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Concise stereoselective synthesis of marine sesterterpene, 16-deacetoxy-12-*epi*-scalarafuran acetate and its 14-epimer via intramolecular Diels–Alder addition

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ABSTRACT

The stereoselective synthesis of C12 oxygenated marine scalaranic sesterterpene 16-deacetoxy-12-*epi*-scalarafuran acetate and its 14-epimer were described. A highly stereoselective intramolecular Diels–Alder addition was designed as the key step to construct the ring D, and the absolute configurations of natural 16-deacetoxy-12-*epi*-scalarafuran acetate was supported by the X-ray diffraction analysis of single crystal of corresponding 16-deacetoxy-12-*epi*-scalarafuran.

1. Introduction

A range of scalarane sesterterpenoids,[1] which display a variety of biological activities, such as cytotoxicity,[2] antifeedant activity,[3] anti-inflammatory[4] and platelet-aggregation inhibitory effects,[5] have been isolated from different marine organisms during the past three decades. Many members of this group of scalaranic sesterterpenes possess ABCDE pentacyclic fused ring skeletons **I** (Fig. 1), which contain γ-butenolide or furan as ring E moieties, as well as C12 oxygenated functionality as common structural features. Some representative compounds are depicted in Fig. 1: (+)-scalarolide was first isolated from sponge *Spongia idia* in 1980;[3a] sesterstatins 4–5 and scalarafuran have been found to have potent cytotoxic[6] and HIV-1 integrase inhibiting activities;[7] 16-deacetoxy-scalarafuran, isolated from genus *Spongia*, was reported to have the cytotoxicity against HeLa cells.[8] 16-Deacetoxy-12-*epi*-scalarafuran acetate has the cytotoxicity against brine shrimp.[9]

Due to their important ecological roles, interesting biological properties and unique structural skeleton, many efforts[10–13] have been developed for the construction of the scalarane framework. In the course of our efforts in developing new methods for producing the scalarane sesterterpenes containing C12 oxygenated functional group, which is supposed to be a prerequisite maintaining the biological activity, we have accomplished the first synthesis of marine scalaranic sesterterpene (+)-scalarolide,[14] and sesterstatins 4/5,[15] respectively, through different strategies. For the synthesis of

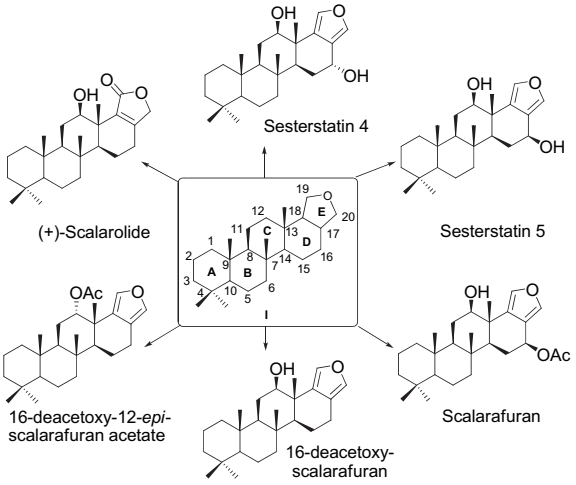

Fig. 1. Representative scalaranic sesterterpenes.

(+)-scalarolide, intermolecular Diels–Alder addition was employed as the key step to construct the ring D; for the latter, a reductive Heck cyclisation was employed as the key step to generate the ring D.

Recently, we further elaborated former synthetic route, and one new member of this series of marine sesterterpene, 16-deacetoxy-scalarafuran and two unnatural analogues of (+)-scalarolide were synthesized.[16] Although, above-mentioned synthetic methods are efficient enough in terms of overall yields and synthetic steps, the stereoselectivity of intermolecular Diels–Alder addition involved in the synthesis of (+)-scalarolide[14] and the yield of reductive Heck reaction for the synthesis of sesterstatins 4/5[15] are still need to be improved. Therefore, we

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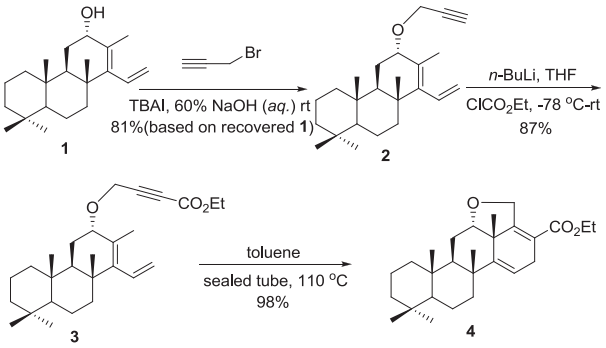
would like to describe herein our recent achievement on the synthesis of natural marine sesterterpene, 16-deacetoxy-12-*epi*-scalarafuran acetate and its 14-epimer, via highly stereoselective intramolecular Diels–Alder addition as key step.

2. Results and discussion

In our previous report,[14] the 12α-OH diene **1**, prepared from starting material sclareol over 13 steps and with an overall 24% yield, was converted to corresponding 12β-OH diene for the intermolecular Diels–Alder addition to construct ring D, however providing a poor stereoselectivity of the angular methyl group at position C-13 (52% yield for major but undesired stereoisomer, 26% yield for desired stereoisomer). On the other hand, intramolecular Diels–Alder strategy has been reported for constructing similar ring system with controlled stereochemistry of corresponding angular methyl group by Abad.[17] Therefore, we further envisaged to employ the similar intramolecular Diels–Alder strategy in order to improve the stereoselectivity of ring D formation.

With this idea in hand, 12α-OH diene **1** was then treated with propargyl bromide under phase-transfer conditions to give corresponding propargyl ether **2** in 81% yield (based on 20% of recovered **1**), which was subjected to sequential treatment with BuLi and ethyl chloroformate in THF at −78 °C, providing **3** in 87% yield. The intramolecular Diels–Alder addition of **3** was then carried out in a sealed tube with heating at 110 °C, and the reaction proceeded smoothly to give corresponding adduct **4** in almost quantitative yield (Scheme 1).[17]



Scheme 1. The intramolecular Diels–Alder addition of **3**.

With the success of constructing ring D with right stereochemistry at C13 angular methyl group, cleavage of the dihydrofuran ring of **4** occurred smoothly and cleanly by treating with Ac_2O and zinc iodide, being accompanied by simultaneous lactonisation to give the scalarane-type lactone **5** in 92% yield.[17] Further hydrogenation of double bond in the presence of 5% Pd/C surprisingly led to two stereoisomers **6a** (desired isomer, 60% yield) and **6b** (undesired one, 20% yield) in 3:1 ratio (determined by NMR). It is worthy noting that two isomers **6a** and **6b** were very difficult to be separated by silica gel column chromatography, which made this process very time-consuming and tedious in order to accumulate enough amount of pure **6a** and **6b** for further transformations. The structure assignment of above two isomers was supported by the X-ray structure of corresponding product 16-deacetoxy-12-*epi*-scalarafuran **7a** derived from isomer **6a** (Fig. 2). Then, the employment of a similar DIBAL-H reduction method in our previous report for the direct furan formation,[16] lactones **6a** and **6b** were smoothly converted two corresponding furans **7a** and **7b** in 80% and 75% yields, respectively. Notably, furan **7a** actually is the 12-epimer of our previous synthetic product, 16-deacetoxy-scalarafuran.[16] Finally, the treatment of both **7a** and **7b** with acetic anhydride afforded the final target compound **8a** and its 14-epimer **8b** in excellent yields (Scheme 2).

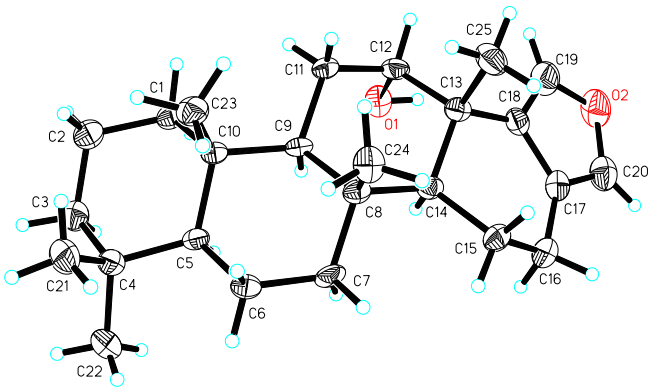
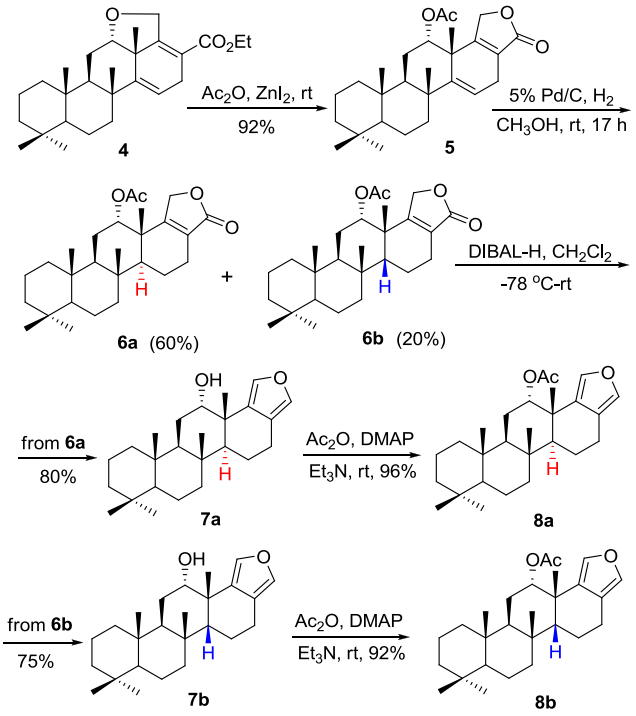


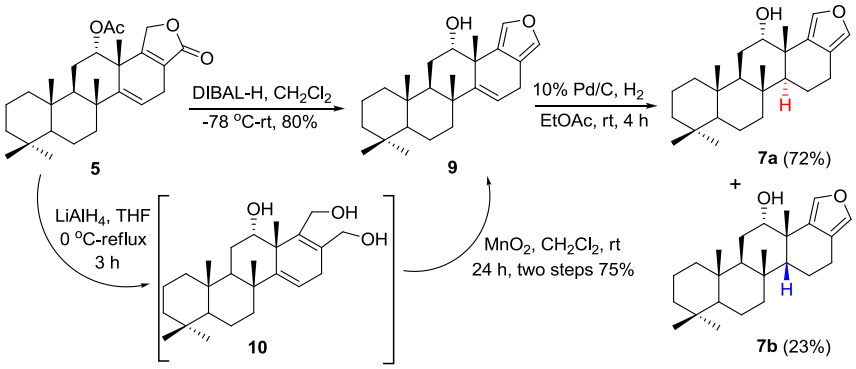
Fig. 2. ORTEP view and atom numbering scheme for **7a**.



Scheme 2. The synthesis of target compound **8a** and its 14-epimer **8b**.

The comparisons of specific optical rotation ($[\alpha]_D^{19}$ +70.0, *c* 0.15, $CHCl_3$) versus ($[\alpha]_D^{25}$ +68.0, *c* 0.5, $CHCl_3$ of lit.[9b]), ^1H NMR, ^{13}C NMR and HRMS data of our synthetic **8a** established the structural identity with the natural 16-deacetoxy-12-*epi*-scalarafuran acetate isolated by Lin.[9b] As shown in Fig. 2, the absolute structure of our synthetic compound **8a** was also supported by the X-ray diffraction analysis of the single crystal of **7a**. Interestingly, both ^1H and ^{13}C NMR spectra of our synthetic **8a** are not completely consistent to that of isolated natural one by De Rosa.[9a]

In view of the poor stereoselectivity in double bond reduction step of lactone **5**, a direct furan formation from lactone **5** using DIBAL-H was therefore tested. Although, corresponding furan **9** was obtained in 80% yield, the stereoselectivity of double bond reduction step was unfortunately still the same as that of previous one. Further investigation showed that furan **9** can also be obtained by the LAH reduction and subsequent MnO_2 oxidation in a similar yield as that of the DIBAL-H reduction process (Scheme 3).



Scheme 3. Alternative routes for the synthesis of furan **7a** from lactone **5**.

3. Conclusion

In summary, we have developed a concise, highly efficient stereoselective synthesis of 16-deacetoxy-12-*epi*-scalarafuran acetate **8a** and its 14-epimer **8b** over 20 steps in overall yields of 8.3% and 2.5%, respectively. It is believed that the developed synthetic method will be of great benefit to the synthesis of other sesterterpenes containing C12 oxygenated functionality, which will further facilitate the pharmacological evaluation of corresponding marine natural or unnatural scalaranic products. Further investigations are currently underway to extend this new synthetic method to generate more analogues of this series of scalaranic sesterterpenes and corresponding investigation of their pharmacological properties.

4. Experimental

4.1. General methods

Melting points were obtained in open capillary tubes using a micro melting point apparatus SGW X-4, which were uncorrected. Mass spectra were recorded by the HP5989A service; HRMS (EI) spectra were obtained on a Finigann MAT8401 instrument. Optical rotations were measured on a AUTOPOLO III polarimeter operating at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL) and solvent. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the residual protons in $CDCl_3$ (δ_H=7.26) at ambient temperatures on the following instruments: Bruker AVANCE DPX-400 (400 MHz). Data are presented as follows: chemical shift (in parts per million on the scale relative to δ_{TMS}=0), integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet), coupling constant (*J*/Hz) and interpretation. ^{13}C NMR spectra were recorded by broadband spin decoupling using an internal deuterium lock for $CDCl_3$ (δ=77.2) at ambient temperatures on the following instruments: Bruker AVANCE DPX-400 (100.6 MHz). Chemical shift values are reported in ppm on the scale (δ_{TMS}=0). Infrared spectra were recorded on NICOLET 5SXC instrument as thin film, frequencies are given as wavenumbers (cm^{-1}). All reagents and solvents were used as purchased if not otherwise stated.

4.2. Preparation of compound 2

The dienol **1** (260 mg, 0.86 mmol), tetrabutylammonium iodide (TBAI) (160 mg, 0.43 mmol) and propargyl bromide (0.67 mL, 8.6 mmol) were added to a cylindrical flask. The mixture was stirred while a 60% aqueous solution of NaOH (2 mL) was added dropwise and the two phase reaction mixture was vigorously stirred at room temperature for 24 h. After this time, the brownish reaction mixture was poured into ice water, extracted with ether, the organic layer was washed with 10% HCl, and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, chromatography on silica gel (2%, EtOAc/petroleum ether) gave **2** (190 mg, 65%) as a white solid, and unreacted starting dienol **1** (52 mg, 20%). Mp: 60–61 °C. HRMS (EI) calcd for $C_{24}H_{36}O$ $[M]^+$ 340.2766, found: 340.2768. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (dd, *J*=17.7, 11.3 Hz, 1H), 5.29 (dd, *J*=11.4, 2.6 Hz, 1H), 4.98 (dd, *J*=17.7, 2.6 Hz, 1H), 4.26 (dd, *J*=15.9, 2.4 Hz, 1H), 4.15 (dd, *J*=15.9, 2.3 Hz, 1H), 3.86 (d, *J*=3.8 Hz, 1H), 2.40 (t, *J*=2.3 Hz, 1H), 1.89 (d, *J*=13.7 Hz, 1H), 1.77 (s, 3H), 1.74–1.63 (m, 3H), 1.63–1.52 (m, 2H), 1.51–1.33 (m, 4H), 1.32–1.20 (m, 2H), 1.17–1.08 (m, 1H), 0.97 (s, 3H), 0.92–0.87 (m, 1H), 0.86 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 133.4, 124.6, 118.2, 79.6, 76.1, 72.8, 55.1, 54.9, 49.1, 41.1, 38.3, 38.0, 37.7, 36.0, 32.2, 32.2, 21.0, 20.2, 18.4, 17.6, 17.6, 17.5, 15.5. IR (film): 3311, 2998, 2956, 2925, 2848, 1384, 1261, 1067, 917, 803, 666, 618 cm^{-1}.

4.3. Preparation of compound 3

Butyl lithium (1.6 M solution in hexane; 1.4 mL, 2.24 mmol) was added dropwise to a solution of **2** (630 mg, 1.85 mmol) in THF (50 mL) at −78 °C under N_2 atmosphere, and the mixture was stirred at the same temperature for 50 min. Ethyl chloroformate (0.23 mL, 2.24 mmol) was added dropwise to the mixture, which was stirred at −78 °C for 1 h, and then automatically risen to room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and concentrated under reduced pressure. The resulting solution was extracted with Et_2O (3×30 mL). The organic layer was washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5%, EtOAc/petroleum ether) to give **3** (664 mg, 87%) as a white amorphous solid. Mp: 60–62 °C. HRMS (EI) calcd for $C_{27}H_{40}O_3$ $[M]^+$ 412.2977, found: 412.2980. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10 (dd, *J*=17.7, 11.4 Hz, 1H), 5.28 (dd, *J*=11.4, 2.5 Hz, 1H), 4.96 (dd, *J*=17.7, 2.5 Hz, 1H), 4.37–4.26 (m, 2H), 4.22 (q, *J*=7.1 Hz, 2H), 3.82 (d, *J*=3.6 Hz, 1H), 1.88 (d, *J*=14.1 Hz, 1H), 1.76 (s, 3H), 1.72–1.63 (m, 3H), 1.61–1.50 (m, 2H), 1.48–1.40 (m, 2H), 1.35 (d, *J*=12.8 Hz, 3H), 1.30 (t, *J*=7.1 Hz, 3H), 1.26–1.19 (m, 1H), 1.12 (td, *J*=13.4, 3.9 Hz, 1H), 0.95 (s, 3H), 0.90–0.87 (m, 1H), 0.85(s, 3H), 0.82 (s, 3H), 0.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 147.4, 134.2, 125.2, 119.3, 84.1, 78.1, 77.7, 62.0, 56.1, 55.9, 50.1, 42.0, 39.3, 39.0, 38.7, 37.0, 33.2, 33.2, 22.1, 21.2, 19.3, 18.5, 18.5, 16.4, 13.9. IR (film): 2998, 2932, 1713, 1388, 1248, 1075, 1053, 800 cm^{-1}.

4.4. Preparation of compounds 4

A solution of diene **3** (200 mg, 0.48 mmol) in degassed anhydrous toluene (4 mL) was heated in a vacuum sealed tube at 110 °C for 24 h. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel (5%, EtOAc/

petroleum ether) to afford the Diels–Alder adduct **4** (196 mg, 98%) as a white solid. Mp: 168–170 °C. HRMS (EI) calcd for $C_{27}H_{40}O_3$ $[M]^+$ 412.2977, found: 412.2961. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.66 (d, J=6.2 Hz, 1H), 4.96 (dd, J=14.1, 1.7 Hz, 1H), 4.32 (dd, J=14.1, 3.7 Hz, 1H), 4.25–4.12 (m, 2H), 3.90 (t, J=3.1 Hz, 1H), 3.33 (dd, J=20.6, 6.5 Hz, 1H), 2.64 (d, J=20.6 Hz, 1H), 1.95–1.92 (m, 3H), 1.72–1.58 (m, 3H), 1.54–1.43 (m, 2H), 1.40–1.32 (m, 3H), 1.29 (t, J=7.1 Hz, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.05 (d, J=8.9 Hz, 2H), 0.88 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H), 0.78 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 163.7, 155.0, 121.7, 117.8, 83.1, 68.7, 60.4, 56.1, 48.5, 45.5, 41.8, 40.4, 39.7, 38.6, 37.4, 33.4, 33.2, 26.9, 24.2, 23.4, 22.8, 21.6, 18.5, 18.5, 15.6, 14.3. IR (film): 2977, 2959, 2925, 2861, 1705, 1448, 1259, 1033 cm^{-1}.

4.5. Preparation of compound 5

A mixture of the Diels–Alder adduct **4** (150 mg, 0.36 mmol) and ZnI_2 (147 mg, 0.46 mmol) in acetic anhydride (2 mL) was stirred at room temperature for 24 h. The reaction mixture was poured into water and extracted with ether. The organic extracts were washed with saturated aqueous $NaHCO_3$, brine, dried with Na_2SO_4 and concentrated under reduced pressure. The resulting residue was then purified by silica gel column chromatography (15%, EtOAc/petroleum ether) to afford the lactone **5** (143 mg, 92%) as a white solid. Mp: 81–83 °C. HRMS (EI) calcd for $C_{27}H_{38}O_4$ $[M]^+$ 426.2770, found: 426.2775. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76–5.74 (m, 1H), 4.96 (t, J=2.6 Hz, 1H), 4.84–4.80 (m, 1H), 4.48 (dt, J=16.6, 2.4 Hz, 1H), 2.99–2.93 (m, 1H), 2.86–2.79 (m, 1H), 2.00 (s, 3H), 1.96–1.83 (m, 3H), 1.72–1.61 (m, 4H), 1.54–1.46 (m, 2H), 1.43 (s, 3H), 1.39–1.36 (m, 2H), 1.31 (dd, J=12.0, 3.1 Hz, 1H), 1.22 (s, 3H), 1.15–1.07 (m, 1H), 0.87 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H), 0.60–0.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 170.4, 164.6, 148.2, 123.4, 116.8, 75.8, 68.6, 56.4, 49.9, 41.8, 41.6, 40.9, 40.4, 39.8, 37.4, 33.3, 33.2, 27.5, 25.0, 22.4, 21.8, 21.4, 21.3, 18.7, 18.5, 16.0. IR (film): 2934, 1764, 1737, 1377, 1244, 1040, 750 cm^{-1}.

4.6. Preparation of compounds 6a and 6b

A solution of lactone **5** (50 mg, 0.12 mmol) in anhydrous CH_3OH (5 mL) containing 5% palladium on charcoal catalyst (100 mg) was stirred under an atmosphere of H_2 for 17 h. The catalyst was removed by filtration and the solvent evaporated to obtain a mixture, which after silica gel column chromatography (15%, EtOAc/petroleum ether) afforded **6a** (30 mg, 60%) as colourless viscous oil and **6b** (10 mg, 20%) as a white solid. Data for **6a**: HRMS (EI) calcd for $C_{27}H_{41}O_4$ $[M+H]^+$ 429.3005, found: 429.3003. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.96 (s, 1H), 4.70 (d, J=16.8 Hz, 1H), 4.42 (dd, J=16.8, 2.4 Hz, 1H), 2.42–2.37(m, 1H), 2.18–2.10 (m, 1H), 2.05 (s, 3H), 1.94–1.84 (m, 3H), 1.74–1.63 (m, 3H), 1.56–1.48 (m, 2H), 1.45–1.36 (m, 3H), 1.26 (d, J=7.5 Hz, 3H), 1.21 (s, 3H), 1.16–1.02 (m, 2H), 0.93 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H), 0.82 (s, 3H), 0.61–0.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 170.3, 167.3, 125.5, 75.0, 68.1, 56.6, 52.9, 50.5, 41.9, 41.3, 40.8, 39.8, 37.7, 36.9, 33.3, 33.2, 22.1, 21.5, 21.4, 21.4, 21.3,18.5, 18.1, 17.3, 16.7, 16.0. Data for **6b**: mp: 188–190 °C. HRMS (EI) calcd for $C_{27}H_{40}O_4$ $[M]^+$ 428.2927, found: 428.2925. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07 (t, J=4.0 Hz, 1H), 4.77 (dd, J=16.8, 1.6 Hz, 1H), 4.69 (d, J=16.9 Hz, 1H), 2.42–2.37 (m, 1H), 2.13–2.03 (m, 2H), 1.97 (s, 3H), 1.88–1.76 (m, 3H), 1.66–1.57 (m, 5H), 1.56–1.39 (m, 5H), 1.37 (s, 3H), 1.23 (s, 3H), 1.17–1.09 (m, 1H), 0.88 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H), 0.81–0.77 (m, 1H), 0.69–0.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 169.9, 165.4, 127.0, 75.6, 69.8, 56.9, 54.5, 41.8, 41.0, 39.7, 39.1, 38.0, 37.4, 33.4, 33.3, 27.9, 27.3, 23.4, 21.7, 21.6, 21.2, 20.1, 18.5, 18.4, 16.0. IR (film): 2990, 2925, 2849, 1758, 1729, 1691, 1372, 1249,1032 cm^{-1}.

4.7. Preparation of compound 7a

A solution of the reduced adduct **6a** (15 mg, 0.035 mmol) in anhydrous CH_2Cl_2 (2 mL) was treated with DIBAL-H (1.0 M solution in hexane; 0.124 mL, 0.124 mmol) at −78 °C under N_2 atmosphere. The solution was stirred at the same temperature for 2 h, and then automatically risen to room temperature, quenched by the addition of saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with 5% HCl and water, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (5%, EtOAc/petroleum ether) to afford the furan **7a** (10 mg, 80%) as a white solid. Mp: 270–272 °C. HRMS (EI) calcd for $C_{25}H_{38}O_2$ $[M]^+$ 370.2872, found: 370.2873. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, J=1.2 Hz, 1H), 7.13 (s, 1H), 4.10 (s, 1H), 2.73 (dd, J=16.0, 5.2 Hz, 1H), 2.43–2.34 (m, 1H), 1.96 (s, 1H), 1.87–1.82 (m, 2H), 1.81–1.72 (m, 2H), 1.68–1.61 (m, 3H), 1.58 (s, 3H), 1.55–1.53 (m, 1H), 1.44–1.34 (m, 3H), 1.24 (s, 3H), 1.14 (td, J=13.4, 4.1 Hz, 1H), 1.05 (td, J=12.4, 3.8 Hz, 1H), 0.91 (s, 3H), 0.88 (d, J=4.0 Hz, 1H), 0.85 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 134.8, 132.5, 121.4, 73.4, 56.6, 51.3, 50.2, 42.1, 41.7, 40.9, 39.6, 38.1, 37.0, 33.3, 33.3, 26.7, 23.0, 21.3, 21.1, 18.6, 18.3, 17.8, 17.5, 16.2. IR (film): 3568, 2959, 2925, 2847, 1386, 1042, 887, 789, 593 cm^{-1}. The X-ray crystallography data of **7a** are listed below: a colourless monoclinic crystal from *n*-hexane/ethyl acetate (3:1) was exposed to graphite-monochromated Mo Kα irradiation. The structures were solved by direct methods and refined on F^2 using all the reflections. $C_{25}H_{38}O_2$, M=370.55, monoclinic, a=13.497(4) Å, b=6.2157(16) Å, c=24.920(6) Å, β=94.080(9)°, V=2085.4(10) Å^3, space group $P2_1/c$, Z=4, μ=0.072 mm^{-1}, D_x=1.180 Mg/m^3, 5427 data (2126 unique, R_{int}=0.0949) were measured in the range $1.64<\theta<25.50°$. $R_1(I>2\sigma(I))$=0.0628 and wR_2(all data)=0.1489. Goodness of fit on F^2=1.012. CCDC No. 201429.

4.8. Preparation of compound 7b

A solution of furan **9** (50 mg, 0.13 mmol) in anhydrous EtOAc (5 mL) containing 10% palladium on charcoal catalyst (100 mg) was stirred under an atmosphere of H_2 for 4 h. The catalyst was removed by filtration and the solvent evaporated to obtain a mixture, which after silica gel column chromatography (5%, EtOAc/petroleum ether) afforded **7a** (36 mg, 72%) and **7b** (21 mg, 23%) as white solids. Data for **7b**: mp: 171–173 °C. HRMS (EI) calcd for $C_{25}H_{38}O_2$ $[M]^+$ 370.2872, found: 370.2865. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J=1.3 Hz, 1H), 7.15 (s, 1H), 3.84 (s, 1H), 2.71 (dt, J=15.6, 3.8 Hz, 1H), 2.34–2.25 (m, 1H), 2.14–2.07 (m, 1H), 1.96–1.85 (m, 2H), 1.83–1.79 (m, 1H), 1.76–1.66 (m, 2H), 1.62–1.55 (m, 4H), 1.50 (s, 1H), 1.46 (s, 3H), 1.43–1.35 (m, 2H), 1.31–1.26 (m, 3H), 1.20 (s, 3H), 1.16 (dd, J=13.8, 4.6 Hz, 1H), 1.11 (s, 1H), 0.87 (s, 6H), 0.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 136.7, 131.4, 123.0, 78.1, 57.1, 55.5, 44.5, 42.0, 39.8, 39.7, 38.4, 37.3, 33.5, 33.3, 32.6, 27.4, 24.5, 23.4, 21.7, 20.6, 18.7, 18.6, 16.2. IR (film): 3576, 2957, 2922, 2851, 1387, 1044, 889, 781, 595 cm^{-1}.

4.9. Preparation of compound 8a

DMAP (3.0 mg, 0.025 mmol) was added to a solution of the furan **7a** (6 mg, 0.016 mmol), acetic anhydride (0.4 mL, 4.1 mmol) and Et_3N (0.4 mL) in dry dichloromethane (1 mL) and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with CH_2Cl_2 and then washed successively with 5% HCl, 5% $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and evaporated to afford a residue, which was purified on silica gel (3%, EtOAc/petroleum ether) to give pure furan acetate **8a** (6.3 mg, 96%) as a white solid. Mp: 130–132 °C (lit.[9b] 130–132 °C). $[\alpha]_D^{19}$ +70.0 (*c* 0.15, $CHCl_3$) (lit.[9b] $[\alpha]_D^{25}$ +68.0 (*c* 0.5, $CHCl_3$)). HRMS (EI) calcd for $C_{27}H_{40}O_3$ $[M]^+$

412.2977, found: 412.2975. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (s, 1H), 6.96 (s, 1H), 5.35 (t, J=2.8 Hz, 1H), 2.74 (dd, J=15.3, 4.5 Hz, 1H), 2.45–2.36 (m, 1H), 1.91 (s, 3H), 1.83–1.77 (m, 3H), 1.63–1.58 (m, 4H), 1.49–1.34 (m, 5H), 1.27 (s, 3H), 1.19–1.04 (m, 3H), 0.93 (s, 3H), 0.88 (d, J=2.1 Hz, 1H), 0.86 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H), 0.68–0.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 136.8, 135.1, 132.1, 120.4, 75.3, 56.7, 52.7, 51.4, 42.0, 41.7, 39.7, 38.8, 37.8, 37.0, 33.3, 33.3, 26.7, 22.3, 21.3, 20.9, 18.5, 18.2, 18.0, 17.4, 16.1. IR (film): 2960, 2924, 2852, 1732, 1385, 1243,1040, 806, 600 cm^{-1}.

4.10. Preparation of compound 8b

This experimental procedure was the same as the preparation of compound **8a**. After silica gel column chromatography (3%, EtOAc/petroleum ether) to afford the furan **8b** in 92% yield as a white solid. HRMS (EI) calcd for $C_{27}H_{40}O_3$ [M]$^+$ 412.2977, found: 412.2975. ^{1}H NMR (400 MHz, $CDCl_3$) 7.22 (s, 1H), 7.06 (s, 1H), 5.15 (t, J=4.3 Hz, 1H), 2.70 (dt, J=15.7, 5.0 Hz, 1H), 2.39–2.31 (m, 1H), 2.09–2.02 (m, 1H), 1.95–1.84 (m, 3H), 1.82 (s, 3H), 1.61–1.54 (m, 4H), 1.46 (s, 3H), 1.37–1.32 (m, 5H), 1.25 (s, 1H), 1.21 (s, 3H), 1.15–1.07 (m, 1H), 0.87 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H), 0.79–0.81 (m, 1H), 0.66–0.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 138.3, 135.7, 130.2, 121.7, 79.3, 56.9, 55.2, 46.5, 41.9, 39.7, 39.3, 38.1, 38.0, 37.5, 33.4, 33.3, 32.3, 27.9, 23.8, 22.8, 21.7, 21.1, 19.9, 18.7, 18.5, 16.0. IR (film): 2955, 2920, 2852, 1731, 1386, 1247, 1040, 785, 597 cm^{-1}.

4.11. Preparation of compound 9 through DIBAL-H reduction; LAH reduction and subsequent MnO_2 oxidation

4.11.1. Through DIBAL-H reduction. This experimental procedure was the same as the preparation of compound **7a**. After silica gel column chromatography (5%, EtOAc/petroleum ether) to afford the furan **9** in 80% yield as a white solid.

4.11.2. Through LAH reduction and subsequent MnO_2 oxidation. To a solution of **5** (30 mg, 0.07 mmol) in dry THF (5 mL), $LiAlH_4$ (14 mg, 0.37 mmol) was added at 0 °C. Then the reaction was refluxed for 3 h. Water was added to quench the unreacted $LiAlH_4$. The mixture was extracted with Et_2O (3×5 mL), and the organic phase was washed successively with brine, dried over Na_2SO_4. After removing the solvent, the residue was directly used for the next step. To a solution of the residue in CH_2Cl_2 (5 mL), MnO_2 (50 mg, 0.57 mmol) was added. The mixture was stirred at room temperature for 24 h. The catalyst was removed by filtration and the solvent was evaporated to obtain the residue, which after silica gel column chromatography (5%, EtOAc/petroleum ether) afforded **9** (20 mg, two steps 75%) as a white solid. Data for **9**. Mp: 162–164 °C. HRMS (EI) calcd for $C_{25}H_{36}O_2$ [M]$^+$ 368.2715, found: 368.2724. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J=1.0 Hz, 1H), 7.22 (d, J=1.0 Hz, 1H), 5.79 (dd, J=5.2, 2.5 Hz, 1H), 4.11 (s, 1H), 3.27 (dd, J=20.9, 5.2 Hz, 1H), 3.11 (dt, J=20.9, 1.9 Hz, 1H), 2.00 (s, 1H), 1.94–1.91 (m, 3H), 1.71–1.65 (m, 2H), 1.62–1.58 (m, 2H), 1.54–1.46 (m, 2H), 1.44 (s, 3H), 1.42–1.37 (m, 1H), 1.33 (s, 1H), 1.27 (d, J=11.7 Hz, 2H), 1.21 (s, 3H), 1.11 (td, J=13.3, 4.0 Hz, 1H), 0.90 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 137.3, 135.3, 130.6, 119.6, 117.5, 74.3, 56.3, 48.5, 42.0, 41.3, 41.0, 40.5, 39.6, 37.4, 33.3, 33.3, 32.1, 25.3, 23.4, 21.4, 20.8, 18.9, 18.6, 16.3. IR (film): 2959, 2921, 2854, 1461, 1382, 1081, 1034, 811, 595 cm^{-1}.

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Supplementary data

The ^{1}H NMR and ^{13}C NMR copies of all compounds were attached. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.072.

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