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Stereoselective synthesis of marine sesterterpenes, 16-deacetoxy-scalarafuran, (+)-scalarolide and their analogs

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ABSTRACT

The stereoselective synthesis of C12 oxygenated marine scalaranic sesterterpenes 16-deacetoxy-scalarafuran, (+)-scalarolide and their unnatural analogs were described. Three key transformations were involved in their synthesis, which are the ring-opening rearrangement of epoxide, stereoselective Diels–Alder addition, and one-pot γ-butenolide formation process, and the absolute configurations of natural (+)-scalarolide and 16-deacetoxy-scalarafuran were confirmed.

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 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] have been developed for the construction of the scalarane framework, such as: (i) biomimetic cyclization sequence of suitably constructed aliphatic[11] or bicyclic[12] C25 substrates; (ii) Diels–Alder addition constructing of the D ring from an ABC tricyclic ring precursor.[13] However, to the best of our knowledge, all the above-mentioned synthetic methods end up with the construction of the tetracyclic ring skeleton, none of them has been successfully utilized to produce the scalarane sesterterpenes containing C12 oxygenated group, which is supposed to be a prerequisite maintaining the biological activity.

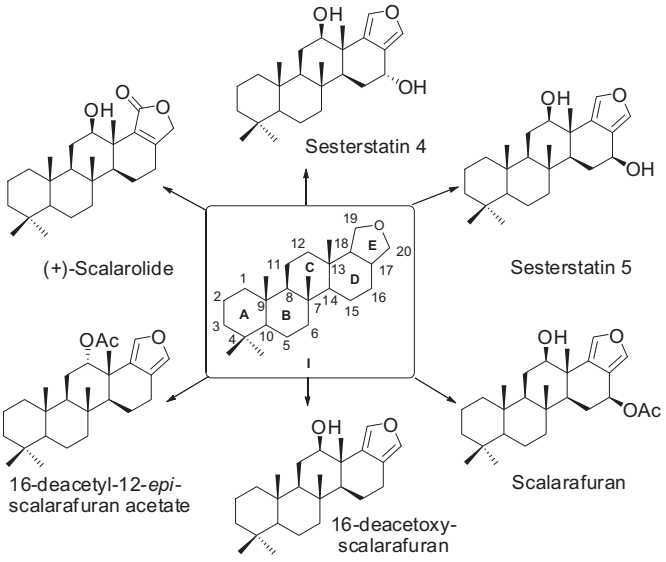

Fig. 1. Representative scalaranic sesterterpenes.

Recently, we reported the first synthesis of marine scalaranic sesterterpene (+)-scalarolide,[14] and sesterstatins 4/5,[15] respectively, through different strategies. For the synthesis of (+)-scalarolide, Diels–Alder addition was employed as the key step to construct the ring D; for the latter, a reductive Heck cyclization was employed as the key step to afford the ring D. In the continuation of our efforts to the synthesis of small library of marine scalaranic sesterterpenes for the marine lead compound discovery, we further elaborated former synthetic route, and one new member of this series, 16-deacetoxy-scalarafuran and two unnatural analogues

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of (+)-scalarolide were synthesized. Herein, we would like to describe our recent achievement on the synthesis of 16-deacetoxy-scalarafuran, (+)-scalarolide and their derivatives in details.

2. Results and discussion

A retrosynthetic analysis of 16-deacetoxy-scalarafuran is shown in Fig. 2. The furan moiety could be synthesized from the diester compound, which could be prepared from the Diels–Alder addition of tricyclic diene with DMAD to construct the ring D. The 12-OH group can be introduced from an epoxide via epoxidation of tricyclic methyl *ent*-isocopalate, which can be easily synthesized using sclareol **1** as starting material according to a published method.[12b,13a,16,17]

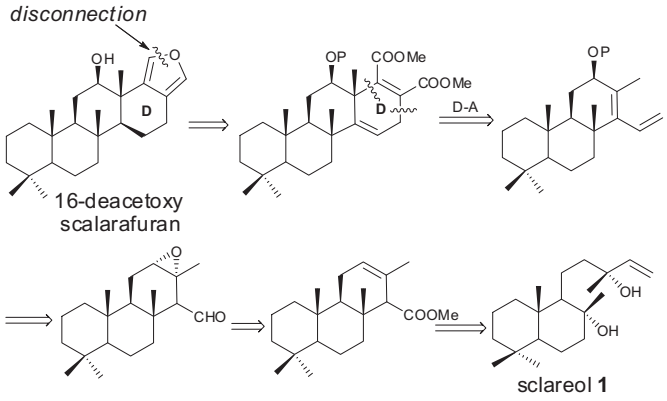
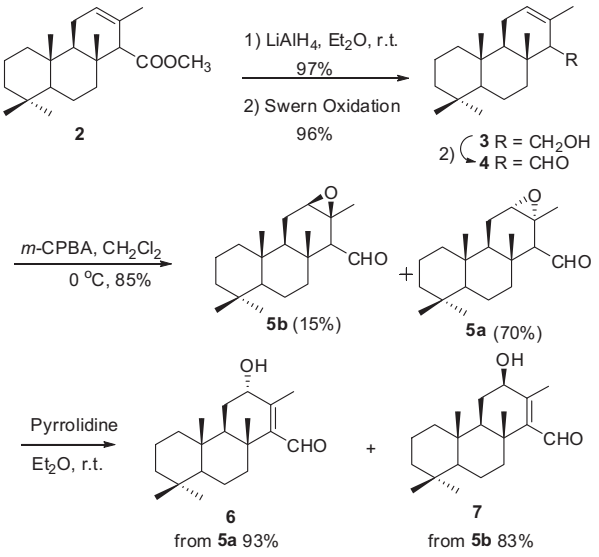


Fig. 2. The retrosynthetic analysis of 16-deacetoxy-scalarafuran.

Tricyclic intermediate **2** was prepared by a published procedure[12b,13a,16] from readily available sclareol **1**. LAH reduction of **2** and subsequent Swern oxidation afforded aldehyde **4**, which was subjected to an epoxidation to generate the epoxide **5a** as major product in 70% yield, accompanied by a minor product **5b** in 15% yield (Scheme 1). The epoxide **5a** underwent smoothly a ring-opening rearrangement to afford 12α-OH-α, β-unsaturated aldehyde **6** using pyrrolidine as base in ether at room temperature.[18] It was notable that 12β-OH-α, β-unsaturated aldehyde **7** can be also synthesized from compound **5b** under the same condition (Scheme 1). Therefore, the both epimers of **6** and **7** were prepared via the same procedure and can be utilized for further synthesis.



Scheme 1. The establishment of C12 hydroxy group.

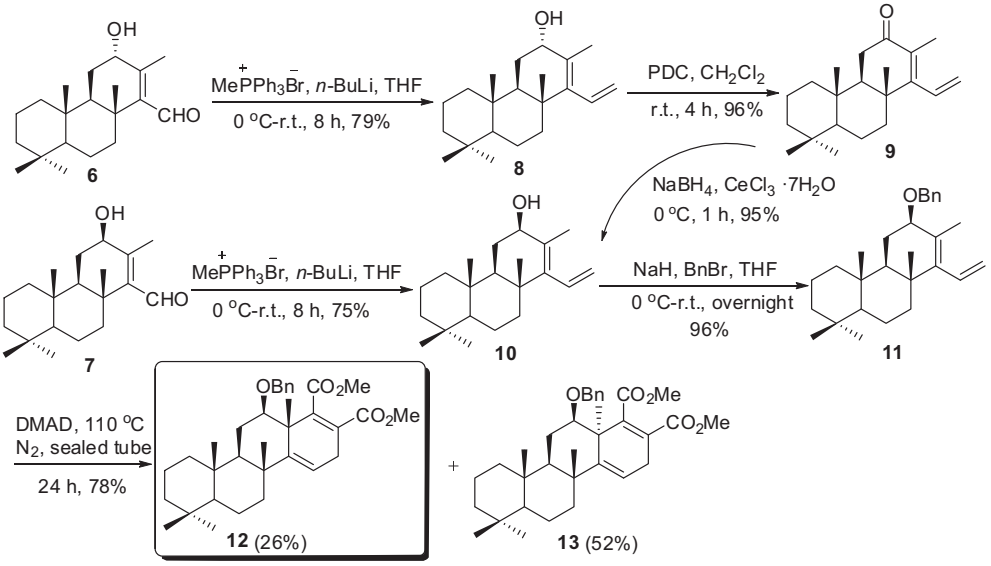
With the success of the establishment of C12 hydroxy group on the tricyclic ring skeleton, we then focused on the stereoselective Diels–Alder addition. As shown in Scheme 2, Wittig olefination of enal **6** provided the 12α-OH diene **8** in 79% yield, followed by a consecutive oxidation with PDC and stereoselective Luche reduction to produce the 12β-OH diene **10**, which can be also prepared through Wittig reaction of **7** in one-step. The benzyl protection of **10** with benzyl bromide gave diene **11**, which was then subjected to Diels–Alder addition with DMAD in sealed tube at 110 °C. As expected, the Diels–Alder addition afforded desired **12** in 26% yield and undesired **13** in 52% yield. The 2D NOESY spectra of **12** and **13** established the above stereochemical assignment due to an obvious crosspeak between newly formed angular methyl group and the axial proton at C12 for **13**, while the absence of such a crosspeak for **12**. This stereochemical result is different from that of previous report.[13b] Unfortunately, many attempts to improve the stereoselectivity by changing the benzyl protecting group to other group, such as MOM, Acyl, and TBS turned out unsuccessful.

With two diastereoisomers **12** and **13** in hands, we initially try to reduce the diester group to form furan ring using major isomer **13** as model substrate. Interestingly, reduction of diester **13** with LAH (0.75 equiv) in ether resulted in the regioselective reduction of less hindered methyl ester group, and spontaneous lactonization afforded γ-butenolide **14** in 80% yield. This one-pot process of regioselective construction of γ-butenolide moiety is superior to that of previously reported synthetic route of (+)-12-deoxyscalarolide.[19] Further hydrogenation of **14** using 10% Pd/C accomplished the synthesis of 25-*epi*-scalarolide **15** in 95% yield. However, if an excess of LAH was used (10 equiv), both two esters of **13** were reduced to afford diol **16** in 69% yield, and further oxidation with pyridinium chlorochromate afforded the expected furan **17** in 92% yield. Finally, deprotection of benzyl group and reduction of double bond catalyzed by 10% Pd/C in ethyl acetate in one step afforded 25-*epi*-16-deacetoxy-scalarafuran **18**, an epimer of natural 16-deacetoxy-scalarafuran in 86% yield (Scheme 3).

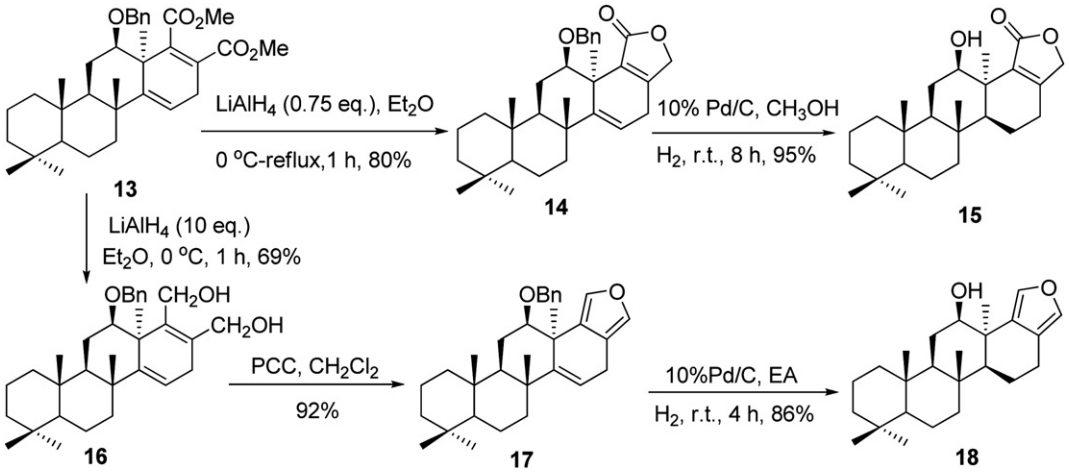
Encouraged by the success of model reaction, we then turned to the transformation of minor, but desired isomer **12**. Using the above-mentioned methods, γ-butenolide **19** was synthesized via the LAH (0.75 equiv) reduction of **12**, followed by debenzylation and hydrogenation with 10% Pd/C to obtain **20** in high yield. Comparisons of specific optical rotation ($[\alpha]_D^{18}$ +23.6, *c* 0.13, CH_2Cl_2) versus ($[\alpha]_D^{20}$ +26.3, *c* 0.15, CH_2Cl_2 of lit.[2b]), ^{1}H NMR, ^{13}C NMR, and HRMS data of our synthetic **20** established the structural identity with the natural (+)-scalarolide isolated by Youssef[2b] and Faulkner.[3a] Likewise, when the amount of LAH was increased to 10 equiv, the diol **21** was afforded in 65% yield, which was then oxidized by pyridinium chlorochromate to form the furan **22** in 90% yield. Unfortunately, hydrogenation of compound **22** led to the reduction of the furan to form a saturated furan ring, which differs from the transformation of **17** to **18**. Fortunately, when DIBAL-H was used instead of LAH for the reduction of the γ-butenolide **20**, the product **24** was obtained in 65% yield (Scheme 4). Comparisons of specific optical rotation ($[\alpha]_D^{18}$ −6.8, *c* 0.08, $CHCl_3$) versus ($[\alpha]_D^{25}$ −9.1, *c* 0.076, $CHCl_3$ of lit.[8a]), ^{1}H NMR, ^{13}C NMR, and HRMS data of our synthetic **24** established the structural identity with the natural 16-deacetoxy-scalarafuran isolated by Tsukamoto.[8a]

3. Conclusion

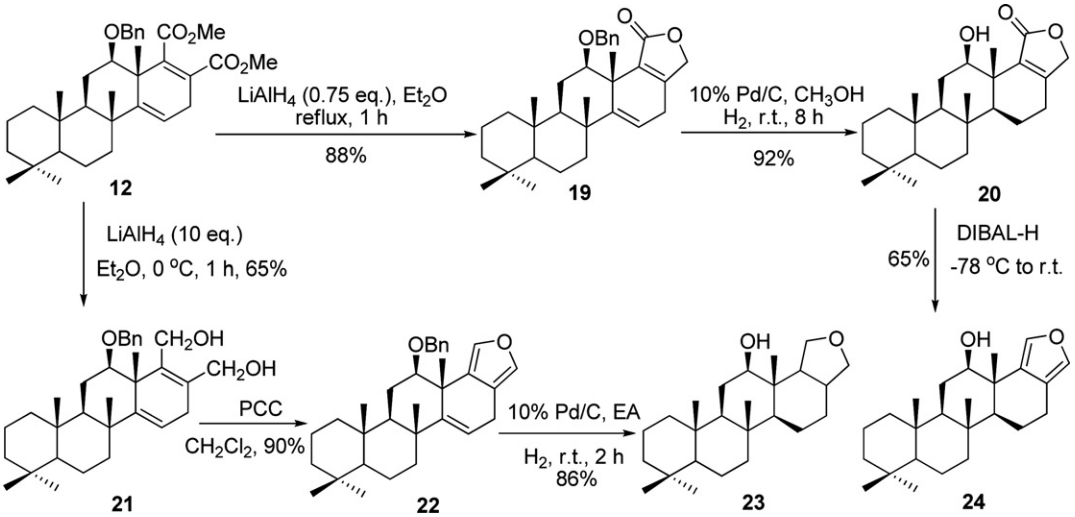
In summary, the first stereoselective synthesis of 16-deacetoxy-scalarafuran **24** was finished in 20 steps with overall yield of 2.9%, and also a series of scalaranic unnatural compounds, such as 25-*epi*-scalarolide **15** and 25-*epi*-16-deacetoxy-scalarafuran **18** etc., were synthesized in an efficient way. It is believed that the developed synthetic method will be of benefit to the synthesis of other sesterterpenes containing C12 oxygenated functionality,



Scheme 2. Synthesis of Diels–Alder adducts **12** and its stereoisomer **13**.



Scheme 3. Synthesis of 25-*epi*-16-deacetoxy-scalarafuran **18**.



Scheme 4. Synthesis of (+)-scalarolide **20** and 16-deacetoxy-scalarafuran **24**.

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 analogs of 16-deacetoxy-scalarafuran 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 ppm 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 parts per million 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 3

To a solution of **2** (420 mg, 1.32 mmol) in dry Et_2O (30 mL) $LiAlH_4$ (50 mg, 1.32 mmol) was added at 0 °C, and the reaction was stirred at 0 °C for 6 h. Once the reaction was finished as judged by TLC, water (2 mL) was added to quench the unreacted $LiAlH_4$. The mixture was then extracted with CH_2Cl_2 (3×10 mL), and the organic phase was washed with saturated NaCl, dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (10%, EtOAc/petroleum ether) to give **3** (372 mg, 97%) as a white solid. R_f=0.2, petroleum ether/EtOAc (20/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.50 (s, 1H), 3.88–3.82 (m, 1H), 3.76–3.69 (m, 1H), 2.07 (dt, J=3.2, 12.6 Hz, 1H), 1.95–1.83 (m, 3H), 1.78 (s, 3H), 1.67–1.57 (m, 2H), 1.55–1.51 (m, 1H), 1.43–1.31 (m, 3H), 1.25–1.07 (m, 4H), 0.89 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H), 0.81–0.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.7, 123.8, 60.8, 57.8, 56.2, 54.8, 41.9, 41.5, 39.9, 37.2, 36.2, 33.4, 33.1, 22.6, 21.9, 21.7, 18.8, 18.5, 15.8, 15.8.

4.3. Preparation of compound 4

A solution of dimethyl sulfoxide (1.2 mL, 15.2 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a stirred solution of oxalyl chloride (0.7 mL, 7.6 mmol) in CH_2Cl_2 (25 mL) under dry nitrogen at −60 °C. After 3 min at −60 °C, a solution of the alcohol **3** (2.0 g, 6.9 mmol) in CH_2Cl_2/dimethyl sulfoxide (3/1; 10 mL) was added dropwise over 5 min. The reaction mixture was stirred for a further 20 min, triethylamine (4.8 mL, 36.1 mmol) was added at −60 °C, and stirring was continued for a further 10 min. The cooling bath was removed, water was added at room temperature, and the product was extracted with ether (3×10 mL). The ether was evaporated off and the remaining dimethyl sulfoxide was removed under reduced pressure, yielding a crude product as a gum. Chromatography on silica gel using 3% EtOAc/petroleum ether as the eluant afforded the aldehyde **4** (1.95 g, 96%). The procedure of Nakano et al. was used.[13a] R_f=0.4, petroleum ether/EtOAc (50/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (d, J=5.1 Hz, 1H), 5.66 (s, 1H), 2.60 (s, 1H), 2.04–1.95 (m, 2H), 1.79–1.73 (m, 1H), 1.68–1.63 (m, 1H), 1.62 (s, 3H), 1.59–1.52 (m, 2H), 1.44–1.31 (m, 4H), 1.18–1.06 (m, 2H), 1.05 (s, 3H), 0.92 (s, 3H), 0.86 (s, 3H), 0.85–0.82 (m, 1H), 0.81 (s, 3H), 0.81–0.75 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 127.6, 125.2, 68.0, 56.4, 53.9, 41.8, 41.8, 39.8, 37.5, 37.3, 33.4, 33.2, 22.6, 21.7, 21.5, 18.4, 18.3, 16.6, 15.9. The data is in agreement with that reported by Nakano et al.[13a]

4.4. Preparation of compounds 5a and 5b

To an ice-cooled solution of **4** (2.00 g, 6.93 mmol) in dry CH_2Cl_2 (60 mL) was added *m*-CPBA (85%, 1.55 g, 7.63 mmol), the mixture was stirred at 0 °C for 12 h. The CH_2Cl_2 solution was filtered, and the filtrate was washed successively with saturated Na_2SO_3 (40 mL), then washed with 0.1 N NaOH (3×20 mL) and saturated brine, dried over Na_2SO_4, and concentrated in vacuo to give a solid residue, which was purified by column chromatography (5%, EtOAc/petroleum ether) to give **5a** (1.47 g, 70%) and **5b** (316 mg, 15%). R_f=0.20 for **5a** and 0.25 for **5b**, petroleum ether/EtOAc (30/1). Data for **5a**: mp: 139–141 °C. EI(MS) m/z 304.1 $[M]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (d, J=5.3 Hz, 1H), 3.09 (s, 1H), 2.24 (d, J=5.2 Hz, 1H), 2.09 (dd, J=4.4, 15.2 Hz, 1H), 1.82–1.72 (m, 1H), 1.68–1.37 (m, 6H), 1.34 (s, 3H), 1.31–1.20 (m, 2H), 1.15 (s, 3H), 1.13–1.07 (m, 1H), 0.99 (dd, J=4.7, 12.5 Hz, 1H), 0.92 (s, 3H), 0.84 (s, 3H), 0.83–0.81 (m, 1H), 0.80 (s, 3H), 0.79–0.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.6, 67.2, 60.4, 56.1, 55.7, 49.2, 41.6, 41.1, 39.3, 37.3, 36.2, 33.4, 33.1, 22.8, 21.6, 21.6, 18.3, 18.2, 17.0, 16.0. Data for **5b**: mp: 183–185 °C. HRMS(EI) calcd for $C_{20}H_{32}O_2^+$ $[M]^+$ 304.2402, found 304.2402. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (d, J=4.8 Hz, 1H), 3.18 (t, J=1.9 Hz, 1H), 2.14–2.09 (m, 1H), 1.94 (d, J=4.8 Hz, 1H), 1.81–1.64 (m, 3H), 1.54–1.48 (m, 2H), 1.47–1.44 (m, 1H), 1.41–1.39 (m, 1H), 1.38–1.36 (m, 1H), 1.34 (s, 3H), 1.32–1.27 (m, 2H), 1.26 (s, 1H), 0.96 (s, 3H), 0.92 (s, 3H), 0.89–0.87 (m, 1H), 0.85 (s, 3H), 0.82 (s, 3H), 0.81–0.79 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.9, 62.6, 59.2, 57.3, 56.5, 44.6, 41.7, 39.6, 38.4, 37.1, 34.6, 33.4, 33.2, 24.8, 22.7, 21.8, 21.7, 18.4, 18.3, 16.2.

4.5. Preparation of compound 6

To a solution of **5a** (150 mg, 0.49 mmol) in Et_2O (30 mL) was added pyrrolidine (0.1 mL, 1.09 mmol) at room temperature, and the reaction was stirred over night. Once the reaction was finished as judged by TLC, water (5 mL) was added. The mixture was extracted with EtOAc (3×10 mL), the organic layer washed successively with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (10%, EtOAc/petroleum ether) to give **6** (139 mg, 93%) as a white solid. R_f=0.2, petroleum ether/EtOAc (6/1). Mp: 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 4.05 (d, J=4.1 Hz, 1H), 2.49 (dt, J=3.2, 12.9 Hz, 1H), 2.13 (s, 3H), 1.82 (d, J=14.2 Hz, 1H), 1.72–1.58 (m, 4H), 1.47–1.36 (m, 3H), 1.27 (dd, J=1.8, 12.9 Hz, 1H), 1.17 (s, 3H), 1.16–1.08 (m, 2H), 0.92–0.89 (m, 1H), 0.88 (s, 3H), 0.87–0.85 (m, 1H), 0.84 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 148.4, 145.0, 70.7, 56.5, 56.3, 50.3, 42.0, 39.6, 38.9, 37.6, 37.0, 33.2, 27.1, 21.2, 19.8, 18.5, 18.4, 16.8, 16.5.

4.6. Preparation of compound 7

To a solution of **5b** (150 mg, 0.49 mmol) in Et_2O (30 mL) was added pyrrolidine (0.1 mL, 1.09 mmol) at room temperature, and the reaction was stirred over night. Once the reaction was finished as judged by TLC, water (5 mL) was added. The mixture was extracted with EtOAc (3×10 mL), the organic layer washed successively with brine, dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (10%, EtOAc/petroleum ether)

to give **7** (125 mg, 83%) as a white solid and was directly used for the next step. R_f=0.2, petroleum ether/EtOAc (6/1). Mp: 183–184 °C. EIMS *m*/*z* 304.3 $[M]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (s, 1H), 4.15 (dd, *J*=8.0, 16.7 Hz, 1H), 2.52 (dt, *J*=3.2, 12.9 Hz, 1H), 2.18–2.11 (m, 1H), 2.10 (s, 3H), 1.75–1.62 (m, 2H), 1.58–1.54 (m, 1H), 1.49–1.33 (m, 4H), 1.26 (s, 3H), 1.18–1.05 (m, 3H), 0.88 (s, 3H), 0.84 (br s, 4H), 0.81 (s, 3H), 0.80–0.73 (m, 1H).

4.7. Preparation of compound 8

To a suspension of methyltriphenylphosphonium bromide (411 mg, 1.15 mmol) in THF (25 mL) at 0 °C under nitrogen atmosphere, a solution of *n*-BuLi in hexane (1.6 M, 0.6 mL, 0.96 mmol) was added dropwise. The solution was stirred for a further 40 min, then a solution of aldehyde **6** (158 mg, 0.52 mmol) in THF (5 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 8 h, then quenched with aqueous NH_4Cl (2 mL), and extracted with Et_2O (3×10 mL). The organic layer was washed with saturated brine and dried over Na_2SO_4. The residue was obtained after removing the solvent and purified by chromatography (5%, EtOAc/petroleum ether) afforded **8** (124 mg, 79%) as a white solid. R_f=0.3, petroleum ether/EtOAc (20/1). Mp: 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (dd, *J*=11.3, 17.7 Hz, 1H), 5.30 (dd, *J*=2.6, 11.3 Hz, 1H), 4.96 (dd, *J*=2.6, 17.7 Hz, 1H), 4.00 (d, *J*=3.8 Hz, 1H), 1.79 (s, 3H), 1.77–1.72 (m, 2H), 1.71–1.68 (m, 1H), 1.67–1.60 (m, 1H), 1.58–1.54 (m, 1H), 1.50 (s, 1H), 1.47–1.41 (m, 1H), 1.40–1.34 (m, 2H), 1.33–1.28 (m, 1H), 1.23–1.09 (m, 2H), 0.97 (s, 3H), 0.92–0.87 (m, 2H), 0.86 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 134.3, 127.1, 119.2, 70.5, 56.5, 50.2, 42.1, 39.6, 39.3, 38.8, 37.0, 33.3 (2C), 27.5, 21.3, 19.4, 18.7, 18.6, 18.5, 16.5. IR (film): 3414, 2996, 2932, 1623, 1401, 1200, 967, 917 cm^{-1}.

4.8. Preparation of compound 9

To a solution of **8** (120 mg, 0.40 mmol) in CH_2Cl_2 (20 mL) was added PDC (752 mg, 2.0 mmol), and the solution was stirred at room temperature for 4 h. Once the reaction was finished, PDC was filtered, and the solvent was concentrated in vacuo to give a solid residue, which was purified by column chromatography (3%, EtOAc/petroleum ether) to give **9** (114 mg, 96%) as a white solid. R_f=0.3, petroleum ether/EtOAc (40/1). Mp: 116–118 °C. EI(MS) *m*/*z* 300.2 $[M]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (dd, *J*=11.7, 17.7 Hz, 1H), 5.48 (dd, *J*=2.0, 11.7 Hz, 1H), 5.12 (dd, *J*=2.0, 17.7 Hz, 1H), 2.48 (dd, *J*=4.2, 17.6 Hz, 1H), 2.37 (dd, *J*=13.9, 17.6 Hz, 1H), 1.86–1.80 (m, 1H), 1.78 (s, 3H), 1.72–1.58 (m, 4H), 1.54 (s, 2H), 1.47–1.35 (m, 4H), 1.12 (s, 3H), 0.93 (s, 3H), 0.91–0.87 (m, 1H), 0.86 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 165.0, 133.2, 128.7, 120.8, 56.0, 54.2, 41.9, 39.9, 39.1, 38.9, 37.3, 34.4, 33.2, 33.1, 21.4, 19.2, 18.5, 18.3, 15.8, 13.2. IR (film): 3445, 2958, 2929, 1656, 936, 804 cm^{-1}.

4.9. Preparation of compound 10 from 9

To a solution of **9** (123 mg, 0.41 mmol) in MeOH (10 mL) and CH_2Cl_2 (3 mL) at 0 °C was added $CeCl_3\cdot 7H_2O$ (167 mg, 0.45 mmol), followed by $NaBH_4$ (17.0 mg, 0.45 mmol). Once the reaction was finished as judged by TLC, the solvent was removed in vacuo. CH_2Cl_2 was added, the organic solution was washed with saturated NaCl, dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (10%, EtOAc/petroleum ether) to give **10** (115 mg, 95%) as a white solid. R_f=0.3, petroleum ether/EtOAc (20/1). Mp: 159–161 °C. HRMS-EI calcd for $C_{21}H_{34}O^+$ $[M]^+$ 302.2610, found 302.2614. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (dd, *J*=11.7, 17.2 Hz, 1H), 5.30 (dd, *J*=2.6, 11.2 Hz, 1H), 4.96 (dd, *J*=2.6, 17.7 Hz, 1H), 4.09 (m, 1H), 2.08 (dd, *J*=7.2, 12.3 Hz, 1H), 1.80–1.75 (m, 1H), 1.73 (s, 3H), 1.72–1.69 (m, 1H), 1.66–1.60 (m, 1H), 1.57–1.53 (m, 1H), 1.46–1.34 (m, 5H), 1.27–1.19 (m, 1H), 1.19–1.11 (m, 2H), 1.04 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H), 0.80–0.75 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 134.4, 128.5, 119.6, 73.6, 56.3, 54.0, 42.1, 39.6, 39.4, 39.0, 37.2, 33.2, 33.2, 28.6, 21.3, 21.1, 18.5, 18.5, 16.6, 16.4. IR (film): 3247, 2996, 2932, 2850, 1377, 1013, 918 cm^{-1}.

4.10. Preparation of compound 10 from 7

To a suspension of methyltriphenylphosphonium bromide (411 mg, 1.15 mmol) in THF (25 mL), a solution of *n*-BuLi in hexane (1.6 M, 0.6 mL, 0.96 mmol) was added dropwise at 0 °C under nitrogen atmosphere. The solution was stirred for a further 40 min, then a solution of aldehyde **7** (158 mg, 0.52 mmol) in THF (5 mL) was added dropwise. Then the mixture was stirred at room temperature for 8 h, then quenched with aqueous NH_4Cl (2 mL), and extracted with Et_2O (3×10 mL). The organic layer was washed with saturated brine and dried over Na_2SO_4. The residue was obtained after removing the solvent and was purified by chromatography (5%, EtOAc/petroleum ether) afforded **10** (118 mg, 75%) as a white solid.

4.11. Preparation of compound 11

To a solution of NaH (220 mg, 5.5 mmol) in 15 mL dry THF was added BnBr (0.66 mL) under N_2 atmosphere at 0 °C. After stirring at room temperature for 10 min, Bu_4NBr (35.5 mg 0.11 mmol) was added at 0 °C, and the reaction was stirred for another 10 min. Then a solution of compound **10** (165 mg, 0.55 mmol) in 10 mL dry THF was added dropwise to the solution. The reactant was warmed to 35 °C. Once the reaction was finished as judged by TLC, water was added to quench any unreacted NaH. The mixture was extracted with CH_2Cl_2 (3×10 mL), and the organic phase was washed with saturated NaCl, dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (1%, EtOAc/petroleum ether) to give **11** (207 mg, 96%) as a white solid. R_f=0.3, petroleum ether/EtOAc (100/1). EIMS *m*/*z* 392.3 $[M]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 5H), 6.10 (dd, *J*=11.3, 17.5 Hz, 1H), 5.27 (dd, *J*=2.5, 11.2 Hz, 1H), 4.97 (dd, *J*=2.5, 11.2 Hz, 1H), 4.63 (d, *J*=11.4 Hz, 1H), 4.49 (d, *J*=11.4 Hz, 1H), 3.95 (t, *J*=8.4 Hz, 1H), 2.10 (dd, *J*=7.4, 12.2 Hz, 1H), 1.78–1.74 (m, 1H), 1.73 (s, 3H), 1.68–1.57 (m, 2H), 1.53–1.41 (m, 2H), 1.37–1.34 (m, 1H), 1.28–1.22 (m, 1H), 1.22–1.11 (m, 3H), 1.11–1.08 (m, 1H), 1.05 (s, 3H), 0.88 (s, 3H), 0.87–0.85 (m, 1H), 0.84 (s, 3H), 0.81 (s, 3H), 0.80–0.75 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 139.1, 134.5, 128.3, 127.8, 127.6, 127.4, 119.5, 80.4, 69.9, 56.4, 53.9, 42.1, 39.6, 39.5, 38.8, 37.3, 33.3, 33.2, 24.1, 21.3, 21.0, 18.6, 18.5, 17.1, 16.4. IR (film): 3431, 2996, 2851, 1621, 1452, 1376, 1068, 918, 741, 697 cm^{-1}.

4.12. Preparation of compounds 12 and 13

A mixture of the diene **11** (100 mg, 0.25 mmol) and freshly distilled DMAD (0.5 mL, 4.1 mmol) was heated under nitrogen atmosphere in a seal tube at 110 °C for 24 h. Then the reaction was cooled to room temperature, DMAD was removed under reduced pressure. The residue was purified by column chromatography (4% EtOAc/petroleum ether) to give compounds **12** (35 mg, 26%) and **13** (70 mg, 52%) as white solid. R_f=0.15 for **13** and 0.10 for **12**, petroleum ether/EtOAc (30/1). Data for **12**: mp: 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.30 (m, 4H), 7.25–7.20 (m, 1H), 5.61 (d, *J*=3.6 Hz, 1H), 4.65 (d, *J*=12.2 Hz, 1H), 4.26 (d, *J*=12.2 Hz, 1H), 3.70 (s, 3H), 3.64 (dd, *J*=4.5, 11.3 Hz, 1H), 3.34 (s, 3H), 3.09 (dd, *J*=5.6, 22.5 Hz, 1H), 2.83 (dd, *J*=1.7, 22.5 Hz, 1H), 2.13 (dd, *J*=3.6, 12.6 Hz, 1H), 1.97 (d, *J*=11.5 Hz, 1H), 1.75–1.58 (m, 3H), 1.54–1.49 (m, 1H), 1.47 (s, 3H), 1.44–1.41 (m, 1H), 1.41–1.30 (m, 3H), 1.21 (s, 3H), 1.18–1.08 (m, 1H), 0.91–0.87 (m, 1H), 0.86 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H), 0.80–0.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 166.3, 151.8, 148.6, 139.4, 128.1 (2C), 126.8, 126.4 (2C), 124.8, 116.4,

80.7, 68.3, 56.1, 53.1, 52.0, 51.9, 46.0, 41.9, 41.2, 40.5, 39.8, 37.8, 33.2 (2C), 26.7, 25.6, 21.9, 21.5, 21.4, 18.7, 18.6, 16.2. IR (film): 3438, 2945, 2929, 2864, 1730, 1258, 738, 689 cm^{-1}. Data for **13**: mp: 86–88 °C. HRMS (ESI) calcd for $C_{34}H_{46}O_5NH_4^+$ $[M+Na]^+$ 552.3689, found 552.3677. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.26 (m, 4H), 7.24–7.18 (m, 1H), 5.71 (d, J=5.3 Hz, 1H), 4.62 (d, J=11.9 Hz, 1H), 4.16 (d, J=11.9 Hz, 1H), 4.00 (d, J=7.8 Hz, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.26 (dd, J=5.9, 22.5 Hz, 1H), 2.77 (d, J=22.6 Hz, 1H), 2.14 (d, J=11.7 Hz, 1H), 2.01–1.90 (m, 1H), 1.77 (m, 1H), 1.65–1.60 (m, 1H), 1.58–1.50 (m, 3H), 1.46–1.40 (m, 1H), 1.39 (s, 4H), 1.38–1.33 (m, 2H), 1.20 (s, 3H), 1.17–1.08 (m, 1H), 0.94–0.87 (m, 1H), 0.85 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H), 0.80–0.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 168.0, 153.5, 145.9, 138.6, 131.8, 128.1 (2C), 126.9 (2C), 116.6, 70.5, 56.7, 52.1, 51.5, 48.8, 44.2, 43.4, 42.0, 39.7, 39.2, 37.9, 33.3, 33.1, 28.0, 27.1, 26.1, 21.9, 21.5, 19.3, 18.5, 15.8. IR (film): 3450, 2946, 2929, 2881, 1725, 1253, 736, 701 cm^{-1}.

4.13. Preparation of compound 14

To a solution of compound **13** (56 mg, 0.105 mmol) in 5 mL Et_2O was added $LiAlH_4$ (3.0 mg, 0.079 mmol) at 0 °C. Then the reaction was refluxed for 1 h. Once the reaction was finished, water was added to quench the $LiAlH_4$. The mixture was extracted with Et_2O (3×5 mL), and the organic phase was washed successively with brine, dried over Na_2SO_4. The residue was purified by column chromatography to give **14** (40 mg, 80%) as a white solid. R_f=0.2, petroleum ether/EtOAc (10/1). Mp: 69–72 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.26 (m, 1H), 7.25–7.18 (m, 4H), 5.68 (dd, J=2.4, 4.8 Hz, 1H), 4.70–4.57 (m, 4H), 4.47 (d, J=11.2 Hz, 1H), 3.02–2.85 (m, 2H), 2.16–2.10 (m, 1H), 2.06–1.96 (m, 1H), 1.79–1.67 (m, 2H), 1.66–1.54 (m, 4H), 1.47–1.34 (m, 4H), 1.32 (s, 3H), 1.23 (s, 3H), 1.19–1.09 (m, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H), 0.82–0.76 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 157.3, 154.7, 139.3, 132.9, 128.2, 128.1, 127.1, 115.7, 76.3, 71.6, 70.4, 57.0, 48.7, 43.5, 42.0, 40.1, 39.9, 39.7, 37.8, 33.3, 33.2, 27.3, 26.8, 25.7, 22.6, 21.5, 19.4, 18.5, 16.1. IR (film): 3446, 1753, 1450, 1062, 991, 697 cm^{-1}.

4.14. Preparation of compound 15

To a solution of compound **14** (10 mg, 0.021 mmol) in MeOH (5 mL) 10% Pd/C (30 mg) was added under hydrogen atmosphere. The reaction mixture was stirred at room temperature for 8 h. Once the reaction was finished as judged by TLC, Pd/C was filtrated, and the solvent was evaporated in vacuo to obtain the crude product, which was purified by column chromatography (20% EtOAc/petroleum ether) to get compound **15** (7.7 mg, 95%) as a white solid. R_f=0.2, petroleum ether/EtOAc (6/1). Mp: >300 °C. HRMS (EI) calcd for $C_{25}H_{38}O_3^+$ $[M]^+$ 386.2829, found 386.2825. ^1H NMR (400 MHz, $CDCl_3$): δ 5.80 (d, J=12.1 Hz, 1H), 4.79 (d, J=17.5 Hz, 1H), 4.61 (d, J=17.5 Hz, 1H), 3.30 (td, J=12.0, 3.6 Hz, 1H), 2.43 (dd, J=6.1, 8.7 Hz, 2H), 2.17–2.00 (m, 2H), 1.96–1.90 (m, 1H), 1.85 (dt, J=3.2, 12.6 Hz, 1H), 1.72 (d, J=12.6 Hz, 1H), 1.61–1.51 (m, 2H), 1.47–1.31 (m, 5H), 1.30 (s, 3H), 1.29–1.24 (m, 1H), 1.16–1.06 (m, 1H), 1.01–0.88 (m, 2H), 0.83 (s, 3H), 0.81–0.79 (m, 1H), 0.78 (s, 3H), 0.76 (s, 3H), 0.61 (s, 3H). ^1H NMR (400 MHz, $CDCl_3$ add D_2O): δ 5.82 (d, J=12.0 Hz, 0.3H), 4.79 (d, J=17.5 Hz, 1H), 4.61 (d, J=17.5 Hz, 1H), 3.30 (d, J=12.0 Hz, 1H), 2.43 (dd, J=6.1, 8.7 Hz, 2H), 2.17–2.00 (m, 2H), 1.96–1.90 (m, 1H), 1.85 (dt, J=3.2, 12.6 Hz, 1H), 1.72 (d, J=12.6 Hz, 1H), 1.61–1.51 (m, 2H), 1.47–1.31 (m, 5H), 1.30 (s, 3H), 1.29–1.24 (m, 1H), 1.16–1.06 (m, 1H), 1.01–0.88 (m, 2H), 0.83 (s, 3H), 0.81–0.79 (m, 1H), 0.78 (s, 3H), 0.76 (s, 3H), 0.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 166.2, 131.6, 79.9, 72.7, 59.2, 56.6, 55.0, 42.3, 42.0, 41.8, 40.1, 39.4, 37.3, 33.3, 33.2, 28.9, 28.6, 21.9, 21.2, 18.5, 18.1, 17.5, 16.9, 15.8. IR (film): 3425, 2921, 1708, 1645, 1459, 1054, 788 cm^{-1}.

4.15. Preparation of compound 16

To a solution of compound **13** (20 mg, 0.037 mmol) in dry ether (10 mL) was added $LiAlH_4$ (14.2 mg, 0.37 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Once the reaction was finished as judged by TLC, water was added to quench any 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. The residue was purified by column chromatography to give **16** (12.2 mg, 69%) as a white solid. R_f=0.2, petroleum ether/EtOAc (3/1). Mp: 87–89 °C. HRMS (EI) calcd for $C_{32}H_{46}O_3^+$ $[M]^+$ 478.3447, found 478.3446. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.27 (m, 5H), 5.72 (dd, J=2.6, 5.2 Hz, 1H), 4.83 (d, J=11.2 Hz, 1H), 4.27 (dd, J=3.5, 11.5 Hz, 2H), 4.15 (s, 2H), 4.11–4.07 (m, 1H), 4.00 (d, J=11.9 Hz, 1H), 2.90–2.74 (m, 2H), 2.69–2.40 (br, 2H), 2.20–2.13 (m, 1H), 2.02–1.96 (m, 2H), 1.73–1.61 (m, 4H), 1.48–1.36 (m, 4H), 1.26 (t, J=7.2 Hz, 1H), 1.22 (s, 3H), 1.19–1.13 (m, 1H), 1.11 (s, 3H), 0.94 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H), 0.83–0.79 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 142.1, 137.2, 136.6, 128.6, 128.1, 127.9, 118.1, 78.9, 69.9, 63.7, 57.8, 56.8, 48.8, 43.5, 43.5, 42.0, 39.8, 39.3, 37.9, 33.3, 33.2, 31.0, 27.9, 26.4, 21.5, 21.5, 19.4, 18.5, 16.0. IR (film): 3386, 2929, 1593, 1459, 1052, 748, 702 cm^{-1}.

4.16. Preparation of compound 17

PCC (205 mg, 0.95 mmol) was added to a solution of compound **16** (30 mg, 0.06 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred at room temperature for 0.5 h. PCC was filtrated, the reaction was evaporated in vacuo to get the crude product, which was purified by column chromatography (2% EtOAc/petroleum ether) to get the product compound **17** (26 mg, 92%) as a white solid. R_f=0.3, petroleum ether/EtOAc (50/1). Mp: 144–146 °C. HRMS (EI) calcd for $C_{32}H_{42}O_2^+$ $[M]^+$ 458.3185, found 458.3183. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.23 (m, 5H), 7.12 (s, 1H), 6.79 (d, J=1.3 Hz, 1H), 5.80 (dd, J=2.1, 6.1 Hz, 1H), 4.67 (d, J=11.9 Hz, 1H), 4.46 (d, J=11.9 Hz, 1H), 3.89 (d, J=7.3 Hz, 1H), 3.22 (dd, J=6.2, 20.0 Hz, 1H), 3.08 (dt, J=1.9, 20.0 Hz, 1H), 2.20–2.13 (m, 1H), 2.07–1.96 (m, 1H), 1.94–1.85 (m, 1H), 1.82–1.73 (m, 1H), 1.66–1.58 (m, 3H), 1.49–1.35 (m, 4H), 1.33 (s, 1H), 1.28 (s, 3H), 1.24 (s, 3H), 1.19–1.10 (m, 1H), 0.93 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H), 0.83–0.79 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 137.2, 134.7, 133.4, 130.8, 127.4, 127.2, 126.4, 119.3, 117.0, 77.0, 69.8, 55.9, 48.0, 42.7, 41.0, 38.8, 38.7, 38.4, 37.1, 32.3, 32.2, 30.5, 25.5, 21.3, 20.5, 20.1, 18.4, 17.5, 15.0.

4.17. Preparation of compound 18

This procedure was the same as for the preparation of the compound **15** with the solvent of ethyl acetate. After column chromatography and evaporated in vacuo, product **18** was obtained in 86% yield as white solid. R_f=0.2, petroleum ether/EtOAc (30/1). Mp: 152–154 °C. HRMS (EI) calcd for $C_{25}H_{38}O_2^+$ $[M]^+$ 370.2872, found 370.2875. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J=1.2 Hz, 1H), 7.09 (d, J=1.3 Hz, 1H), 3.65 (dd, J=4.6, 11.2 Hz, 1H), 2.64 (m, 2H), 2.02–1.94 (m, 2H), 1.87 (dt, J=3.2, 12.7 Hz, 2H), 1.75–1.66 (m, 3H), 1.64–1.60 (m, 1H), 1.52–1.48 (m, 1H), 1.44–1.36 (m, 2H), 1.33 (s, 1H), 1.28 (s, 3H), 1.22 (t, J=4.0 Hz, 1H), 1.16–1.09 (m, 1H), 0.97–0.91 (m, 1H), 0.91–0.86 (m, 2H), 0.84 (s, 3H), 0.77 (s, 3H), 0.75 (s, 3H), 0.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 136.6, 126.2, 121.4, 81.1, 58.2, 56.7, 54.9, 42.4, 42.1, 40.3, 39.7, 39.2, 37.3, 33.3, 33.3, 30.2, 27.0, 21.3, 18.6, 18.2, 16.7, 16.5, 16.2, 15.8. IR (film): 3405, 2929, 1640, 1395, 1026, 614 cm^{-1}.

4.18. Preparation of compound 19

This procedure was the same as for the preparation of the compound **14**. After column chromatography and evaporated in

vacuo, product **19** was obtained in 88% yield as white solid. R_f=0.2, petroleum ether/EtOAc (10/1). Mp: 207–209 °C. HRMS (ESI) calcd for $C_{32}H_{42}O_3^+$ $[M]^+$ 474.3134, found 474.3136. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J=7.3 Hz, 2H), 7.30 (t, J=7.3 Hz, 2H), 7.22 (t, J=7.3 Hz, 1H), 5.59 (t, J=3.6 Hz, 1H), 4.67 (d, J=11.6 Hz, 1H), 4.58 (s, 2H), 4.47 (d, J=11.5 Hz, 1H), 3.33 (dd, J=4.5, 11.2 Hz, 1H), 2.95 (m, 2H), 1.97–1.77 (m, 2H), 1.66–1.62 (m, 1H), 1.62–1.57 (m, 3H), 1.51 (s, 3H), 1.46–1.41 (m, 2H), 1.40–1.34 (m, 2H), 1.18 (s, 3H), 1.14–1.07 (m, 1H), 0.86 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H), 0.78–0.72 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 157.7, 153.5, 139.3, 132.3, 128.3, 128.1, 127.1, 113.7, 83.5, 71.5, 69.2, 56.5, 54.7, 43.2, 42.0, 41.9, 40.8, 39.6, 38.1, 33.3, 33.2, 26.0, 24.4, 23.5, 21.4, 21.3, 18.9, 18.6, 16.0. IR (film): 3424, 2945, 1753, 1400, 993, 705 cm^{-1}

4.19. Preparation of compound 20

This procedure was the same as for the preparation of compound **15**. After column chromatography and evaporated in vacuo, product **20** was obtained in 92% yield as white solid. R_f=0.2, petroleum ether/EtOAc (6/1). Mp: >300 °C. $[\alpha]_D^{18}$ +23.6 (c 0.13, CH_2Cl_2) versus $[\alpha]_D^{20}$ +26.3 (c 0.15, CH_2Cl_2 of lit.[2b]). HRMS (ESI) calcd for $C_{25}H_{39}O_3^+$ $[M+H]^+$ 387.2899, found 387.2896. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (s, 1H), 4.75–4.65 (m, 2H), 3.67 (dd, J=5.2, 10.9 Hz, 1H), 2.49–2.40 (m, 1H), 2.33–2.16 (m, 1H), 1.97–1.78 (m, 3H), 1.78–1.61 (m, 3H), 1.57–1.42 (m, 4H), 1.42–1.24 (m, 3H), 1.13 (s, 3H), 1.12–1.04 (m, 2H), 0.89 (s, 3H), 0.84 (s, 6H), 0.81 (s, 3H), 0.80–0.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 162.1, 135.9, 75.6, 72.1, 58.0, 56.7, 55.2, 42.2, 42.1, 41.7, 39.7, 37.4, 37.3, 33.3, 31.0, 25.8, 25.3, 21.3, 18.6, 18.3, 17.2, 16.8, 16.5, 16.0. IR (film): 3393, 2929, 1711, 1442, 1387, 1061 cm^{-1}.

4.20. Preparation of compound 21

This procedure was the same as for the preparation of compound **16**. After column chromatography and evaporated in vacuo, product **21** was obtained in 65% yield as white solid. R_f=0.2, petroleum ether/EtOAc (3/1). Mp: 122–124 °C. HRMS (EI) calcd for $C_{32}H_{46}O_3^+$ $[M]^+$ 478.3447, found 478.3441. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.29 (m, 5H), 5.65 (t, J=3.9 Hz, 1H), 4.81 (d, J=11.2 Hz, 1H), 4.48 (m, 2H), 4.20 (d, J=1.8 Hz, 2H), 4.15–4.09 (m, 1H), 3.65 (dd, J=4.7, 11.2 Hz, 1H), 2.82 (d, J=3.6 Hz, 2H), 2.23 (dd, J=4.2, 12.6 Hz, 1H), 1.99 (m, 1H), 1.81–1.58 (m, 5H), 1.50–1.31 (m, 5H), 1.27 (s, 3H), 1.22 (s, 3H), 1.15–1.08 (m, 1H), 0.89 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H), 0.81–0.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 142.0, 137.9, 135.3, 128.6, 127.9, 118.0, 84.1, 69.5, 63.2, 59.1, 56.1, 53.2, 44.6, 42.0, 41.5, 40.4, 39.9, 37.8, 33.3, 33.2, 30.8, 25.9, 23.7, 22.1, 21.4, 18.8, 18.6, 16.2. IR (film): 3425, 2918, 2359, 1621, 1395, 1062, 975 cm^{-1}.

4.21. Preparation of compound 22

This procedure was the same as for the preparation of compound **17**. After column chromatography and evaporated in vacuo, product **22** was obtained in 90% yield as white solid. R_f=0.3, petroleum ether/EtOAc (50/1). Mp: 85–87 °C. HRMS (EI) calcd for $C_{32}H_{42}O_2^+$ $[M]^+$ 458.3185, found 458.3181. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J=1.4 Hz, 1H), 7.46–7.36 (m, 4H), 7.34–7.30 (m, 1H), 7.14 (s, 1H), 5.76 (dd, J=2.4, 5.6 Hz, 1H), 4.84 (d, J=11.8 Hz, 1H), 4.54 (d, J=11.9 Hz, 1H), 3.50 (dd, J=4.2, 10.5 Hz, 1H), 3.26 (dd, J=5.6, 10.6 Hz, 1H), 3.12 (dt, J=1.9, 20.5 Hz, 1H), 2.15 (dd, J=2.8, 12.6 Hz, 1H), 2.04–1.96 (m, 1H), 1.77 (d, J=12.4 Hz, 1H), 1.73–1.60 (m, 3H), 1.53–1.47 (m, 1H), 1.45 (s, 3H), 1.43–1.36 (m, 2H), 1.25 (s, 3H), 1.18–1.08 (m, 1H), 0.95–0.93 (m, 1H), 0.92 (s, 3H), 0.88 (s,3H), 0.85 (s, 3H), 0.91–0.89 (m, 1H), 0.82–0.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 139.1, 137.5, 135.1, 133.2, 128.4, 127.3, 127.0, 118.7, 117.3, 86.6, 70.3, 56.2, 54.7, 42.0, 41.6, 40.6, 40.3, 39.9, 38.0, 33.3, 33.3, 25.9, 25.3, 22.1, 21.4, 21.0, 18.9, 18.6, 16.3.

4.22. Preparation of compound 23

This procedure was the same as for the preparation of compound **18**. After column chromatography and evaporated in vacuo, product **23** was obtained in 86% yield as white solid. R_f=0.2, petroleum ether/EtOAc (4/1). Mp: 179–181 °C EI/MS m/z 374.3 $[M]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35 (dd, J=2.1, 9.2 Hz, 1H), 3.85–3.79 (m, 2H), 3.41 (dd, J=7.9, 10.2 Hz, 1H), 3.33 (m, 1H), 2.36 (br, 1H), 1.93 (t, J=6.0 Hz, 1H), 1.77 (dt, J=3.0, 12.5 Hz, 1H), 1.71–1.59 (m, 5H), 1.55–1.34 (m, 8H), 1.26 (s, 1H), 1.19–1.07 (m, 2H), 0.97 (s, 3H), 0.93–0.87 (m, 2H), 0.86 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H), 0.79–0.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 84.8, 72.1, 71.7, 58.8, 56.7, 56.4, 53.1, 42.1, 41.7, 41.1, 39.9, 37.9, 37.6, 37.4, 33.3 (2C), 27.8, 24.3, 21.3, 18.6, 18.2, 17.5, 16.4 (2C), 11.7. IR (film): 3433, 2926, 2842, 1462, 1379, 1058, cm^{-1}. The data is in agreement with that reported by Kamel et al.[20]

4.23. Preparation of compound 24

To a solution of compound **20** (5 mg, 0.013 mmol) in dry toluene was added DIBAL-H (1 M in hexane, 0.06 mL, 0.06 mmol,) dropwise at −78 °C under nitrogen atmosphere. After 2 h at −78 °C, the reaction was gradually rised up to room temperature. Once the reaction was finished as judged by TLC, saturated NH_4Cl (1 mL) was added, and the mixture was extracted with CH_2Cl_2 (3×5 mL). The organic phase was washed successively with brine, dried over Na_2SO_4. The residue was purified by column chromatography (3%, EtOAc/petroleum ether) to give **24** (3.1 mg, 65%) as a white solid. R_f=0.1, petroleum ether/EtOAc (20/1). $[\alpha]_D^{18}$ −6.8 (c 0.08, $CHCl_3$) versus $[\alpha]_D^{25}$ −9.1 (c 0.076, $CHCl_3$ of lit.[8a]). HRMS (EI) calcd for $C_{25}H_{38}O_2^+$ $[M]^+$ 370.2872, found 370.2873. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (br s, 1H), 7.04 (br s, 1H), 3.64 (m, 1H), 2.75 (dd, J=5.8, 16.0 Hz, 1H), 2.41 (m, 1H), 1.86 (dt, J=3.2, 12.5 Hz, 1H), 1.83–1.75 (m, 2H), 1.73–1.65 (m, 2H), 1.65–1.57 (m, 2H), 1.51–1.42 (m, 2H), 1.42–1.33 (m, 3H), 1.20 (s, 3H), 1.14–1.10 (m, 2H), 0.97–0.91 (m, 2H), 0.89 (s, 3H), 0.85 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H), 0.79–0.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 136.2, 134.6, 120.0, 80.0, 58.8, 56.7, 55.8, 42.1, 41.7, 40.4, 39.9, 37.5, 37.5, 33.3, 33.3, 28.0, 21.3, 21.0, 19.2, 18.6, 18.2, 17.7, 17.6, 16.3.

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Supplementary data

The ^{1}H NMR and ^{13}C NMR copies of all compounds were attached as Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.092.

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