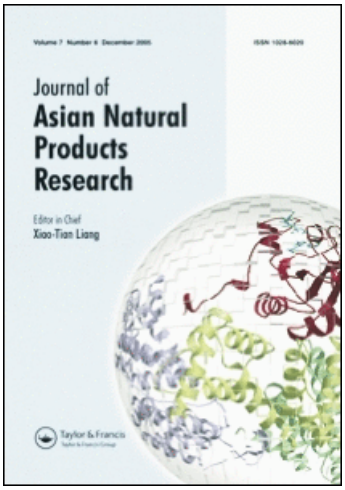


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# Conversional studies towards taxoids from $C_{19}$-diterpenoid alkaloids by the BAC sequence

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The conversional synthesis of taxoids by the BAC sequence from the $C_{19}$-diterpenoid alkaloids, 14-acetyltalatisamine (**1**), yunaconitine (**12**), and 14-acetylchasmanine (**19**), was designed and explored. Two aconane-type diterpenes **17** and **28**, the advanced intermediates for our conversional synthesis, were synthesized. The key steps include the rupture of the C(7)—C(17) bond, the formation of imine, and the denitrogenation.

**Keywords:** taxoids; $C_{19}$-diterpenoid alkaloids; aconane-type diterpene; conversional synthesis



## 1. Introduction

The discovery of the anticancer drug paclitaxel (Taxol®) [1] is one of the major milestones in the medicinal natural products. It spurred an intense research on the biology and chemistry of both paclitaxel and its related taxoids. At present, the majority of the commercially available paclitaxel and docetaxel (Taxotere®) are obtained via semi-synthetic processes starting from 10-deacetyl baccatin III. Therefore, searching for an alternate source of these two important anticancer drugs is still in need. Considering abundant natural sources of certain $C_{19}$-diterpenoid alkaloids and our extensive research experience in the chemistry of diterpenoid alkaloids, we have sequentially envisioned four strategies towards the conversion from the $C_{19}$-diterpenoid alkaloids to taxoids [2]. After a decade-long and persistent exploration on this research program since 1994, we have successfully achieved a novel approach to the taxane ABC core system from $C_{19}$-diterpenoid alkaloid deltaline [3]. Surprisingly, our journey along this conversional synthesis provided us with chance to find numerous intriguing reactions of $C_{19}$-diterpenoid alkaloids [2].

We have designed and explored an approach towards the taxoids from the $C_{19}$-diterpenoid alkaloids via a modification sequence from the ring B, ring A, to ring C (BAC sequence), which was planned with 14-acetyltalatisamine (**1**), yunaconitine (**12**), and 14-acetylchasmanine (**19**) as starting materials. During the course of this study, we have synthesized two aconane-type diterpenes **17** and **28**, the advanced intermediates for our conversional synthesis. The synthesis of these two key intermediates and the exploitation on the BAC sequence are herein described.

## 2. Results and discussion

14-Acetyltalatisamine (**1**), a simpler diterpenoid alkaloid, was initially employed as

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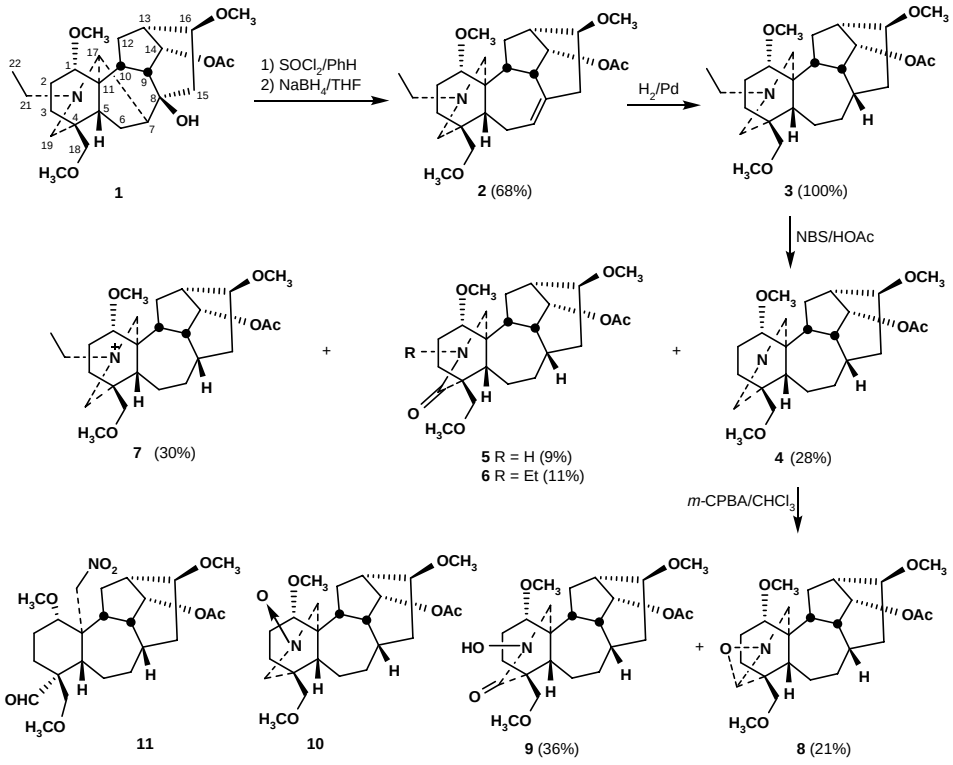
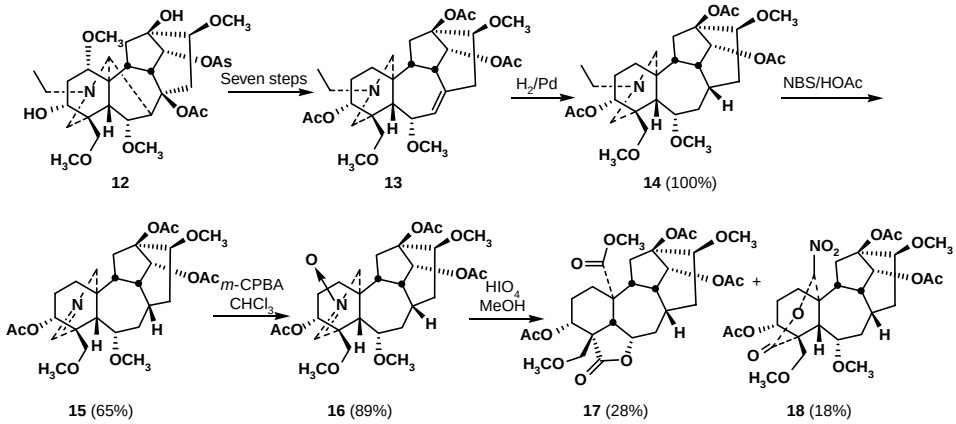
a starting material of our conversional synthesis of the taxoids through the BAC sequencing (Scheme 1). The 7,17-*seco* diterpenoid alkaloid **3** was prepared from **1** in 68% yield by the cleavage of the C(17)—C(7) bond using the procedure that we have developed [4] followed by hydrogenation. Reaction of **3** with NBS [5–7] gave imine **4** in 28% yield and the by-products **5**–**7**. It is indicated that the products of this type of reactions are highly dependent on the substituents of the substrates since we have quantitatively synthesized the imines from yunaconitine or its derivatives [5–7]. Unfortunately, oxidation of **4** with *m*-CPBA only generated the oxidative products **8** (21%) and **9** (36%) instead of the desired nitrone **10**. An attempt to cleave the *N*—C(19) bond of **8** and **9** by treating with $HIO_4$ failed. We have also tried to directly convert the imine **4** to the corresponding diterpene **11** through a one-pot reaction (*m*-CPBA–LTA)[8], but it is not successful.

We considered that the aldehyde group at C-19 from the breakage of the *N*—C(19) bond might be detrimental to the reaction and that the methoxyl group at C-6 in imine **15** might be able to trap the aldehyde group. As shown in Scheme 2, the 7,17-*seco* diterpenoid alkaloid **13** was prepared from **12** using a seven-step reaction sequence that was reported by us [4]. The $\Delta^{7,8}$ double bond in **13** was subsequently saturated to avoid some unexpected reactions. The imine **15** was smoothly prepared from **14** in 65% yield by reacting with NBS in HOAc. The characteristic imine signals at $\delta_H$ 7.30 s and $\delta_C$ 160.9 d in its NMR spectra can be assigned to C-19 due to the presence of the HMBC correlations of H-




Scheme 1. Attempt to convert 14-acetyltalatisamine to taxoids via the BAC sequence.




Scheme 2. Attempt to convert yunaconitine to taxoids via the BAC sequence.



19 with C-4 ($\delta_C$ 46.9 s) and C-18 ($\delta_C$ 70.2 t), and of C-19 ($\delta_C$ 160.9 d) with H-3 ($\delta_H$ 4.97, 1H, dd, $J = 10.8$, 5.2 Hz) (Table 1). These results suggested that the *N*,19-imine, rather than the *N*,17-imine, could be favorably formed from the 7,17-*seco*-$C_{19}$-diterpenoid alkaloids probably due to the steric effect. The nitrone **16** was obtained in 89% yield by treatment of **15** with *m*-CPBA at room temperature. However, an attempt to break the *N*—C(19) bond of **16** with $NaIO_4$ or LTA failed. Compound **16** was subsequently exposed to a molar excess of a solution of $HIO_4$ in MeOH overnight at room temperature to furnish **17** and **18**. These two products have negative response to Dragendorff's reagent. The NMR spectra of **17** exhibited the presence of a typical methyl ester group ($\delta_H$ 3.69, 3H, s; $\delta_C$ 168.1 s, 51.9 q) and a five-membered lactone moiety ($\delta_C$ 178.0 s and IR 1778 $cm^{-1}$). The NMR spectra of **18** displayed the existence of a lactone moiety ($\delta_C$ 168.2 s) and a special methine group ($\delta_H$ 5.62, 1H, br s, $\delta_C$ 103.3 d). Its IR spectrum exhibited absorbance for the nitro group (1563–1372 $cm^{-1}$).

We then chose 14-acetylchasmanine **19**, a simpler diterpenoid alkaloid relative to yunaconitine but with a methoxyl group at C-6, as the starting material to observe the applicability of this approach (Scheme 3). According to the procedure described in the literature [4], 7,17-*seco* diterpenoid alkaloids **20** and **21** were obtained in 52 and 31% yield from **19**. Hydrogenation of **20** followed by exposure to NBS in HOAc furnished imine **23** and iminium **24**. Oxidation of imine **23** with *m*-CPBA provided the desired nitrone **25** in 43% yield. During the subsequent denitrogenation by treating with $HIO_4$, we observed that an old bottle of $HIO_4{\cdot}2H_2O$ appeared to be liquid led to the quantitative conversion of **25** to the expected ester **26**. To avoid the generation of cycloether by the simultaneous reduction of the methyl ester and the γ-lactone, we tried to selectively reduce the methyl ester. However, $NaBH_4$-GDE only reduced the ester group at C-14 of **26** to give compound **27**. The expected product **28** could be obtained when an excess amount of $NaBH_4$ was used in the presence of $AlCl_3$. Reduction of **26** with a stoichiometric amount of $LiAlH_4$ afforded **28** in 51% yield.

In conclusion, a BAC-sequencing approach to the taxoids from three diterpenoid alkaloids was exploited. To this end, two advanced intermediates were synthesized, demonstrating the BCA

Table 1. 1D and 2D NMR spectral data of compound **15** in $CDCl_3$ (400 MHz for $^1H$, 100 MHz for $^{13}C$).

| No. | $\delta_C$ | $\delta_H$ mult. ($J$ in Hz) | HMBC (H → C) |
|---|---|---|---|
| 1 | 29.0 t | 1.62 m | C-2, C-3, C-5, C-11 |
| | | 1.73 m | C-2, C-3, C-5, C-11 |
| 2 | 27.1 t | 1.44 m | C-1, C-3, C-11 |
| | | 1.98 m | C-1, C-4, C-11 |
| 3 | 73.3 d | 4.97 dd ($J$ = 10.8, 5.2) | C-2, C-4, C-18, C-19 |
| 4 | 46.9 s | – | – |
| 5 | 45.7 d | 1.64 d ($J$ = 3.2) | C-1, C-3, C-11 |
| 6 | 79.9 d | 3.73 br s | C-5, C-7, C-8, C-11, 6-$OCH_3$ |
| 7 | 32.7 t | 2.07 m | C-8, C-9 |
| | | 2.18 m | C-9 |
| 8 | 28.9 d | 1.76 m | C-6, C-7, C-9, C-16 |
| 9 | 45.4 d | 2.38 m | C-7, C-8, C-10, C-11, C-12 |
| 10 | 44.4 d | 2.36 m | C-9, C-11, C-12, C-13, C-14 |
| 11 | 36.1 s | – | – |
| 12 | 33.5 t | 1.28 dt ($J$ = 14.6, 5.2) | C-10 |
| | | 1.92 m | C-9, C-11 |
| 13 | 85.1 s | – | – |
| 14 | 77.3 d | 5.22 d ($J$ = 4.4) | C-8, C-10, C-13, C-16 |
| 15 | 46.8 t | 1.43 m | C-7, C-8, C-9, C-13, C-16 |
| | | 1.76 m | C-8, C-9, C-13, C-16 |
| 16 | 81.1 d | 4.00 br s | C-8, C-13, C-14, 16-$OCH_3$ |
| 17 | 59.5 t | 3.39 dd ($J$ = 18.5, 2.4) | C-5, C-11 |
| | | 4.16 dd ($J$ = 18.5, 2.4) | C-5, C-11 |
| 18 | 70.2 t | 3.31 ABq ($J$ = 9.6) | C-3, C-5, 18-$OCH_3$ |
| | | 3.58 ABq ($J$ = 10.0) | C-3, C-5, 18-$OCH_3$ |
| 19 | 160.9 d | 7.30 s | C-4, C-18 |
| 6-OMe | 59.2 q | 3.19 s | C-6 |
| 16-OMe | 58.4 q | 3.35 s | C-16 |
| 18-OMe | 55.9 q | 3.27 s | C-18 |
| 3-OAc | 170.8 s | – | – |
| | 20.9 q | 2.05 s | 3-OCO |
| 13-OAc | 170.7 s | – | – |
| | 22.0 q | 2.11 s | 13-OCO |
| 14-OAc | 169.8 s | – | – |
| | 21.2 q | 2.05 s | 14-OCO |

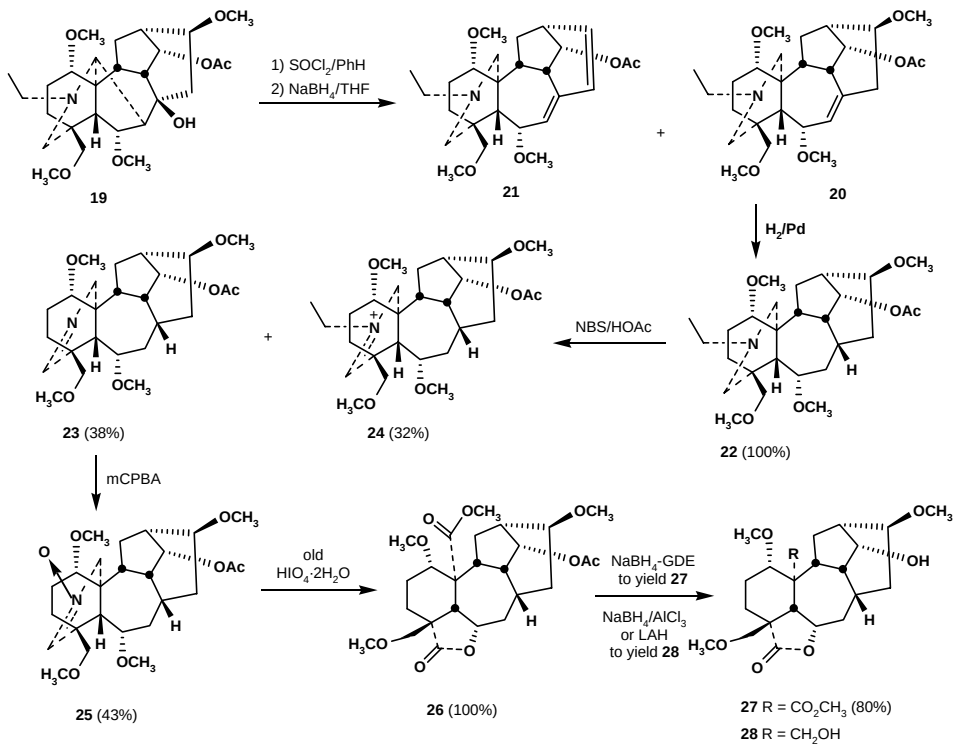


sequence to be a potential route for the conversion of $C_{19}$-diterpenoid alkaloids to the taxoids. It has been reported that the oxidation of the nitrones (e.g. **16**, **25**) with $HIO_4$ could generate the corresponding nitro compounds [6,7,9], and that nitro compounds could be converted to the corresponding carboxylic acids or esters under some oxidants [10,11]. However, for the first time, it was observed that the treatment of the nitrones with $HIO_4$ could directly produce the corresponding carboxylic esters.

## 3. Experimental

### *3.1 General experimental procedures*

Melting points were determined on a Kofler block (uncorrected). IR spectra were recorded on a Nicolet FT-IR 200 SXV spectrometer. $^1H$ and $^{13}C$ NMR spectra were acquired on a Varian INOVA 400/54 or a Bruker AC-E 200 spectrometer in $CDCl_3$ with TMS as the internal standard. Mass spectra were obtained on a Finnigan LCQ and Micromass Auto Spec Ultima-Tof spectrometer.




Scheme 3. Attempt to convert 14-chasmanine to taxoids via the BAC sequence.

Silica gel $GF_{254}$ and H (10–40 μm; Qingdao Sea Chemical Factory, Qingdao, China) were used for TLC, Chromatotron, and column chromatography.

### *3.2 Compound 2*

To a solution of compound **1** (1.34 g, 2.89 mmol) in anhydrous benzene (60 ml) was added $SOCl_2$ (3 ml), and the subsequent solution was stirred at room temperature overnight. The removal of the solvent gave a residue, to which $NaBH_4$ (1.12 g) in THF (60 ml) was added. The reaction mixture was heated at 60°C for 12 h. After the removal of the solvents, the residue was diluted with water (90 ml) and extracted with chloroform (70 ml × 3). The combined extracts were dried ($Na_2SO_4$) and the solvents were removed. The residue was subjected to column chromatography (silica gel H, 30 g) eluted with cyclohexane–acetone (12:1) to afford **2** (a white amorphous powder, 756 mg, 68%). The structure of **2** was identified by comparison with the authentic sample [TLC: cyclohexane–acetone (6:1), $CHCl_3$–$CH_3OH$ (99:1), $CHCl_3$–acetone (12:1)].

### *3.3 Compound 3*

To a solution of **2** (500 mg, 1.1 mmol) in 95% EtOH (15 ml) was added 10% Pd/C (20 mg), and the solution was stirred under the atmosphere of hydrogen at room temperature for 1 h. After filtration, the filtrate was concentrated to give **3** (a white amorphous powder, 500 mg, 100%), which was identified by comparison with the authentic sample [TLC: cyclohexane–acetone (6:1), $CHCl_3$–$CH_3OH$ (99:1), $CHCl_3$–acetone (12:1)].

### *3.4 Compounds 4–7*

To a solution of **3** (350 g, 0.78 mmol) in HOAc (12 ml) was added NBS (1.11 g,

6.23 mmol), and the solution was allowed to stand at room temperature for 1 h prior to being poured into ice water (5 ml). The mixture was basified with conc. $NH_4OH$ solution to pH 9 and extracted with chloroform (15 ml × 3). The extracts were dried ($Na_2SO_4$) and concentrated. Column chromatography (silica gel H, 10 g) of the residue, using cyclohexane–acetone (5:1) as the eluent, afforded **4** (a white amorphous powder, 91 mg, 28%), **5** (a white amorphous powder, 30 mg, 9%), **6** (a white amorphous powder, 40 mg, 11%), and **7** (a white amorphous powder, 98 mg, 30%). Compound **4**: mp 81–83°C; $[\alpha]_D^{20}$ + 4.44 ($c$ = 3.6, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2928, 1734, 1654, 1252, 1098 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 2.06 (3H, s, OAc), 3.26, 3.30, 3.36 (each 3H, s, 3 × OMe), 3.70, 3.81 (each 1H, ABq, $J$ = 19.2 Hz, $H_2$-18), 4.67 (1H, t, $J$ = 4.8 Hz, H-14β), 7.35 (1H, br s, H-19); $^{13}C$ NMR spectral data, see Table 2; ESI-MS $m/z$ (%): 420 ($[M + H]^+$, 100). Compound **5**: mp 137–139°C; $[\alpha]_D^{20}$ − 1.00 ($c$ = 1.0, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 3440, 2930, 1713, 1649, 1254, 1098 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 2.04 (3H, s, OAc), 3.24, 3.32, 3.32 (each 3H, s, 3 × OMe), 4.65 (1H, t, $J$ = 4.4 Hz, H-14β); $^{13}C$ NMR spectral data, see Table 2; HR-ESI-MS: $m/z$ 436.2697 $[M + H]^+$ (calcd for $C_{24}H_{38}O_6N$, 436.2699). Compound **6**: mp 69–71°C; $[\alpha]_D^{20}$ − 2.3 ($c$ = 1.0, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2931, 1734, 1634, 1253, 1098 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 1.10 (3H, t, $J$ = 7.0 Hz, $NCH_2CH_3$), 2.03 (3H, s, OAc), 3.24, 3.30, 3.30 (each 3H, s, 3 × OMe), 3.44, 3.67 (each 1H, ABq, $J$ = 10.0 Hz, $H_2$-18), 4.63 (1H, t, $J$ = 4.0 Hz, H-14β); $^{13}C$ NMR spectral data, see Table 2; ESI-MS $m/z$ (%): 478 (M + Na, 100); HR-ESI-MS: $m/z$ 464.3020 $[M + H]^+$ (calcd for $C_{26}H_{42}O_6N$, 464.3012). Compound **7**: mp 142–144°C; $[\alpha]_D^{20}$ − 13.3 ($c$ = 4.0, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2934, 1730, 1649, 1456, 1368, 1255, 1096 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 1.54 (3H, t, $J$ = 7.2 Hz, $NCH_2CH_3$), 2.04 (3H, s, OAc), 3.24, 3.32, 3.41 (each 3H, s, 3 × OMe), 4.50 (2H, dd, $J$ = 13.6, 7.2 Hz, $H_2$-17), 4.63 (1H, t, $J$ = 4.8 Hz, H-14β), 9.49 (1H, br s, H-19); $^{13}C$ NMR spectral data, see Table 2; ESI-MS $m/z$ (%): 449 $[M + H]^+$(26), 448 ($M^+$, 100); HR-ESI-MS: $m/z$ 448.3068 $[M]^+$ (calcd for $C_{26}H_{42}O_5N$, 448.3063).

### 3.5 Compounds 8 and 9

To a solution of **4** (103 mg, 0.25 mmol) in $CHCl_3$ (5 ml) was added *m*-CPBA (127 mg, 0.74 mmol), and the solution was stirred at room temperature for 1 h. The reaction was quenched by the addition of 10% $Na_2CO_3$ (9 ml) with stirring. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (5 ml × 3). The combined extracts were dried ($Na_2SO_4$) and concentrated. The residue was subjected to column chromatography (silica gel H, 3 g) eluted with cyclohexane–acetone (6:1) to afford **8** (a white amorphous powder, 22 mg, 21%) and **9** (a white amorphous powder, 40 mg, 36%). Compound **8**: mp 96–98°C; $[\alpha]_D^{20}$ − 15.38 ($c$ = 3.9, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2929, 1734, 1648, 1254, 1097 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 2.05 (3H, s, OAc), 3.25, 3.31, 3.35 (each 3H, s, 3 × OMe), 3.88 (1H, s, H-19β), 4.64 (1H, t, $J$ = 4.6 Hz, H-14β); $^{13}C$ NMR spectral data, see Table 2; ESI-MS $m/z$ (%): 436 ($[M + H]^+$, 100), 420 ($M^+ - CH_3$, 18); HR-ESI-MS: $m/z$ 436.2713 $[M + H]^+$ (calcd for $C_{24}H_{38}O_6N$, 436.2699). Compound **9**: mp 100–102°C; $[\alpha]_D^{20}$ − 28.9 ($c$ = 3.4, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 3441, 2929, 1735, 1637, 1369, 1253, 1099 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 2.05 (3H, s, OAc), 3.25, 3.31, 3.31 (each 3H, s, 3 × OMe), 4.65 (1H, t, $J$ = 4.6 Hz, H-14β); $^{13}C$ NMR spectral data, see Table 2; ESI-MS $m/z$ (%): 452 ($[M + H]^+$, 100), 420 ($M^+ - OCH_3$, 32), HR-ESI-MS: $m/z$ 452.2663 $[M + H]^+$ (calcd for $C_{24}H_{38}O_7N$ 452.2648).

### 3.6 Compound 14

This compound was prepared from **13** in quantitative yield employing a similar

Table 2. $^{13}C$ NMR spectral data of compounds **4**–**9**, **14**, **16**–**18**, and **20**–**28** (50 MHz, $CDCl_3$).

| No. | **4** | **5** | **6** | **7** | **8** | **9** | **14** | **16** | **17** | **18** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 90.7 | 90.0 | 90.1 | 88.1 | 88.4 | 89.3 | 28.0 | 26.5 | 23.3 | 25.3 | 89.4 | 92.9 | 90.2 | 90.9 | 88.3 | 89.1 | 82.2 | 83.1 | 83.4 |
| 2 | 26.9 | 27.0 | 27.1 | 27.3 | 27.0 | 27.3 | 28.8 | 29.0 | 29.2 | 30.5 | 25.9 | 25.3 | 22.4 | 27.4 | 27.4 | 27.4 | 24.6 | 24.6 | 24.2 |
| 3 | 30.5 | 32.6 | 33.0 | 31.3 | 30.5 | 32.3 | 74.3 | 73.2 | 70.9 | 71.0 | 36.2 | 34.0 | 35.8 | 31.0 | 33.3 | 32.5 | 29.3 | 36.9 | 36.8 |
| 4 | 43.2 | 41.9 | 42.1 | 43.5 | 42.6 | 43.5 | 43.2 | 47.2 | 44.9 | 45.0 | 39.7 | 41.2 | 41.7 | 42.2 | 42.5 | 43.5 | 49.2 | 52.1 | 52.2 |
| 5 | 34.1 | 34.3 | 34.4 | 34.1 | 33.6 | 34.3 | 47.2 | 45.5 | 45.9 | 50.4 | 41.4 | 43.1 | 41.9 | 34.2 | 34.0 | 34.0 | 35.5 | 37.6 | 37.6 |
| 6 | 24.1 | 24.1 | 24.3 | 24.1 | 24.6 | 24.0 | 81.2 | 79.6 | 80.4 | 77.8 | 84.3 | 84.4 | 85.2 | 81.6 | 80.6 | 81.1 | 80.9 | 82.1 | 83.1 |
| 7 | 21.2 | 20.9 | 20.9 | 21.4 | 21.2 | 21.0 | 33.4 | 32.4 | 31.4 | 32.9 | 127.5 | 123.7 | 32.6 | 24.6 | 23.9 | 24.2 | 20.7 | 20.7 | 21.7 |
| 8 | 44.5 | 44.5 | 44.6 | 44.3 | 43.6 | 44.6 | 29.2 | 28.6 | 27.5 | 29.3 | 133.1 | 135.4 | 28.7 | 44.8 | 44.5 | 44.9 | 44.7 | 45.5 | 46.4 |
| 9 | 43.2 | 43.1 | 43.3 | 42.3 | 43.4 | 43.5 | 46.2 | 45.2 | 45.5 | 45.5 | 44.3 | 47.1 | 41.8 | 43.9 | 43.7 | 44.0 | 43.0 | 45.5 | 45.3 |
| 10 | 44.6 | 44.6 | 44.7 | 44.5 | 45.0 | 44.6 | 43.7 | 44.5 | 42.9 | 43.4 | 44.0 | 43.3 | 45.7 | 46.5 | 45.0 | 46.4 | 48.6 | 48.6 | 48.7 |
| 11 | 44.6 | 47.0 | 46.9 | 43.5 | 40.3 | 46.9 | 38.2 | 38.2 | 53.4 | 45.0 | 43.0 | 44.3 | 44.1 | 43.8 | 46.1 | 44.1 | 52.0 | 49.2 | 40.0 |
| 12 | 28.5 | 28.5 | 28.5 | 28.4 | 28.4 | 28.6 | 33.7 | 33.2 | 31.5 | 37.0 | 29.9 | 33.7 | 27.2 | 28.8 | 28.5 | 28.7 | 26.3 | 26.0 | 25.9 |
| 13 | 29.1 | 29.0 | 29.0 | 28.8 | 28.9 | 29.0 | 85.5 | 84.5 | 85.2 | 85.2 | 36.4 | 38.9 | 37.7 | 29.4 | 28.6 | 29.1 | 28.2 | 27.2 | 27.1 |
| 14 | 77.1 | 76.9 | 76.9 | 76.5 | 77.1 | 76.8 | 77.7 | 76.7 | 75.9 | 76.6 | 78.1 | 73.3 | 76.0 | 77.4 | 76.1 | 76.8 | 75.4 | 75.9 | 76.0 |
| 15 | 34.3 | 34.0 | 33.9 | 34.2 | 35.4 | 33.9 | 46.5 | 45.7 | 35.6 | 43.0 | 37.4 | 132.2 | 38.6 | 34.4 | 31.1 | 34.0 | 36.8 | 28.5 | 28.5 |
| 16 | 81.5 | 81.5 | 81.5 | 80.9 | 81.5 | 81.3 | 81.3 | 80.9 | 80.7 | 82.0 | 80.4 | 130.5 | 78.9 | 81.6 | 80.3 | 80.5 | 80.8 | 81.0 | 79.6 |
| 17 | 51.5 | 42.4 | 47.4 | 57.1 | 49.5 | 49.7 | 53.7 | 66.1 | 168.1 | 103.3 | 52.1 | 52.8 | 50.1 | 52.8 | 56.1 | 60.0 | 173.8 | 173.9 | 64.9 |
| 18 | 76.6 | 74.7 | 75.4 | 73.6 | 76.8 | 74.5 | 72.8 | 69.5 | 73.0 | 70.4 | 79.7 | 81.4 | 80.1 | 76.9 | 73.7 | 76.2 | 77.5 | 77.5 | 80.2 |
| 19 | 164.8 | 174.9 | 171.3 | 179.6 | 80.8 | 166.4 | 52.1 | 135.0 | 178.0 | 168.2 | 56.3 | 52.4 | 56.6 | 162.7 | 179.0 | 137.9 | 176.2 | 176.5 | 177.2 |
| 21 | | | 41.4 | 51.9 | | | 50.4 | | | | 52.0 | 50.9 | 51.2 | | 53.0 | | | | |
| 22 | | | 11.7 | 14.1 | | | 12.2 | | | | 12.1 | 11.9 | 11.9 | | 13.6 | | | | |
| 1-OMe | 56.5 | 56.5 | 56.5 | 56.5 | 56.5 | 56.6 | | | | | 55.8 | 56.8 | 56.0 | 55.9 | 55.6 | 56.0 | 56.5 | 56.7 | 56.7 |
| 6-OMe | | | | | | | 55.1 | 56.2 | | 56.7 | 57.4 | 57.2 | 57.2 | 57.1 | 56.3 | 56.7 | | | |
| 16-OMe | 56.9 | 57.0 | 57.0 | 57.0 | 57.0 | 56.9 | 58.3 | 58.5 | 58.3 | 58.3 | 56.3 | | 56.3 | 56.4 | 56.7 | 56.4 | 57.4 | 57.3 | 58.1 |
| 18-OMe | 59.4 | 59.3 | 59.2 | 59.4 | 59.3 | 59.4 | 58.9 | 59.2 | 59.2 | 59.3 | 58.9 | 59.2 | 59.4 | 59.4 | 59.1 | 59.3 | 59.3 | 59.3 | 59.4 |
| O*CO* | 171.6 | 171.7 | 171.6 | 171.4 | 171.6 | 171.5 | 170.8, 170.8, 170.2 | 170.7, 170.5, 169.5 | 170.9, 170.3, 169.7 | 170.9, 170.7, 169.3 | 171.1 | 171.3 | 171.4 | 171.7 | 171.7 | 171.5 | 171.5 | | |
| CO*CH*$_3$ | 21.3 | 21.2 | 21.2 | 21.0 | 21.2 | 21.2 | 22.1, 21.3, 21.2 | 21.9, 21.1, 20.9 | 21.6, 21.2, 21.0 | 22.1, 21.1, 20.4 | 21.3 | 21.2 | 21.0 | 21.2 | 20.8 | 21.1 | 21.1 | | |
| COO*CH*$_3$ | | | | | | | | | 51.9 | | | | | | | | 51.6 | 51.6 | |

procedure as described for the synthesis of **3**. Compound **14**: a white amorphous powder; mp 78–80°C; $[\alpha]_D$ −15.9 ($c = 4.4$, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 1737, 1450, 1369, 1250 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 0.95 (3H, t, $J = 7.2$ Hz, $NCH_2CH_3$), 1.99, 1.99, 2.04 (each 3H, s, 3 × OAc), 3.13, 3.20, 3.28 (each 3H, s, 3 × OMe), 3.76 (1H, br s, H-16α), 3.92 (1H, d, $J = 4.2$ Hz, H-6β), 4.92 (1H, dd, $J = 11.6$, 6.8 Hz, H-3β), 5.44 (1H, br s, H-14β); $^{13}C$ NMR spectral data, see Table 2; HR-ESI-MS: *m/z* 566.3318 $[M + H]^+$ (calcd for $C_{30}H_{48}ON_9$, 566.3329).

### 3.7 Compound 15

Employing a similar procedure as described for the synthesis of compounds **4**–**7**, imine **15** (384 mg, 65%) was prepared from **14**. Imine **15**: a white amorphous powder; mp 204–205°C; $[\alpha]_D^{20}$ + 8.2 ($c = 3.7$, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 1773, 1705, 1247, 1192 $cm^{-1}$; $^1H$ and $^{13}C$ NMR spectral data, see Table 1; HR-ESI-MS: *m/z* 558.6250 $[M + Na]^+$ (calcd for $C_{28}H_{41}O_9NNa$, 558.6246).

### 3.8 Compound 16

This compound (95 mg) was prepared from **15** in 89% yield by a similar procedure as described for the synthesis of compounds **8** and **9**. Compound **16**: mp 184–186°C; $^1H$ NMR (200 MHz) $\delta$ 2.01, 2.01, 2.07 (each 3H, s, 3 × OAc), 3.22, 3.22, 3.32 (each 3H, s, 3 × OMe), 3.77 (1H, br s, H-6β), 3.89 (1H, br s, H-16α), 4.39 (1H, d, $J = 15.6$ Hz, H-17), 4.94 (1H, dd, $J = 10.8$, 4.8 Hz, H-3β), 5.20 (1H, d, $J = 2.8$ Hz, H-14β), 6.68 (1H, s, H-19); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 574 ($M^+$ + Na, 100); HR-ESI-MS: *m/z* 574.2609 $[M + Na]^+$ (calcd for $C_{28}H_{41}O_{10}NNa$, 574.2623).

### 3.9 Compounds 17 and 18

To a solution of **16** (175 mg, 0.32 mmol) in MeOH (7 ml) was added $HIO_4 \cdot 2H_2O$ (580 mg, 2.55 mmol), and the mixture was stirred at room temperature for 12 h. After the removal of methanol, the residue was diluted with water and extracted with ethyl acetate. The combined extracts were dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel H, 5 g) eluted with cyclohexane–acetone (5:1) to afford **17** (a white amorphous powder, 41 mg, 28%) and **18** (a white amorphous powder, 27 mg, 18%). Compound **17**: mp 102–104°C; $[\alpha]_D^{20}$ + 20.0 ($c = 2.7$, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2933, 1778, 1736, 1608, 1514, 1460, 1258, 1099 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 1.98, 2.03, 2.11 (each 3H, s, 3 × OAc), 3.27, 3.32, 3.69 (each 3H, s, 3 × OMe), 3.89 (1H, d, $J = 4.0$ Hz, H-6β), 3. 98 (1H, d, $J = 4.8$ Hz, H-16α), 4.99 (1H, dd, $J = 10.6$, 4.6 Hz, H-3β), 5.18 (1H, d, $J = 2.4$ Hz, H-14β); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 589 ($M^+$ + Na, 100); HR-ESI-MS: *m/z* 589.5928 $[M + Na]^+$ (calcd for $C_{28}H_{38}O_{12}Na$, 589.5923). Compound **18**: mp 96–98°C; $[\alpha]_D^{20}$ −15.4 ($c = 2.2$, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2928, 1746, 1733, 1563, 1458, 1372, 1243, 1106 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 2.00, 2.06, 2.08 (each 3H, s, 3 × OAc), 3.31, 3.36, 3.38 (each 3H, s, 3 × OMe), 3.84 (1H, d, $J = 5.6$ Hz, H-6β), 3.92 (1H, d, $J = 4.0$ Hz, H-16α), 4.99 (1H, dd, $J = 10.6$, 4.8 Hz, H-3β), 5.57 (1H, d, $J = 3.6$ Hz, H-14β), 5.62 (1H, br s, H-17); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 620 ($M^+$ + Na, 100), 589 ($M^+ - OCH_3$, 45); HR-ESI-MS: *m/z* 620.6059 $[M + Na]^+$ (calcd for $C_{28}H_{39}O_{13}NNa$, 620.6064).

### 3.10 Compounds 20 and 21

Using a similar procedure as described for the synthesis of **2**, olefin **20** (a white amorphous powder, 82 mg, 52%) and diene **21** (a white amorphous powder, 46 mg, 31%) were prepared from **19**. Olefin **20**: mp 88–90°C; $[\alpha]_D^{20}$ + 41.6 ($c = 1.2$, $CH_2Cl_2$);

IR (KBr) $\nu_{max}$: 2930, 1736, 1635, 1458, 1367, 1249, 1094 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 0.96 (3H, t, $J = 7.6$ Hz, $NCH_2CH_3$), 2.03 (3H, s, OAc), 3.26, 3.30, 3.31 (each 3H, s, 3 × OMe), 4.13 (1H, m, H-16α), 4.77 (1H, t, $J = 4.0$ Hz, H-14β), 5.51 (1H, t, $J = 2.0$ Hz, H-7); $^{13}C$ NMR spectral data, see Table 2; HR-ESI-MS: *m/z* 478.3174 $[M + H]^+$ (calcd for $C_{27}H_{44}O_6N$, 478.3169). Diene **21**: mp 99–101°C; IR (KBr) $\nu_{max}$: 2934, 1734, 1647, 1454, 1248, 1098 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 0.96 (3H, t, $J = 7.2$ Hz, $NCH_2CH_3$), 2.02 (3H, s, OAc), 3.25, 3.29, 3.29 (each 3H, s, 3 × OMe), 4.80 (1H, t, $J = 4.0$ Hz, H-14β), 5.43 (1H, d, $J = 6.8$ Hz, H-7), 5.88 (1H, t, $J = 9.2$ Hz, H-16), 6.24 (1H, d, $J = 8.8$ Hz, H-15); $^{13}C$ NMR spectral data, see Table 2. ESI-MS: *m/z* 446 ($[M + H]^+$, 100); HR-ESI-MS: *m/z* 446.2911 $[M + H]^+$ (calcd for $C_{26}H_{40}ON_5$, 446.2906).

### 3.11 Compound 22

This compound was prepared from **20** in quantitative yield by a similar procedure as described for the synthesis of **3**. A white amorphous power (60 mg); mp 55–57°C; $[\alpha]_D^{20}$ −30.0 ($c = 1.1$, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2924, 1735, 1458, 1367, 1254, 1096 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 0.99 (3H, t, $J = 7.0$ Hz, $NCH_2CH_3$), 2.05 (3H, s, OAc), 3.23, 3.24, 3.28, 3.32 (each 3H, s, 4 × OMe), 3.78 (1H, br s, H-6β), 4.70 (1H, t, $J = 4.8$ Hz, H-14β); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 480 ($[M + H]^+$, 100). HR-ESI-MS: *m/z* 480.3320 $[M + H]^+$ (calcd for $C_{27}H_{46}O_6N$, 480.3325).

### 3.12 Compounds 23 and 24

These two compounds were prepared from **22** according to a similar procedure as described for the synthesis of compounds **4**–**7**. Compound **23**: a white amorphous powder; 104 mg, 38%; mp 59–61°C; $[\alpha]_D^{20}$ −1.29 ($c = 1.5$, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2926, 1730, 1642, 1254, 1096 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 2.06 (3H, s, OAc), 3.17, 3.27, 3.30, 3.35 (each 3H, s, 4 × OMe), 3.66 (1H, br s, H-6β), 3.78, 3.91 (each 1H, dd, $J = 17.6$, 2.0 Hz, $H_2$-17), 4.74 (1H, t, $J = 4.4$ Hz, H-14β), 7.57 (1H, s, H-19); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 450 ($[M + H]^+$, 100); HR-ESI-MS: *m/z* 450.2856 $[M + H]^+$ (calcd for $C_{30}H_{45}O_{12}$, 450.2850). Compound **24**: a white amorphous powder; 93 mg, 32%; mp 87–89°C; $[\alpha]_D^{20}$ + 0.54 ($c = 1.8$, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2923, 1725, 1640, 1455, 1369, 1254, 1094 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 1.52 (3H, t, $J = 7.2$ Hz, $NCH_2CH_3$), 2.07 (3H, s, OAc), 3.21, 3.27, 3.34, 3.38 (each 3H, s, 4 × OMe), 3.70, 3.78 (each 1H, ABq, $J = 9.6$ Hz, $H_2$-17), 3.64, 3.97 (each 1H, ABq, $J = 16.0$ Hz, $H_2$-18), 3.81 (1H, br s, H-6β), 4.09, 4.40 (each 1H, m, $H_2$-21), 4.68 (1H, t, $J = 4.4$ Hz, H-14β), 10.00 (1H, s, H-19); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 479 ($[M + H]^+$, 30), 478 ($M^+$, 100); HR-ESI-MS: *m/z* 478.3152 $[M]^+$ (calcd for $C_{27}H_{44}O_6N$, 478.3169).

### 3.13 Compound 25

This compound was prepared from **23** in 43% yield by a similar procedure as described for the synthesis of **8** and **9**. Compound **25**: a white amorphous powder, 48 mg; mp 99–101°C; $[\alpha]_D^{20}$ −48.5 ($c = 2.8$, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2928, 1730, 1637, 1457, 1371, 1254, 1097 $cm^{-1}$; $^1H$ NMR (400 MHz) $\delta$ 2.07 (3H, s, OAc), 3.23, 3.26, 3.31, 3.34 (each 3H, s, 4 × OMe), 3.74 (1H, br s, H-6β), 3.80, 4.14 (each 1H, ABq, $J = 15.6$ Hz, $H_2$-17), 4.69 (1H, t, $J = 4.4$ Hz, H-14β), 6.76 (1H, s, H-19); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 448 ($[M + Na]^+$, 100); HR-ESI-MS: *m/z* 488.2612 $[M + Na]^+$ (calcd for $C_{25}H_{39}O_7NNa$, 488.2619).

### 3.14 Compound 26

This compound was prepared from **25** in quantitative yield by a similar procedure as

described for the synthesis of **17** and **18**. The only difference being that an old $HIO_4{\cdot}2H_2O$ was used this time that appeared to be a liquid. Compound **26**: a white amorphous powder (11 mg, 100%), mp 88–90°C; $[\alpha]_D^{20} + 5.7$ ($c = 2.1$, $CH_2Cl_2$); IR (KBr) $\nu_{max}$: 2938, 1771, 1741, 1608, 1514, 1443, 1257, 1100 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 2.03 (3H, s, OAc), 3.19, 3.30, 3.30 (each 3H, s, 3 × OMe), 3.63 (3H, s, 17-COO*CH*$_3$), 4.71 (1H, d, $J = 2.6$ Hz, H-6β), 4.75 (1H, t, $J = 4.0$ Hz, H-14β); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 503 ($[M + Na]^+$, 100), 465 ($M^+ - CH_3$, 25); HR-ESI-MS: *m/z* 503.2264 $[M + Na]^+$ (calcd for $C_{25}H_{36}O_9Na$, 503.2252).

### 3.15 Compound 27

Compound **26** (69 mg, 0.14 mmol) was dissolved in anhydrous GDE (2 ml) and added $NaBH_4$ (83 mg, 0.65 mmol), and the solution was stirred at 50°C for 5 h. After the removal of the solvent, the residue was diluted with water (5 ml), the mixture was extracted with ethyl acetate (5 ml × 3), the extracts were dried ($Na_2SO_4$), and the organic solvent was removed *in vacuo* to afford **27** (a white amorphous powder, 49 mg, 80%), mp 195–196°C; $^1H$ NMR (400 MHz) $\delta$ 3.31, 3.32, 3.32 (each 3H, s, 3 × OMe), 3.65 (3H, s, COO*CH*$_3$), 3.98 (1H, m, H-14β), 4.80 (1H, d, $J = 3.2$ Hz, H-6β), 5.15 (1H, d, $J = 8.4$ Hz, exchangeable with $D_2O$, OH); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 439 ($M^+ + H$, 100); HR-ESI-MS: *m/z* 439.5266 $[M + H]^+$ (calcd for $C_{23}H_{35}O_8$, 439.5261).

### 3.16 Compound 28

To a solution of **26** (69 mg, 0.14 mmol) in anhydrous THF (2 ml) was added $LiAlH_4$ (8 mg, 0.21 mmol), and the solution was stirred at room temperature for 10 h prior to being quenched with water (0.5 ml). The mixture was diluted with 20% $NH_4Cl$ solution (5 ml) and extracted with ethyl acetate (5 ml × 3), and the combined extracts were dried ($Na_2SO_4$) and concentrated. The residue was purified over column chromatography (silica gel H, 1.5 g) eluted with cyclohexane–acetone (5:1) to afford **28** as a white amorphous powder (29 mg, 51%), mp 202–203°C; $^1H$ NMR (200 MHz) $\delta$ 3.29, 3.31, 3.35 (each 3H, s, 3 × OMe), 3.94 (1H, m, H-14β), 5.01 (1H, d, $J = 2.9$ Hz, H-6β), 5.11 (1H, d, $J = 8.6$ Hz, exchangeable with $D_2O$, OH); $^{13}C$ NMR spectral data, see Table 2; ESI-MS *m/z* (%): 449 ($[M + K]^+$, 100); HR-ESI-MS: *m/z* 449.6057 $[M + K]^+$ (calcd for $C_{22}H_{34}O_7K$, 449.6061).

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