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Construction of AE ring system for the C_{19}-diterpenoid alkaloids with a 5β-hydroxyl group

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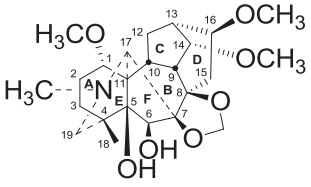
ABSTRACT

An AE azabicyclic fragment, with a β-hydroxyl group at C-5 and a substituent at C-1, of the C_{19}-diterpenoid alkaloids, was synthesized. The key reactions include an intramolecular Claisen-type condensation, double Mannich reaction, and stereoselective nucleophilic addition of carbonyl group with the assistance of steric effect of 1β-substituent.

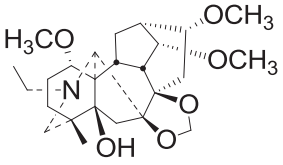
1. Introduction

Diterpenoid alkaloids, the largest and most complex group of terpenoid alkaloids, could be divided into three broad categories: C_{20}-diterpenoid alkaloids, C_{19}-diterpenoid alkaloids, and C_{18}-diterpenoid alkaloids. The structural diversity and complexity, as well as the important pharmacological activities, of the diterpenoid alkaloids pose an alluring target for synthetic chemists and medicinal chemists. Of them, the C_{19}-diterpenoid alkaloids (674 in total by the end of July 2008), a class of highly substituted alkaloids composed of one seven-, three six-, and two five-membered rings, may be divided into six types, including 13 subtypes and 19 groups.[1] So far, only three C_{19}-diterpenoid alkaloids belonging to one type have been totally synthesized, all of which were contributed by the Wiesner group.[2–4] The challenge of the synthesis of C_{19}-diterpenoid alkaloids is mostly because of its polycyclic and highly bridged core structure and heavily substituted feature. The diversity of substituent makes it very difficult to explore a general synthetic approach to the C_{19}-diterpenoid alkaloids with same core structure. However, it should be feasible to build a general synthetic route to the C_{19}-diterpenoid alkaloids with some unique substituents.

It is not common for the C_{19}-diterpenoid alkaloids to possess a 5β-hydroxyl group, which were so far isolated from four species of plants.[5–8] Two representatives of this type C_{19}-diterpenoid alkaloids were listed in Fig. 1. Among them, bonvalol represents the first example, which was isolated by Jiang and Sung in 1984.[5a]



Bonvalol 1



Nordhagenii A 2

Fig. 1. Representatives of 5β-hydroxyl-containing C_{19}-diterpenoid alkaloids.

There is no report yet on the total synthesis of 5β-hydroxyl-containing C_{19}-diterpenoid alkaloids. Even though the 5β-hydroxyl-containing AE fragments have been synthesized by Kraus et al. and Brimble et al.,[9,10] these fragments do not contain a substituent at C-1. Considering that most of the naturally occurring 5β-hydroxyl-containing C_{19}-diterpenoid alkaloids do contain an oxygenated group at C-1, we selected the C_{19}-diterpenoid alkaloids that contain an oxygenated group at C-1 and a hydroxyl group at C-5β as our first synthetic targets. Here, we report the construction of AE fragment with a substituent at C-1 and a hydroxyl group at C-5.

2. Results and discussion

We planned to introduce an oxygenated substituent at C-1 of ring A of C_{19}-diterpenoid alkaloids prior to the construction of ring E. As shown in Scheme 1, our synthesis started with Michael addition of cyclohex-2-enone (**3**) with vinylmagnesium bromide, using the procedure described in the literature.[11] The ketone carbonyl in olefin

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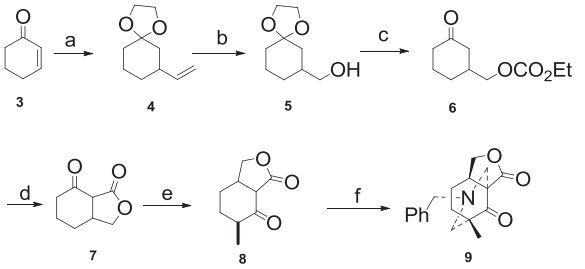
4 was protected as ketal, which can also avoid the rapid evaporation of volatile **4** at room temperature. The olefinic double bond in **4** was then oxidized with ozone to furnish the corresponding aldehyde, which is readily reduced with $NaBH_4$ to generate alcohol **5**. Introduction of carbonate followed by deprotecting ketone carbonyl furnished ethyl carbonate **6**. At this stage, a lactone moiety was installed through an intramolecular Claisen-type condensation with a pendent carbonate moiety. Initially, the procedure described in the literature[12] was employed to make the lactone **7**, leading to only 35% yield with 12 equiv of sodium hydride. Considering that excess sodium hydride might cause decomposition of the product or starting material, we explored the effect of amount of sodium hydride on yield. It was observed that yield was significantly increased to 93% when the amount of sodium hydride was reduced to 2 equiv. Having made the β-keto lactone **7** in high yield, the methyl group at the future C-4 position was readily introduced via methylation of 1,3-dianion of **7** at the γ carbon.[13] Note that the optimal temperature for the formation of dianion of our substrate was −20 °C instead of 0 °C as reported in the literature.



Scheme 1. Synthesis of AE ring analog **9**. Reagents and conditions: (a) (i) $CH_2CHMgBr$, CuI, (ii) ethylene glycol, TsOH, 60% for two steps; (b) (i) −78 °C, O_3, CH_2Cl_2, (ii) $NaBH_4$, 75% for two steps; (c) (i) $ClCO_2Et$, Py, (ii) PPTS, acetone, H_2O, 95% for two steps; (d) 60% NaH, THF, 93%, dr=100:0; (e) −20 °C, LDA, CH_3I, 85% based on 42% conversion, dr=100:0; (f) 37% formaldehyde, $BnNH_2$, EtOH, 30%, dr=100:0.

With 1,4-disubstituted ring A analog **8** in hand, next step is to construct ring E. Double Mannich reaction has been proved to be a reliable strategy to construct azabicyclo[3.3.1]-nonane core structure, corresponding to the AE part of C_{19}-diterpenoid alkaloids.[14–16] Treatment of β-keto lactone **8** with formaldehyde and benzylamine in ethanol under reflux generated the racemic bicyclic compound **9** with a 1β-substituent in 30% yield (Scheme 1). It is worth noting that no diastereoisomer of **9** was observed in this reaction. The structure of **9** was established based on the interpretation of its 2D NMR spectra (Fig. 2), and its relative configuration was deduced from the key NOESY correlations (Fig. 3). Both of them were confirmed by its X-ray crystallographic analysis (Fig. 4).

We next proceeded to stereoselectively introduce a 5β-hydroxyl group. During the course of our investigation on AE ring analogs of C_{18}-diterpenoid alkaloids, it was observed that 1β-substituent in compound **10** could hinder the approach of borane from Si face, leading to exclusive formation of compound **11** that contains a

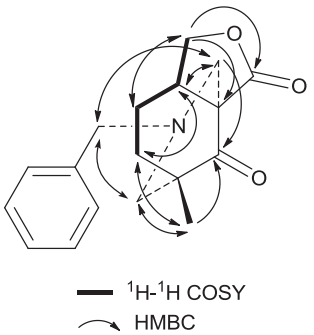


Fig. 2. Key ^{1}H−^{1}H COSY and HMBC correlations of **9**.

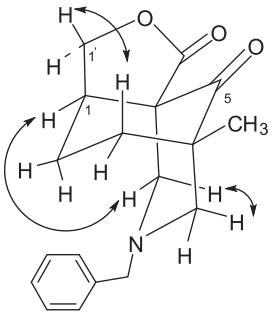


Fig. 3. Key NOESY correlations of **9**.

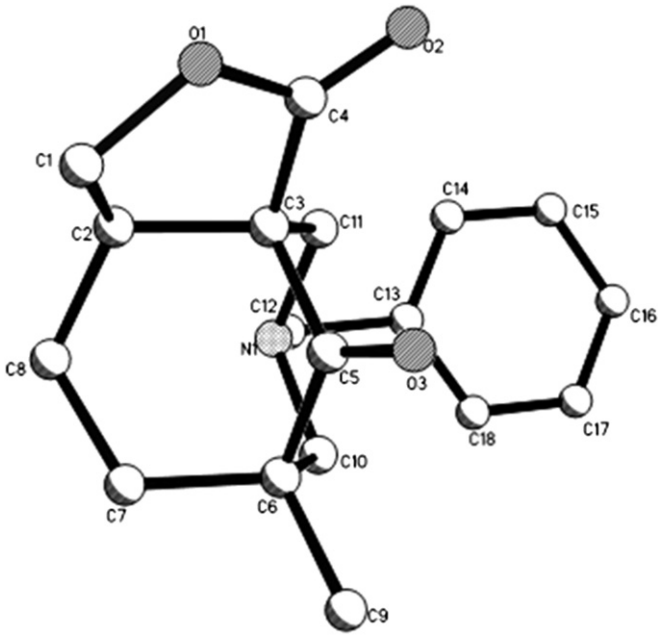
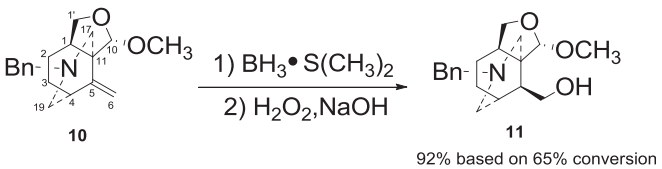
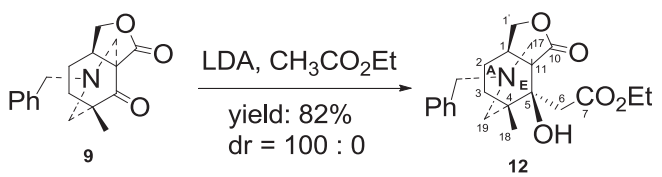


Fig. 4. ORTEP drawing of **9**.

5β-substituent (Scheme 2). This inspired us to envision that the 5β-hydroxyl group might be introduced through the nucleophilic addition of the carbonyl group at C-5 in the presence of 1β-substituent. Consequently, compound **9** was treated with the enolate of ethyl acetate (Scheme 3), which gave the desired AE ring analog **12**, possessing a 5β-hydroxyl group, of the C_{19}-diterpenoid alkaloids. The hydroxyl group at C-5 was established as β orientation based on the NOE correlations between the hydroxyl proton and H-1′, and between the hydroxyl proton and H-3β (Fig. 5).



Scheme 2. Hydroborylation of the double bond between C-5 and C-6.



Scheme 3. Synthesis of AE ring analog **12**.

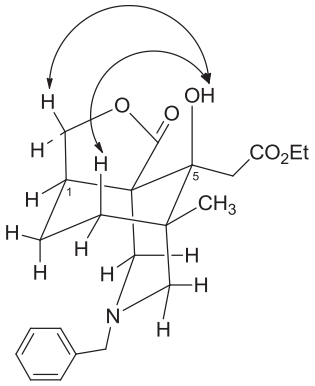


Fig. 5. NOEDS correlations of **12**.

3. Conclusion

In conclusion, the AE analog, with a heavily substituted ring A and a 5β-hydroxyl group, of the C_{19}-diterpenoid alkaloids was synthesized from cyclohex-2-enone. The key reactions include: (i) installation of the lactone moiety at C-1 and C-11 through an intramolecular Claisen-type condensation; (ii) construction of ring E by double Mannich reaction; and (iii) stereoselective introduction of a hydroxyl group at 5β through nucleophilic addition of carbonyl group with the assistance of steric effect of 1β-substituent.

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; ^{1}H 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 olefin 4

To a solution of vinylmagnesium bromide (90 mL, 1.0 M in THF, 90 mmol), CuI (1.44 g, 7.6 mmol) was added under argon at −5 °C, and the resulting black mixture was stirred at 0 °C for 20 min. A solution of 2-cyclohexen-1-one (4.30 g, 45 mmol) in THF (50 mL) was slowly added dropwise over 30 min. The solution was stirred at 5 °C for 1 h. A cold aqueous solution of ammonia and NH_4Cl (pH 8.0, 100 mL) was added and the mixture was extracted with ether (150 mL×2). The combined extracts were dried over $MgSO_4$ and concentrated. The crude residue was dissolved in THF (100 mL), to which was added ethylene glycol (11.2 g, 180 mmol) and TsOH (0.774 g, 9 mmol). The reaction solution was stirred at 25 °C for 8 h prior to being diluted with water (100 mL). The subsequent mixture was extracted with dichloroform (100 mL×2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography eluting with petroleum ether/ether (30:1) to afford compound **4** (colorless oil, 4.54 g, 60% for two steps). IR (KBr) ν_{max}: 3079, 1640, 1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80–0.86 (1H, m), 0.95–1.05 (1H, m), 1.30 (1H, t, J=12.8 Hz), 1.36–1.44 (1H, m), 1.48–1.59 (1H, m), 1.69–1.78 (3H, m), 2.25–2.28 (1H, m), 3.89–3.94 (4H, m), 4.88 (1H, d, J=10.4 Hz), 4.95 (1H, d, J=17.2 Hz), 5.74 (1H, ddd, J=17.2, 10.4, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9 (t), 31.2 (t), 34.5 (t), 39.3 (d), 40.5 (t), 64.1 (t), 64.2 (t), 108.9 (s), 112.2 (t), 143.1 (d); HRMS calcd for $C_{10}H_{17}O_2$: 169.1223. Found: 169.1231.

4.3. Preparation of alcohol 5

A solution of olefin **4** (4.00 g, 24 mmol) in CH_2Cl_2 (150 mL) at −78 °C was flushed with ozone until the reaction mixture turned to blue. Dimethyl sulfide (3.50 mL, 48 mmol) was then added to quench the reaction. The subsequent mixture was allowed to warm to room temperature and washed with water (100 mL×2). The organic layer was concentrated in vacuum to give a crude residue, which was dissolved in CH_3OH (100 mL) followed by the addition of $NaBH_4$ (1.83 g, 48 mmol) at 25 °C. The resultant mixture was stirred at the same temperature for 2 h prior to being quenched with saturated NH_4Cl solution (100 mL). The mixture was extracted with ether (100 mL×3), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated in vacuo. The obtained residue was chromatographed over silica gel, using petroleum ether/ethyl acetate (1:1) as eluent, to afford **5** (colorless oil, 3.08 g, 75%). IR (KBr) ν_{max}: 3407, 2926, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89–0.99 (1H, m), 1.17–1.26 (1H, m), 1.39–1.48 (1H, m), 1.48–1.59 (1H, m), 1.50–1.58 (1H, m), 1.71–1.84 (5H, m), 3.45–3.47 (2H, m), 3.91–3.95 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7 (t), 28.0 (t), 34.9 (d), 37.9 (t), 38.3 (t), 64.1 (t), 64.2 (t), 67.7 (t), 109.1 (s); HRMS calcd for $C_9H_{17}O_3$: 173.1172. Found: 173.1180.

4.4. Preparation of carbonate 6

To a solution of alcohol **5** (3.44 g, 20 mmol) in CH_2Cl_2 (150 mL) at 0 °C were sequentially added pyridine (4.59 mL, 60 mmol) and ethyl chloroformate (3.82 mL, 40 mmol), and the reaction was allowed to proceed with stirring at room temperature for 5 h prior to being rinsed with 1 N HCl (100 mL×2). The organic layer was concentrated under reduced pressure to furnish a residue, which was dissolved in acetone (70 mL) and water (3.5 mL). To this mixture was added pyridine *p*-toluenesulfonate (1.69 g, 6 mmol), and the mixture was refluxed for 24 h before being concentrated in vacuo. The obtained residue was purified over chromatography eluting with petroleum ether/ethyl acetate (20:1) to give compound **6** (colorless oil, 3.80 g, 95%). IR (KBr) ν_{max}: 2930, 1745, 1713, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, t, J=7.2 Hz), 1.42–1.52 (1H, m), 1.61–1.72 (2H, m), 1.92–1.95 (1H, m), 2.05–2.11 (1H, m), 2.14–2.18 (1H, m), 2.20–2.30 (1H, m), 2.36–2.45 (2H, m), 4.04 (2H, d, J=5.2 Hz), 4.18 (2H, d, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (q), 24.7 (t), 27.6 (t), 38.2 (d), 41.1 (t), 44.2 (t), 64.1 (t), 70.9 (t), 155.0 (s), 210.1 (s); HRMS calcd for $C_{10}H_{16}NaO_4$: 223.0941. Found: 223.0954.

4.5. Preparation of lactone 7

To a solution of carbonate **6** (1.50 g, 7.5 mmol) in THF (250 mL) was added NaH (60%, 0.60 g, 15 mmol), and the resulting mixture was refluxed for 10 h prior to being quenched with saturated NH_4Cl (100 mL) and 3 N HCl solution (15 mL). The mixture was extracted with ethyl acetate (100 mL×3), the combined extracts were dried over $MgSO_4$ and concentrated in vacuo to furnish a residue, which was purified by column chromatography eluting with petroleum ether/ethyl acetate (2.5:1) to afford lactone **7** (pale yellow solid, 1.07 g, 93%). The lactone **7** exists as a mixture of ketone form and enol form with a ratio of 10:2. IR (KBr) ν_{max}: 2937, 2870, 1770, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) ketone/enol=10:2, δ (ketone form) 1.59–1.80 (2H, m), 2.02–2.06 (2H, m), 2.28–2.35 (1H, m), 2.45–2.50 (1H, m), 2.94–3.01 (1H, m), 3.47 (1H, d, J=7.2 Hz), 4.14 (1H, d, J=8.8 Hz), 4.30 (1H, dd, J=8.8, 5.2 Hz); δ (typical signals for enol form) 3.84 (1H, t, J=8.8 Hz), 4.57 (1H, t, J=8.4 Hz), 8.95 (1H, br s, enol-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (t), 26.2 (t), 39.4 (d), 39.8 (t), 54.1 (d), 71.8 (t), 172.1 (s), 203.2 (s); these data are consistent with those reported in the literature.[16]

4.6. Preparation of lactone 8

A solution of **7** (1.00 g, 6.49 mmol) in THF (10 mL) was added to lithium diisopropylamide solution (14.2 mL, 1.0 M in THF, 14.2 mmol) at −20 °C. After 30 min, CH_3I (0.48 mL, 7.71 mmol) was slowly added dropwise at −20 °C. The reaction solution was stirred at 0 °C for 2 h, and diluted with water (20 mL). The mixture was extracted with CH_2Cl_2 (30 mL×2), and the combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give a residue. This residue was purified by column chromatography, using petroleum ether/ethyl acetate (4:1) as eluent, to give lactone **8** (colorless oil, 0.39 g, 85% based on 42% conversion). IR (KBr) ν_{max}: 2970, 2935, 1767, 1712, 1454, 1372 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (3H, d, J=6.0 Hz), 1.40–1.49 (1H, m), 1.69–1.79 (1H, m), 2.03–2.07 (2H, m), 2.34–2.40 (1H, m), 2.91–2.97 (1H, m), 3.46 (1H, d, J=7.2 Hz), 4.15 (1H, d, J=9.2 Hz), 4.28 (1H, dd, J=9.2, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (q), 26.9 (t), 32.5 (t), 40.7 (d), 44.0 (d), 54.4 (d), 72.1 (t), 172.2 (s), 204.3 (s); HRMS calcd for $C_9H_{12}NaO_3$: 191.0679. Found: 191.0685.

4.7. Preparation of compound 9

To a solution of **8** (0.20 g, 1.2 mmol) in EtOH (300 mL) was added aqueous formaldehyde solution (37%, 0.29 mL, 3.6 mmol) and phenylmethanamine (0.2 mL, 1.8 mmol), and the reaction mixture was refluxed for 48 h before cooling down to room temperature. After removing the solvents, the crude residue was purified by column chromatography, employing petroleum ether/ethyl acetate (10:1) as eluent, to afford **9** (white solid, 107 mg, 30%): mp: 119–161 °C; IR (KBr) ν_{max}: 3028, 2923, 1778, 1715, 1455, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, s), 1.39–1.44 (1H, m), 1.87–1.92 (1H, m), 2.20–2.26 (1H, m), 2.38, 3.05 (each 1H, ABX, J=12.0, 2.4 Hz), 2.81–2.75 (1H, m), 2.85, 3.07 (each 1H, ABq, J=11.2 Hz), 3.12–3.14 (1H, m), 3.51, 3.61 (each 1H, ABq, J=13.0 Hz), 3.83 (1H, dd, J=10.4, 9.2 Hz), 4.29 (1H, t, J=9.2 Hz), 7.27–7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7 (q), 22.0 (t), 39.2 (t), 46.1 (s), 47.5 (d), 58.6 (s), 59.8 (t), 61.5 (t), 65.8 (t), 69.2 (t), 127.5 (d), 128.5 (d), 128.7 (d), 137.7 (s), 173.4 (s), 210.7 (s); HRMS calcd for $C_{18}H_{21}NNaO_3$: 322.1414. Found: 322.1418. The X-ray crystallography data of **9** are listed below: a colorless orthorhombic crystal from petroleum ether/ethyl acetate (4:1) was mounted on a P_4 four circle diffractometer and exposed to graphite-monochromated Mo Kα irradiation. The unit cell parameters are a=10.795 (2) Å, b=14.386 (3) Å, c=9.797 (2) Å, V=1521.5 (5) $Å^3$, Z=4, d_x=1.307 g/cm^3, in space group Pna2_1, of the 10,268 measured with $2.50 \le \theta \le 26.00°$ scan, 1584 were independently observed at the level of $F_0 > 4\sigma$ (F_0). The structure was solved by the directed method using the program SHELXL–97 and the atomic parameters were refined by the full-matrix least squares on F^2 method. The final R indices [$I > 2\sigma$ (I)] was $R1$=0.067, $WR2$=0.167. CCDC reference number: CCDC 801408.

4.8. Preparation of compound 11

To a solution of **10** (0.30 g, 1.0 mmol) in THF (25 mL) was added borane methyl sulfide complex (0.29 mL, 5.0 mmol) at −15 °C, and the reaction mixture was stirred for 48 h. Aqueous H_2O_2 solution (30%, 1.02 mL, 10.0 mmol) and aqueous NaOH solution (1N, 10.0 mL, 10.0 mmol) were added, and the resulting mixture was stirred for an additional 4 h at room temperature. The mixture was extracted with ethyl acetate (50 mL×2), and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The obtained residue was purified by column chromatography, eluting with petroleum ether/ethyl acetate (2.5:1) to afford **11** (colorless oil, 190 mg, 92% based on 65% conversion). IR (KBr) ν_{max}: 3406, 3027, 2920, 1452, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36–1.47 (2H, m, H-2β, H-3β), 1.64–1.71 (2H, m, H-3α, H-5), 1.89–1.94 (1H, m, H-4), 2.10, 2.97 (each 1H, ABq, J=10.4 Hz, H_2-17), 2.18, 2.85 (each 1H, ABX, J=10.8, 2.0 Hz, H_2-19), 2.32–2.40 (1H, m, H-2α), 2.53–2.61 (1H, m, H-1), 3.27 (3H, s, OCH_3), 3.37, 3.56 (each 1H, ABq, J=13.6 Hz, NCH_2Ph), 3.60, 3.92 (each 1H, ABX, J=11.6, 7.2 Hz, H-6), 3.55, 4.09 (each 1H, ABX, J=9.6, 8.8 Hz, H-1′), 7.22–7.31 (5H, m, aromatic protons); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3 (t, C-2), 21.9 (t, C-3), 30.6 (d, C-4), 38.7 (d, C-1), 45.9 (d, C-5), 47.5 (s, C-11), 54.6 (q, OCH_3), 60.5 (t, C-19), 61.2 (t, C-17), 64.1 (t, C-6), 73.8 (t, C-1), 108.1 (d, C-10), 126.7, 128.2, 128.6, 139.4 (CH_2*Ph*); HRMS calcd for $C_{19}H_{27}NNaO_3$: 340.1883. Found: 340.1880.

4.9. Preparation of compound 12

A solution of ethyl acetate (23.5 μL, 0.24 mmol) in THF (3 mL) was added to lithium diisopropylamide solution (1.0 mL, 1.0 M in THF, 0.25 mmol) at −78 °C. After stirring at the same temperature for 30 min, a solution of **9** (59.8 mg, 0.20 mmol) in THF (3 mL) was added and the mixture was stirred for 15 h at −40 °C. The reaction solution was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (25 mL×2). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuum. Column chromatography of the residue, using petroleum ether/ethyl acetate (2:1) as eluent, gave **12** (white solid, 63 mg, 82%): mp: 151–153 °C; IR (KBr) ν_{max}: 3443, 3026, 2913, 1753, 1703, 1469, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.75 (3H, s, H-18), 1.27 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.30–1.36 (1H, m), 1.56–1.62 (1H, m), 2.16–2.24 (1H, m, H-3β), 2.31 (1H, d, J=12.0 Hz), 2.31, 2.65 (each 1H, ABq, J=12.0 Hz), 2.43–2.50 (1H, m), 2.50, 2.59 (each 1H, ABq, J=11.2 Hz), 2.67–2.73 (1H, overlapped), 2.83, 3.12 (each 1H, ABq, J=16.8 Hz, H-6), 3.39, 3.54 (each 1H, ABq, J=13.2 Hz, NCH_2Ph), 4.15–4.19 (1H, overlapped, H-1′α), 4.16 (2H, t, J=7.2 Hz, OCH_2CH_3), 4.39 (1H, dd, J=11.6, 7.6 Hz, H-1′β), 5.87 (1H, s, *OH*), 7.25–7.33 (5H, m, aromatic protons); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (q), 19.9 (t), 22.1 (d), 31.5 (t), 32.1 (t), 39.0 (s), 42.5 (d), 50.7 (s), 57.5 (t), 61.2 (t), 62.2 (t), 62.7 (t), 72.7 (t), 75.3 (s), 127.1 (d), 128.3 (d), 128.5 (d), 138.3 (s), 174.7 (s), 179.0 (s); HRMS calcd for $C_{22}H_{29}NNaO_5$: 410.1938. Found: 410.1928.

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