixture was stirred at 50 °C for 24 h. Then the mixture was filtered through a pad of Celite. Remove of solvent under reduced pressure afforded a crude residue which was purified by preparative thin layer chromatography on silica gel (ethyl acetate:petroleum ether = 1:8) to afford alkyne **33** (12.2 mg, 64%) as a yellowish solid: mp = 219.4−222.4 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.59−7.51 (m, 2H), 7.41−7.29 (m, 3H), 7.16 (d, J = 10.0 Hz, 1H), 6.45 (s, 1H), 5.92 (d, J = 10.0 Hz, 1H), 5.63 (s, 1H), 3.83 (s, 3H), 2.84 (dd, J = 13.9, 6.3 Hz, 1H), 2.68 (t, J = 13.0 Hz, 1H), 2.44 (s, 3H), 2.44−2.37 (m, 1H), 2.27 (d, J = 13.1 Hz, 1H), 2.13 (t, J = 13.9 Hz, 1H), 1.90 (s, 3H), 1.90−1.82 (m, 1H), 1.33 (s, 3H), 1.18 (s, 3H), 1.14 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$/TMS) δ 204.8, 170.9, 159.9, 158.3, 151.0, 138.3, 131.8, 131.6 (2C), 128.4 (2C), 128.0, 125.9, 124.1, 110.2, 101.1, 97.4, 85.1, 71.5, 56.2, 51.8, 51.7, 47.7, 44.6, 39.5, 27.3, 26.0, 25.1, 23.3, 21.3, 21.2, 19.0, 17.9; IR (KBr): 2958, 2855, 2201, 1731, 1662, 1593, 1575, 1463, 1439, 1376, 1324, 1296, 1248, 1215, 1092, 1026 cm^{-1}; HRMS (ESI-ion trap) m/z: $[M + Na]^+$ Calcd for $C_{33}H_{36}O_4Na$ 519.2506; Found 519.2508.

General Procedure for Compounds 34−37. To a flame-dried, nitrogen-flushed tube were added ketone **23** (20.0 mg, 0.0383 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (8.8 mg, 0.00762 mmol, 0.2 equiv), Na_2CO_3 (40.6 mg, 0.383 mmol, 10.0 equiv), and the corresponding boronic acid (0.191 mmol, 5.0 equiv). The tube was immediately sealed and flushed with nitrogen. Then deoxygenated water/dioxane (1.2 mL, 1:2, v/v) was added. The reaction mixture was heated at 105 °C for 3 h, then allowed to gradually reach the room temperature. The mixture was neutralized with HCl solution (1 M) and extracted with ethyl acetate (3 × 2.0 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum to give the crude material, which was purified by preparative thin layer chromatography on silica gel (ethyl acetate:petroleum ether = 1:8) to afford the product.

*rac-9-(Furan-2-yl)-8-methoxy-4,4,6a,10,11b-pentamethyl-3-oxo-4,4a,5,6,6a,11,11a,11b-octahydro-3H-benzo[a]fluoren-6-yl Acetate ((±)-**34**).* (15.5 mg, 87%) as a yellowish solid: mp = 164.1−168.4 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.51 (s, 1H), 7.16 (d, J = 9.9 Hz, 1H), 6.49 (s, 2H), 6.38 (s, 1H), 5.91 (d, J = 9.9 Hz, 1H), 5.64 (s, 1H), 3.70 (s, 3H), 2.84 (dd, J = 14.0, 6.3 Hz, 1H), 2.69 (t, J = 13.0 Hz, 1H), 2.43 (dd, J = 12.4, 6.3 Hz, 1H), 2.28 (d, J = 13.1 Hz, 1H), 2.16 (s, 3H), 2.12 (d, J = 15.1 Hz, 1H), 1.92 (s, 3H), 1.92−1.85 (m, 1H), 1.34 (s, 4H), 1.19 (s, 3H), 1.14 (s, 3H), 1.14 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$/TMS) δ 204.9, 170.9, 158.4, 157.7, 151.2, 150.0, 141.7, 136.0, 132.2, 125.8, 118.2, 110.7, 110.2, 101.6, 71.6, 56.2, 51.9, 51.6, 47.7, 44.6, 39.5, 27.3, 26.1, 25.1, 23.4, 21.4, 21.2, 19.0, 17.5; IR (KBr): 2936, 2853, 1733, 1670, 1609, 1462, 1376, 1317, 1246, 1212, 1149, 1078, 1030 cm^{-1}; HRMS (ESI-ion trap) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{34}O_5Na$ 485.2299; Found 485.2300.

*rac-8-Methoxy-4,4,6a,10,11b-pentamethyl-3-oxo-9-(thiophen-3-yl)-4,4a,5,6,6a,11,11a,11b-octahydro-3H-benzo[a]fluoren-6-yl Acetate ((±)-**35**).* (12.3 mg, 67%) as a brown solid: mp = 207.2−209.6 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.38−7.32 (m, 1H), 7.17 (d, J = 9.9 Hz, 1H), 7.10 (s, 1H), 7.01 (d, J = 4.9 Hz, 1H), 6.48 (s, 1H), 5.91 (d, J = 9.9 Hz, 1H), 5.65 (s, 1H), 3.65 (s, 3H), 2.84 (dd, J = 13.8, 6.3 Hz, 1H), 2.70 (t, J = 13.0 Hz, 1H), 2.45 (dd, J = 12.3, 6.3 Hz, 1H), 2.28 (d, J = 13.2 Hz, 1H), 2.15 (t, J = 14.1 Hz, 1H), 2.08 (s, 3H), 1.94 (s, 3H), 1.91 (d, J = 14.4 Hz, 1H), 1.35 (s, 3H), 1.21 (s, 3H), 1.14 (s, 3H), 1.14 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$/TMS) δ 204.9, 170.9, 158.5, 156.8, 149.6, 137.4, 134.6, 132.0, 130.1, 125.8, 124.2, 123.64, 123.56, 101.5, 71.7, 56.1, 52.1, 51.4, 47.8, 44.7, 39.5, 27.3, 26.2, 25.1, 23.5, 21.4, 21.2, 19.0, 17.6; IR (KBr): 2970, 2946, 1730, 1668, 1465, 1427, 1375, 1314, 1244, 1212, 1107, 1029 cm^{-1}; HRMS (ESI-ion trap) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{34}O_4SNa$ 501.2070; Found 501.2075.

*rac-8-Methoxy-4,4,6a,9,10,11b-hexamethyl-3-oxo-4,4a,5,6,6a,11,11a,11b-octahydro-3H-benzo[a]fluoren-6-yl Acetate ((±)-**36**).* (5.3 mg, 34%) as a white solid: mp = 189.6−193.1 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.16 (d, J = 10.0 Hz, 1H), 6.41 (s, 1H), 5.90 (d, J = 10.0 Hz, 1H), 5.61 (s, 1H), 3.74 (s, 3H), 2.83 (dd, J = 13.8, 6.3 Hz, 1H), 2.68 (t, J = 13.0 Hz, 1H), 2.39 (dd, J = 12.2, 6.4 Hz, 1H), 2.31−2.18 (m, 1H), 2.20 (s, 3H), 2.17−2.06 (m, 1H), 2.12 (s, 3H), 1.91 (s, 3H), 1.94−1.83 (m, 1H), 1.33 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 1.13 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$/TMS) δ 205.0, 170.9, 158.6, 156.8, 147.5, 134.2, 131.6, 125.8, 122.7, 101.0, 71.7, 55.9, 52.1, 51.3, 47.8, 44.7, 39.5, 27.3, 26.2, 25.1, 23.7, 21.4, 21.2, 19.0, 16.5, 11.9; IR (KBr): 2967, 2931, 1725, 1664,

https://doi.org/10.1021/acs.joc.1c00401
J. Org. Chem. XXXX, XXX, XXX−XXX

1462, 1368, 1315, 1248, 1216, 1109, 1028 cm^{-1}; HRMS (ESI-ion trap) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{34}O_4Na$ 433.2349; Found 433.2350.

*rac-8-Methoxy-4,4,6a,10,11b-pentamethyl-3-oxo-9-phenyl-4,4a,5,6,6a,11,11a,11b-octahydro-3H-benzo[a]fluoren-6-yl Acetate ((±)-**37**).* (13.4 mg, 74%) as a brown solid: mp = 232.9−234.8 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.43−7.36 (m, 2H), 7.35−7.28 (m, 1H), 7.24−7.14 (m, 3H), 6.49 (s, 1H), 5.92 (d, *J* = 10.0 Hz, 1H), 5.65 (s, 1H), 3.62 (s, 3H), 2.84 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.71 (t, *J* = 13.0 Hz, 1H), 2.47 (dd, *J* = 12.1, 6.3 Hz, 1H), 2.29 (d, *J* = 13.0 Hz, 1H), 2.16 (t, *J* = 14.0 Hz, 1H), 2.00 (s, 3H), 1.96 (s, 3H), 1.92 (d, *J* = 15.4 Hz, 1H), 1.35 (s, 3H), 1.23 (s, 3H), 1.15 (s, 3H), 1.15 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$/TMS) δ 205.0, 170.9, 158.6, 156.3, 149.4, 138.1, 133.9, 131.9, 130.5, 130.3, 128.9, 128.1 (2C), 126.7, 125.8, 101.5, 71.8, 56.1, 52.1, 51.4, 47.8, 44.7, 39.5, 27.3, 26.2, 25.1, 23.6, 21.5, 21.2, 19.0, 17.4; IR (KBr): 2933, 2853, 1732, 1668, 1461, 1424, 1375, 1316, 1246, 1212, 1030 cm^{-1}; HRMS (ESI-ion trap) *m/z*: $[M + Na]^+$ Calcd for $C_{31}H_{36}O_4Na$ 495.2506; Found 495.2509.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00401.

X-ray crystallographic data for **23** and spectral data of synthetic compounds (PDF)

Accession Codes

CCDC 2053477 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Gong Xu − *College of Plant Protection, Northwest A&F University, Yangling 712100, Shaanxi, China; State Key Laboratory of Crop Stress Biology for Arid Areas, Key Laboratory of Botanical Pesticide R&D in Shaanxi Province, Shaanxi Key Laboratory of Natural Products & Chemical Biology, Yangling 712100, Shaanxi, China;* orcid.org/0000-0002-4305-4370; Email: gongxu@nwafu.edu.cn

Authors

Danyang Zhang − *College of Plant Protection, Northwest A&F University, Yangling 712100, Shaanxi, China*

Dan Xu − *College of Chemistry & Pharmacy, Northwest A&F University, Yangling 712100, Shaanxi, China; State Key Laboratory of Crop Stress Biology for Arid Areas, Key Laboratory of Botanical Pesticide R&D in Shaanxi Province, Shaanxi Key Laboratory of Natural Products & Chemical Biology, Yangling 712100, Shaanxi, China*

Xinyue Chen − *College of Plant Protection, Northwest A&F University, Yangling 712100, Shaanxi, China*

Huan Zhou − *College of Plant Protection, Northwest A&F University, Yangling 712100, Shaanxi, China; State Key Laboratory of Crop Stress Biology for Arid Areas, Key Laboratory of Botanical Pesticide R&D in Shaanxi Province, Shaanxi Key Laboratory of Natural Products & Chemical Biology, Yangling 712100, Shaanxi, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00401

Author Contributions

‖D.Z. and D.X. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (21801207), the Department of Science and Technology of Shaanxi Province (2021NY-140, 2021JQ-157), the Program for Science & Technology Innovation Team of Shaanxi Province (2020TD-035), and the Scientific Research Foundation of Northwest A&F University. Partial instrumentation support was provided by the State Key Laboratory of Crop Stress Biology for Arid Areas in Northwest A&F University. We thank Mr. Hongli Zhang (Northwest A&F University) for NMR spectroscopic assistance. KeeCloud Biotech is acknowledged for HRMS analysis.

■ REFERENCES

(1) Jin, Y.-p.; Yan, S.; Liu, J.-x.; Yang, Y.; Wang, Y.-s.; Wang, Y.-p. Research Progress on Nortriterpenoids in Plants of Schisandraceae and Their Pharmacological Activities. *Zhongcaoyao* **2014**, *45* (11), 1643−1650.

(2) Yang, Z. The Journey of Schinortriterpenoid Total Syntheses. *Acc. Chem. Res.* **2019**, *52* (2), 480−491.

(3) Fang, X.; Di, Y. T.; Hao, X. J. The Advances in the Limonoid Chemistry of the Meliaceae Family. *Curr. Org. Chem.* **2011**, *15* (9), 1363−1391.

(4) Xiao, W.-L.; Gong, Y.-Q.; Wang, R.-R.; Weng, Z.-Y.; Luo, X.; Li, X.-N.; Yang, G.-Y.; He, F.; Pu, J.-X.; Yang, L.-M.; Zheng, Y.-T.; Lu, Y.; Sun, H.-D. Bioactive Nortriterpenoids from Schisandra grandiflora. *J. Nat. Prod.* **2009**, *72* (9), 1678−1681.

(5) Xiao, W.-L.; Huang, S.-X.; Zhang, L.; Tian, R.-R.; Wu, L.; Li, X.-L.; Pu, J.-X.; Zheng, Y.-T.; Lu, Y.; Li, R.-T.; Zheng, Q.-T.; Sun, H.-D. Nortriterpenoids from Schisandra lancifolia. *J. Nat. Prod.* **2006**, *69* (4), 650−653.

(6) Trinh, B. T. D.; Nguyen, H. D.; Nguyen, H. T.; Pham, P. D.; Ngo, N. T. N.; Nguyen, L.-T. T.; Nguyen, L. T. T.; Bui, D. N.; Dang, S. V.; Nguyen, L.-H. D. Cytotoxic Limonoids from the Bark of Walsura cochinchinensis. *Fitoterapia* **2019**, *133*, 75−79.

(7) Han, M.-L.; Shen, Y.; Leng, Y.; Zhang, H.; Yue, J.-M. New Rearranged Limonoids from Walsura cochinchinensis. *RSC Adv.* **2014**, *4* (37), 19150−19158.

(8) Han, M.-L.; Shen, Y.; Wang, G.-C.; Leng, Y.; Zhang, H.; Yue, J.-M. 11β-HSD1 Inhibitors from Walsura cochinchinensis. *J. Nat. Prod.* **2013**, *76* (7), 1319−1327.

(9) Han, M.-L.; Zhang, H.; Yang, S.-P.; Yue, J.-M. Walsucochinoids A and B: New Rearranged Limonoids from Walsura cochinchinensis. *Org. Lett.* **2012**, *14* (2), 486−489.

(10) Zhou, Z.-W.; Yin, S.; Zhang, H.-Y.; Fu, Y.; Yang, S.-P.; Wang, X.-N.; Wu, Y.; Tang, X.-C.; Yue, J.-M. Walsucochins A and B with an Unprecedented Skeleton Isolated from Walsura cochinchinensis. *Org. Lett.* **2008**, *10* (3), 465−468.

(11) Scott, J. S.; Goldberg, F. W.; Turnbull, A. V. Medicinal Chemistry of Inhibitors of 11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1). *J. Med. Chem.* **2014**, *57* (11), 4466−4486.

(12) Morton, N. M. Obesity and Corticosteroids: 11β-Hydroxysteroid Type 1 as a Cause and Therapeutic Target in Metabolic Disease. *Mol. Cell. Endocrinol.* **2010**, *316* (2), 154−64.

(13) Webster, S. P.; Pallin, T. D. 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors as Therapeutic Agents. *Expert Opin. Ther. Pat.* **2007**, *17* (12), 1407−1422.

(14) Wamil, M.; Seckl, J. R. Inhibition of 11β-Hydroxysteroid Dehydrogenase Type 1 as a Promising Therapeutic Target. *Drug Discovery Today* **2007**, *12* (13-14), 504−520.

(15) Walker, B. R.; Seckl, J. R. 11β-Hydroxysteroid Dehydrogenase Type 1 as a Novel Therapeutic Target in Metabolic and Neurodegenerative Disease. *Expert Opin. Ther. Targets* **2003**, *7* (6), 771−783.
(16) Goclik, E.; Koenig, G. M.; Wright, A. D.; Kaminsky, R. Pelorol from the Tropical Marine Sponge Dactylospongia elegans. *J. Nat. Prod.* **2000**, *63* (8), 1150−1152.
(17) Kwak, J. H.; Schmitz, F. J.; Kelly, M. Sesquiterpene Quinols/Quinones from the Micronesian Sponge Petrosaspongia metachromia. *J. Nat. Prod.* **2000**, *63* (8), 1153−1156.
(18) Yang, L.; Williams, D. E.; Mui, A.; Ong, C.; Krystal, G.; van Soest, R.; Andersen, R. J. Synthesis of Pelorol and Analogs: Activators of the Inositol 5-Phosphatase SHIP. *Org. Lett.* **2005**, *7* (6), 1073−1076.
(19) Ong, C. J.; Ming-Lum, A.; Nodwell, M.; Ghanipour, A.; Yang, L.; Williams, D. E.; Kim, J.; Demirjian, L.; Qasimi, P.; Ruschmann, J.; Cao, L.-P.; Ma, K.; Chung, S. W.; Duronio, V.; Andersen, R. J.; Krystal, G.; Mui, A. L. F. Small-Molecule Agonists of SHIP1 Inhibit the Phosphoinositide 3-Kinase Pathway in Hematopoietic Cells. *Blood* **2007**, *110* (6), 1942−1949.
(20) Mukku, V. J. R. V.; Edrada, R. A.; Schmitz, F. J.; Shanks, M. K.; Chaudhuri, B.; Fabbro, D. New Sesquiterpene Quinols from a Micronesian Sponge, Aka sp. *J. Nat. Prod.* **2003**, *66* (5), 686−689.
(21) Liermann, J. C.; Kolshorn, H.; Anke, H.; Thines, E.; Opatz, T. Tetracyclic Terpenoids from Dasyscyphus niveus, Dasyscyphins D and E. *J. Nat. Prod.* **2008**, *71* (9), 1654−1656.
(22) Xu, S.; Gu, J.; Li, H.; Ma, D.; Xie, X.; She, X. Enantioselective Total Synthesis of (−)-Walsucochin B. *Org. Lett.* **2014**, *16* (7), 1996−1999.
(23) Chen, X.; Zhang, D.; Xu, D.; Zhou, H.; Xu, G. Remote C−H Activation Strategy Enables Total Syntheses of Nortriterpenoids (±)-Walsucochin B and (±)-Walsucochinoids M and N. *Org. Lett.* **2020**, *22* (17), 6993−6997.
(24) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. Iodine(V) Reagents in Organic Synthesis. Part 4. o-Iodoxybenzoic Acid as a Chemospecific Tool for Single Electron Transfer-Based Oxidation Processes. *J. Am. Chem. Soc.* **2002**, *124* (10), 2245−2258.
(25) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. A New Method for the One-Step Synthesis of α,β-Unsaturated Carbonyl Systems from Saturated Alcohols and Carbonyl Compounds. *J. Am. Chem. Soc.* **2000**, *122* (31), 7596−7597.
(26) Deng, X.; Kong, L.-M.; Zhao, Y.; He, J.; Peng, L.-Y.; Li, Y.; Zhao, Q.-S. Exploring of Drug Leads from Diversity-Oriented Michael-Acceptor Library Derived from Natural Products. *Nat. Prod. Bioprospect.* **2012**, *2* (5), 210−216.
(27) Martin, S. F.; Dodge, J. A. Efficacious Modification of the Mitsunobu Reaction for Inversions of Sterically Hindered Secondary Alcohols. *Tetrahedron Lett.* **1991**, *32* (26), 3017−3020.
(28) Shi, X.-X.; Shen, C.-L.; Yao, J.-Z.; Nie, L.-D.; Quan, N. Inversion of Secondary Chiral Alcohols in Toluene with the Tunable Complex of R3NR′COOH. *Tetrahedron: Asymmetry* **2010**, *21* (3), 277−284.
(29) Snider, B. B.; Hawryluk, N. A. Synthesis of (−)-Dysiherbaine. *Org. Lett.* **2000**, *2* (5), 635−638.
(30) Hawryluk, N. A.; Snider, B. B. Alcohol Inversion Using Cesium Carboxylates and DMAP in Toluene. *J. Org. Chem.* **2000**, *65* (24), 8379−8380.
(31) Brown, H. C.; Krishnamurthy, S. Lithium Tri-Sec-Butylborohydride. New Reagent for the Reduction of Cyclic and Bicyclic Ketones with Super Stereoselectivity. Remarkably Simple and Practical Procedure for the Conversion of Ketones to Alcohols in Exceptionally High Stereochemical Purity. *J. Am. Chem. Soc.* **1972**, *94* (20), 7159−7161.
(32) Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. Annulative Methods Enable a Total Synthesis of the Complex Meroterpene Berkeleyone A. *J. Am. Chem. Soc.* **2016**, *138* (45), 14868−14871.
(33) Yusubov, M. S.; Postnikov, P. S.; Yusubova, R. Y.; Yoshimura, A.; Juerjens, G.; Kirschning, A.; Zhdankin, V. V. 2-Iodoxybenzoic Acid Tosylates: the Alternative to Dess-Martin Periodinane Oxidizing Reagents. *Adv. Synth. Catal.* **2017**, *359* (18), 3207−3216.

https://doi.org/10.1021/acs.joc.1c00401
J. Org. Chem. XXXX, XXX, XXX−XXX