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Construction of A/E/F ring systems of C_{19}-diterpenoid alkaloids with both C-1 and C-6 oxygen functions

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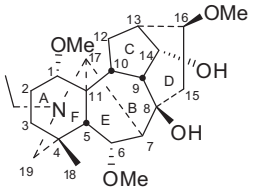
ABSTRACT

An tricyclic AEF fragment of C_{19}-diterpenoid alkaloid bearing an angular methyl group and the oxygen function groups at C-1 and C-6 was successfully synthesized. The synthesis features a stereoselective intramolecular Diels–Alder reaction and a highly efficient intramolecular Mannich reaction as well as efficient functional groups transformations.

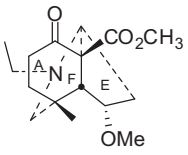
1. Introduction

C_{19}-diterpenoid alkaloids comprise a large class of structurally complex natural products mainly distributing in plants of *Aconitium* and *Delphinium* genera, which display a range of biological activities including antiinflammatory, analgesic, antiarrhythmic, antipyretic, anti-epileptic, hypotensive, and bradycardic properties.[1] Until now, over 674 members of these compounds have been identified, with new alkaloids ongoing to be isolated. The structures of C_{19}-diterpenoid alkaloids are characterized by a congested hexacyclic ring system containing 9–16 stereogenic centers and 5–9 oxygen functions involving hydroxyl, methoxy, and acyloxy groups. Differences among the numerous members of these alkaloids are determined by type, number, and position of the substituents on the basic skeleton, which is mostly represented by the carbon frame work of the aconane-type diterpene.

The total synthesis of C_{19}-diterpenoid alkaloids is a conspicuous challenge due to their intricate structures. So far, only three C_{19}-diterpenoid alkaloids have been practically synthesized, all of which were contributed by Wiesner and co-workers in 1970s.[2–4] Accordingly, partial ring systems synthesis of the six rings of C_{19}-diterpenoid alkaloids has attracted much attention of synthetic chemists, resulting in many elegant synthetic works and useful methodologies.[5–7] The unique nitrogen-containing A/E/F tricycle section is the commonly observed subunit in the C_{19}-diterpenoid alkaloid, almost invariably functionalized by oxygenation. Construction of this subunit can be regarded as one of the key points for total synthesis of this family of alkaloids.[8–10] In connection with an interest in total synthesis of royleinine,[1,11] one of the aconitine-type C_{19}-diterpenoid alkaloids bearing an unique C-18 angular methyl group as well as C-1 and C-6 methoxyl groups, we planned to develop a new methodology for construction of the A/E/F ring system with both C-1 and C-6 oxygen substituents. We now wish to describe a synthetic procedure leading to tricyclic amine **2** as the model for A/E/F ring system of royleinine using stereoselective intramolecular Diels–Alder reaction and intramolecular Mannich cyclization as the key steps.



Royleinine 1



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2. Results and discussion

The intramolecular Mannich reaction is a highly efficient approach to assemble of nitrogen-containing complex ring systems. Despite the pioneering application of this methodology by Taber[10]

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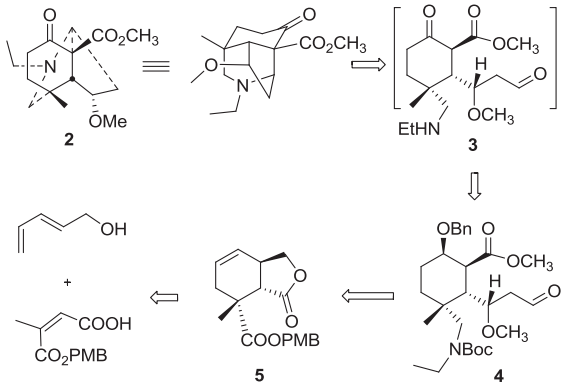
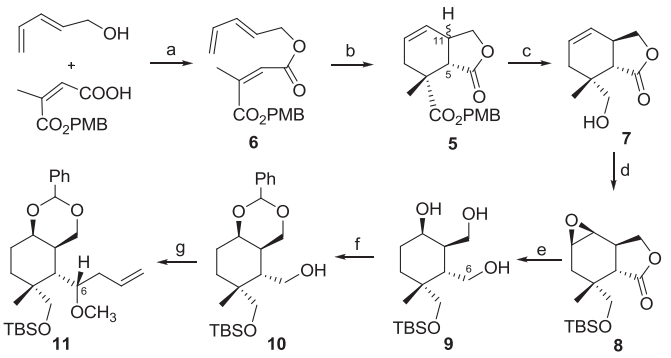
in construction of A/E/F ring of the C_{18}-diterpenoid alkaloid containing an oxygenated quaternary carbon at C-4,[12] we planned to employ the similar reaction as the key step to form the E/F rings by generation of a highly reactive β-ketoester **3** (**4**→**2**, Scheme 1). The polysubstituted six-membered ring-A **5** should be available by intramolecular Diels–Alder reaction followed by facile functional group transformations.



Scheme 1. Retrosynthetic analysis for A/E/F ring **2**.

Following the work of Sherburn and co-workers,[13] the intramolecular Diels–Alder reaction of the ester **6** that prepared from the facile condensation of known (*E*)-2,4-pentadien-1-ols and (*Z*)-2-methylbut-2-enedioic acid 1-(4-methoxybenzyl) ester,[14] was conducted in xylene at 130 °C to give the cycloadduct as a 5:1 mixture of the *exo* and *endo* isomers in 97% yield, which could be easily separated by column chromatography (Scheme 2). The relative stereochemistry of *exo*-adduct **5** was established by the observed large coupling constant ($J_{5,11}$=13.6 Hz) in ^{1}H NMR spectrum and the NOE correlation between the angular methyl protons and H-5. Subsequently, selective hydrolysis of PMB ester with TFA in DCM delivered an acid, which was reduced to an alcohol **7** by in situ formation of active mixed anhydride and then reduction with $NaBH_4$ in 90% yield over two steps. The alcohol function of **7** was then protected as a TBS ether by using standard conditions and the olefin was subjected to *m*-CPBA/$NaHCO_3$ to give the epoxide **8** as a single stereoisomer in 91% yield over two steps. After screening various bulky nucleophilic hydride reagents and reaction conditions, regioselective opening of epoxide with simultaneous reduction of lactone was effected by treatment with $LiBHEt_3$ in THF to deliver the desired triol **9** in 81% separated yield,[15] along with a small amount of unwanted regioisomer with hydroxyl at C-2.



Scheme 2. Synthesis of intermediate **11**. Reagents and conditions: (a) DIC, DMAP, CH_2Cl_2, 89%; (b) xylene, BHT, 130 °C, 97%; (c) (i) TFA, CH_2Cl_2, (ii) Et_3N, $ClCO_2Et$, THF, then $NaBH_4$, 90% for two steps; (d) (i) TBSCl, Et_3N, DMF, (ii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 91% for two steps; (e) $LiBHEt_3$, THF, 81%; (f) $Bn(OMe)_2$, CSA, CH_2Cl_2, 86% based on 90% conversion; (g) (i) PCC, Na_2CO_3, 4 Å MS, CH_2Cl_2, (ii) Zn, allyl bromide, aq NH_4Cl–THF, (iii) NaH, CH_3I, THF, 84% for three steps.

With the desired triol **9** in hand, the selective protection of 1,3-diol and installation of C-6α methoxyl group were addressed next. Treatment of **9** with $Bn(OMe)_2$ in DCM in presence of catalytic amount of CSA gave rise to 1,3-benzylidene acetal **10** in 86% yield based on 90% conversion. The remaining primary alcohol in **10** was then oxidized with PCC/Na_2CO_3 in DCM to furnish an aldehyde, which was subjected to a mild zinc powder promoted allylation in saturated aqueous NH_4Cl/THF (5:1)[16] and in turn methylation of resulting homoallylic alcohol with CH_3I, affording the desired α methyl ether **11** as a single diastereoisomer in 84% yield over three steps. Careful analysis of the plausible stereo transition state of allyation reaction reveals that the bulky TBS group may hinder the *Re* face of carbonyl group, leading to exclusive nucleophilic attack of allyl anion from *Si* face (Fig. 1). The stereochemistry of the methoxyl group in **11** was confirmed at last E/F ring closure stage based on NOE difference experiments.

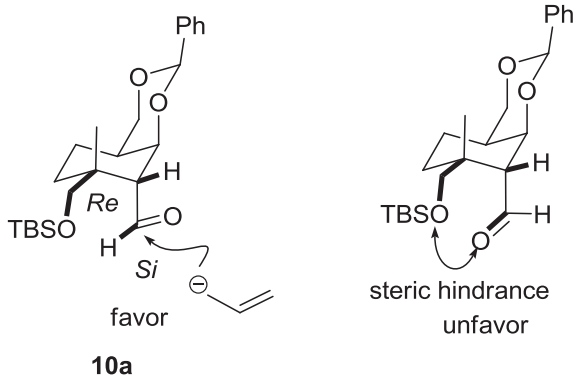
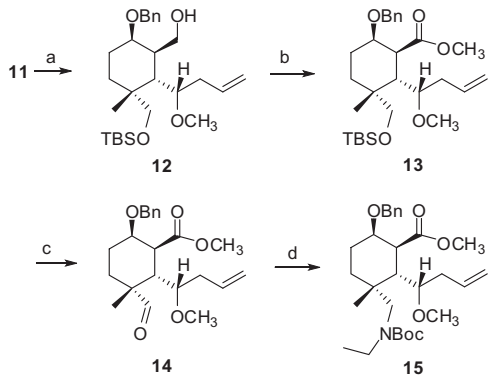


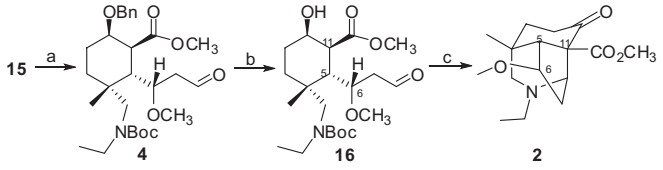
Fig. 1. Stereochemical analysis of allylation of aldehyde **10a**.

The next phase of the synthesis is outlined in Scheme 3. Regioselective cleavage of the 1,3-benzylidene acetal **11** was achieved under classical conditions (DIBAL-H/DCM) to give primary alcohol **12**. The alcohol was then converted into methyl carboxylate **13** in three steps: (1) oxidation of alcohol **12** with PCC/NaOAc to the aldehyde; (2) the aldehyde was further oxidized to carboxylic acid with $NaClO_2$; (3) conversion of carboxylic acid to the methylate **13** in 86% yield over three steps. With one single ester group in place, attention turned to installation of nitrogen at C-19 position. Thus, after a clean removal of TBS group with 5% HF/CH_3CN, the resulting alcohol was oxidized to aldehyde **14** by Dess–Martin periodinane reagent in 96% yield over two steps. Treatment of **14** with ethyl amine in methanol followed by reduction in situ with $NaBH(OAc)_3$ furnished the secondary amine, which was further protected with Boc_2O to give **15** in 88% yield over two steps.



Scheme 3. Synthesis of intermediate **15**. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, 89%; (b) (i) PCC, NaOAc, 4 Å MS, CH_2Cl_2, (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH/H_2O, iii) K_2CO_3, CH_3I, DMF, 86% for three steps; (c) (i) 5% aq HF/CH_3CN, (ii) DMP, CH_2Cl_2, 96% for two steps; (d) (i) $EtNH_2$, MeOH, then $NaBH(OAc)_3$, (ii) $(Boc)_2O$, Na_2CO_3, THF, 88% for two steps.

The final stage of the synthesis involved in the key intramolecular Mannich reaction (Scheme 4). Thus, oxidative cleavage of terminal olefin **15** with $OsO_4/NaIO_4$ gave an aldehyde **4** that was subsequently hydrogenated to an alcohol **16.** Oxidation of alcohol **16** with Dess–Martin periodinane formed the key keto ester intermediate. Without further purification, this keto ester intermediate was exposed to 5% TFA in DCM at room temperature to remove the Boc group. To our surprise, it was found that the Mannich cyclization occurred simultaneously upon removal of the Boc group, giving the desired A/E/F ring **2** in 73% yield. The relative configuration of the methoxy group at C-6 could be confirmed by NOE difference experiments of compound **2**, which show the correlations between protons of angular methyl group (δ 1.20) and C-6 methoxy (δ 3.31), as well as between H-5 (δ 2.72) and H-6 (δ 3.62).



Scheme 4. Synthesis of A/E/F ring **2**. Reagents and conditions: (a) OsO_4, NMO, 1,4-dioxane/H_2O, then $NaIO_4$, 85%; (b) $Pd(OH)_2/C$, H_2, 95% EtOH, 94%; (c) DMP, Na_2CO_3, CH_2Cl_2, then 5% TFA/CH_2Cl_2, 73%.

3. Conclusion

In conclusion, the desired tricycle amine **2** containing C-1 and C-6 oxygen functions as the model of A/E/F ring system of royleinine has been successfully synthesized from the commercial available 2,4-pentadien-1-ols. The synthesis features: (a) stereoselective synthesis of the model intermediate polysubstituted six-membered ring A through an intramolecular Diels–Alder reaction and efficient functional group transformations; (b) stereoselective installation of C-6α hydroxyl group through nucleophilic allylation of carbonyl group with the assistance of steric effect of neighboring bulky TBS group; (c) highly efficient construction of E/F ring by intramolecular Mannich reaction of β-ketoester under mild reaction conditions.

4. Experimental section

4.1. General information

Melting points were determined on a Kofler block (uncorrected); IR spectra were recorded on a Nicolet 200 SXV spectrometer; HRMS were obtained with a Bruker BioTOFQ mass spectrometer; ^1H and ^{13}C NMR spectra were acquired on a Varian INOVA-400/54 spectrometer, with TMS as internal standard; silica gel GF_{254} and H (10–40 mm, Qingdao Marine Chemical Factory, China) were used for TLC and CC. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone. Unless otherwise noted, all reactions were carried out under an atmosphere of argon or nitrogen.

4.2. Preparation of ester 6

To a solution of (*Z*)-2-methylbut-2-enedioic acid 1-(4-methoxybenzyl) ester (40.2 g, 0.16 mol) and (*E*)-2,4-pentadien-1-ols (13.5 g, 0.16 mol) in CH_2Cl_2 (400 mL) were added dropwise DIC (22.2 g, 0.176 mol) and DMAP (980 mg, 8 mmol) in one portion at 0 °C. After stirring for 3 h, the mixture was filtered and the solvent was removed in vacuo. The residue was purified by silica gel chromatography with PE/EtOAc (15:1) to give ester **6** (45 g, 89%). Colorless oil; IR (film) ν_{max}: 2956, 2838, 1722, 1652, 1613, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J*=8.1 Hz, 2H), 6.89 (d, *J*=8.1 Hz, 2H), 6.41–6.19 (m, 2H), 5.87 (s, 1H), 5.79–5.65 (m, 1H), 5.26 (d, *J*=16.0 Hz, 1H), 5.17 (s, 2H), 5.16 (d, *J*=12.1 Hz, 1H), 4.59 (d, *J*=6.3 Hz, 2H), 3.81 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 164.2, 159.3, 145.1, 135.5, 134.7, 129.9, 127.2, 126.2, 120.6, 118.5, 113.5, 66.0, 65.0, 54.8, 29.9; HRMS calcd for $C_{18}H_{20}NaO_5$ 339.1208, found 339.1202.

4.3. Preparation of compound 5

A solution of ester **6** (20.9 g, 66 mmol) in xylene (550 mL) was heated to 130 °C under Ar in the presence of BHT (1.45 g, 6.6 mmol) for 48 h. The mixture was concentrated in vacuo to leave a brown oil, which was purified by silica gel chromatography with PE/EtOAc (5:1) to afford *exo*-**5**: 16.9 g, 81%; *endo*-**5**: 3.3 g, 16%. For *exo*-**5**: white solid; mp: 69–71 °C; IR (KBr) ν_{max}: 2961, 1771, 1716, 1613, 1517, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J*=8.3 Hz, 2H), 6.87 (d, *J*=8.3 Hz, 2H), 5.70 (s, 2H), 5.15 (d, *J*=12.0 Hz, 1H), 5.04 (d, *J*=12.0 Hz, 1H), 4.36 (t, *J*=7.5 Hz, 1H), 3.81 (s, 3H), 3.76 (dd, *J*=11.3, 8.0 Hz, 1H), 2.94 (d, *J*=18.8 Hz, 1H), 2.94–2.90(m, 1H), 2.14 (d, *J*=13.5 Hz, 1H), 2.05 (dd, *J*=18.8, 3.7 Hz, 1H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 173.8, 159.5, 129.8, 129.0, 127.6, 123.5, 113.8, 69.8, 66.5, 55.2, 48.8, 43.0, 38.5, 37.8, 23.7; HRMS calcd for $C_{18}H_{20}NaO_5$ 339.1208, found 339.1202. For *endo*-**5**: white solid; mp: 53–55 °C; IR (KBr) ν_{max}: 2965, 2914, 1767, 1725, 1613, 1517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J*=8.3 Hz, 2H), 6.89 (d, *J*=8.3 Hz, 2H), 5.89–5.78 (m, 1H), 5.57 (d, *J*=10.0 Hz, 1H), 5.14 (q, *J*=11.9 Hz, 2H), 4.34 (dd, *J*=8.7, 5.8 Hz, 1H), 4.12 (d, *J*=8.7 Hz, 1H), 3.81 (s, 3H), 3.23 (d, *J*=7.2 Hz, 1H), 3.15–3.00 (m, 1H), 2.58 (d, *J*=18.2 Hz, 1H), 2.19–1.98 (m, 1H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 175.5, 159.4, 129.9, 128.2, 127.9, 124.0, 113.7, 71.6, 66.4, 55.1, 45.4, 39.9, 35.2, 29.4, 23.4; HRMS calcd for $C_{18}H_{20}NaO_5$ 339.1208, found 339.1202.

4.4. Preparation of alcohol 7

To a stirred solution of *exo*-**5** (14.2 g, 45 mmol) in CH_2Cl_2 (250 mL) was added trifluoroacetic acid (17.2 mL, 0.225 mol) at 0 °C. After stirring at the same temperature for 2 h, the red reaction mixture was concentrated in vacuo. The residue was dissolved in 100 mL EtOAc and adjusted to pH=8 with saturated aqueous $NaHCO_3$. The organic layer was separated and discarded. The aqueous layer was acidified using 3 N aqueous HCl and extracted twice with EtOAc. The combined organics were dried over $MgSO_4$, evaporated to give the pure acid **5a**. White solid; mp 184–186 °C; IR (KBr) ν_{max}: 3437, 2896, 2249, 2091, 1781, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86–5.66 (m, 2H), 4.48 (t, *J*=7.4 Hz, 1H), 3.82 (t, *J*=10.4 Hz, 1H), 3.37–3.11 (m, 1H), 2.94 (d, *J*=19.0 Hz, 1H), 2.16 (d, *J*=13.9 Hz, 1H), 2.12 (d, *J*=19.0 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ 176.4, 175.0, 128.4, 122.8, 69.8, 48.2, 42.2, 38.0, 37.4, 23.2; HRMS calcd for $C_{10}H_{12}NaO_4$ 219.0633, found 219.0631.

To a stirred solution of the crude acid **5a** in THF (200 mL) at 0 °C were added Et_3N (7.5 mL, 54 mmol) and ethyl chloroformate (5.2 mL, 54 mmol). After stirring at the same temperature for 20 min, the inorganic salts were filtered off and washed with cold THF (50 mL). The filtrate was placed in a 500 mL flask, followed by addition of $NaBH_4$ (3.4 g, 90 mmol) in portions and CH_3OH (10 mL) dropwise at −40 °C. The reaction mixture was allowed to stir for 3 h at the same temperature and quenched by addition of water. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by silica gel chromatography with PE/EtOAc (4:1) to yield alcohol **7** (7.4 g, 90% for two steps). White solid; mp 105–107 °C; IR (KBr)

ν_{max}: 3471, 2957, 2887, 1766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91–5.39 (m, 2H), 4.47 (t, J=8.0 Hz, 1H), 3.82 (dd, J=11.3, 8.0 Hz, 1H), 3.66 (d, J=11.2 Hz, 1H), 3.47 (d, J=11.2 Hz, 1H), 3.21–3.01 (m, 1H), 2.16 (d, J=13.7 Hz, 1H), 2.05 (d, J=18.8 Hz, 1H), 1.95 (d, J=18.8 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 129.7, 123.3, 70.2, 66.9, 49.3, 37.9, 37.0, 35.7, 23.0; HRMS calcd for $C_{10}H_{14}NaO_3$ 205.0841, found 205.0846.

4.5. Preparation of epoxide 8

To a stirred solution of alcohol **7** (7.4 g, 40.6 mmol) in DMF (60 mL) were added Et_3N (6.8 mL, 48.7 mmol), DMAP (249 mg, 2.0 mmol), and TBSCl (6.7 g, 44.7 mmol) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was diluted with EtOAc (600 mL), washed with water (3×100 mL) and brine. The organics were dried over $MgSO_4$ and concentrated in vacuo to give crude product **7a**, which was directly used in next step. A small portion was purified for characterization of **7a**. White solid; mp 41–43 °C; IR (KBr) ν_{max}: 2953, 2855, 1776, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78–5.63 (m, 2H), 4.40 (t, J=7.3 Hz, 1H), 3.74 (dd, J=11.6, 8.0 Hz, 1H), 3.54 (d, J=9.8 Hz, 1H), 3.44 (d, J=9.8 Hz, 1H), 3.15–2.94 (m, 1H), 2.13 (d, J=19.0 Hz, 1H), 2.09 (d, J=13.7 Hz, 1H), 1.88 (d, J=19.0 Hz, 1H), 1.33 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 130.2, 123.4, 69.7, 66.3, 49.4, 37.6, 37.3, 35.8, 25.7, 23.4, 18.1, −5.7, −5.8; HRMS calcd for $C_{16}H_{28}NaO_3Si$ 319.1705, found 319.1702.

To a stirred solution of crude **7a** in CH_2Cl_2 (250 mL) at 0 °C were added $NaHCO_3$ (5.0 g, 60 mmol) and *m*-CPBA (14.8 g, 70%, 60 mmol) in portions. After 10 min, the ice bath was removed and stirring was continued for 10 h at room temperature. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (30 mL), and the resulting mixture was stirred until it became clear. The organic phases were washed with water, dried over Na_2SO_4, and evaporated to leave a residue, which was purified by silica gel chromatography with PE/EtOAc (20:1) to yield epoxide **8** (11.6 g, 91% for two steps). White solid; mp 108–110 °C; IR (KBr) ν_{max}: 2927, 2855, 1781, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (t, J=7.3 Hz, 1H), 3.96 (dd, J=11.6, 8.0 Hz, 1H), 3.57 (d, J=10.1 Hz, 1H), 3.32 (d, J=10.1 Hz, 1H), 3.30–3.26 (m, 1H), 3.23–3.12 (m, 2H), 2.35 (d, J=13.9 Hz, 1H), 1.96 (dd, J=16.0, 3.7 Hz, 1H), 1.73 (d, J=16.0 Hz, 1H), 1.19 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 67.9, 67.6, 51.8, 51.2, 42.7, 38.6, 34.4, 34.1, 25.7, 23.8, 18.0, −5.7, −5.8; HRMS calcd for $C_{16}H_{28}NaO_4Si$ 335.1655, found 335.1651.

4.6. Preparation of triol 9

To a stirred solution of epoxide **8** (6.0 g, 19.2 mmol) in dry THF (200 mL) at −20 °C was added dropwise $LiBHEt_3$ (77 mL, 1 M in THF, 77 mmol). The reaction mixture was slowly warmed to 15 °C and stirred overnight. Then 50 mL water was added dropwise to quench the reaction, followed by addition of 1 N aqueous NaOH (40 mL) and 30% H_2O_2 (40 mL). The mixture was stirred over additional 30 min before extracting with EtOAc. The combined organics were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EtOAc (2:1) to yield triol **9** (4.9 g, 81%). White solid; mp 65–67 °C; IR (KBr) ν_{max}: 3298, 2930, 2857, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$+D_2O) δ 4.24 (s, 1H), 4.05 (d, J=11.1 Hz, 1H), 3.99–3.84 (m, 3H), 3.74 (d, J=12.3 Hz, 1H), 3.22 (d, J=10.5 Hz, 1H), 1.90 (s, 2H), 1.83–1.71 (m, 1H), 1.61–1.52 (m, 2H), 1.28–1.22 (m, 1H), 1.04 (s, 3H), 0.91 (s, 9H), 0.09 (d, J=3.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.0, 66.6, 65.3, 59.1, 41.8, 39.2, 37.8, 32.7, 29.2, 25.8, 25.4, 18.2, −5.6, −5.6; HRMS calcd for $C_{16}H_{35}O_4Si$ 319.2305, found 319.2303.

4.7. Preparation of compound 10

Benzaldehyde dimethylacetal (2.15 mL, 14.3 mmol) and CSA (139.4 mg, 0.6 mmol) were added to a solution of triol **9** (3.8 g, 11.9 mmol) in CH_2Cl_2 (120 mL) at 0 °C. The reaction mixture was stirred for 1 h at the same temperature and then quenched with saturated aqueous $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organics were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EtOAc (10:1) to afford compound **10** (3.7 g, 86% based on 90% conversion). Colorless oil; IR (film) ν_{max}: 3466, 2930, 2885, 1459 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J=7.1 Hz, 2H), 7.42–7.30 (m, 3H), 5.57 (s, 1H), 4.50 (d, J=12.0 Hz, 1H), 4.18 (s, 1H), 4.11 (d, J=11.4 Hz, 1H), 4.06 (d, J=10.6 Hz, 1H), 4.00–3.91 (m, 2H), 3.86–3.72 (m, 1H), 3.23 (d, J=10.6 Hz, 1H), 2.15 (dd, J=11.9, 2.9 Hz, 1H), 1.96 (d, J=11.9 Hz, 1H), 1.87–1.74 (m, 2H), 1.71–1.63 (m, 1H), 1.34–1.21 (m, 1H), 1.05 (s, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 128.8, 128.3, 126.1, 102.0, 75.8, 69.1, 66.9, 57.4, 41.9, 37.6, 34.2, 32.1, 27.1, 25.7, 25.5, 18.2, −5.5, −5.7; HRMS calcd for $C_{23}H_{38}NaO_4Si$ 429.2437, found 429.2435.

4.8. Preparation of compound 11

To a stirred solution of **10** (3.8 g, 9.3 mmol) in CH_2Cl_2 (100 mL) were sequentially added Na_2CO_3 (3.0 g, 27.9 mmol), 4 Å MS (7.6 g), and PCC (6.0 g, 27.9 mmol) at 0 °C. After 10 min, the ice bath was removed and stirring was continued for 1 h at room temperature. Then ether (100 mL) was added and the mixture was filtered over a pad of silica, washed with ether. The filtrate was concentrated in vacuo to give crude product **10a**, which was directly used in next step. A small portion was purified for characterization of **10a**. Colorless oil; IR (film) ν_{max}: 2930, 2857, 1717, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.49 (d, J=6.9 Hz, 2H), 7.42–7.34 (m, 3H), 5.52 (s, 1H), 4.32–4.08 (m, 2H), 4.03 (d, J=12.0 Hz, 1H), 3.70 (d, J=10.0 Hz, 1H), 3.33 (d, J=10.0 Hz, 1H), 3.04 (d, J=11.7 Hz, 1H), 2.02 (d, J=11.7 Hz, 1H), 1.88–1.63 (m, 3H), 1.42 (d, J=10.8 Hz, 1H), 1.29 (s, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 138.5, 128.9, 128.3, 126.1, 101.6, 74.4, 69.7, 66.0, 53.2, 39.8, 31.1, 30.7, 26.8, 25.9, 25.8, 18.2, −5.7, −5.8; HRMS calcd for $C_{23}H_{36}NaO_4Si$ 427.2281, found 427.2286.

Zinc powder (2.35 g, 36 mmol) was successively added in portions to a stirred solution of the crude **10a** and allyl bromide (3.1 mL, 36 mmol) in saturated NH_4Cl solution (100 mL) and THF (20 mL). The mixture was continued stirring for 1 h at room temperature, then extracted with CH_2Cl_2. The combined organics were dried on Na_2SO_4 and concentrated in vacuo to give crude alcohol **10b**, which was directly used in next step. A small portion was purified for characterization of **10b**. White solid; mp 58–60 °C; IR (KBr) ν_{max}: 3512, 3040, 2931, 2851, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J=7.7 Hz, 2H), 7.41–7.33 (m, 3H), 5.94–5.75 (m, 1H), 5.59 (s, 1H), 5.12 (d, J=17.1 Hz, 1H), 5.06 (d, J=10.1 Hz, 1H), 4.69 (d, J=12.0 Hz, 1H), 4.21 (td, J=7.3, 3.2 Hz, 1H), 4.12 (s, 1H), 4.01–3.89 (m, 2H), 3.32 (d, J=10.6 Hz, 1H), 3.26 (d, J=3.3 Hz, 1H), 2.65–2.50 (m, 1H), 2.50–2.38 (m, 1H), 2.27 (d, J=11.7 Hz, 1H), 1.88 (d, J=11.7 Hz, 1H), 1.73–1.62 (m, 3H), 1.32–1.21 (m, 1H), 1.00 (s, 3H), 0.92 (s, 9H), 0.10 (d, J=3.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 136.5, 128.9, 128.2, 126.4, 116.8, 102.4, 77.2, 70.5, 68.5, 67.1, 43.1, 42.5, 38.0, 33.3, 33.0, 27.2, 26.0, 25.8, 18.3, −5.6, −5.7; HRMS calcd for $C_{26}H_{43}O_4Si$ 447.2931, found 447.2920.

To a stirred solution of crude **10b** in dry THF (90 mL) was added NaH (1.5 g, 60% in oil, 36.8 mmol) in one portion. After stirring at room temperature for 20 min, CH_3I (1.2 mL, 18.4 mmol) was added and the suspension was heated to reflux for 3 h. The reaction mixture was cooled to 0 °C, and quenched with water. The organic layer was separated and the water layer was extracted with EtOAc.

The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EtOAc (50:1) to give **11** (4.15 g, 84% for three steps). Colorless oil; IR (film) ν_{max}: 3069, 2931, 2856, 1469 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J=7.0 Hz, 2H), 7.41–7.29 (m, 3H), 5.84–5.68 (m, 1H), 5.56 (s, 1H), 5.14 (d, J=17.1 Hz, 1H), 5.09 (d, J=10.1 Hz, 1H), 4.46 (d, J=11.9 Hz, 1H), 4.07 (s, 1H), 3.87 (d, J=11.9 Hz, 1H), 3.79 (d, J=10.1 Hz, 1H), 3.43 (dd, J=9.7, 3.9 Hz, 1H), 3.31 (s, 3H), 3.23 (d, J=10.1 Hz, 1H), 2.63–2.52 (m, 1H), 2.40–2.31 (m, 2H), 1.81 (d, J=11.8 Hz, 1H), 1.74–1.63 (m, 3H), 1.43–1.32 (m, 1H), 0.91 (s, 3H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.7, 128.9, 128.3, 126.5, 117.6, 102.5, 79.3, 77.1, 70.7, 63.4, 56.6, 42.4, 39.0, 38.3, 32.5, 28.5, 27.2, 26.0, 25.9, 18.3, −5.5, −5.6; HRMS calcd for $C_{27}H_{44}NaO_4Si$ 483.2907, found 483.2897.

4.9. Preparation of alcohol 12

DIBAL (29.6 mL, 1.0 M in Tol, 29.6 mmol) was added dropwise to a stirred solution of **11** (3.4 g, 7.4 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was warmed to 10 °C and stirred overnight. With cooling (0 °C), saturated potassium sodium tartrate solution (100 mL) was added, and the suspension was stirred until it became clear. The organic layer was washed with water, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel chromatography with PE/EtOAc (25:1) to afford alcohol **12** (3.0 g, 89%). Colorless oil; IR (film) ν_{max}: 3512, 3031, 2930, 2856, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.82–5.59 (m, 1H), 5.14 (d, J=17.0 Hz, 1H), 5.05 (d, J=10.1 Hz, 1H), 4.63 (d, J=11.7 Hz, 1H), 4.35 (d, J=11.7 Hz, 1H), 3.88–3.78 (m, 3H), 3.74 (d, J=10.2 Hz, 1H), 3.61 (d, J=8.2 Hz, 1H), 3.41 (dd, J=9.5, 4.6 Hz, 1H), 3.31 (s, 3H), 3.19 (d, J=10.2 Hz, 1H), 2.57–2.36 (m, 2H), 2.03–1.90 (m, 2H), 1.87 (dd, J=14.0, 3.2 Hz, 1H), 1.69 (d, J=13.1 Hz, 1H), 1.43 (t, J=14.0 Hz, 1H), 1.34–1.21 (m, 1H), 0.89 (s, 12H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.8, 128.4, 127.6, 127.5, 117.4, 80.1, 80.0, 69.8, 66.3, 63.7, 56.2, 43.0, 39.1, 38.3, 37.0, 27.4, 26.1, 25.9, 23.4, 18.3, −5.6, −5.6; HRMS calcd for $C_{27}H_{46}NaO_4Si$ 485.3063, found 485.3059.

4.10. Preparation of ester 13

To a stirred solution of **12** (3.6 g, 7.8 mmol) in CH_2Cl_2 (100 mL) were sequentially added 4 Å MS (7.2 g), NaOAc (1.92 g, 23.4 mmol), and PCC (5.0 g, 23.4 mmol) at 0 °C. After 10 min, the ice bath was removed and stirring was continued for 1 h at room temperature. Then ether (100 mL) was added and the mixture was filtered over a pad of silica, washed with ether. The filtrate was concentrated in vacuo to give crude aldehyde **12a**, which was directly used in next step. A small portion was purified for characterization of **12a**. Colorless oil; IR (film) ν_{max}: 3068, 2931, 2857, 1718, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, J=3.4 Hz, 1H), 7.37–7.27 (m, 5H), 5.90–5.66 (m, 1H), 5.16–5.03 (m, 2H), 4.54 (d, J=11.8 Hz, 1H), 4.33 (d, J=11.8 Hz, 1H), 4.00 (d, J=2.8 Hz, 1H), 3.56 (d, J=10.0 Hz, 1H), 3.52–3.45 (m, 1H), 3.42 (d, J=10.0 Hz, 1H), 3.22 (s, 3H), 2.60–2.52 (m, 1H), 2.49–2.39 (m, 2H), 2.26–2.14 (m, 1H), 1.90–1.78 (m, 1H), 1.65–1.59 (m, 1H), 1.54–1.48 (m, 1H), 1.41 (td, J=12.4, 3.6 Hz, 1H), 0.93 (s, 3H), 0.89 (s, 9H), 0.03 (d, J=1.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 138.5, 134.8, 128.2, 127.4, 127.3, 117.4, 79.5, 76.9, 70.3, 65.3, 57.0, 50.7, 44.3, 40.0, 37.3, 29.4, 25.9, 25.8, 23.9, 18.2, −5.7, −5.6; HRMS calcd for $C_{27}H_{44}NaO_4Si$ 483.2907, found 483.2897.

To a stirred solution of crude aldehyde **12a** in $^tBuOH/H_2O$ (125 mL, 3.5/1) were added sequentially 2-methyl-2-butene (16.6 mL, 156 mmol), $NaH_2PO_4 \cdot 2H_2O$ (6.1 g, 39 mmol), and $NaC1O_2$ (3.5 g, 39 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h, followed by addition of saturated aqueous $Na_2S_2O_3$ (30 mL) to quench the reaction. The mixture was extracted with EtOAc. The combined organics were dried over $MgSO_4$, and concentrated to give crude acid **12b**, which was directly used in next step. A small portion was purified for characterization of **12b**. White solid; mp 82–84 °C; IR (KBr) ν_{max}: 3458, 2936, 2855, 1717, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 5H), 5.82–5.66 (m, 1H), 5.08 (d, J=19.4 Hz, 1H), 5.04 (d, J=11.7 Hz, 1H), 4.67 (d, J=11.4 Hz, 1H), 4.53 (d, J=11.4 Hz, 1H), 4.13 (s, 1H), 3.52 (s, 1H), 3.48–3.35 (m, 2H), 3.28 (s, 3H), 2.92 (s, 1H), 2.58–2.37 (m, 2H), 2.20–2.08 (m, 1H), 1.91–1.45 (m, 4H), 0.92 (s, 3H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 137.9, 135.8, 128.3, 127.6, 127.5, 116.7, 79.9, 74.9, 70.6, 69.2, 57.7, 44.6, 37.4, 28.8, 25.8, 25.2, 23.9, 18.2, 16.4, −5.6, −5.7; HRMS calcd for $C_{27}H_{45}O_5Si$ 477.3036, found 477.3040.

To a stirred solution of crude acid **12b** in DMF (75 mL) at 0 °C were added K_2CO_3 (2.15 g, 15.6 mmol) and CH_3I (1.9 mL, 31.2 mmol). The reaction mixture was stirred at the same temperature for 2 h. Then EtOAc (500 mL) was added, and the mixture was washed with H_2O (3×100 mL) and brine. The organic layer was dried on $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EtOAc (60:1) to afford ester **13** (3.3 g, 86% for three steps). White solid; mp 52–54 °C; IR (KBr) ν_{max}: 3029, 2931, 2859, 1750,1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.27 (m, 5H), 5.97–5.73 (m, 1H), 5.10 (d, J=17.1 Hz, 1H), 5.02 (d, J=10.1 Hz, 1H), 4.56 (d, J=12.4 Hz, 1H), 4.34 (d, J=12.4 Hz, 1H), 3.86 (s, 1H), 3.65 (d, J=10.0 Hz, 1H), 3.59 (s, 3H), 3.35 (d, J=10.0 Hz, 1H), 3.33–3.28 (m, 1H), 3.24 (s, 3H), 2.75 (dd, J=12.1, 2.8 Hz, 1H), 2.62–2.45 (m, 1H), 2.34–2.20 (m, 2H), 1.91–1.78 (m, 1H), 1.66–1.59 (m, 1H), 1.53–1.34 (m, 2H), 0.90 (s, 3H), 0.89 (s, 9H), 0.03 (d, J=1.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 138.7, 136.5, 128.1, 127.5, 127.3, 116.3, 79.7, 74.6, 70.2, 64.1, 58.2, 51.1, 44.9, 44.8, 41.0, 37.4, 28.5, 25.8, 25.3, 23.7, 18.2, −5.5, −5.6; HRMS calcd for $C_{28}H_{46}NaO_5Si$ 513.3012, found 513.2996.

4.11. Preparation of aldehyde 14

To a stirred solution of ester **13** (1.5 g, 3.06 mmol) in CH_3CN (120 mL) at 0 °C was added aqueous HF (6.0 mL, 40% in H_2O). After stirring at 20 °C for 4 h, saturated aqueous $NaHCO_3$ (30 mL) was added dropwise to quench the reaction. The mixture was extracted with EtOAc, and the combined organics were dried on $MgSO_4$, concentrated to give crude alcohol **13a**, which was directly used in next step. A small portion was purified for characterization of **13a**. Colorless oil; IR (film) ν_{max}: 3487, 3028, 2934, 1746, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 5.96–5.70 (m, 1H), 5.13 (d, J=17.1 Hz, 1H), 5.05 (d, J=10.1 Hz, 1H), 4.57 (d, J=12.4 Hz, 1H), 4.34 (d, J=12.4 Hz, 1H), 3.88 (s, 1H), 3.65 (d, J=11.4 Hz, 1H), 3.59 (s, 3H), 3.51–3.38 (m, 2H), 3.29 (s, 3H), 2.87 (dd, J=12.1, 3.1 Hz, 1H), 2.59–2.44 (m, 1H), 2.36 (d, J=12.1 Hz, 1H), 2.34–2.25 (m, 1H), 2.01 (s, 1H), 1.87 (dd, J=13.6, 3.2 Hz, 1H), 1.78–1.43 (m, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 138.6, 136.0, 128.1, 127.5, 127.3, 116.9, 79.7, 74.5, 70.2, 66.5, 57.5, 51.1, 44.9, 43.8, 39.0, 37.2, 29.8, 25.5, 23.9; HRMS calcd for $C_{22}H_{32}NaO_5$ 399.2147, found 399.2136.

To a stirred solution of crude alcohol **13a** in CH_2Cl_2 (60 mL) was added Dess–Martin periodinane (1.95 g, 4.6 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, followed by addition of saturated aqueous $NaHCO_3$ (15 mL) and saturated aqueous $Na_2S_2O_3$ (15 mL) to quench the reaction. After being vigorously stirred for 30 min, the mixture was extracted with CH_2Cl_2. The combined organics were dried on Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EtOAc (15:1) to afford aldehyde **14** (1.1 g, 96% for two steps). Colorless oil; IR (film) ν_{max}: 3029, 2934, 1746, 1705, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.43–7.27 (m, 5H), 5.99–5.60 (m, 1H), 5.09 (d, J=17.1 Hz, 1H), 5.03 (d, J=10.1 Hz, 1H), 4.55 (d, J=12.3 Hz, 1H), 4.35 (d, J=12.3 Hz, 1H), 3.93 (d, J=2.5 Hz, 1H), 3.61 (s, 3H), 3.29 (s, 3H), 3.24–3.16 (m, 1H), 3.08 (dd, J=12.2, 3.2 Hz, 1H),

2.62–2.45 (m, 1H), 2.41 (dd, *J*=12.2, 3.0 Hz, 1H), 2.30–2.12 (m, 1H), 2.01–1.88 (m, 1H), 1.81 (td, *J*=14.1, 3.7 Hz, 1H), 1.65–1.56 (m, 1H), 1.51–1.39 (m, 1H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 173.6, 138.3, 135.9, 128.2, 127.6, 127.5, 116.7, 81.0, 74.0, 70.4, 58.8, 51.2, 48.5, 45.4, 44.0, 40.8, 28.5, 24.3, 23.1; HRMS calcd for $C_{22}H_{30}NaO_5$ 397.1991, found 397.1995.

4.12. Preparation of compound 15

To a solution of aldehyde **14** (1.8 g, 4.8 mmol) in dry MeOH (60 mL) was added 30% $EtNH_2$ in methanol (28.9 mL, 192 mmol). After stirring at room temperature for 5 h, the TLC analysis showed the complete consumption of **14**. Then the mixture was cooled at 0 °C, and $NaBH(OAc)_3$ (2.0 g, 9.6 mmol) was added. The reaction mixture was stirred for another 30 min, and quenched with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, and the combined organics were dried on $MgSO_4$, concentrated to give crude amine **14a**, which was directly used in next step. A small portion was purified for characterization of **14a**. Colorless oil; IR (film) ν_{max}: 3328, 3028, 2928, 1748, 1727, 1435 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 5.94–5.76 (m, 1H), 5.10 (d, *J*=17.1 Hz, 1H), 5.02 (d, *J*=10.1 Hz, 1H), 4.57 (d, *J*=12.4 Hz, 1H), 4.34 (d, *J*=12.4 Hz, 1H), 3.87 (s, 1H), 3.59 (s, 3H), 3.39–3.29 (m, 1H), 3.26 (s, 3H), 2.80–2.51 (m, 5H), 2.39 (d, *J*=11.8 Hz, 1H), 2.35–2.22 (m, 2H), 1.85 (d, *J*=11.2 Hz, 1H), 1.60–1.35 (m, 3H), 1.10 (t, *J*=7.1 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 138.7, 136.6, 128.1, 127.5, 127.3, 116.3, 79.7, 74.5, 70.3, 58.3, 51.0, 50.6, 46.3, 45.3, 44.9, 41.4, 36.0, 29.0, 26.1, 23.8, 15.3; HRMS calcd for $C_{24}H_{38}NO_4$ 404.2801, found 404.2809.

To a stirred solution of crude **14a** in THF (80 mL) were added Na_2CO_3 (1.53 g, 14.4 mmol) and $(Boc)_2O$ (1.57 g, 7.2 mmol). After stirring at room temperature for 10 h, the mixture was diluted with EtOAc, and washed with water and brine. The organic layer was dried on $MgSO_4$, concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EtOAc (20:1) to afford compound **15** (2.1 g, 88% for two steps). Colorless oil; IR (film) ν_{max}: 3067, 2930, 1749, 1692, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 5.98–5.68 (m, 1H), 5.12 (d, *J*=17.0 Hz, 1H), 5.03 (d, *J*=10.0 Hz, 1H), 4.56 (d, *J*=12.4 Hz, 1H), 4.34 (d, *J*=12.4 Hz, 1H), 3.86 (s, 1H), 3.59 (s, 3H), 3.53–3.32 (m, 2H), 3.30 (s, 3H), 3.26–2.97 (m, 3H), 2.78–2.55 (m, 2H), 2.49–2.33 (m, 1H), 2.29 (d, *J*=12.5 Hz, 1H), 1.93–1.80 (m, 1H), 1.64–1.54 (m, 1H), 1.52–1.39 (m, 11H), 1.09 (t, *J*=6.5 Hz, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 156.6, 138.7, 136.5, 128.2, 127.5, 127.3, 116.6, 80.1 (79.7), 79.0, 74.4, 70.3, 58.1, 51.1, 46.1 (45.8), 45.0, 44.8, 44.4(43.8), 40.9(40.6), 38.6, 29.5, 28.6 (28.4), 26.4 (25.8), 24.2, 13.2 (12.5); HRMS calcd for $C_{29}H_{45}NNaO_6$ 526.3145, found 526.3150.

4.13. Preparation of aldehyde 4

OsO_4 (0.64 mL, 5 wt % in 1,4-dioxane, 0.125 mmol) and NMO (588 mg, 5.0 mmol) were added to a stirred solution of olefin **15** (1.24 g, 2.5 mmol) in 1,4-dioxane/H_2O (50 mL, 3:1). After stirring at room temperature for 2 h, the TLC analysis showed the complete consumption of **15**. Then $NaIO_4$ (1.07 g, 5.0 mmol) was added, and the mixture was stirred overnight. The reaction was quenched with saturated aqueous $Na_2S_2SO_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2, and the combined organics were dried on Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel chromatography with PE/EtOAc (5:1) to afford aldehyde **4** (1.06 g, 85%). Colorless oil; IR (film) ν_{max}: 2930, 1746, 1722, 1693, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.51–7.27 (m, 5H), 4.57 (d, *J*=12.4 Hz, 1H), 4.33 (d, *J*=12.4 Hz, 1H), 4.03 (s, 1H), 3.87 (s, 1H), 3.57 (s, 3H), 3.44–3.22 (m, 1H), 3.25 (s, 3H), 3.20–2.89 (m, 3H), 2.87–2.60 (m, 2H), 2.22 (d, *J*=12.4 Hz, 1H), 1.88 (s, 1H), 1.56–1.40 (m, 13H), 1.10 (t, *J*=6.7 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9 (201.3), 173.9 (173.7), 156.6 (156.1), 139.3 (139.2), 128.2, 127.7, 127.5, 80.0 (79.1), 74.0, 73.7 (73.4), 70.1, 58.2, 52.4 (52.2), 51.2, 47.7, 46.1, 44.7, 44.6 (43.8), 38.8, 29.4, 28.4, 26.3 (25.5), 23.8, 13.2 (12.5); HRMS calcd for $C_{28}H_{44}NO_7$ 506.3118, found 506.3123.

4.14. Preparation of compound 16

$Pd(OH)_2$ on carbon (20%) (45 mg) was added to a solution of aldehyde **4** (898 mg, 1.8 mmol) in 95% EtOH (20 mL). The mixture was stirred under hydrogen for 20 h at room temperature. Filtration of the reaction product through Celite and evaporation of the solvent afforded compound **16** (690 mg, 94%), which was used in next step without purification. A small portion was purified for characterization of **16**. Colorless oil; IR (film) ν_{max}: 3433, 2931, 1723, 1690, 1415 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 4.08–3.99 (m, 2H), 3.71 (s, 3H), 3.66–3.58 (m, 1H), 3.55–3.44 (m, 1H), 3.29 (s, 3H), 3.23–3.02 (m, 2H), 2.92–2.50 (m, 3H), 2.19 (d, *J*=12.1 Hz, 1H), 2.03–1.69 (m, 3H), 1.46 (s, 10H), 1.11 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (200.7), 176.5 (176.3), 156.6 (156.1), 80.1 (79.2), 73.6 (73.4), 66.9, 58.0, 51.9, 51.1, 47.5, 46.3, 44.6, 44.4, 38.8, 29.2, 28.4, 27.5, 26.3 (25.6), 13.1 (12.4); HRMS calcd for $C_{21}H_{37}NNaO_7$ 438.2468, found 438.2465.

4.15. Preparation of compound 2

To a stirred solution of **16** (491 mg, 1.2 mmol) in CH_2Cl_2 (24 mL) was added Dess–Martin periodinane (1.02 g, 2.4 mmol) and $NaHCO_3$ (403 mg, 4.8 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then quenched with saturated aqueous $Na_2S_2O_3$ (5 mL). After being vigorously stirred for 30 min, the mixture was extracted with CH_2Cl_2. The combined organics were dried on Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), and TFA (0.92 mL, 1.2 mmol) was added dropwise to the solution at 0 °C. The mixture was stirred at room temperature for 2 h, and then the solvent was removed in vacuo. The residue was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried on Na_2SO_4, concentrated to give the crude product, which was purified by silica gel chromatography with PE/EtOAc (20:1) to afford compound **2** (259 mg, 73%). Colorless oil; IR (film) ν_{max}: 2921, 2850, 1742, 1700, 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.70 (d, *J*=6.0 Hz, 1H), 3.66–3.58 (m, 1H), 3.31 (s, 3H), 3.09–2.92 (m, 1H), 2.72 (d, *J*=5.1 Hz, 1H), 2.62 (d, *J*=11.6 Hz, 1H), 2.51 (d, *J*=11.6 Hz, 1H), 2.42 (dd, *J*=17.9, 6.8 Hz, 1H), 2.37–2.20 (m, 2H), 2.08–1.95 (m, 1H), 1.94–1.80 (m, 1H), 1.78–1.65 (m, 2H), 1.20 (s, 3H), 0.99 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 171.5, 83.1, 67.7, 64.0, 58.2, 56.8, 52.4, 50.6, 48.3, 40.2, 38.6, 33.5, 26.8, 26.1, 12.9; HRMS calcd for $C_{16}H_{25}NNaO_4$ 318.1681, found 318.1684.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.10.073.

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