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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and biological evaluation of (20*S*,24*R*)-epoxy-dammarane-3β,12β,25-triol derivatives as α-glucosidase and PTP1B inhibitors

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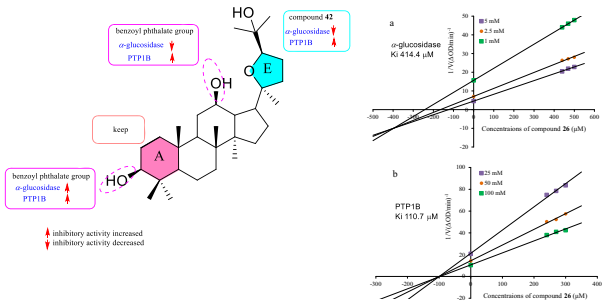
Abstract

The dammarane triterpenoid (20*S*,24*R*)-epoxy-dammarane-3β,12β,25-triol obtained from *Cyclocarya paliurus* in our previous study showed inhibitory activity on α-glucosidase in vitro with an inhibitory ratio of 32.2% at the concentration of 200 μM. In order to reveal the structure-activity relationships (SARs) and get more active compounds, 42 derivatives of (20*S*,24*R*)-epoxy-dammarane-3β,12β,25-triol were synthesized by chemical modification on the hydroxyls (C-3 and C-12), rings A and E, and assayed for their α-glucosidase and PTP1B inhibitory activities. Two compounds (**8**, **26**) increased activity against α-glucosidase, and four compounds (**8**, **15**, **26**, **42**) significantly inhibited PTP1B. It was noted that compounds **8** and **26** could inhibit both α-glucosidase and PTP1B as dual-target inhibitors with IC_{50} values of 489.8, 467.7 μM (α-glucosidase) and 319.7, 269.1 μM (PTP1B). Compound **26** was revealed to be a mix-type inhibitor on α-glucosidase and a noncompetitive-type inhibitor on PTP1B based on enzyme kinetic study. Furthermore, compound **42** could selectively inhibited PTP1B as a mix-type inhibitor with IC_{50} value of 134.9 μM, which was 2.5-fold higher than the positive control, suramin sodium (IC_{50} 339.0 μM), but not inhibit α-glucosidase.

Graphical Abstract



Keywords (20S,24*R*)-epoxy-dammarane-3β,12β,25-triol · α-glucosidase inhibitors · PTP1B inhibitors · Enzyme kinetics

Introduction

Diabetes mellitus is a chronic metabolic disease due to that pancreas is unable to produce sufficient insulin or body cannot take full advantage of insulin, its complications including blurred vision, cardiovascular diseases, kidney failure, and organ damage [1–3]. Diabetes mellitus is mainly divided into type 1 and type 2 diabetes mellitus (T1DM and T2DM), and ~90% of diabetic patients suffers from T2DM. α-Glucosidase and protein tyrosine phosphatase 1B (PTP1B) are two enzymes close related to T2DM. α-Glucosidase is the crucial enzyme for hydrolyzing the

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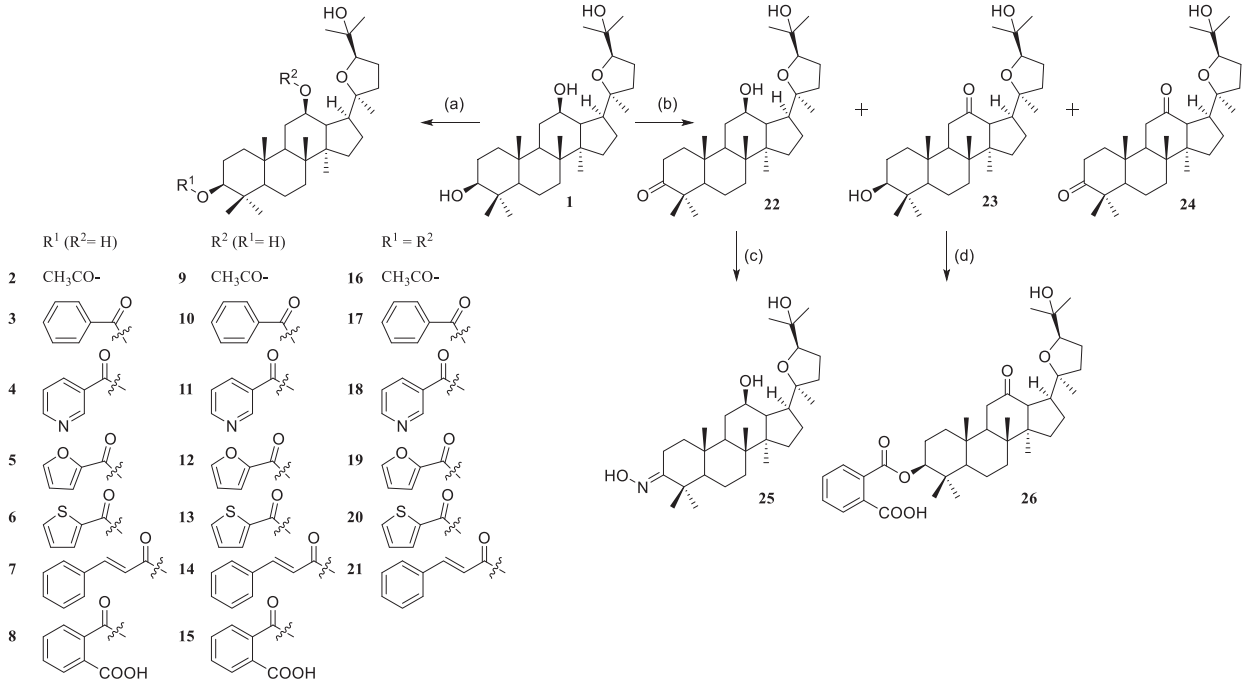


Scheme 1 Reagents and conditions: (**a**) DCC, DMAP, appropriate carboxylic acid, dry DCM, 0 °C– r.t., 59 % (**3**, **10**, **17**, 19% + 23% + 16%), 43% (**4**, **11**, **18**, 16% + 13% + 14%), 53% (**5**, **12**, **19**, 17% + 30% + 6%), 42% (**6**, **13**, **20**, 13% + 23% + 6%), 37% (**7**, **14**, **21**, 13% + 16% + 8%) or *o*-phthalic anhydride, pyridine, DMAP, 80 °C, 38% (**8**, **15**, 10% + 28%) or Ac_2O, pyridine, r.t., 68% (**2**, **9**, **16**, 20% + 24% + 24%); **b** $Al(Oi\text{-}Pr)_3$, acetone, toluene, reflux, 70% (**22**) or PCC, DCM, r.t., 68% (**22**, **23**, **24**, 18% + 20% + 30%); **c** NH_2OH•HCl, CH_3COONa•$3H_2O$, EtOH-H_2O (10:1), reflux, 93%; **d** *o*-phthalic anhydride, pyridine, DMAP, 80 °C, 76%

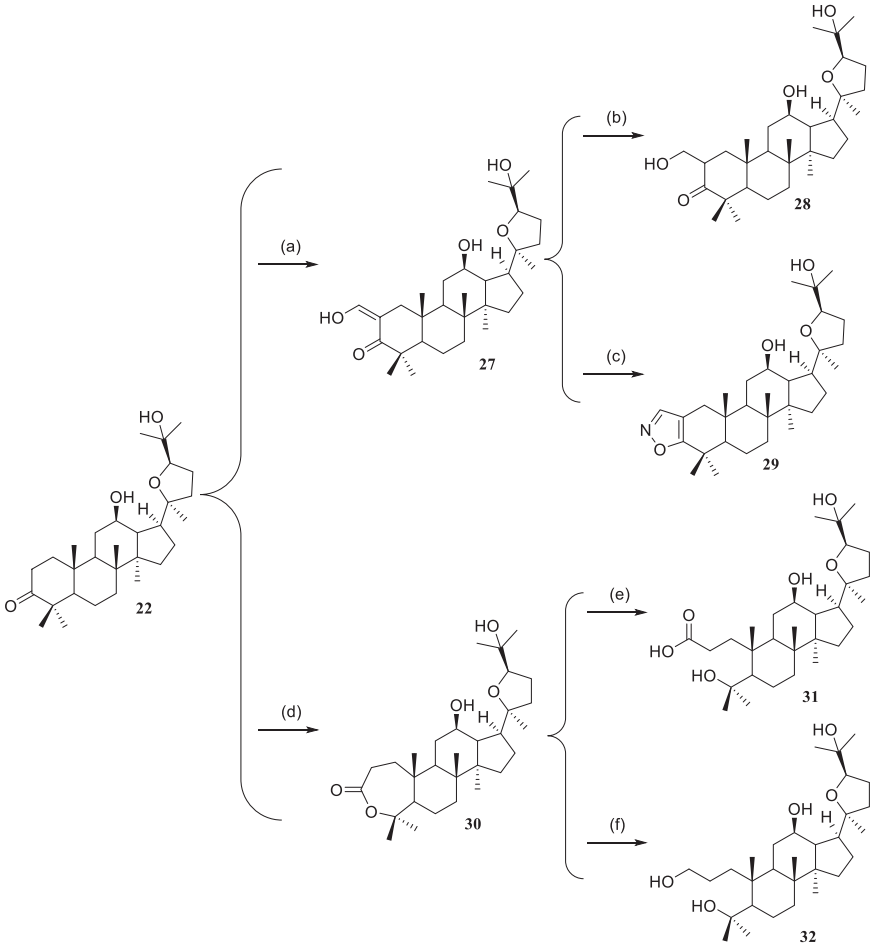
1,4-α-glucosidic linkages of oligosaccharides to release absorbable monosaccharides in small intestine. α-Glucosidase inhibitors can delay the absorption of carbohydrates, and reduce the effect of postprandial hyperglycaemia [4–6]. Protein tyrosine phosphatase 1B is a key negative regulator of leptin and insulin signaling pathways due to its ability to dephosphorylate and inactivate the insulin receptor [7, 8]. The gene knockout studies indicate PTP1B acts as a major negative regulator of insulin signaling [9, 10]. α-Glucosidase inhibitors are the preferred drugs for controlling postprandial blood glucose, and PTP1B inhibitors can improve insulin sensitivity. Therefore, compounds with α-glucosidase and PTP1B dual inhibition could be more effective and will provide important clues for the development of new antidiabetic candidates.

Natural products are rich sources for searching new antidiabetic agents [11, 12], and the discovery of natural products and their derivatives as potential antidiabetic lead compounds are continuing goals of our laboratory [13–21]. The leaves of *Cyclocarya paliurus* were widely used to treat obesity and diabetes in China. Dammarane-type triterpenoids were characteristic components of *C. paliurus*, which had shown potent α-glucosidase inhibitory and anti-inflammatory activities [22, 23]. Our previous antidiabetic investigation of *C. paliurus* indicated (20*S*,24*R*)-epoxydammarane-3β,12β,25-triol (**1**) exhibited inhibitory activity on α-glucosidase in vitro with an inhibitory ratio of 32.2% at the concentration of 200 μM. Compound **1** also showed weak inhibition on PTP1B with an inhibitory ratio of 16.4% at concentration of 400 μM. Compound **1** was one of the main constituents of *C. paliurus*, which provides possibilities for the chemical modification to explore the structure-activity relationships (SARs) and search for new antidiabetic candidates. In current investigation, 42 derivatives of compound **1** were synthesized and assayed for their α-glucosidase and PTP1B inhibitory activities.

Results and discussion

Chemistry

To figure out the roles of hydroxyls at C-3 and C-12 for inhibiting α-glucosidase and PTP1B, a series of derivatives were synthesized as shown in Scheme 1. Compound **1** was treated with anhydrides or carboxylic acids in the presence of *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) to yield compounds **2–8** with acyl groups at C-3, compounds **9–15** with acyl groups at C-12 and di-esterified products **16–21**. Oxidation of compound **1** using pyridinium chlorochromate (PCC) afforded ketones **22–24** with different oxidation location at C-3 and C-12, while compound **22** could be selectively obtained in 70% yield via Oppenauer oxidation [24]. When



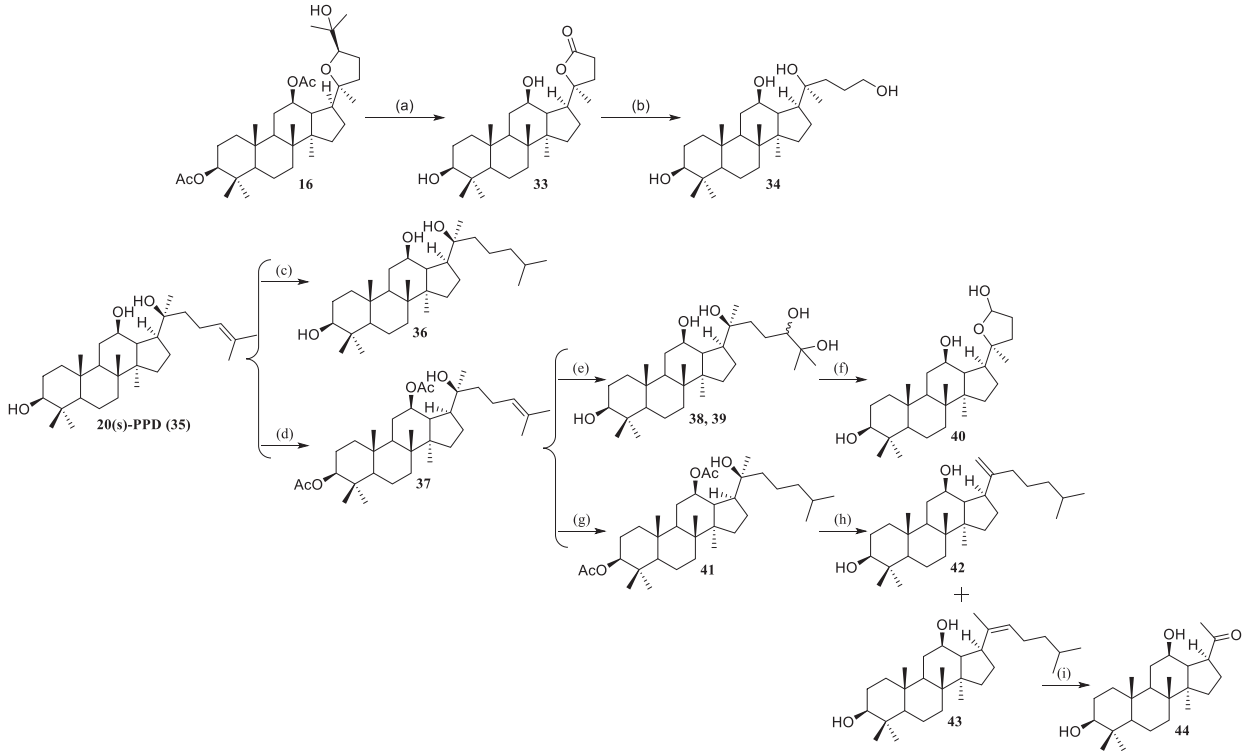
Scheme 2 Reagents and conditions: (**a**) HCOOEt, Na, Et_2O, reflux, 76%; **b** $NaBH_4$, MeOH, r.t., 69%; **c** NH_2OH•HCl, EtOH-H_2O (10:1), reflux, 56%; **d** *m*-CPBA, $NaHCO_3$, DCM, r.t., 71%; **e** 10% NaOH aqueous, MeOH, reflux, 82%; **f** $LiAlH_4$, dry THF, r.t.−50 °C, 50%

compound **22** and hydroxylamine hydrochloride were heated in the presence of sodium acetate trihydrate, the oxime derivative **25** was afforded in 93% yield [25]. From compound **23**, phthalic derivative **26** was provided in 76% yield by esterification with *o*-phthalic anhydride.

Next, different functionalities were introduced on ring A (Scheme 2). The formylation of compound **22** with ethyl formate in the presence of Na gave compound **27** [26], and subsequent reduction with sodium borohydride delivered 2-hydroxymethyl derivative **28**. Treatment of compound **27** with hydroxylamine hydrochloride provided isoxazole **29** in good yield [27]. Exposure of compound **22** to Baeyer–Villiger conditions delivered ring expansion product **30** [28, 29], which was further transformed into ring A opening derivatives **31** and **32** by hydrolysis or reduction of ester [30].

Oxidative cleavage of compound **16** with PCC and subsequent hydrolysis with NaOH resulted in lactone **33**, and reduction of the lactone with $LiAlH_4$ afforded ring-opening product **34**. To get more ring-opening products and study the influence of substituted tetrahydrofuran side chain on the activity, nine derivatives with different oxidation location on the side chain were synthesized from naturally abundant dammarane triterpenoid, 20(S)-PPD. Alkene hydrogenation of compound **35** with H_2 and Pd/C gave derivative **36**. A protection/dihydroxylation/deprotection sequence produced compounds **38** and **39** as a 1.2:1 mixture of diastereomers, and oxidative cleavage of the diol using $NaIO_4$ delivered hemiacetal **40**. Pd/C-catalyzed regioselective hydrogenation of compound **37** followed by one pot dehydration and deacetylation afforded compounds **42** and **43** Scheme 3. Compound **44** was synthesized via Lemieux-Johnson oxidation in 61% yield.

Taking compound **26** as an example, the structural characterization of the synthesized compounds was explained as follows. Compound **26** had a molecular formula of $C_{38}H_{54}O_7$ deduced by the (-)-HRESIMS ion at *m/z* 621.3787 $[M\text{-}H]^-$ (Calcd. for 621.3797). The ^1H NMR data of compound **26** displayed signals of eight singlet methyl groups at δ_H 1.23 (3H, s), 1.20 (3H, s), 1.19 (3H, s), 1.13 (3H, s), 1.10 (3H, s), 1.08 (3H, s), 0.94 (3H, s) and 0.89 (3H, s), two oxygenated methines at δ_H 4.92 (1H, m, H-3) and 3.70 (1H, t, $J = 7.4$ Hz, H-24), and four aromatic hydrogens at δ_H 7.90 (1H, m, H-4′), 7.59 (3H, m, H-5′, H-6’, H-7′); the ^{13}C NMR (DEPT) spectrum revealed 38 carbon resonances attributable to three carbonyls (δ_C 212.1, 168.2, 168.2), four unsubstituted aryl carbons (δ_C 129.5, 130.7, 131.1 and 129.1), two substituted



Scheme 3 Reagents and conditions: (**a**) (i) PCC, DCM, 40 °C, 54%; (ii) 10% NaOH aqueous, MeOH, reflux, 91%; **b** $LiAlH_4$, dry THF, r.t. −50 °C, 35%; **c** Pd/C, H_2, EtOH, r.t, 80%; **d** Ac_2O, pyridine, DMAP, r.t., 86%; **e** (i) $KMnO_4$, EtOH-H_2O (15:1), −40 °C; (ii) 10% NaOH aqueous, MeOH, reflux, **38** (52%), **39** (42%); **f** $NaIO_4$, MeOH, H_2O, r.t., 82%; **g** Pd/C, H_2, r.t., 87%; **h** (i) $POCl_3$, pyridine, 40 °C; (ii) 10% NaOH aqueous, MeOH, reflux, **42** (16%), **43** (43%); (i) OsO_4, $NaIO_4$, MeOH-H_2O, r.t., 61%

aryl carbons (δ_C 133.5, 133.5), eight methyls, seven sp^3 methines (three oxygenated, δ_C 80.3, 71.4, 83.4), and six sp^3 quaternary carbons (two oxygenated, δ_C 86.1, 71.6). From the above characteristic signals, the structure of compound **26** was concluded.

Biology

The inhibitory activities of all the synthesized derivatives on α-glucosidase and PTP1B were tested with acarbose and suramin sodium as the positive control, respectively. (Table 1). The inhibitory ratio of derivatives on α-glucosidase was primarily tested at the concentration of 200 μM. For compounds **2**–**8** with different acyloxy group at C-3, only phthalic derivative **3** maintained activity. Among C-12 esterification derivatives **9**–**15**, acetylation product **9** exhibited the similar inhibitory potency with that of compound **1**. Di-esterification products **16**–**21** lost suppressant properties on α-glucosidase. When the hydroxyl group at C-3 was oxidized to be carbonyl group, compound **10** showed better inhibitory ratio than that of compound **1** (46.6% vs 32.2%). Compounds **27**–**32** modified on ring A were inactive, which indicated that ring A of compound **1** is essential for α-glucosidase inhibitory effects. For compounds **33**–**44** with different oxidation location on the side chain, compounds **34** and **35** maintained activity at the concentration of 200 μM.

For PTP1B, the phthalate compounds **8**, **15** and **26** increased 3.8, 3.6 and 4.8-folds of inhibitory activity at the concentration of 400 μM, suggesting the additional carboxyl groups were favorable. For derivatives **27**–**44** with different functionalities on ring A and the side chain, compound **42** exhibited activity with an inhibitory ratio of 73.6%, which was 4.5 times stronger than that of compound **1**. Different with its double bond positional isomers **42**, derivative **43** was almost inactive, which indicated that the location of the double bond on the side chain had significant influence on PTP1B inhibitory effects.

Dose-response relationships of the active compounds were further studied to measure their IC_{50} values (Table 2). Interestingly, compounds **8** and **26** containing a phthalic acid moiety at C-3 showed inhibitory activity on both enzymes with IC_{50} values of 489.8, 467.7 μM (α-glucosidase) and 319.7, 269.1 μM (PTP1B), which were superior to compound **1** (IC_{50} values higher than 800 μM). When the phthalic acid was located at C-12, the resulted compound **15** was only active against PTP1B with an IC_{50} value of 341.7 μM; and all the three phthalate derivatives showed the similar inhibitory activity and compound **42** showed about 2.5-fold higher by comparison with the positive control suramin sodium.

Table 1 α-Glucosidase and PTP1B inhibitory activities of derivatives **1**–**44**[a]

Compounds	Inhibitory ratio (%)[b]		Compounds	Inhibitory ratio (%)[b]	
	α-Glucosidase	PTP1B		*α*-Glucosidase	PTP1B
1	32.2	16.4	**23**	46.6	15.1
2	6.7	13.2	**24**	5.3	3.7
3	11.9	22.3	**25**	–	20.0
4	20.3	9.6	**26**	26.5	79.2
5	11.2	19.7	**27**	–	8.5
6	8.6	14.4	**28**	–	9.6
7	21.0	26.0	**29**	–	20.2
8	31.9	62.8	**30**	–	12.8
9	38.7	17.8	**31**	–	9.4
10	10.8	15.3	**32**	–	–
11	4.8	21.3	**33**	–	6.6
12	9.8	13.7	**34**	36.5	16.6
13	21.2	14.8	**35**	36.5	15.5
14	5.7	20.2	**36**	2.3	15.7
15	0.8	58.8	**37**	–	10.8
16	5.9	4.6	**38**	12.3	21.2
17	–[c]	9.4	**39**	15.0	15.4
18	6.7	23.6	**40**	–	–
19	–	18.0	**41**	–	8.5
20	3.3	16.6	**42**	–	73.6
21	6.5	20.6	**43**	5.4	–
22	8.6	1.3	**44**	–	3.8

[a]Data were expressed as means of two tests

[b]The tested concentrations were 200 μM (α-glucosidase) and 400 μM (PTP1B)

[c]"–" means no activity

Table 2 *α*-Glucosidase and PTP1B inhibitory activities of the selected derivatives[a]

Compounds	IC_{50} (μM)	
	α-Glucosidase	PTP1B
1	>800	>800
8	489.8	319.7
15	–	341.7
26	467.7	269.1
42	–	134.9
Acarbose[b]	0.018	
Suramin sodium[c]		339.0

[a]Data were expressed as means of two tests

[b]Acarbose was used as the positive control against *α*-glucosidase

[c]Suramin sodium was used as the positive control against PTP1B

Compound **26** showed activity against both *α*-glucosidase and PTP1B with IC_{50} values of 467.7 and 269.1 μM, respectively. Enzyme kinetic studies by Lineweaver–Burk plot and Dixon plot showed the lines of compound **26** intersected at the third quadrant and the V_{max} and K_i values were decreased with the increase of concentration (Fig. 1A), indicating compound **26** was a mixed-type inhibitor against *α*-glucosidase with K_i value of 414.4 μM. Meanwhile, the line of compound **26** intersected on the *x*-axis (Fig. 1B), indicating it was a noncompetitive-type inhibitor against PTP1B (K_i value: 110.7 μM). Compound **42** showed the highest activity against PTP1B with an IC_{50} value of 134.9 μM, and enzyme kinetics study manifested it was a mixed-type inhibitor with a K_i value of 139.2 μM.

Conclusions

In summary, 42 derivatives of (20*S*,24*R*)-epoxy-dammarane-3*β*,12*β*,25-triol were synthesized and assayed for their *α*-glucosidase and PTP1B inhibitory activities. Two compounds (**8, 26**) increased activity on *α*-glucosidase. Four compounds (**8, 15, 26, 42**) were active on PTP1B, of which compound **42** showed the highest activity with the IC_{50} value superior to suramin sodium. Especially, phthalic derivatives **8** and **26** showed inhibitory activity on both *α*-glucosidase and PTP1B. Enzyme kinetic study consolidated

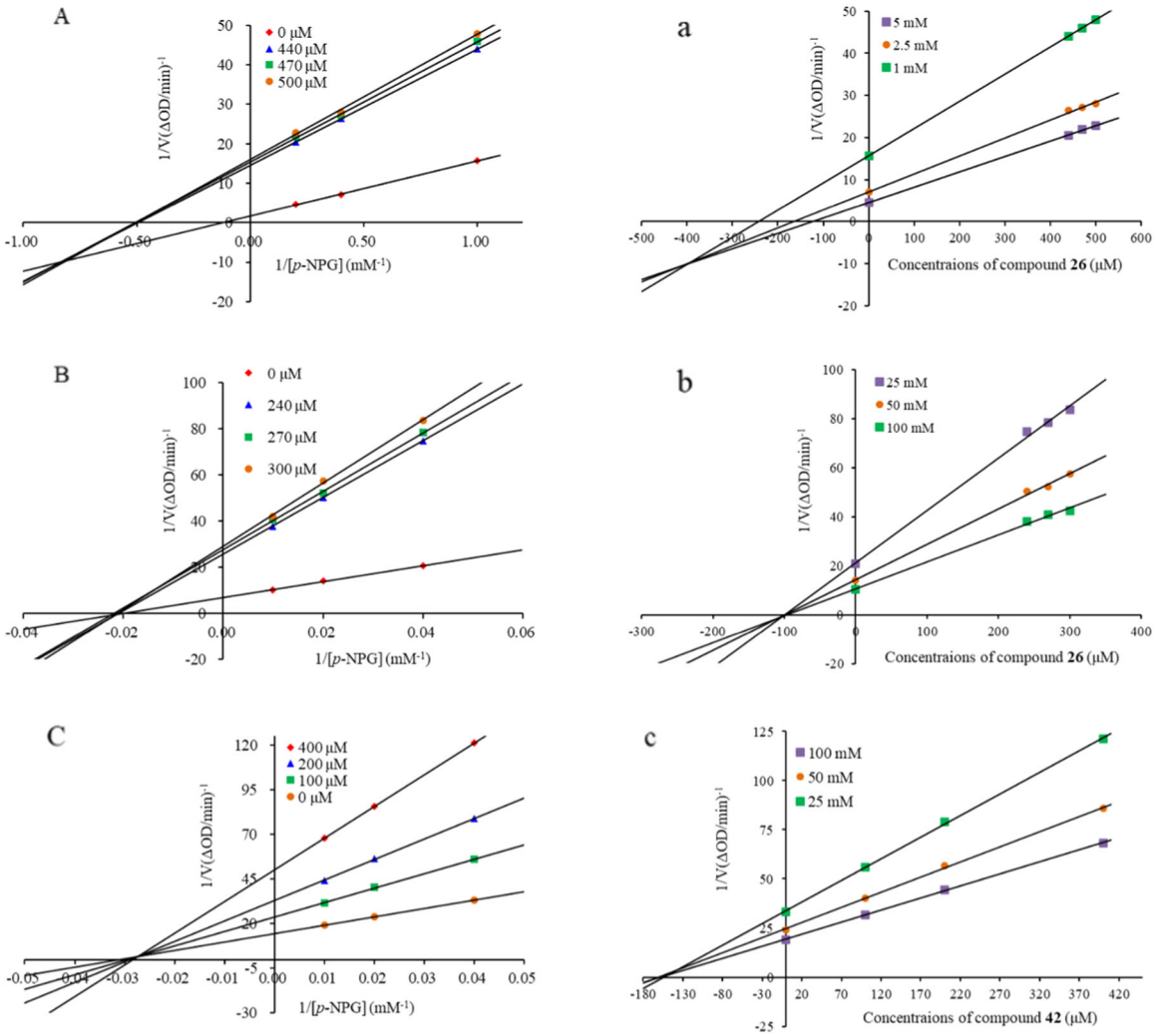


Fig. 1 Lineweaver–Burk and Dixon plots of compound **26** against α-glucosidase (**A/a**), PTP1B (**B/b**) and compound **42** against PTP1B(**C/c**)

that compound **26** was a mix-type inhibitor against α-glucosidase and a noncompetitive-type inhibitor against PTP1B with K_i values of 414.4 μM and 110.7 μM, respectively. The primary SARs were concluded as: (a) ring A is crucial for maintaining α-glucosidase and PPT1B inhibitory activity; (b) the incorporation of carboxyl groups at C-3 is favorable. These results provide valuable clues for the discovery of PTP1B and α-glucosidase dual inhibitors.

Experimental

Chemistry

General

All reagents and solvents were obtained from commercial supplies and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were tested on Avance III HD 400 (Bruker, Germany), Avance III 500 (Bruker, Germany) and Avance III 600 (Bruker, Germany) spectrometers with TMS as the internal standard. (20*S*,24*R*)-Epoxy- dammarane-3β,12β,25-triol was isolated from *Cyclocarya paliurus*. All synthetic compounds were purified by column chromatography on silica gel (200–300 mesh, Qingdao Makall Group Co., Ltd., Qingdao, China).

Synthesis

General procedure for the synthesis of compounds 2, 9 and 16

To a solution of (20*S*,24*R*)-epoxy-dammarane-3β,12β,25-triol (56.0 mg, 0.12 mmol) in pyridine (1.2 mL) was added acetic anhydride (1.2 mL) at room temperature, and the mixture was stirred at room temperature for 12 h. The

reaction mixture was then diluted with EtOAc and washed with 5% HCl aqueous solution. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc-petroleum ether, 10:90) to give compounds **2**, **9**, and **16**.

(20*S*,24*R*)-epoxy-3*β*-acetyl-dammarane-12*β*,25-diol (2) White powder, 20% yield, ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (1H, m, H-3), 3.92 (1H, td, $J = 10.5$, 5.5 Hz, H-12), 3.73 (1H, t, $J = 7.5$ Hz, H-24), 2.08 (3H, s, H-2′), 1.21 (3H, s), 1.13 (3H, s), 1.12 (3H, s), 1.06 (3H, s), 0.96 (3H, s), 0.95 (3H, s), 0.91 (3H, s), 0.84 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.8 (CH_2, C-1), 23.0 (CH_2, C-2), 78.2 (CH, C-3), 37.0 (C, C-4), 50.6 (CH, C-5), 17.9 (CH_2, C-6), 36.0 (CH_2, C-7), 41.0 (C, C-8), 55.5 (CH, C-9), 39.1 (C, C-10), 39.8 (CH_2, C-11), 71.2 (CH, C-12), 41.3 (CH, C-13), 50.0 (C, C-14), 31.1 (CH_2, C-15), 25.7 (CH_2, C-16), 49.4 (CH, C-17), 16.8 (CH_3, C-18), 16.5 (CH_3, C-19), 86.0 (C, C-20), 23.3 (CH_3, C-21), 36.3 (CH_2, C-22), 26.3 (CH_2, C-23), 83.4 (CH, C-24), 71.4 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 28.4 (CH_3, C-28), 21.5 (CH_3, C-29), 16.5 (CH_3, C-30), 170.9 (CO, C-1′), 21.9 (CH_3, C-2′); HRMS (ESI^-) m/z calcd for $C_{33}H_{55}O_7$ 563.3953, found 563.3958 ($M + HCOO^-$).

(20*S*,24*R*)-epoxy-12*β*-acetyl-dammarane-3*β*,25-diol (9) White powder, 24% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (1H, m, H-3), 5.11 (1H, td, $J = 10.7$, 5.5 Hz, H-12), 3.70 (1H, t, $J = 7.4$ Hz, H-24), 1.20 (3H, s), 1.11 (3H, s), 1.10 (3H, s), 0.99 (3H, s), 0.96 (3H, s), 0.94 (3H, s), 0.94 (3H, s), 0.84 (3H, s), 1.96 (3H, s, H-2′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.9 (CH_2, C-1), 25.5 (CH_2, C-2), 75.8 (CH, C-3), 37.9 (C, C-4), 49.1 (CH, C-5), 18.0 (CH_2, C-6), 35.0 (CH_2, C-7), 41.3 (C, C-8), 52.6 (CH, C-9), 39.0 (C, C-10), 34.5 (CH_2, C-11), 73.2 (CH, C-12), 40.6 (CH, C-13), 49.8 (C, C-14), 31.1 (CH_2, C-15), 26.0 (CH_2, C-16), 49.0 (CH, C-17), 16.8 (CH_3, C-18), 16.8 (CH_3, C-19), 86.1 (C, C-20), 23.9 (CH_3, C-21), 35.7 (CH_2, C-22), 26.0 (CH_2, C-23), 83.6 (CH, C-24), 71.2 (C, C-25), 27.4 (CH_3, C-26), 24.9 (CH_3, C-27), 28.8 (CH_3, C-28), 22.2 (CH_3, C-29), 16.3 (CH_3, C-30), 170.4 (CO, C-1'), 22.1 (CH_3, C-2′); HRMS (ESI^+) m/z calcd for $C_{32}H_{54}O_5Na$ 541.3863, found 541.3838 ($M + Na^+$).

(20*S*,24*R*) -epoxy-3*β*,12*β*-diacetyl-dammarane-25-ol (16) White powder, 24% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (1H, m, H-3), 5.12 (1H, td, $J = 10.5$, 5.5 Hz, H-12), 3.71 (1H, t, $J = 7.4$ Hz, H-24), 1.24 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.00 (3H, s), 0.98 (3H, s), 0.97 (3H, s), 0.88 (3H, s), 0.84 (3H, s), 1.96 (3H, s, H-2′), 2.09 (3H, s, H-2″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.6 (CH_2, C-1), 23.0 (CH_2, C-2), 78.1 (CH, C-3), 37.0 (C, C-4), 50.2 (CH, C-5), 17.9 (CH_2, C-6), 35.6 (CH_2, C-7), 40.6 (C, C-8), 52.5 (CH, C-9), 38.8 (C, C-10), 34.8 (CH_2, C-11), 73.3 (CH, C-12), 41.3 (CH, C-13), 49.8 (C, C-14), 31.2 (CH_2, C-15), 25.9 (CH_2, C-16), 49.0 (CH, C-17), 16.7 (CH_3, C-18), 16.7 (CH_3, C-19), 86.1 (C, C-20), 24.1 (CH_3, C-21), 35.6 (CH_2, C-22), 26.1 (CH_2, C-23), 83.6 (CH, C-24), 71.2 (C, C-25), 27.4 (CH_3, C-26), 24.9 (CH_3, C-27), 28.4 (CH_3, C-28), 22.1 (CH_3, C-29), 16.4 (CH_3, C-30), 170.9 (CO, C-1′), 21.9 (CH_3, C-2′), 170.3 (CO, C-1″), 21.5 (CH_3, C-2″); HRMS (ESI^+) m/z calcd for $C_{34}H_{56}O_6Na$ 583.3969, found 583.4012 ($M + Na^+$).

General procedure for the synthesis of compounds 3–7, 10–14, 17–21

To a solution of appropriate carboxylic acid (0.06 mmol) in anhydrous dichloromethane (2 mL) was added DCC (27.3 mg, 0.132 mmol) and DMAP (1.2 mg, 0.01 mmol) at 0 °C. After stirred for 10 min, (20 *S*,24 *R*)-epoxy-dammarane-3*β*,12*β*,25-triol (25.0 mg, 0.05 mmol) was added. The mixture was then warmed to room temperature and stirred until the reaction completed (monitored by TLC). After completion of the reaction, placed the flask in the freezer at −10 °C for 6 h, and the suspension was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (acetone-petroleum ether, 6:94) to give target compounds.

(20*S*,24*R*)-epoxy-3*β*-benzoyl-dammarane-12*β*,25-diol (3) Light yellow powder, 19% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (1H, m, H-3), 3.99 (1H, m, H-12), 3.73 (1H, t, $J = 7.4$ Hz, H-24), 1.21 (3H, s), 1.14 (3H, s), 1.13 (3H, s), 1.12 (3H, s), 1.00 (3H, s), 0.99 (3H, s), 0.98 (3H, s), 0.94 (3H, s), 8.07 (2H, m, H-3′, H-7′), 7.47 (2H, m, H-4′, H-6′), 7.57 (1H, m, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.4 (CH_2, C-1), 23.1 (CH_2, C-2), 79.0 (CH, C-3), 37.5 (C, C-4), 51.3 (CH, C-5), 18.0 (CH_2, C-6), 36.0 (CH_2, C-7), 41.1 (C, C-8), 55.8 (CH, C-9), 39.2 (C, C-10), 39.8 (CH_2, C-11), 71.3 (CH, C-12), 41.4 (CH, C-13), 50.0 (C, C-14), 31.1 (CH_2, C-15), 25.7 (CH_2, C-16), 49.4 (CH, C-17), 16.8 (CH_3, C-18), 16.5 (CH_3, C-19), 85.9 (C, C-20), 23.2 (CH_3, C-21), 36.4 (CH_2, C-22), 26.3 (CH_2, C-23), 83.4 (CH, C-24), 71.4 (C, C-25), 27.5 (CH_3, C-26), 24.3 (CH_3, C-27), 28.7 (CH_3, C-28), 22.0 (CH_3, C-29), 16.5 (CH_3, C-30), 166.1 (CO, C-1′), 131.2 (C, C-2′), 130.0 (CH, C-3′, C-7′), 128.4 (CH, C-4′, C-6′), 132.7 (CH, C-5′); HRMS (ESI^-) m/z calcd for $C_{38}H_{57}O_7$ 625.4110, found 625.4097 ($M + HCOO^-$).

(20*S*,24*R*)-epoxy-3*β*-nicotinoyl-dammarane-12*β*,25-diol (4) Light yellow powder, 16% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (1H, m, H-3), 3.99 (1H, m, H-12), 3.73 (1H, t, $J = 7.4$ Hz, H-24), 1.21 (3H, s), 1.14 (3H, s), 1.13 (3H, s),

1.12 (3H, s), 1.00 (3H, s), 0.99 (3H, s), 0.97 (3H, s), 0.94 (3H, s), 9.28 (1H, dd, $J = 2.2$, 0.9 Hz, H-3′), 8.79 (1H, dd, $J = 4.9$, 2.0 Hz, H-4′), 7.43 (1H, ddd, $J = 7.9$, 4.9, 0.9 Hz, H-5′), 8.32 (1H, dt, $J = 7.9$, 2.0 Hz, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3 (CH_2, C-1), 23.1 (CH_2, C-2), 79.8 (CH, C-3), 37.5 (C, C-4), 51.4 (CH, C-5), 18.0 (CH_2, C-6), 36.0 (CH_2, C-7), 41.0 (C, C-8), 55.8 (CH, C-9), 39.2 (C, C-10), 39.9 (CH_2, C-11), 71.2 (CH, C-12), 41.4 (CH, C-13), 50.0 (C, C-14), 31.1 (CH_2, C-15), 25.7 (CH_2, C-16), 49.3 (C, C-17), 16.8 (CH_3, C-18), 16.6 (CH_3, C-19), 85.9 (C, C-20), 23.4 (CH_3, C-21), 36.3 (CH_2, C-22), 26.3 (CH_2, C-23), 83.4 (CH, C-24), 71.4 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 28.7 (CH_3, C-28), 22.0 (CH_3, C-29), 16.5 (CH_3, C-30), 164.8 (CO, C-1′), 126.9 (C, C-2′), 150.8 (CH, C-3′), 153.2 (CH, C-4′), 123.4 (CH, C-5′), 137.2 (CH, C-6′); HRMS (ESI^+) m/z calcd for $C_{36}H_{56}NO_5$ 582.4153, found 582.4113 ($M + H^+$).

(20*S*,24*R*)-epoxy-3*β*-furoyl-dammarane-12*β*,25-diol (5) Light yellow powder, 17% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (1H, m, H-3), 3.98 (1H, m, H-12), 3.39 (1H, t, $J = 7.3$ Hz, H-24), 1.21 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.10 (3H, s), 0.98 (3H, s), 0.97 (3H, s), 0.97 (3H, s), 0.92 (3H, s), 7.15 (1H, dd, $J = 3.4$, 0.9 Hz, H-3′), 6.52 (1H, dd, $J = 3.4$, 1.8 Hz, H-4′), 7.59 (1H, dd, $J = 1.8$, 0.9 Hz, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3 (CH_2, C-1), 23.1 (CH_2, C-2), 79.1 (CH, C-3), 37.4 (C, C-4), 51.0 (CH, C-5), 18.0 (CH_2, C-6), 35.9 (CH_2, C-7), 41.0 (C, C-8), 55.7 (CH, C-9), 39.1 (C, C-10), 39.8 (CH_2, C-11), 71.3 (CH, C-12), 41.4 (CH, C-13), 50.0 (C, C-14), 31.1 (CH_2, C-15), 25.7 (CH_2, C-16), 49.4 (CH, C-17), 16.8 (CH_3, C-18), 16.5 (CH_3, C-19), 86.0 (C, C-20), 23.4 (CH_3, C-21), 36.2 (CH_2, C-22), 26.3 (CH_2, C-23), 83.4 (CH, C-24), 71.5 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 28.6 (CH_3, C-28), 21.9 (CH_3, C-29), 16.5 (CH_3, C-30), 158.5 (CO, C-1′), 145.3 (C, C-2′), 117.2 (CH, C-3′), 111.7 (CH, C-4’), 146.1 (CH, C-5′); HRMS (ESI^+) m/z calcd for $C_{35}H_{54}O_6Na$ 593.3813, found 593.3778 ($M + Na^+$).

(20*S*,24*R*)-epoxy-3*β*-thenoyl-dammarane-12*β*,25-diol (6) Light yellow powder, 13% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (1H, m, H-3), 3.96 (1H, m, H-12), 3.72 (1H, t, $J = 7.4$ Hz, H-24), 1.20 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.10 (3H, s), 0.98 (3H, s), 0.97 (3H, s), 0.97 (3H, s), 0.93 (3H, s), 7.80 (1H, dd, $J = 3.8$, 1.3 Hz, H-3’), 7.12 (1H, dd, $J = 5.0$, 3.8 Hz, H-4′), 7.55 (1H, dd, $J = 5.0$, 1.3 Hz, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.3 (CH_2, C-1), 23.0 (CH_2, C-2), 79.4 (CH, C-3), 37.4 (C, C-4), 51.0 (CH, C-5), 17.9 (CH_2, C-6), 36.0 (CH_2, C-7), 41.0 (C, C-8), 55.7 (CH, C-9), 39.1 (C, C-10), 39.7 (CH_2, C-11), 71.3 (CH, C-12), 41.4 (CH, C-13), 49.9 (C, C-14), 31.1 (CH_2, C-15), 25.7 (CH_2, C-16), 49.4 (CH, C-17), 16.8 (CH_3, C-18), 16.5 (CH_3, C-19), 86.0 (C, C-20), 23.3 (CH_3, C-21), 36.2 (CH_2, C-22), 26.3 (CH_2, C-23), 83.4 (CH, C-24), 71.5 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 28.7 (CH_3, C-28), 21.8 (CH_3, C-29), 16.4 (CH_3, C-30), 161.8 (CO, C-1′), 134.8 (C, C-2′), 132.9 (CH, C-3′), 127.9 (CH, C-4′), 132.0 (CH, C-5′); HRMS (ESI^+) m/z calcd for $C_{35}H_{54}O_5SNa$ 609.3584, found 609.3606 ($M + Na^+$).

(20*S*,24*R*)-epoxy-3*β*-cinnamoyl-dammarane-12*β*,25-diol (7) Light yellow powder, 13% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (1H, m, H-3), 3.98 (1H, m, H-12), 3.73 (1H, t, $J = 7.4$ Hz, H-24), 1.21 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.09 (3H, s), 0.99 (3H, s), 0.99 (3H, s), 0.96 (3H, s), 0.90 (3H, s), 6.51 (1H, d, $J = 16.0$ Hz, H-2’), 7.68 (1H, d, $J = 16.0$ Hz, H-3′), 7.56 (2H, m, H-5′, H-9′), 7.39 (3H, m, H-6′, H-7′, H-8′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2 (CH_2, C-1), 23.3 (CH_2, C-2), 78.4 (CH, C-3), 37.3 (C, C-4), 50.9 (CH, C-5), 17.9 (CH_2, C-6), 35.9 (CH_2, C-7), 41.1 (C, C-8), 55.7 (CH, C-9), 39.2 (C, C-10), 39.8 (CH_2, C-11), 71.3 (CH, C-12), 41.4 (CH, C-13), 50.0 (C, C-14), 31.1 (CH_2, C-15), 25.7 (CH_2, C-16), 49.4 (CH, C-17), 16.8 (CH_3, C-18), 16.6 (CH_3, C-19), 86.0 (C, C-20), 23.1 (CH_3, C-21), 36.4 (CH_2, C-22), 26.3 (CH_2, C-23), 83.4 (CH, C-24), 71.5 (C, C-25), 27.5 (CH_3, C-26), 24.3 (CH_3, C-27), 28.6 (CH_3, C-28), 22.0 (CH_3, C-29), 16.5 (CH_3, C-30), 166.7 (CO, C-1′), 119.0 (CH, C-2′), 144.3 (CH, C-3′), 134.6 (C, C-4′), 128.1 (CH, C-5′, C-9′), 128.9 (CH, C-6′, C-8′), 130.1 (CH, C-7′); HRMS (ESI^-) m/z calcd for $C_{40}H_{59}O_7$ 651.4266, found 651.4265 ($M + HCOO^-$).

(20*S*,24*R*)-epoxy-12*β*-benzoyl-dammarane-3*β*,25-diol (10) White powder, 23% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 (1H, m, H-3), 5.44 (1H, td, $J = 10.8$, 5.5 Hz, H-12), 3.71 (1H, t, $J = 7.4$ Hz, H-24), 1.20 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.07 (3H, s), 1.00 (3H, s), 0.99 (3H, s), 0.96 (3H, s), 0.83 (3H, s), 8.03 (2H, m, H-3′, H-7′), 7.42 (2H, m, H-4′, H-6′), 7.55 (1H, m, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.1 (CH_2, C-1), 25.4 (CH_2, C-2), 75.9 (CH, C-3), 37.9 (C, C-4), 49.1 (CH, C-5), 18.0 (CH_2, C-6), 35.3 (CH_2, C-7), 41.4 (C, C-8), 52.8 (CH, C-9), 39.0 (C, C-10), 34.6 (CH_2, C-11), 74.0 (CH, C-12), 40.7 (CH, C-13), 49.9 (C, C-14), 31.2 (CH_2, C-15), 29.7 (CH_2, C-16), 49.0 (CH, C-17), 16.8 (CH_3, C-18), 16.8 (CH_3, C-19), 86.1 (C, C-20), 23.8 (CH_3, C-21), 35.8 (CH_2, C-22), 26.0 (CH_2, C-23), 83.6 (CH, C-24), 71.2 (C, C-25), 27.4 (CH_3, C-26), 24.9 (CH_3, C-27), 28.8 (CH_3, C-28), 22.2 (CH_3, C-29), 16.4 (CH_3, C-30), 165.7 (CO, C-1′), 131.0 (C, C-2′), 129.8 (CH, C-3′, C-7′), 128.3 (CH, C-4′, C-6′), 132.8 (CH, C-5′); HRMS (ESI^+) m/z calcd for $C_{37}H_{56}O_5Na$ 603.4020, found 603.4041 ($M + Na^+$).

(20*S*,24*R*)-epoxy-12*β*-nicotinoyl-dammarane-3*β*,25-diol (11) White powder, 13% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 (1H, m, H-3), 5.47 (1H, td, $J = 10.5$, 5.5 Hz,

H-12), 3.71 (1H, t, $J = 7.4$ Hz, H-24), 1.20 (3H, s), 1.13 (3H, s), 1.12 (3H, s), 1.07 (3H, s), 1.01 (3H, s), 1.00 (3H, s), 0.96 (3H, s), 0.83 (3H, s), 9.21 (1H, d, $J = 2.1$ Hz, H-3'), 8.76 (1H, dd, $J = 4.8$, 1.8 Hz, H-4′), 7.37 (1H, dd, $J = 7.9$, 4.8 Hz, H-5′), 8.27 (1H, dt, $J = 7.9$, 2.0 Hz, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.0 (CH_2, C-1), 25.4 (CH_2, C-2), 75.7 (CH, C-3), 37.9 (C, C-4), 49.0 (CH, C-5), 18.1 (CH_2, C-6), 35.4 (CH_2, C-7), 41.5 (C, C-8), 52.7 (CH, C-9), 39.0 (C, C-10), 34.7 (CH_2, C-11), 74.7 (CH, C-12), 40.6 (CH, C-13), 49.9 (C, C-14), 31.2 (CH_2, C-15), 29.7 (CH_2, C-16), 48.9 (CH, C-17), 16.9 (CH_3, C-18), 16.8 (CH_3, C-19), 86.1 (C, C-20), 24.0 (CH_3, C-21), 35.7 (CH_2, C-22), 25.9 (CH_2, C-23), 83.2 (CH, C-24), 71.3 (C, C-25), 27.4 (CH_3, C-26), 24.9 (CH_3, C-27), 28.8 (CH_3, C-28), 22.2 (CH_3, C-29), 16.4 (CH_3, C-30), 164.5 (CO, C-1′), 126.7 (C, C-2′), 151.2 (CH, C-3′), 153.3 (CH, C-4′), 123.3 (CH, C-5′), 137.2 (CH, C-6′); HRMS (ESI^+) m/z calcd for $C_{36}H_{56}NO_5$ 582.4153, found 582.4129 ($M + H^+$).

(20*S*,24*R*)-epoxy-12β-furoyl-dammarane-3β,25-diol (12) White powder, 30% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.35 (1H, m, H-3), 5.37 (1H, td, $J = 10.8$, 5.5 Hz, H-12), 3.70 (1H, t, $J = 7.4$ Hz, H-24), 1.20 (3H, s), 1.12 (3H, s), 1.11 (3H, s), 1.04 (3H, s), 0.98 (3H, s), 0.98 (3H, s), 0.95 (3H, s), 0.84 (3H, s), 7.08 (1H, dd, $J = 3.5$, 0.8 Hz, H-3′), 6.47 (1H, dd, $J = 3.5$, 1.7 Hz, H-4′), 7.56 (1H, d, $J =$ 1.7 Hz, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.0 (CH_2, C-1), 25.5 (CH_2, C-2), 75.8 (CH, C-3), 37.9 (C, C-4), 49.2 (CH, C-5), 18.0 (CH_2, C-6), 35.5 (CH_2, C-7), 41.4 (C, C-8), 52.7 (CH, C-9), 39.0 (C, C-10), 34.5 (CH_2, C-11), 74.0 (CH, C-12), 40.7 (CH, C-13), 49.9 (C, C-14), 31.1 (CH_2, C-15), 25.8 (CH_2, C-16), 49.0 (CH, C-17), 16.8 (CH_3, C-18), 16.8 (CH_3, C-19), 86.0 (C, C-20), 23.6 (CH_3, C-21), 35.8 (CH_2, C-22), 26.0 (CH_2, C-23), 83.5 (CH, C-24), 71.3 (C, C-25), 27.4 (CH_3, C-26), 24.8 (CH_3, C-27), 28.8 (CH_3, C-28), 22.2 (CH_3, C-29), 16.4 (CH_3, C-30), 158.1 (CO, C-1'), 145.4 (C, C-2′), 117.8 (CH, C-3′), 111.8 (CH, C-4′), 146.3 (CH, C-5′); HRMS (ESI^+) m/z calcd for $C_{35}H_{54}O_6Na$ 593.3813, found 593.3785 ($M + Na^+$).

(20*S*,24R)-epoxy-12β-thenoyl-dammarane-3β,25-diol (13) White powder, 23% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.35 (1H, m, H-3), 5.37 (1H, td, $J = 10.8$, 5.5 Hz, H-12), 3.71 (1H, t, $J = 7.4$ Hz, H-24), 1.21 (3H, s), 1.12 (3H, s),1.11 (3H, s), 1.05 (3H, s), 1.00 (3H, s), 1.00 (3H, s), 0.96 (3H, s), 0.84 (3H, s), 7.75 (1H, dd, $J = 3.7$, 1.3 Hz, H-3′), 7.0 (1H, dd, $J = 5.0$, 3.7 Hz, H-4′), 7.53 (1H, dd, $J = 5.0$, 1.3 Hz, H-5′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.2 (CH_2, C-1), 25.5 (CH_2, C-2), 75.8 (CH, C-3), 37.9 (C, C-4), 49.1 (CH, C-5), 18.0 (CH_2, C-6), 35.4 (CH_2, C-7), 41.4 (C, C-8), 52.7 (CH, C-9), 39.0 (C, C-10), 34.5 (CH_2, C-11), 74.3 (CH, C-12), 40.7 (CH, C-13), 49.9 (C, C-14), 31.1 (CH_2, C-15), 25.6 (CH_2, C-16), 48.9 (CH, C-17), 16.8 (CH_3, C-18), 16.7 (CH_3, C-19), 86.0 (C, C-20), 23.8 (CH_3, C-21), 35.8 (CH_2, C-22), 26.0 (CH_2, C-23), 83.6 (CH, C-24), 71.2 (C, C-25), 27.3 (CH_3, C-26), 25.0 (CH_3, C-27), 28.8 (CH_3, C-28), 22.2 (CH_3, C-29), 16.4 (CH_3, C-30), 161.5 (CO, C-1′), 135.0 (C, C-2′), 133.3 (CH, C-3′), 127.7 (CH, C-4′), 132.4 (CH, C-5′); HRMS (ESI^+) m/z calcd for $C_{35}H_{54}O_5SNa$ 609.3584, found 609.3589 ($M + Na^+$).

(20*S*,24*R*)-epoxy-12β-cinnamoyl-dammarane-3β,25-diol (14) White powder, 16% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (1H, m, H-3), 5.28 (1H, td, $J = 10.7$, 5.4 Hz, H-12), 3.71 (1H, t, $J = 7.4$ Hz, H-24), 1.21 (3H, s), 1.12 (3H, s), 1.11 (3H, s), 1.04 (3H, s), 0.99 (3H, s), 0.98 (3H, s), 0.95 (3H, s), 0.84 (3H, s), 6.36 (1H, d, $J = 16.0$ Hz, H-2′), 7.63 (1H, d, $J = 16.0$ Hz, H-3′), 7.51 (2H, m, H-5′, H-9′), 7.37 (3H, m, H-6′, H-7′, H-8′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.1 (CH_2, C-1), 25.6 (CH_2, C-2), 75.9 (CH, C-3), 37.9 (C, C-4), 49.1 (CH, C-5), 18.1 (CH_2, C-6), 35.1 (CH_2, C-7), 41.4 (C, C-8), 52.8 (CH, C-9), 39.1 (C, C-10), 34.7 (CH_2, C-11), 73.4 (CH, C-12), 40.7 (CH, C-13), 49.9 (C, C-14), 31.2 (CH_2, C-15), 26.9 (CH_2, C-16), 49.0 (CH, C-17), 16.8 (CH_3, C-18), 16.8 (CH_3, C-19), 86.1 (C, C-20), 23.9 (CH_3, C-21), 35.8 (CH_2, C-22), 26.0 (CH_2, C-23), 83.6 (CH, C-24), 71.2 (C, C-25), 27.4 (CH_3, C-26), 24.9 (CH_3, C-27), 28.8 (CH_3, C-28), 22.2 (CH_3, C-29), 16.4 (CH_3, C-30), 166.2 (CO, C-1′), 119.1 (CH, C-2′), 144.6 (CH, C-3′), 134.5 (C, C-4′), 128.1 (CH, C-5′, C-9′), 128.9 (CH, C-6′, C-8′), 130.2 (CH, C-7′); HRMS (ESI^+) m/z calcd for $C_{39}H_{58}O_5Na$ 629.4176, found 629.4166 ($M + Na^+$).

(20*S*,24*R*)-epoxy-3β,12β-dibenzoyl-dammarane-25-ol (17) Light yellow powder, 16% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (1H, m, H-3), 5.47 (1H, td, $J = 10.8$, 5.2 Hz, H-12), 3.71 (1H, t, $J = 7.4$ Hz, H-24), 1.21 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.12 (3H, s), 1.06 (3H, s), 1.04 (3H, s), 0.96 (3H, s), 0.95 (3H, s), 8.12 (2H, m, H-3′, H-7′), 7.45 (2H, m, H-4′, H-6′), 7.61 (1H, m, H-5′), 7.97 (2H, m, H-3″, H-7″), 7.39 (2H, m, H-4″, H-6″), 7.53 (1H, m, H-5″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.7 (CH_2, C-1), 23.1 (CH_2, C-2), 78.9 (CH, C-3), 37.5 (C, C-4), 50.9 (CH, C-5), 17.9 (CH_2, C-6), 36.0 (CH_2, C-7), 40.8 (C, C-8), 53.0 (CH, C-9), 38.9 (C, C-10), 34.9 (CH_2, C-11), 74.1 (CH, C-12), 41.5 (CH, C-13), 49.8 (C, C-14), 31.3 (CH_2, C-15), 25.9 (CH_2, C-16), 49.0 (CH, C-17), 16.8 (CH_3, C-18), 16.7 (CH_3, C-19), 86.1 (C, C-20), 24.0 (CH_3, C-21), 36.3 (CH_2, C-22), 26.0 (CH_2, C-23), 83.6 (CH, C-24), 71.2 (C, C-25), 27.4 (CH_3, C-26), 25.0 (CH_3, C-27), 28.7 (CH_3, C-28), 22.0 (CH_3, C-29), 16.5 (CH_3, C-30), 166.1 (CO, C-1′), 130.8 (C, C-2′), 129.7 (CH, C-3′, C-7′), 128.5 (CH, C-4′, C-6′), 132.8 (CH, C-5′), 165.7 (CO, C-1″), 130.7 (C, C-2″), 129.6 (CH, C-3″, C-7″), 128.4 (CH, C-4″, C-6″), 132.8 (CH, C-5″); HRMS (ESI^+) m/z calcd for $C_{44}H_{60}O_6Na$ 707.4282, found 707.4279 ($M + Na^+$).

(20*S*,24*R*)-epoxy-3*β*,12*β*-dinicotinoyl-dammarane-25-ol (18) White powder, 14% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (1H, m, H-3), 5.50 (1H, td, $J = 10.8$, 5.3 Hz, H-12), 3.72 (1H, t, $J = 7.4$ Hz, H-24), 1.21 (3H, s), 1.14 (3H, s), 1.13 (3H, s), 1.11 (3H, s), 1.06 (6H, s), 0.97 (3H, s), 0.95 (3H, s), 9.33 (1H, m, H-3'), 8.82 (1H, m, H-4′), 7.48 (1H, dd, $J = 7.9$, 4.8 Hz, H-5′), 8.36 (1H, dt, $J = 7.9$, 1.9 Hz, H-6′), 9.15 (1H, m, H-3″), 8.72 (1H, m, H-4″), 7.34 (1H, dd, $J = 8.0$, 4.8 Hz, H-5″), 8.23 (1H, dt, $J = 8.0$, 1.9 Hz, H-6″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.6 (CH_2, C-1), 25.0 (CH_2, C-2), 79.3 (CH, C-3), 37.5 (C, C-4), 50.9 (CH, C-5), 17.9 (CH_2, C-6), 35.8 (CH_2, C-7), 40.7 (C, C-8), 53.0 (CH, C-9), 39.0 (C, C-10), 34.8 (CH_2, C-11), 74.8 (CH, C-12), 41.6 (CH, C-13), 49.8 (C, C-14), 31.3 (CH_2, C-15), 25.8 (CH_2, C-16), 48.8 (CH, C-17), 16.8 (CH_3, C-18), 16.8 (CH_3, C-19), 86.1 (C, C-20), 23.2 (CH_3, C-21), 36.3 (CH_2, C-22), 26.1 (CH_2, C-23), 83.6 (CH, C-24), 71.2 (C, C-25), 27.4 (CH_3, C-26), 24.2 (CH_3, C-27), 28.7 (CH_3, C-28), 21.9 (CH_3, C-29), 16.7 (CH_3, C-30), 164.7 (CO, C-1′), 127.0 (C, C-2′), 151.0 (CH, C-3′), 153.3 (CH, C-4′), 123.6 (CH, C-5′), 137.4 (CH, C-6′), 164.5 (CO, C-1″), 126.6 (C, C-2″), 150.8 (CH, C-3″), 153.3 (CH, C-4″), 123.4 (CH, C-5″), 137.1 (CH, C-6″); HRMS (ESI$^+$) m/z calcd for $C_{42}H_{59}N_2O_6$ 687.4368, found 687.4406 ($M + H^+$).

(20*S*,24*R*)-epoxy-3*β*,12*β*-difuroyl-dammarane-25-ol (19) White powder, 6% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (1H, m, H-3), 5.39 (1H, td, $J = 10.9$, 5.3 Hz, H-12), 3.72 (1H, t, $J = 7.5$ Hz, H-24), 1.21 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.08 (3H, s), 1.03 (3H, s), 1.02 (3H, s), 0.94 (3H, s), 0.93 (3H, s), 7.20 (1H, dd, $J = 3.4$, 0.9 Hz, H-3′), 6.56 (1H, dd, $J = 3.4$, 1.8 Hz, H-4′), 7.63 (1H, dd, $J = 1.7$, 0.9 Hz, H-5′), 7.05 (1H, dd, $J = 3.5$, 0.9 Hz, H-3″), 6.46 (1H, dd, $J = 3.5$, 1.7 Hz, H-4″), 7.53 (1H, dd, $J = 1.7$, 0.8 Hz, H-5″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.6 (CH_2, C-1), 23.8 (CH_2, C-2), 79.0 (CH, C-3), 37.4 (C, C-4), 50.6 (CH, C-5), 17.9 (CH_2, C-6), 35.8 (CH_2, C-7), 40.8 (C, C-8), 52.8 (CH, C-9), 38.8 (C, C-10), 35.2 (CH_2, C-11), 74.2 (CH, C-12), 41.5 (CH, C-13), 49.8 (C, C-14), 31.2 (CH_2, C-15), 29.7 (CH_2, C-16), 49.0 (CH, C-17), 16.8 (CH_3, C-18), 16.7 (CH_3, C-19), 86.0 (C, C-20), 23.2 (CH_3, C-21), 35.9 (CH_2, C-22), 25.9 (CH_2, C-23), 83.6 (CH, C-24), 71.3 (C, C-25), 27.4 (CH_3, C-26), 24.9 (CH_3, C-27), 28.6 (CH_3, C-28), 21.9 (CH_3, C-29), 16.6 (CH_3, C-30), 158.6 (CO, C-1′), 145.3 (C, C-2′), 118.0 (CH, C-3′), 111.9 (CH, C-4′), 146.4 (CH, C-5′), 158.0 (CO, C-1″), 145.2 (C, C-2″), 117.3 (CH, C-3″), 111.8 (CH, C-4″), 146.2 (CH, C-5″); HRMS (ESI$^+$) m/z calcd for $C_{40}H_{56}O_8Na$ 687.3867, found 687.3847 ($M + Na^+$).

(20*S*,24*R*)-epoxy-3*β*,12*β*-dithenoyl-dammarane-25-ol (20) White powder, 6% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (1H, m, H-3), 5.37 (1H, td, $J = 10.8$, 5.3 Hz, H-12), 3.72 (1H, t, $J = 7.4$ Hz, H-24), 1.22 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.09 (3H, s), 1.05 (3H, s), 1.03 (3H, s), 0.94 (3H, s), 0.94 (3H, s), 7.85 (1H, dd, $J = 3.7$, 1.3 Hz, H-3′), 7.17 (1H, dd, $J = 5.0$, 3.7 Hz, H-4′), 7.60 (1H, dd, $J = 5.0$, 1.2 Hz, H-5′), 7.70 (1H, dd, $J = 3.7$, 1.3 Hz, H-3″), 7.05 (1H, m, H-4′), 7.50 (1H, dd, $J = 5.0$, 1.2 Hz, H-5″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.6 (CH_2, C-1), 23.9 (CH_2, C-2), 79.2 (CH, C-3), 37.5 (C, C-4), 50.6 (CH, C-5), 17.9 (CH_2, C-6), 36.0 (CH_2, C-7), 40.8 (C, C-8), 52.9 (CH, C-9), 38.8 (C, C-10), 35.0 (CH_2, C-11), 74.5 (CH, C-12), 41.5 (CH, C-13), 49.8 (C, C-14), 31.2 (CH_2, C-15), 26.0 (CH_2, C-16), 49.0 (CH, C-17), 16.8 (CH_3, C-18), 16.8 (CH_3, C-19), 86.1 (C, C-20), 23.2 (CH_3, C-21), 36.3 (CH_2, C-22), 25.9 (CH_2, C-23), 83.6 (CH, C-24), 71.2 (C, C-25), 27.4 (CH_3, C-26), 24.9 (CH_3, C-27), 28.7 (CH_3, C-28), 21.8 (CH_3, C-29), 16.5 (CH_3, C-30), 161.8 (CO, C-1'), 134.9 (C, C-2′), 133.4 (CH, C-3′), 132.5 (CH, C-4′), 127.9 (CH, C-5′), 161.5 (CO, C-1″), 134.8 (C, C-2″), 133.0 (CH, C-3″), 132.1 (CH, C-4″), 127.7 (CH, C-5″); HRMS (ESI$^+$) m/z calcd for $C_{40}H_{56}O_6S_2Na$ 719.3411, found 719.3389 ($M + Na^+$).

(20*S*,24*R*)-epoxy-3*β*,12*β*-dicinnamoyl-dammarane-25-ol (21) Light yellow powder, 8% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (1H, m, H-3), 5.30 (1H, td, $J = 10.7$, 5.3 Hz, H-12), 3.72 (1H, t, $J = 7.4$ Hz, H-24), 1.23 (3H, s), 1.14 (3H, s), 1.13 (3H, s), 1.08 (3H, s), 1.05 (3H, s), 1.03 (3H, s), 0.94 (3H, s), 0.91 (3H, s), 6.57 (1H, d, $J = 16.0$ Hz, H-2′), 7.70 (1H, d, $J = 16.0$ Hz, H-3'), 7.59 (2H, m, H-5′, H-9′), 7.38 (3H, m, H-6′, H-7′, H-8′), 7.66 (1H, d, $J = 16.0$ Hz, H-3″), 7.47 (2H, m, H-5″, H-9″), 7.35-7.34 (3H, m, H-6″, H-7″, H-8″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.7 (CH_2, C-1), 24.0 (CH_2, C-2), 78.3 (CH, C-3), 37.2 (C, C-4), 50.5 (CH, C-5), 17.9 (CH_2, C-6), 35.8 (CH_2, C-7), 40.7 (C, C-8), 52.8 (CH, C-9), 39.0 (C, C-10), 34.9 (CH_2, C-11), 73.5 (CH, C-12), 41.4 (CH, C-13), 49.8 (C, C-14), 31.2 (CH_2, C-15), 26.0 (CH_2, C-16), 49.0 (CH, C-17), 16.8 (CH_3, C-18), 16.8 (CH_3, C-19), 86.1 (C, C-20), 23.1 (CH_3, C-21), 35.8 (CH_2, C-22), 25.9 (CH_2, C-23), 83.6 (CH, C-24), 71.2 (C, C-25), 27.4 (CH_3, C-26), 25.0 (CH_3, C-27), 28.5 (CH_3, C-28), 21.9 (CH_3, C-29), 16.5 (CH_3, C-30), 166.7 (CO, C-1′), 119.0 (CH, C-2′), 144.9 (CH, C-3′), 134.8 (C, C-4′), 128.1 (CH, C-5′, C-9′), 128.9 (CH, C-6′, C-8′), 130.3 (CH, C-7′), 166.2 (CO, C-1″), 118.8 (CH, C-2″), 144.4 (CH, C-3″), 134.6 (C, C-4″), 128.0 (CH, C-5″, C-9″), 128.9 (CH, C-6″, C-8″), 130.2 (CH, C-7″); HRMS (ESI$^+$) m/z calcd for $C_{48}H_{64}O_6Na$ 759.4595, found 759.4600 ($M + Na^+$).

General procedure for the synthesis of compounds 8 and 15

To a solution of (20 *S*,24 *R*)-epoxy-dammarane-3*β*,12*β*,25-triol (23.8 mg, 0.05 mmol) in pyridine (0.6 mL) was added phthalic anhydride (13.3 mg, 0.09 mmol) at room

temperature. The solution was then heated to 80 °C and stirred for 24 h. Then, the reaction mixture was diluted with EtOAc and washed with 5% HCl aqueous solution. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (chloroform-methanol-acetic acid, 98:2:0.01) to give compounds **8** and **15**.

(20*S*,24*R*)-epoxy-3*β*-(2-carboxybenzoyl)-dammarane-12β,25-diol (8) White powder, 10% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.93 (1H, m, H-3), 3.99 (1H, m, H-12), 3.72 (1H, t, $J = 7.1$ Hz, H-24), 1.25 (3H, s), 1.17 (3H, s), 1.12 (3H, s), 1.11 (3H, s), 1.06 (6H, s), 0.95 (3H, s), 0.91 (6H, s), 0.84 (3H, s), 7.83 (1H, m, H-4′), 7.83 (1H, m, H-7′), 7.55 (2H, m, H-5′, H-6′); ^{13}C NMR(150 MHz, $CDCl_3$) δ 31.9 (CH_2, C-1), 22.3 (CH_2, C-2), 80.3 (CH, C-3), 37.2 (C, C-4), 49.9 (CH, C-5), 16.6 (CH_2, C-6), 35.7 (CH_2, C-7), 41.2 (C, C-8), 54.9 (CH, C-9), 38.9 (C, C-10), 39.3 (CH_2, C-11), 71.4 (CH, C-12), 41.0 (CH, C-13), 50.4 (C, C-14), 31.0 (CH_2, C-15), 25.8 (CH_2, C-16), 49.2 (CH, C-17), 16.5 (CH_3, C-18), 17.8 (CH_3, C-19), 86.1 (C, C-20), 23.9 (CH_3, C-21), 36.2 (CH_2, C-22), 26.3 (CH_2, C-23), 83.4 (CH, C-24), 71.6 (C, C-25), 27.3 (CH_3, C-26), 24.3 (CH_3, C-27), 28.3 (CH_3, C-28), 21.9 (CH_3, C-29), 16.5 (CH_3, C-30), 168.2 (C, C-1′, C-8′), 133.2 (C, C-2′, C-3′), 129.5 (C, C-4′), 130.7 (C, C-5′), 131.1 (C, C-6′), 129.1 (C, C-7′); HRMS (ESI^-) m/z calcd for $C_{38}H_{55}O_7$ 623.3953, found 623.3935 ($M\text{-}H^-$).

(20*S*,24*R*)-epoxy-12*β*-(2-carboxybenzoyl)-dammarane-3*β*,25-diol (15) White powder, 28% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.36 (1H, m, H-3), 5.48 (1H, td, $J =$ 10.8, 5.7 Hz, H-12), 3.80 (1H, t, $J = 7.0$ Hz, H-24), 1.21 (3H, s), 1.18 (3H, s), 1.15 (3H, s), 1.06 (6H, s), 0.98 (3H, s), 0.95 (3H, s), 0.85 (3H, s), 7.84 (1H, m, H-4'), 7.52 (3H, m, H-5′-H-7′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.2 (CH_2, C-1), 25.3 (CH_2, C-2), 75.8 (CH, C-3), 37.9 (C, C-4), 48.5 (CH, C-5), 18.0 (CH_2, C-6), 35.0 (CH_2, C-7), 41.5 (C, C-8), 52.7 (CH, C-9), 38.9 (C, C-10), 32.9 (CH_2, C-11), 75.1 (C, C-12), 40.4 (CH, C-13), 49.9 (C, C-14), 31.1 (CH_2, C-15), 26.1 (CH_2, C-16), 48.9 (CH, C-17), 16.9 (CH_3, C-18), 16.7 (CH_3, C-19), 86.7 (C, C-20), 23.6 (CH_3, C-21), 35.8 (CH_2, C-22), 26.6 (CH_2, C-23), 83.5 (CH, C-24), 72.4 (C, C-25), 27.3 (CH_3, C-26), 24.7 (CH_3, C-27), 28.8 (CH_3, C-28), 22.2 (CH_3, C-29), 16.4 (CH_3, C-30), 167.5 (C, C-1′, C-8′), 133.7 (C, C-2′, C-3′), 129.8 (C, C-4′), 130.5 (C, C-5′), 131.3 (C, C-6′), 127.9 (C, C-7′); HRMS (ESI^-) m/z calcd for $C_{38}H_{55}O_7$ 623.3953, found 623.3922 ($M\text{-}H^-$).

(20*S*,24*R*)-epoxy-12*β*,25-dihydroxy-dammarane-3-one (22) The (20 *S*,24 *R*)-epoxy-dammarane-3*β*,12*β*,25-triol (100.0 mg, 0.21 mmol) was dissolved in toluene (3.0 mL) followed by the addition of aluminium isopropoxide (107.2 mg, 0.53 mmol). After stirred at room temperature for 1 h, acetone was added and the reaction was heated to reflux for 7 h. The reaction was cooled to room temperature and quenched by the addition of 5% HCl aqueous solution. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to remove EtOAc. The residue was purified by column chromatography on silica gel (EtOAc-petroleum ether, 25:75, 35:65) to give compound **22** (70% yield) as a white powder, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (1H, m, H-12), 3.73 (1H, t, $J = 7.4$ Hz, H-24), 1.25 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 1.11 (3H, s), 1.06 (3H, s), 1.04 (3H, s), 1.00 (3H, s), 0.89 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.0 (CH_2, C-1), 20.7 (CH_2, C-2), 218.8 (CO, C-3), 38.2 (C, C-4), 54.8 (CH, C-5), 19.6 (CH_2, C-6), 35.1 (CH_2, C-7), 40.6 (C, C-8), 55.2 (CH, C-9), 47.7 (C, C-10), 39.5 (CH_2, C-11), 71.2 (CH, C-12), 41.6 (CH, C-13), 49.8 (C, C-14), 31.0 (CH_2, C-15), 25.7 (CH_2, C-16), 49.2 (CH, C-17), 16.7 (CH_3, C-18), 16.4 (CH_3, C-19), 85.9 (C, C-20), 23.3 (CH_3, C-21), 36.3 (CH_2, C-22), 26.3 (CH_2, C-23), 83.4 (CH, C-24), 71.5 (C, C-25), 27.5 (CH_3, C-26), 24.3 (CH_3, C-27), 29.7 (CH_3, C-28), 22.7 (CH_3, C-29), 16.2 (CH_3, C-30); HRMS (ESI^-) m/z calcd for $C_{31}H_{51}O_6$ 519.3691, found 519.3693 ($M + HCOO^-$).

General procedure for the synthesis of compounds 23 and 24

To a solution of (20 *S*,24 *R*)-epoxy-dammarane-3*β*,12*β*,25-triol (30.0 mg, 0.06 mmol) in dry CH_2Cl_2 (2 mL) was added pyridinium chlorochromate (PCC, 25.8 mg, 0.12 mmol) and the mixture was stirred at room temperature for 24 h. The suspension was then filtered by a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc-petroleum ether, 35:65) to afford compounds **23** and **24**.

(20*S*,24*R*)-epoxy-12-oxo-dammarane-3*β*,25-diol (23) White powder, 20% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.37 (1H, m, H-3), 3.70 (1H, t, $J = 7.4$ Hz, H-24), 1.23 (3H, s), 1.18 (3H, s), 1.13 (3H, s), 1.09 (3H, s), 1.09 (3H, s), 0.95 (3H, s), 0.91 (3H, s), 0.83 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 32.6 (CH_2, C-1), 25.3 (CH_2, C-2), 76.2 (CH, C-3), 36.8 (C, C-4), 49.5 (CH, C-5), 18.0 (CH_2, C-6), 34.5 (CH_2, C-7), 43.5 (C, C-8), 44.3 (CH, C-9), 37.6 (C, C-10), 46.9 (CH_2, C-11), 212.2 (CO, C-12), 63.5 (CH, C-13), 50.0 (C, C-14), 30.5 (CH_2, C-15), 26.0 (CH_2, C-16), 48.9 (CH, C-17), 17.9 (CH_3, C-18), 16.8 (CH_3, C-19), 85.9 (C, C-20), 23.4 (CH_3, C-21), 36.1 (CH_2, C-22), 26.3 (CH_2, C-23), 83.7 (CH, C-24), 71.6 (C, C-25), 27.6 (CH_3, C-26), 24.8 (CH_3, C-27), 28.6 (CH_3, C-28), 22.4 (CH_3, C-29), 16.6 (CH_3, C-30);

HRMS (ESI^+) m/z calcd for $C_{30}H_{50}O_4Na$ 497.3601, found 497.3573 ($M + Na^+$).

(20*S*,24*R*)-epoxy-3,12-dioxo-dammarane-25-ol (24) White powder, 30% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 3.71 (1H, t, $J = 7.4$ Hz, H-24), 1.33 (3H, s), 1.18 (3H, s), 1.14 (3H, s), 1.11 (6H, s), 1.06 (3H, s), 1.04 (3H, s), 0.99 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.8 (CH_2, C-1), 33.8 (CH_2, C-2), 217.0 (CO, C-3), 36.3 (C, C-4), 55.7 (CH, C-5), 19.2 (CH_2, C-6), 34.1 (CH_2, C-7), 43.0 (C, C-8), 44.0 (CH, C-9), 47.7 (C, C-10), 46.5 (CH_2, C-11), 211.4 (CO, C-12), 62.8 (CH, C-13), 49.7 (C, C-14), 30.4 (CH_2, C-15), 25.8 (CH_2, C-16), 49.3 (CH, C-17), 17.5 (CH_3, C-18), 16.4 (CH_3, C-19), 85.6 (C, C-20), 23.3 (CH_3, C-21), 35.8 (CH_2, C-22), 26.1 (CH_2, C-23), 83.5 (CH, C-24), 71.4 (C, C-25), 26.2 (CH_3, C-26), 24.6 (CH_3, C-27), 27.3 (CH_3, C-28), 21.5 (CH_3, C-29), 15.7 (CH_3, C-30); HRMS (ESI^+) m/z calcd for $C_{30}H_{48}O_4Na$ 495.3445, found 495.3416 ($M + Na^+$).

(20*S*,24*R*)-epoxy-3-oxime-dammarane-12β,25-diol (25) To a stirred solution of compound **22** (30.0 mg, 0.06 mmol) in 2.2 mL of ethanol-water (10:1, *v*/*v*) was added hydroxylamine hydrochloride (NH_2OH•HCl, 11.0 mg, 0.16 mmol) and sodium acetate trihydrate (CH_3COONa•$3H_2O$, 21.6 mg, 0.16 mmol) in sequence. The reaction mixture was refluxed for 3 h. After cooling to room temperature, the organic solvent was removed under reduced pressure. The residue was taken up in EtOAc (5.0 mL) and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (acetone-petroleum ether, 15:85, 25:75) to provide compound **25** (91% yield) as a white solid, ^1H NMR (400 MHz, $CDCl_3$) δ 3.93 (1H, td, $J = 10.6$, 4.9 Hz, H-12), 3.73 (1H, t, $J = 7.2$ Hz, H-24), 1.20 (3H, s), 1.15 (3H, s), 1.14 (3H, s), 1.13 (3H, s), 1.10 (6H, br s), 0.99 (3H, s), 0.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1 (CH_2, C-1), 19.0 (CH_2, C-2), 167.2 (C, C-3), 38.7 (C, C-4), 55.2 (CH, C-5), 17.5 (CH_2, C-6), 35.5 (CH_2, C-7), 40.7 (C, C-8), 55.4 (CH, C-9), 40.6 (C, C-10), 39.4 (CH_2, C-11), 71.2 (CH, C-12), 41.6 (CH, C-13), 49.8 (C, C-14), 30.9 (CH_2, C-15), 25.6 (CH_2, C-16), 49.2 (CH, C-17), 16.7 (CH_3, C-18), 16.4 (CH_3, C-19), 85.9 (C, C-20), 23.3 (CH_3, C-21), 36.3 (CH_2, C-22), 26.3 (CH_2, C-23), 83.4 (CH, C-24), 71.5 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 28.2 (CH_3, C-28), 22.6 (CH_3, C-29), 16.2 (CH_3, C-30); HRMS (ESI^-) m/z calcd for $C_{31}H_{52}NO_6$ 534.3800, found 534.3794 ($M + HCOO^-$).

(20*S*,24*R*)-epoxy-3β-(2-carboxybenzoyl)-12-oxo-dammarane-25-ol (26) To a solution of compound **23** (12.0 mg, 0.03 mmol) in pyridine (0.6 mL) was added *o*-phthalic anhydride (22.2 mg, 0.15 mmol) and the mixture was refluxed for 72 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, and washed with 5% HCl aqueous solution. The aqueous phase was extracted with EtOAc, the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (acetone-petroleum ether-acetic acid, 20:80:0.1, 25:75:0.1) to give compound **26** (76% yield) as a white solid, ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (1H, m, H-3), 3.70 (1H, t, $J =$ 7.4 Hz, H-24), 1.23 (3H, s), 1.20 (3H, s), 1.19 (3H, s), 1.13 (3H, s), 1.10 (3H, s), 1.08 (3H, s), 0.94 (3H, s), 0.89 (3H, s), 7.90 (1H, m, H-4'), 7.59 (3H, m, H-5′-H-7′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.3 (CH_2, C-1), 22.2 (CH_2, C-2), 80.1 (CH, C-3), 36.5 (C, C-4), 50.0 (CH, C-5), 17.7 (CH_2, C-6), 34.2 (CH_2, C-7), 43.3 (C, C-8), 44.1 (CH, C-9), 36.9 (C, C-10), 46.6 (CH_2, C-11), 212.1 (C, C-12), 63.1 (CH, C-13), 49.8 (C, C-14), 30.3 (CH_2, C-15), 25.8 (CH_2, C-16), 49.3 (CH, C-17), 17.7 (CH_3, C-18), 16.7 (CH_3, C-19), 85.7 (C, C-20), 23.2 (CH_3, C-21), 35.9 (CH_2, C-22), 26.1 (CH_2, C-23), 83.4 (CH, C-24), 71.5 (C, C-25), 27.3 (CH_3, C-26), 24.5 (CH_3, C-27), 28.0 (CH_3, C-28), 21.9 (CH_3, C-29), 16.4 (CH_3, C-30), 167.9 (C, C-1′, C-8′), 134.1 (C, C-2′, C-3′), 130.0 (C, C-4′), 130.6 (C, C-5′), 131.9 (C, C-6′), 128.5 (C, C-7′); HRMS (ESI^-) m/z calcd for $C_{38}H_{53}O_7$ 621.3797, found 621.3787 ($M\text{-}H^-$).

(20*S*,24*R*)-epoxy-2-hydroxymethlidene-3-oxo-dammarane12β,25-diol (27) To a round-bottom bottle equipped with Na (0.5 g) was added ethyl ether (5.0 mL), and the mixture was refluxed for 1 h. After cooling to 0 °C, a solution of compound **22** (20.0 mg, 0.04 mmol) in ethyl formate (1.0 mL) was added dropwise to the mixture. After 30 min, the solution was allowed to warm to room temperature and stirred for 6 h before it was quenched by the addition of EtOH (2.0 mL). The mixture was poured into 5 mL water. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc-petroleum ether, 6:94) to give compound **27** (76% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 3.39 (2H, d, $J = 14.9$ Hz, H-1), 4.00 (1H, td, $J = 10.7$, 4.9 Hz, H-12), 3.74 (1H, t, $J = 7.2$ Hz, H-24), 1.22 (3H, s), 1.21 (3H, s), 1.15 (3H, s), 1.13 (6H, overlap), 1.03 (6H, overlap), 0.93 (3H, s), 8.60 (1H, s, H-1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.7 (CH_2, C-1), 106.5 (C, C-2), 189.0 (C, C-3), 40.4 (C, C-4), 53.4 (CH, C-5), 19.3 (CH_2, C-6), 35.0 (CH_2, C-7), 40.5 (C, C-8), 53.1 (CH, C-9), 37.4 (C, C-10), 39.7 (CH_2, C-11), 71.3 (CH, C-12), 41.5 (CH, C-13), 49.8 (C, C-14), 31.0 (CH_2, C-15), 25.7 (CH_2, C-16), 49.1 (CH, C-17), 16.2 (CH_3, C-18), 15.2 (CH_3, C-19), 85.9 (C, C-20), 23.5 (CH_3, C-21), 36.1 (CH_2, C-22), 26.2 (CH_2, C-23), 83.3 (CH, C-24), 71.5 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 28.4 (CH_3, C-28), 20.6 (CH_3, C-29), 16.3 (CH_3, C-30),

189.8 (CH, C-1'); HRMS (ESI^-) m/z calcd for $C_{31}H_{49}O_5$ 501.3585, found 501.3592 ($M\text{-}H^-$).

(20*S*,24*R*)-epoxy-2- hydroxymethyl-3-oxo-dammarane12*β*,25 -diol (28) To a solution of compound **27** (20.0 mg, 0.04 mmol) in methanol (1.0 mL) was added $NaBH_4$ (3.0 mg, 0.08 mmol). The reaction mixture was allowed to stir at room temperature for 6 h before it was quenched by the addition of water (1.0 mL). The aqueous phase was extracted with EtOAc, the combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (acetone-petroleum ether, 15:85, 20:80) to give compound **28** (69% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 2.90 (1H, m, H-2), 3.86 (1H, td, $J = 10.9$, 4.7 Hz, H-12), 3.73 (1H, t, $J = 7.3$ Hz, H-24), 1.21 (3H, s), 1.14 (3H, s), 1.12 (6H, s), 1.08 (3H, s), 0.97 (3H, s), 0.94 (3H, s), 0.86 (3H, s), 2.83 (1H, m, H-1′), 3.53 (1H, m, H-1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.5 (CH_2, C-1), 43.5 (CH, C-2), 222.8 (C, C-3), 40.4 (C, C-4), 53.1 (CH, C-5), 19.8 (CH_2, C-6), 34.6 (CH_2, C-7), 41.2 (C, C-8), 54.7 (CH, C-9), 37.7 (C, C-10), 39.2 (CH_2, C-11), 71.1 (CH, C-12), 41.6 (CH, C-13), 49.7 (C, C-14), 30.9 (CH_2, C-15), 25.6 (CH_2, C-16), 49.0 (CH, C-17), 18.3 (CH_3, C-18), 15.7 (CH_3, C-19), 85.9 (C, C-20), 23.4 (CH_3, C-21), 36.2 (CH_2, C-22), 26.3 (CH_2, C-23), 83.3 (CH, C-24), 71.4 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 29.4 (CH_3, C-28), 19.4 (CH_3, C-29), 16.1 (CH_3, C-30), 63.0 (CH_2, C-1′); HRMS (ESI^+) m/z calcd for $C_{31}H_{52}O_5Na$ 527.3707, found 527.3694 ($M + Na^+$).

(20*S*,24*R*)-epoxy-[2,3-d]-isoxazole-dammarane-12*β*,25-diol (29) To a solution of compound **27** (9.0 mg, 0.02 mmol) in 2.2 mL ethanol-water (10:1, *v*/*v*) was added hydroxylamine hydrochloride (NH_2OH•HCl, 3.1 mg, 0.05 mmol). The reaction mixture was refluxed for 3 h. After cooling to room temperature, the solution was diluted with EtOAc, the organic phase was separated and washed by brine. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (acetone-petroleum ether, 5:95) to give compound **29** (56% yield) as a white solid, ^1H NMR (400 MHz, $CDCl_3$) δ 3.43 (1H, dd, $J = 15.9$, 5.4 Hz, H-1), 4.02 (1H, td, $J = 10.7$, 5.0 Hz, H-12), 3.74 (1H, t, $J =$ 7.2 Hz, H-24), 1.32 (3H, s), 1.24 (3H, s), 1.22 (3H, s), 1.16 (3H, s), 1.13 (3H, s), 1.03 (3H, s), 1.01 (3H, s), 0.94 (3H, s), 7.96 (1H, s, H-1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9 (CH_2, C-1), 109.7 (C, C-2), 172.2 (C, C-3), 49.8 (C, C-4), 53.8 (CH, C-5), 18.5 (CH_2, C-6), 35.1 (CH_2, C-7), 40.7 (C, C-8), 54.2 (CH, C-9), 35.1 (C, C-10), 39.8 (CH_2, C-11), 71.2 (CH, C-12), 41.5 (CH, C-13), 49.8 (C, C-14), 31.0 (CH_2, C-15), 25.7 (CH_2, C-16), 49.1 (CH, C-17), 16.2 (CH_3, C-18), 16.2 (CH_3, C-19), 85.9 (C, C-20), 23.6 (CH_3, C-21), 36.1 (CH_2, C-22), 26.2 (CH_2, C-23), 83.3 (CH, C-24), 71.5 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 29.0 (CH_3, C-28), 21.3 (CH_3, C-29), 16.3 (CH_3, C-30), 150.6 (CH, C-1′); HRMS (ESI^+) m/z calcd for $C_{31}H_{50}NO_4$ 500.3734, found 500.3702 ($M + H^+$).

(20*S*,24*R*)-epoxy-3,4-lactone-dammarane-12*β*,25-diol (30) To a solution of compound **22** (15.0 mg, 0.03 mmol) in 1.5 mL of DCM was added $NaHCO_3$ (10.8 mg, 0.12 mmol) and *m*-CPBA (10.4 mg, 0.06 mmol). The resulting suspension was stirred for 12 h at room temperature before it was quenched with sat. aq. $Na_2S_2O_3$ aqueous solution. Layers were separated, and the aqueous layer was extracted with DCM, and the combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (acetone-petroleum ether, 10:90) to give compound **30** (71% yield) as a white solid, ^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (1H, m, H-12), 3.73 (1H, t, $J = 7.3$ Hz, H-24), 1.51 (3H, s), 1.43 (3H, s), 1.30 (3H, s), 1.21 (3H, s), 1.15 (3H, s), 1.13 (3H, s), 1.03 (3H, s), 0.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.1 (CH_2, C-1), 33.1 (CH_2, C-2), 175.4 (C, C-3), 85.6 (C, C-4), 51.8 (CH, C-5), 23.8 (CH_2, C-6), 34.7 (CH_2, C-7), 40.2 (C, C-8), 56.2 (CH, C-9), 39.8 (C, C-10), 39.3 (CH_2, C-11), 71.0 (CH, C-12), 41.9 (CH, C-13), 49.6 (C, C-14), 30.7 (CH_2, C-15), 25.6 (CH_2, C-16), 48.9 (CH, C-17), 15.9 (CH_3, C-18), 19.3 (CH_3, C-19), 85.8 (C, C-20), 23.3 (CH_3, C-21), 36.4 (CH_2, C-22), 26.3 (CH_2, C-23), 83.3 (CH, C-24), 71.4 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 29.6 (CH_3, C-28), 27.8 (CH_3, C-29), 15.7 (CH_3, C-30); HRMS (ESI^+) m/z calcd for $C_{30}H_{50}O_5Na$ 513.3550, found 513.3516 ($M + Na^+$).

(20*S*,24*R*)-epoxy-3-carboxyl-dammarane-4,12*β*,25-triol (31) To a solution of compound **30** (24.0 mg, 0.05 mmol) in 3 mL of methanol was added 10% NaOH aqueous solution (1 mL) and the mixture was heated to reflux for 5 h. After the completion of hydrolysis, the solution was neutralized with 1 M HCl and the mixture was extracted with EtOAc. Combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (chloroform-methanol, 10:90) to give compound **31** (82% yield) as a white solid, ^1H NMR (400 MHz, CD_3OD) δ 2.69 (1H, m, H-2), 3.81 (1H, td, $J = 10.9$, 4.7 Hz, H-12), 3.72 (1H, t, $J = 7.2$ Hz, H-24), 1.27 (6H, s), 1.24 (3H, s), 1.13 (3H, s), 1.12 (6H, s), 1.01 (3H, s), 0.91 (3H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 35.1 (CH_2, C-1), 30.0 (CH_2, C-2), 75.2 (C, C-4), 49.2 (CH, C-5), 21.9 (CH_2, C-6), 35.4 (CH_2, C-7), 41.8 (C, C-8), 51.6 (CH, C-9), 40.0 (C, C-10), 38.6 (CH_2, C-11), 70.8 (CH, C-12), 41.6 (CH, C-13), 49.8 (C, C-14), 30.6 (CH_2, C-15), 25.0 (CH_2, C-16), 49.2 (CH, C-17), 15.4 (CH_3, C-18), 19.6 (CH_3, C-19), 86.0 (C, C-20), 24.1 (CH_3, C-21), 36.0 (CH_2, C-22), 26.0 (CH_2, C-23), 83.4

(CH, C-24), 71.4 (C, C-25), 27.2 (CH_3, C-26), 24.9 (CH_3, C-27), 31.9 (CH_3, C-28), 22.0 (CH_3, C-29), 14.9 (CH_3, C-30); HRMS (ESI^-) m/z calcd for $C_{30}H_{51}O_6$ 507.3691, found 507.3673 ($M\text{-}H^-$).

(20*S*,24*R*)-epoxy-dammarane-3,4,12*β*,25-tetrol (32) Under a nitrogen atmosphere, a solution of compound **30** (19.0 mg, 0.04 mmol) in THF was treated dropwise with solution of $LiAlH_4$ (5.2 mg, 0.12 mmol) in 1.5 mL of dried THF at 0 °C. After complete addition, the solution was heated to 50 °C and stirred at the same temperature for 12 h. After cooling to 0 °C, water and 0.1 M NaOH aqueous solution was added slowly and filtered. The filtrate was extracted with EtOAc, and the combine organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (acetone-petroleum ether, 20:80) to give compound **32** (50% yield) as a white solid, ^1H NMR (400 MHz, $CDCl_3$) δ 2.92 (1H, m, H-3), 3.80 (1H, td, $J = 10.7$, 4.6 Hz, H-12), 3.72 (1H, t, $J = 7.2$ Hz, H-24), 1.32 (3H, s), 1.30 (3H, s), 1.25 (3H, s), 1.23 (3H, s), 1.21 (3H, s), 1.14 (3H, s), 1.12 (3H, s), 0.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3 (CH_2, C-1), 27.3 (CH_2, C-2), 63.3 (CH_2, C-3), 76.6 (C, C-4), 46.0 (CH, C-5), 22.5 (CH_2, C-6), 35.9 (CH_2, C-7), 42.4 (C, C-8), 51.4 (CH, C-9), 40.2 (C, C-10), 39.8 (CH_2, C-11), 71.7 (CH, C-12), 41.6 (CH, C-13), 50.0 (C, C-14), 31.0 (CH_2, C-15), 25.6 (CH_2, C-16), 49.1 (CH, C-17), 16.0 (CH_3, C-18), 20.8 (CH_3, C-19), 86.0 (C, C-20), 23.5 (CH_3, C-21), 37.8 (CH_2, C-22), 26.3 (CH_2, C-23), 83.3 (CH, C-24), 71.6 (C, C-25), 27.4 (CH_3, C-26), 24.3 (CH_3, C-27), 28.2 (CH_3, C-28), 22.0 (CH_3, C-29), 16.3 (CH_3, C-30); HRMS (ESI^+) m/z calcd for $C_{30}H_{54}O_5Na$ 517.3863, found 517.3848 ($M + Na^+$).

Procedure for the synthesis of compounds 33 and 34

To a solution of compound **16** (30.0 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL) was added pyridinium chlorochromate (PCC, 46.6 mg, 0.22 mmol) at room temperature. The resultant mixture was then heated to 40 °C and stirred at the same temperature for 12 h. Upon consumption of starting material, the suspension was filtered by a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc-petroleum ether, 5:95 to 10:90) to afford intermediate. To a solution of intermediate (24.0 mg, 0.05 mmol) in MeOH (3.0 mL) was added 10% NaOH aqueous solution (1.0 mL) at room temperature. Then, the mixture was heated to reflux and stirred overnight. After cooling to room temperature, the organic solvent was removed under reduced pressure. Then the crude was diluted with EtOAc, washed with 5% HCl aqueous solution, sat. aq. $NaHCO_3$, and brine in sequence, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (acetone-petroleum ether, 25:75, 10:90) to give compound **33** (91% yield) as a white powder.

Under a nitrogen atmosphere, a solution of compound **33** (5.3 mg, 0.14 mmol) in THF was treated dropwise with a solution of $LiAlH_4$ (5.2 mg, 0.12 mmol) in 1.5 mL of dried THF at 0 °C. After complete addition, the solution was heated to 50 °C and stirred at the same temperature for 12 h. After cooling to 0 °C, water and 0.1 M NaOH aqueous solution was added slowly and filtered. The filtrate was extracted with EtOAc, and the combine organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (acetone-petroleum ether, 20:80 to 35:65) to give compound **34** (35% yield) as a white solid.

20*S*-epoxy-3*β*,12*β*-dihydroxy-dammarane -24-one (33) White powder, 91% yield; ^1H NMR (400 MHz, CD_3OD) δ 3.30 (1H, m, H-3), 3.90 (1H, td, $J = 10.5$, 5.5 Hz, H-12), 1.37 (3H, s), 1.06 (3H, s), 1.00 (6H, s), 0.98 (3H, s), 0.92 (3H, s), 0.86 (3H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 36.3 (CH_2, C-1), 26.2 (CH, C-2), 76.8 (CH, C-3), 38.9 (C, C-4), 50.5 (CH, C-5), 19.1 (CH_2, C-6), 37.1 (CH_2, C-7), 42.1 (C, C-8), 56.1 (CH, C-9), 40.3 (C, C-10), 39.6 (CH_2, C-11), 71.4 (CH, C-12), 42.9 (CH, C-13), 51.2 (C, C-14), 31.8 (CH_2, C-15), 26.5 (CH_2, C-16), 50.6 (CH, C-17), 17.2 (CH_3, C-18), 17.1 (CH_3, C-19), 91.9 (C, C-20), 25.5 (CH_3, C-21), 31.8 (CH_2, C-22), 30.0 (CH_2, C-23), 179.6 (CO, C-24), 29.6 (CH_3, C-28), 23.0 (CH_3, C-29), 16.5 (CH_3, C-30); HRMS (ESI^-) m/z calcd for $C_{28}H_{45}O_6$ 477.3222, found 477.3203 ($M + HCOO^-$).

20*S*-protopanaxadiol-24-ol (34) White powder, 35% yield; ^1H NMR (400 MHz, CD_3OD) δ 3.53 (1H, m, H-3), 3.91 (1H, td, $J = 11.0$, 5.5 Hz, H-12), 3.73 (1H, t, $J = 7.3$ Hz, H-24), 1.13 (3H, s), 1.06 (3H, s), 0.99 (3H, s), 0.96 (3H, s), 0.92 (3H, s), 0.86 (3H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 35.0 (CH_2, C-1), 24.5 (CH, C-2), 74.5 (CH, C-3), 37.5 (C, C-4), 49.2 (CH, C-5), 17.8 (CH_2, C-6), 35.7 (CH_2, C-7), 40.5 (C, C-8), 54.8 (CH, C-9), 38.9 (C, C-10), 39.1 (CH_2, C-11), 70.3 (CH, C-12), 40.7 (CH, C-13), 50.0 (C, C-14), 30.4 (CH_2, C-15), 25.6 (CH_2, C-16), 49.4 (CH, C-17), 15.8 (CH_3, C-18), 15.7 (CH_3, C-19), 74.2 (C, C-20), 23.9 (CH_3, C-21), 37.1 (CH_2, C-22), 26.4 (CH_2, C-23), 62.3 (CH_2, C-24), 28.2 (CH_3, C-28), 23.9 (CH_3, C-29), 15.4 (CH_3, C-30); HRMS (ESI^-) m/z calcd for $C_{28}H_{49}O_6$ 481.3535, found 481.3530 ($M + HCOO^-$).

20*S*-24,25-dihydro-protopanaxadiol (36) A suspension of 10% Pd/C (2.4 mg) and 20(*S*)-PPD (21.0 mg, 0.05 mmol) in ethanol (1.0 mL) was stirred at room temperature under hydrogen atmosphere. After being stirred for 12 h, the

suspension was filtered through a Celite pad and the pad was washed with CH_2Cl_2. The filtrate was concentrated and purified by column chromatography on silica gel (acetone-petroleum ether, 10:90) to give compound **36** (80% yield) as a white powder, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (1H, dd, $J = 11.2$, 5.0 Hz, H-3), 3.59 (1H, td, $J = 10.3$, 5.2 Hz, H-12), 1.18 (3H, s), 0.99 (3H, s), 0.98 (3H, s), 0.88 (12H, overlap), 0.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.9 (CH_2, C-1), 27.4 (CH_2, C-2), 78.9 (CH, C-3), 39.0 (C, C-4), 55.8 (CH, C-5), 18.3 (CH_2, C-6), 34.8 (CH_2, C-7), 39.7 (C, C-8), 50.1 (CH, C-9), 37.1 (C, C-10), 31.0 (CH_2, C-11), 70.9 (C, C-12), 47.7 (CH, C-13), 51.6 (C, C-14), 31.2 (CH_2, C-15), 26.6 (CH_2, C-16), 53.5 (CH, C-17), 16.1 (CH_3, C-18), 15.6 (CH_3, C-19), 74.3 (C, C-20), 27.1 (CH_3, C-21), 35.1 (CH_2, C-22), 21.3 (CH_2, C-23), 39.8 (CH_2, C-24), 28.2 (CH, C-25), 22.7 (CH_3, C-26), 22.6 (CH_3, C-27), 28.1 (CH_3, C-28), 15.4 (CH_3, C-29), 16.8 (CH_3, C-30); HRMS (ESI^-) m/z calcd for $C_{31}H_{55}O_5$ 507.4055, found 507.4067 ($M + HCOO^-$).

20*S*-3β,12β-diacetyl-protopanaxadiol (37) To a solution of compound 20(*S*)-PPD (150.0 mg, 0.33 mmol) in pyridine (1.0 mL) was added acetic anhydride (1.2 mL) and DMAP (1.8 mg, 0.02 mmol) at room temperature. After being stirred for 4 h, the reaction mixture was diluted with EtOAc, and washed with 5% HCl aqueous solution and brine in sequence. The organic phases were combined, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (acetone-petroleum ether, 10:90) to give compound **37** (86% yield) as a white powder, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (1H, dd, $J = 11.5$, 4.7 Hz, H-3), 4.74 (1H, td, $J = 10.6$, 4.6 Hz, H-12), 5.16 (1H, t, $J = 7.1$ Hz, H-24), 1.71 (3H, s, H-26), 1.64 (3H, s, H-27), 1.13 (3H, s), 1.01 (3H, s), 0.95 (3H, s), 0.88 (3H, s), 0.85 (6H, overlap), 2.04 (6H, s, H-2′, H-2″); HRMS (ESI^+) m/z calcd for $C_{34}H_{56}O_5Na$ 567.4020, found 567.3980 ($M + Na^+$).

Procedure for the synthesis of compounds 38–40

To the solution of compound **37** (24.0 mg, 0.04 mmol) in ethanol-water (15:1, *v*/*v*, 6.4 mL) was added $KMnO_4$ (8.2 mg, 0.05 mmol) at −40 °C and the reaction was stirred for 6 h at the same temperature before it was quenched by the addition of 10% $Na_2S_2O_3$ aqueous solution. The mixture was extracted with EtOAc and the combined organic layers were washed with 5% HCl and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was dissolved in methanol (3.0 mL), followed by the addition 10% NaOH aqueous solution (1.0 mL). The reaction was heated to reflux and stirred for 2 h. After cooling to room temperature, the solution was diluted with EtOAc and washed with 5% HCl aqueous solution and brine in sequence. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (methanol-acetone-petroleum ether, 7.5:15:85) to give compounds **38** and **39**.

The mixture of compounds **38** and **39** were dissolved in methanol-water (3:2, *v*/*v*, 1.0 mL) and followed by the addition of $NaIO_4$ (21.4 mg, 0.10 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with 10% $Na_2S_2O_3$ and extracted with EtOAc. The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (acetone-petroleum ether, 10:90) to give compound **40**.

20*S*-24,25-dihydroxy-protopanaxadiol (38) White powder, 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (1H, dd, $J = 11.2$, 5.1 Hz, H-3), 3.58 (1H, td, $J = 10.4$, 5.0 Hz, H-12), 3.33 (1H, d, $J = 9.6$ Hz, H-24), 1.22 (3H, s), 1.17 (6H, s), 0.99 (3H, s), 0.98 (3H, s), 0.88 (6H, s), 0.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0 (CH_2, C-1), 27.3 (CH_2, C-2), 78.9 (CH, C-3), 39.7 (C, C-4), 55.8 (CH, C-5), 18.3 (CH_2, C-6), 34.8 (CH_2, C-7), 38.9 (C, C-8), 50.2 (CH, C-9), 37.1 (C, C-10), 31.1 (CH_2, C-11), 71.2 (CH, C-12), 47.8 (CH, C-13), 51.6 (C, C-14), 31.1 (CH_2, C-15), 25.6 (CH_2, C-16), 53.1 (CH, C-17), 15.7 (CH_3, C-18), 15.4 (CH_3, C-19), 73.4 (C, C-20), 26.6 (CH_3, C-21), 32.9 (CH_2, C-22), 25.3 (CH_2, C-22), 79.6 (CH, C-24), 73.1 (C, C-25), 26.6 (CH_3, C-26), 23.5 (CH_3, C-27), 28.0 (CH_3, C-28), 16.2 (CH_3, C-29), 16.8 (CH_3, C-30); HRMS (ESI^-) m/z calcd for $C_{31}H_{55}O_7$ 539.3953, found 539.3934 ($M + HCOO^-$).

20*S*-24,25-dihydroxy-protopanaxadiol (39) White powder, 42% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (1H, dd, $J = 11.2$, 5.0 Hz, H-3), 3.59 (1H, td, $J = 10.3$, 5.1 Hz, H-12), 3.45 (1H, d, $J = 10.3$ Hz, H-24), 1.23 (3H, s), 1.18 (6H, s), 0.99 (3H, s), 0.98 (3H, s), 0.88 (6H, s), 0.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.1 (CH_2, C-1), 27.5 (CH_2, C-2), 78.7 (CH, C-3), 39.8 (C, C-4), 56.0 (CH, C-5), 18.4 (CH_2, C-6), 34.9 (CH_2, C-7), 39.1 (C, C-8), 50.3 (CH, C-9), 37.2 (C, C-10), 31.1 (CH_2, C-11), 71.5 (CH, C-12), 47.9 (CH, C-13), 51.8 (C, C-14), 31.5 (CH_2, C-15), 26.7 (CH_2, C-16), 53.9 (CH, C-17), 15.8 (CH_3, C-18), 15.5 (CH_3, C-19), 74.1 (C, C-20), 27.2 (CH_3, C-21), 31.6 (CH_2, C-22), 25.6 (CH_2, C-22), 79.0 (CH, C-24), 73.4 (C, C-25), 26.5 (CH_3, C-26), 23.7 (CH_3, C-27), 28.2 (CH_3, C-28), 16.3 (CH_3, C-29), 17.0 (CH_3, C-30); HRMS (ESI^-) m/z calcd for $C_{31}H_{55}O_7$ 539.3953, found 539.3914 ($M + HCOO^-$).

20*S*-epoxy-3β,12β,24-trihydroxy-dammarane (40) White powder, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (1H, dd, $J = 11.3$, 4.9 Hz, H-3), 3.78 (1H, td, $J = 10.6$, 5.6 Hz, H-12), 5.55 (1H, d, $J = 6.4$ Hz, H-24), 1.29 (3H, s),

0.98 (6H, s), 0.91 (3H, s), 0.87 (3H, s), 0.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.9 (CH_2, C-1), 27.4 (CH_2, C-2), 78.8 (CH, C-3), 40.0 (C, C-4), 55.7 (CH, C-5), 18.2 (CH_2, C-6), 34.6 (CH_2, C-7), 38.9 (C, C-8), 49.7 (CH, C-9), 37.2 (C, C-10), 30.2 (CH_2, C-11), 73.8 (CH, C-12), 47.7 (CH, C-13), 50.0 (C, C-14), 31.9 (CH_2, C-15), 23.7 (CH_2, C-16), 52.8 (CH, C-17), 16.0 (CH_3, C-18), 15.9 (CH_3, C-19), 87.6 (C, C-20), 37.2 (CH_2, C-22), 28.9 (CH_2, C-23), 102.2 (CH, C-24), 28.1 (CH_3, C-28), 15.4 (CH_3, C-29), 16.9 (CH_3, C-30); HRMS (ESI^+) m/z calcd for $C_{27}H_{46}O_4Na$ 457.3288, found 457.3310 ($M + Na^+$).

Procedure for the synthesis of compounds 41–43

A suspension of 10% Pd/C (12.0 mg) and compound **37** (116.0 mg, 0.21 mmol) in ethanol (3.0 mL) was stirred at room temperature under hydrogen atmosphere. After being stirred for 12 h, the suspension was filtered through a Celite pad and the pad was washed with CH_2Cl_2. The filtrate was concentrated and purified by column chromatography on silica gel (acetone- petroleum ether, 10:90) to give compound **41**.

To a solution of compound **41** in pyridine (2.0 mL) was added $POCl_3$ (40.8 µL, 1.32 mmol) at 0 °C. After 20 min, the mixture was heated to 40 °C and stirred overnight. The solution was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude was dissolved in methanol and followed by the addition of 10% NaOH aqueous solution (1.0 mL). The mixture refluxed for 2 h. After cooling to room temperature, the solution was diluted with EtOAc and washed with 5% HCl aqueous solution and brine in sequence. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc-petroleum ether, 4:96) to give compounds **42** and **43**.

20*S*-24,25-dihydro-3β,12β-diacetyl -protopanaxadiol (41) White powder, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (1H, dd, $J = 11.5$, 4.6 Hz, H-3), 4.74 (1H, td, $J = 10.9$, 5.1 Hz, H-12), 1.11 (3H, s), 1.01 (3H, s), 0.95 (3H, s), 0.91 (3H, s), 0.89 (6H, s), 0.85 (6H, s), 2.04 (6H, s, H-2′, H-2″); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.5 (CH_2, C-1), 23.5 (CH_2, C-2), 80.5 (CH, C-3), 37.8 (C, C-4), 55.8 (CH, C-5), 18.1 (CH_2, C-6), 34.5 (CH_2, C-7), 39.7 (C, C-8), 49.9 (CH, C-9), 37.0 (C, C-10), 28.2 (CH_2, C-11), 76.5 (C, C-12), 44.8 (CH, C-13), 52.6 (C, C-14), 31.5 (CH_2, C-15), 27.2 (CH_2, C-16), 52.7 (CH, C-17), 16.2 (CH_3, C-18), 15.5 (CH_3, C-19), 73.7 (C, C-20), 26.3 (CH_3, C-21), 36.4 (CH_2, C-22), 21.3 (CH_2, C-23), 40.0 (CH_2, C-24), 28.1 (CH, C-25), 22.7 (CH_3, C-26), 22.7 (CH_3, C-27), 27.9 (CH_3, C-28), 16.4 (CH_3, C-29), 17.3 (CH_3, C-30), 170.8 (C, C-1′), 21.5 (CH_3, C-2′), 170.0 (C, C-1″), 21.2 (CH_3, C-2″); HRMS (ESI^+) m/z calcd for $C_{34}H_{58}O_5Na$ 569.4176, found 569.4189 ($M + Na^+$).

20*S*-20,21-ene-24,25-dihydro-protopanaxadiol (42) White powder, 16% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (1H, dd, $J = 11.2$, 5.0 Hz, H-3), 3.59 (1H, td, $J = 10.3$, 5.2 Hz, H-12), 5.01 (1H, br s, H-21a), 4.77 (1H, br s, H-21b), 1.18 (3H, s), 0.99 (3H, s), 0.98 (3H, s), 0.88 (12H, overlap), 0.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0 (CH_2, C-1), 27.4 (CH_2, C-2), 78.8 (CH, C-3), 40.1 (C, C-4), 55.9 (CH, C-5), 18.3 (CH_2, C-6), 35.0 (CH_2, C-7), 38.9 (C, C-8), 50.4 (CH, C-9), 37.2 (C, C-10), 30.9 (CH_2, C-11), 73.3 (C, C-12), 48.1 (CH, C-13), 50.8 (C, C-14), 32.3 (CH_2, C-15), 26.0 (CH_2, C-16), 50.9 (CH, C-17), 16.2 (CH_3, C-18), 15.7 (CH_3, C-19), 156.2 (C, C-20), 109.0 (CH_2, C-21), 32.9 (CH_2, C-22), 29.1 (CH_2, C-23), 39.0 (CH_2, C-24), 28.0 (CH, C-25), 22.7 (CH_3, C-26), 22.6 (CH_3, C-27), 28.0 (CH_3, C-28), 15.4 (CH_3, C-29), 16.7 (CH_3, C-30); HRMS (ESI^+) m/z calcd for $C_{30}H_{53}O_2$ 445.4040, found 445.4037 ($M + H^+$).

20*S*-*E*-20,22-ene-24,25-dihydro-protopanaxadiol (43) White powder, 43% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (1H, dd, $J = 11.3$, 5.0 Hz, H-3), 3.74 (1H, td, $J = 10.6$, 5.2 Hz, H-12), 1.64 (3H, s, H-21), 5.42 (1H, t, $J = 7.1$ Hz, H-22), 1.02 (3H, s), 0.98 (3H, s), 0.89 (3H, s), 0.88 (9H, overlap), 0.86 (3H, s), 0.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.6 (CH_2, C-1), 27.4 (CH_2, C-2), 78.8 (CH, C-3), 39.0 (C, C-4), 55.9 (CH, C-5), 18.3 (CH_2, C-6), 35.0 (CH_2, C-7), 40.1 (C, C-8), 50.1 (CH, C-9), 37.2 (C, C-10), 30.4 (CH_2, C-11), 73.4 (C, C-12), 50.3 (CH, C-13), 50.5 (C, C-14), 32.5 (CH_2, C-15), 27.3 (CH_2, C-16), 50.2 (CH, C-17), 16.2 (CH_3, C-18), 15.7 (CH_3, C-19), 140.3 (C, C-20), 12.4 (CH_3, C-21), 126.4 (CH, C-22), 25.8 (CH_2, C-23), 29.0 (CH_2, C-24), 27.7 (CH, C-25), 22.6 (CH_3, C-26), 22.4 (CH_3, C-27), 28.0 (CH_3, C-28), 15.4 (CH_3, C-29), 16.8 (CH_3, C-30); HRMS (ESI^+) m/z calcd for $C_{30}H_{53}O_2$ 445.4040, found 445.4031 ($M + H^+$).

20-oxo-protopanaxadiol (44) To a stirred solution of compound **43** (26.6 mg, 0.06 mmol) in 2.0 mL of methanol-water (3:2) was added $NaIO_4$ (29.7 mg, 0.14 mmol) and OsO_4 (35 µL, 2% aqueous solution, 0.002 mmol) at ambient temperature. After stirred for 12 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered. After removal of the solvent under *vacuum*, the residue was purified by column chromatography on silica gel (acetone-petroleum ether, 10:90) to give compound **44** (61% yield) as a white powder, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (1H, dd, $J = 11.4$, 5.0 Hz, H-3), 3.48 (1H, td, $J = 10.7$, 5.1 Hz, H-12), 2.86 (1H, td, $J = 11.1$, 5.6 Hz, H-17), 2.23 (3H, s, H-21), 1.02

(3H, s), 0.98 (3H, s), 0.89 (3H, s), 0.88 (3H, s), 0.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0 (CH_2, C-1), 27.4 (CH_2, C-2), 78.8 (CH, C-3), 38.9 (C, C-4), 55.9 (CH, C-5), 18.2 (CH_2, C-6), 35.1 (CH_2, C-7), 39.8 (C, C-8), 50.6 (CH, C-9), 37.2 (C, C-10), 31.9 (CH_2, C-11), 71.7 (C, C-12), 50.2 (CH, C-13), 51.2 (C, C-14), 32.5 (CH_2, C-15), 26.8 (CH_2, C-16), 53.2 (CH, C-17), 16.3 (CH_3, C-18), 15.7 (CH_3, C-19), 214.7 (C, C-20), 29.4 (CH_3, C-21), 28.0 (CH_3, C-28), 15.4 (CH_3, C-29), 17.0 (CH_3, C-30); HRMS (ESI^+) m/z calcd for C_{24} $H_{40}O_3Na$ 399.2870, found 399.2832 ($M + Na^+$).

Biology

In vitro inhibition activity of α-glucosidase

The α-glucosidase inhibition activity was investigated by a spectrophotometric method as previous researches [12, 14–16, 18]. Acarbose (Bayer Healthcare Co Ltd, Beijing, China) was utilized as a positive control and was dissolved in phosphate buffer (PB, 0.1 mM, pH = 6.8). Test samples dissolved in methanol-PB (1:1, *v/v*, 20 µL) and *p*-Nitrophenyl-α-D-glucopyranoside (20 µL, 5.0 mM, p-NPG) dissolved in PB (in triplicate) were added to a 96-well plate and incubated at 37 °C for 5 min. Then α-glucosidase dissolved in PB (2.0 U/mL, 20 µL, Shanghai yuanye Bio-Technology Co Ltd, China) was added to each well as a substrate. After incubation for 15 min at 37 °C, the reaction was terminated with Na_2CO_3 solution (40 µL, 0.5 mM). Another preincubation for 5 min, the absorbance was measured at 405 nm via a Bio-Rad 680 microplate reader (Hercules, CA, USA). The system using PB replace test compounds was used as control. The mixtures' reaction without α-glucosidase was used as blank.

The α-glucosidase inhibitory rate $\% = [(\Delta OD_{control} - \Delta OD_{control\ blank}) - (\Delta OD_{sample} - \Delta OD_{sample\ blank})]/(\Delta OD_{control} - \Delta OD_{control\ blank})$. IC_{50} values were tested and calculated through nonlinear regression using Graphpad prism 8 software, which concentration of sample resulting in 50% inhibition.

In vitro inhibition activity of PTP1B

The PTP1B inhibition assay was investigated by the method as previous reports [14, 16, 18]. Working buffer containing MOPS (34.5 mM), DTT (1.9 mM), EDTA·4Na (0.67 mM), BSA (2.0 mg/mL), and NaCl (2.1 mM) in deionized water was prepared before the assay. Suramin sodium was utilized as a positive control dissolved in DMSO. Working buffer (70 µL), test samples dissolved in DMSO (10 µL) and PTP1B dissolved in working buffer (10 µL, 4.9 mg/L) were added to a 96-well plate and incubated at 37 °C for 15 min. Then the substrate in working buffer (10 µL, 100 mM, *p*-NPP) was added to each well. After incubation for 30 min, the reaction was stopped by adding 100 µL of Na_2CO_3 solution (0.1 mM). The absorbance was measured at 405 nm via a Bio-Rad 680 microplate reader (Hercules, CA, USA). The system using DMSO replace test compounds was used as control. The mixtures' reaction without PTP1B was used as blank. The PTP1B inhibitory rate and IC_{50} values of compounds were calculated using the same method as described above.

Enzyme kinetic studies of compounds 26 and 42 for α-glucosidase and PTP1B

The enzyme kinetics of α-glucosidase and PTP1B inhibition for compounds **26** and **42** were investigated according to experiments as described above. For α-glucosidase, enzymatic reactions at four different tested concentrations of compound **26** (0, 440, 470, and 500 µM) were evaluated by monitoring the effects of three different substrate concentrations (5.0, 2.5, and 1.0 mM). And for PTP1B, the inhibitory modes of compounds **26** and **42** were measured using three different concentrations of p-NPP (25, 50, 100 mM), and four different concentrations of tested compounds (compound **26**: 0, 240, 270, 300 µM; compound **42**: 0, 100, 200, 400 µM) to obtain Lineweaver −Burk double reciprocal plots. The inhibition constants (K_i) were calculated by the *x*-axis value of intersection of Dixon plot.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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