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Papyriferic acid derivatives as reversal agents of multidrug resistance in cancer cells

Juan Xiong [a], Masatoshi Taniguchi [a], Yoshiki Kashiwada [a,*], Michiko Sekiya [b], Takashi Yamagishi [c], Yoshihisa Takaishi [a]

[a] Graduate School of Pharmaceutical Sciences, University of Tokushima, Tokushima 770-8505, Japan
[b] Faculty of Pharmaceutical Sciences, Niigata University of Pharmacy and Applied Life Sciences, Niigata 956-8603, Japan
[c] Kitami Institute of Technology, Kitami, Hokkaido 090-8507, Japan

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ABSTRACT

Forty-one derivatives of papyriferic acid were prepared based on our previous finding that methyl papyriferate (**3**) showed potent reversing effect on cytotoxicity of colchicine against multidrug resistance (MDR) human cancer cells (KB-C2), and evaluated for their cytotoxicity and effect on reversing P-gp-mediated MDR against KB-C2 cells. 3-*O*-(Morpholino-β-oxopropanoyl)-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (**37**) significantly increased the sensitivity of colchicine against KB-C2 cells by 185-fold at 5 μg/mL (7.4 μM), and the cytotoxicity of colchicine was recovered to nearly that of sensitive (KB) cells. The other several new amide derivatives also exhibited potent reversal activity comparable to or more potent than methyl papyriferate and verapamil.

1. Introduction

Multidrug resistance (MDR) is one of the major impediments to effective cancer chemotherapy. A primary mechanism of MDR is due to the overexpression of ATP-binding cassette (ABC) transporters, which efflux a broad class of anticancer drugs, remarkably decreasing cellular drug accumulation.[1] So far, at least 12 ABC transporters from four ABC subfamilies have been identified to play important roles in the drug resistance of cancer cells.[2] Among them, P-glycoprotein (P-gp, also known as ABCB1 or MDR1), a member of the ABCB subfamily, is the most crucial and well-studied ABC transporter.[3–6] Many structurally unrelated anticancer drugs used clinically, such as vinca alkaloids, anthracyclines, epipodophyllotoxins, and taxanes, are known to be P-gp substrates.[7,8]

P-gp-mediated drug transport could be inhibited or altered by a wide range of agents (efflux blockers, chemosensitizers, MDR-reversal agents, MDR-modulators, or MDR-inhibitors).[2,9,10] Verapamil, the calcium channel blocker, was the first discovered P-gp modulator.[11,12] Since then, various reversal agents were brought to light, including the first generation inhibitors (e.g., amiodarone, cyclosporine, quinidine, nifedipine), the second generation inhibitors (e.g., PSC-833, dexverapamil) and the third generation modulators (e.g., VX-710, LY335979, XR-9576).[13] However, these compounds were ineffective or toxic at the doses required to attenuate P-gp function,[13] or induced unfavourable pharmacokinetic interactions,[14,15] resulting in failure in their clinical trials. Although progress in the development of ideal P-gp inhibitors has been slow, it is believed that this approach is still realistic and promising for overcoming MDR.

In our previous research for plant-derived MDR-reversal agents, methyl papyriferate (**3**), isolated from the floral spikes of *Betula platyphylla* var. *japonica*, demonstrated potent reversing effect on the cytotoxicity of colchicine against MDR human cancer cells (KB-C2) at 8.1 μM, which was comparable to 5 μM verapamil.[16] In contrast, papyriferic acid (**1**) did not enhance the cytotoxicity of colchicine against KB-C2 cells. These findings prompt our modification of papyriferic acid as new MDR-reversal agents. This paper describes the preparation of forty-one derivatives of papyriferic acid, as well as its related triterpene, and evaluation of their cytotoxicities and MDR-reversing effect against KB-C2 cells.

2. Results and discussion

2.1. Chemistry

Although compounds **1** and **2** (3-*O*-malonyl-epiocotillol-II), both of which containing a 3-*O*-carboxyacetyl group, did not show MDR-reversing effect, a great enhanced MDR-reversal effect was observed in their methyl esters (compounds **3** and **4**, respectively) in our previous research (Fig. 1). These results suggested that the ester group at C-3 position of methyl papyriferate played an

* Corresponding author. Tel./fax: +81 88 633 7276.
E-mail address: kasiwada@ph.tokukshima-u.ac.jp (Y. Kashiwada).

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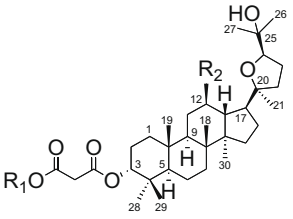


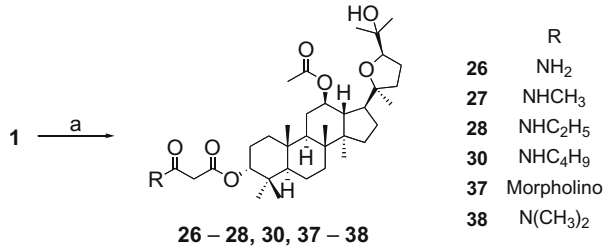
papyriferic acid (**1**) R_1=H, R_2=OAc
3-*O*-malonyl-epiocotillol-II (**2**) R_1=H, R_2=H
methyl papyriferate (**3**) R_1=CH_3, R_2=OAc
3-*O*-methylmalonyl-epiocotillol-II (**4**) R_1=CH_3, R_2=H

Figure 1. Structure of papyriferic acid and its analogues.

important role for MDR-reversing effect. Based on this finding, various alkyl substituents were introduced to the carboxylic acid group of the malonyl moiety in compounds **1** and **2**. In addition, the alkylcarbamoyl derivatives of papyriferic acid were also prepared, and evaluated their cytotoxicity as well as MDR-reversing effects.

Compounds **5**–**14** and **17**–**23** were prepared by treatment of compounds **1** and **2** with appropriate alkyl bromides in the presence of K_2CO_3. In contrast, compounds **15**,**16, 24** and **25** were synthesized by reaction of acyl chloride of **1** or **2** with appropriate alcohols in the presence of NEt_3 (Scheme 1).

The amide derivatives of papyriferic acid were synthesized as outlined in Schemes 2 and 3. Thus, papyriferic acid was treated with oxalyl dichloride, and then reacted with appropriate amines yielding the desired derivatives. However, compounds **39**–**45** were also produced unexpectedly as a by-product in each case, resulting in low yield of the desired amide derivatives. In contrast, reaction of papyriferic acid with appropriate amines using DCC and HOBt as catalysts afforded compounds **26**–**28**, **30**, **37**, and **38** with satisfactory yields.



	R
26	NH_2
27	$NHCH_3$
28	NHC_2H_5
30	NHC_4H_9
37	Morpholino
38	$N(CH_3)_2$

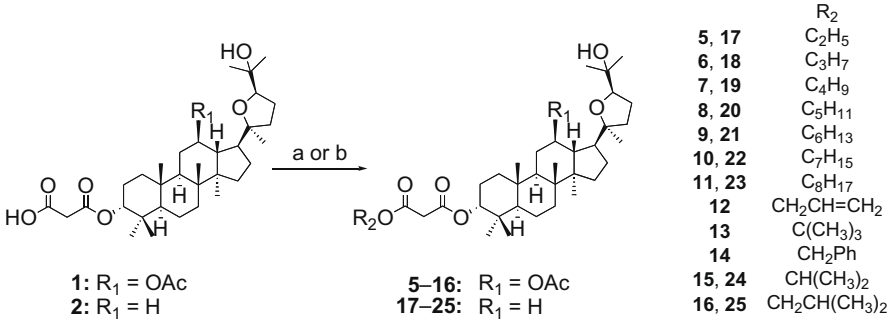
Scheme 3. Reagents and conditions: (a) DCC, HOBt, CH_2Cl_2, rt.

The structures of all the compounds are confirmed by ^{1}H NMR, ^{13}C NMR, 2D NMR (HMBC&HSQC) and MS spectroscopic analyses.

2.2. Biological evaluation

The cytotoxic activities of compounds **3**–**45** against human epidermoid nasopharyngeal carcinoma cell lines, KB (drug-sensitive cells) and KB-C2 (colchicine-resistant KB cells), were evaluated. Results are summarized in Table 1.

All the tested compounds showed little or no antiproliferative effects against KB and KB-C2 cell lines (IC_{50} values greater than 25 μM). No remarkable differences were found in the cytotoxic activities between the sensitive and resistant cell lines, except for compounds **6**–**8**, **13**, **14**, **16**, and **32**. However, some of them exhibited enhanced cytotoxicity against KB-C2 cells in the presence of 2.5 μM colchicine, which had no effect on the growth of KB-C2 cells. This suggested that these analogues might show some MDR-reversing effects.



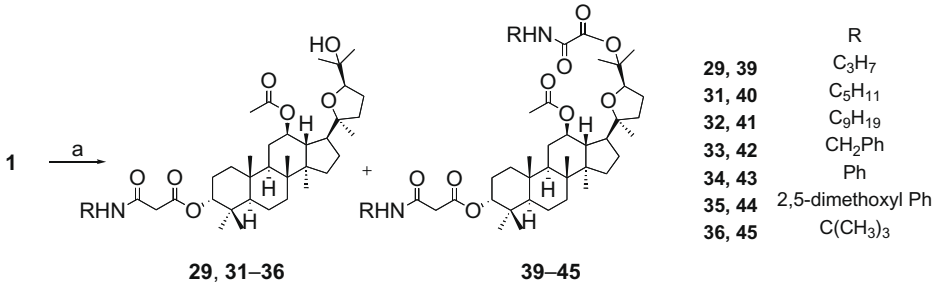
1: R_1 = OAc
2: R_1 = H

5–16: R_1 = OAc
17–25: R_1 = H

	R_2
5, **17**	C_2H_5
6, **18**	C_3H_7
7, **19**	C_4H_9
8, **20**	C_5H_{11}
9, **21**	C_6H_{13}
10, **22**	C_7H_{15}
11, **23**	C_8H_{17}
12	$CH_2CH{=}CH_2$
13	$C(CH_3)_3$
14	CH_2Ph
15, **24**	$CH(CH_3)_2$
16, **25**	$CH_2CH(CH_3)_2$

Scheme 1

Scheme 1. Reagents and conditions: (a) RBr, K_2CO_3, acetone, rt; (b) $(COCl)_2$, CH_2Cl_2, rt; then ROH, NEt_3, CH_2Cl_2, rt.



29, **31**–**36** **39**–**45**

	R
29, 39	C_3H_7
31, 40	C_5H_{11}
32, 41	C_9H_{19}
33, 42	CH_2Ph
34, 43	Ph
35, 44	2,5-dimethoxyl Ph
36, 45	$C(CH_3)_3$

Scheme 2. Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, reflux; (b) then RNH_2, CH_2Cl_2 or benzene, reflux.

Table 1
Cytotoxicity (IC_{50}[a] in μM) of compounds **3–45** against KB and KB-C2 cell lines (with or without colchicine) in vitro

Compound	KB	KB-C2	KB-C2 (+2.5 μM colchicine)	Compound	KB	KB-C2	KB-C2 (+2.5 μM colchicine)
3	26.7 ± 2.1	32.1 ± 0.80	2.5 ± 0.09	26	39.3 ± 1.8	43.7 ± 0.30	3.8 ± 0.38
5	39.1 ± 1.8	64.3 ± 2.7	23.1 ± 0.28	27	40.9 ± 2.3	43.1 ± 0.80	1.9 ± 0.04
6	27.8 ± 1.2	67.8 ± 2.3	24.3 ± 0.53	28	39.7 ± 2.8	43.9 ± 0.67	1.9 ± 0.03
7	40.8 ± 1.5	>100	52.3 ± 1.8	29	46.1 ± 1.0	40.8 ± 0.68	5.6 ± 0.13
8	45.4 ± 2.8	>100	>100	30	24.9 ± 1.2	24.4 ± 0.42	4.8 ± 0.07
9	70.7 ± 5.7	>100	>100	31	38.3 ± 0.82	38.3 ± 0.76	12.2 ± 0.49
10	>100	>100	>100	32	42.8 ± 2.4	>100	>100
11	>100	>100	>100	33	31.9 ± 1.1	33.2 ± 0.77	7.0 ± 0.43
12	34.8 ± 2.2	48.3 ± 0.89	14.9 ± 0.40	34	28.3 ± 1.7	26.2 ± 0.64	4.9 ± 0.01
13	31.5 ± 1.5	>100	51.4 ± 1.0	35	>100	>100	26.3 ± 0.51
14	43.7 ± 2.7	>100	>100	36	40.5 ± 0.72	47.9 ± 1.4	11.5 ± 0.13
15	74.6 ± 2.7	>100	41.4 ± 1.2	37	30.8 ± 0.57	27.5 ± 0.48	1.3 ± 0.07
16	33.3 ± 2.1	>100	44.1 ± 0.79	38	25.2 ± 1.3	28.0 ± 0.56	1.2 ± 0.11
4	45.4 ± 2.3	56.6 ± 1.8	7.5 ± 0.64	39	24.8 ± 0.75	26.6 ± 1.0	5.4 ± 0.12
17	>100	>100	41.9 ± 1.0	40	>100	>100	>100
18	60.3 ± 2.6	>100	66.1 ± 0.98	41	>100	>100	>100
19	>100	>100	>100	42	>100	>100	>100
20	>100	>100	>100	43	>100	>100	>100
21	>100	>100	>100	44	>100	>100	>100
22	>100	>100	>100	45	>100	>100	29.2 ± 1.3
23	>100	>100	>100	Daunorubicin	0.64 ± 0.03	16.2 ± 0.98	18.3 ± 0.74
24	>100	>100	96.5 ± 0.98	Colchicine	0.013 ± 0.0001	10.9 ± 0.60	—
25	97.0 ± 5.8	>100	>100	Verapamil	ND	>100	3.0 ± 0.11

[a] Data are mean ± SE from three or four experiments.

Among the ester derivatives (**3**, **5**–**16**), methyl papyriferate (**3**) showed the most enhanced cytotoxicity in the presence of 2.5 μM colchicine with an IC_{50} value of 2.5 μM, which was 13-fold reversal effect as compared with its cytotoxicity (IC_{50} 32.1 μM) against KB-C2. The reversing activity was reduced according to the chain length, and the reversing activity was totally lost when the alkyl group with the chain length of more than five or benzyl group was introduced (**8**–**11** and **14**). This tendency was also observed in the 3-epiocotillol derivatives (**4**, **17**–**25**), although their potency were less than those found in alkyl papyriferate. This result suggested that the length of alkyl chain as well as the acetoxy group at C-12 plays an important role for the reversing activity.

In the case of the amide derivatives, compounds **27**, **28**, **37**, and **38** demonstrated the significantly enhanced cytotoxicity in the presence of 2.5 μM colchicine with IC_{50} values ranging from 1.2 μM to 1.9 μM, which were more potent than those of verapamil (IC_{50} 3.1 μM) and methyl papyriferate (IC_{50} 2.5 μM). In addition, their reversal effects, which were over 20-fold in each case, as compared with their cytotoxicities against KB-C2 cells, were more potent than that of methyl papyriferate. The other amide derivatives, except for **32**, also showed moderate MDR-reversing activities; their reversal effects ranged from 11- to 3-fold. In overall, the reversing activities of the amide derivatives were more potent than the corresponding ester derivatives. In contrast, the 25-*O*-alkylcarbamoyl formate of the amide derivatives, except for **39** and **45**, did not show cytotoxicity whether colchicine was present or absent, although the corresponding amide derivatives showed weak reversing effect. Compounds **39** and **45** also showed less potent reversing activities than those of the corresponding amide derivatives. These data implied that the free hydroxyl group at C-25 is also important for the reversing activity.

Compounds **3**, **4**, **26**–**28**, and **36**–**39** were selected to determine the recovery of the cytotoxicity of colchicine against KB-C2 cells (Table 2). Compound **37** demonstrated the most potent reversal effect of colchicine resistance of KB-C2 cells. Thus, 5 μg/mL of **37**

Table 2
MDR-reversing effects on the cytotoxicity (IC_{50}[a] in μM) of colchicine against KB-C2 cells and physico-chemical properties[b] of indicated compounds

Compound	IC_{50} value of colchicine (μM)			No. H		MW	MV	TPSA	Log *P* (ACD)
	0	1 μg/mL	5 μg/mL	Acceptors	Donors				
3		7.2 ± 0.18 (1.5)[c]	0.21 ± 0.009 (51.6)	8	1	619	610	108.4	7.3
4		10.0 ± 0.29 (1.1)	0.74 ± 0.024 (14.8)	6	1	561	566	82.1	8.3
26		5.3 ± 0.19 (2.1)	0.22 ± 0.006 (49.3)	8	2	604	596	125.1	6.5
27		2.3 ± 0.12 (4.7)	0.15 ± 0.003 (74.4)	8	2	618	613	111.2	6.7
28		4.2 ± 0.026 (2.6)	0.20 ± 0.007 (53.9)	8	2	632	630	111.2	7.2
36		9.6 ± 0.19 (1.1)	1.1 ± 0.088 (9.8)	8	2	660	663	111.2	7.9
37		0.63 ± 0.065 (17.4)	0.059 ± 0.003 (185.4)	9	1	674	662	111.6	7.4
38		4.5 ± 0.24 (2.4)	0.12 ± 0.001 (87.5)	8	1	632	630	102.4	7.0
39		9.3 ± 0.21 (1.2)	0.16 ± 0.004 (68.8)	11	2	759	748	146.3	8.5
Colchicine	10.9 ± 0.60 (1.0)								
Verapamil[d]									
1 μM	6.4 ± 0.11 (1.7)								
2 μM	2.8 ± 0.12 (3.9)								
5 μM	0.37 ± 0.007 (29.9)								

[a] Data are mean ± SE from three or four experiments.
[b] Physico-chemical parameters were calculated using ACD softwares.
[c] Fold-reversion, was calculated by dividing the corresponding IC_{50} value with the IC_{50} value of colchicine (10.9 μM).
[d] Positive control.

reversed the cytotoxicity of colchicine against KB-C2 cells from the IC_{50} value of 10.9 to 0.059 μM, in which the sensitivity of colchicine against KB-C2 was increased by 185-fold. It is worthy to note that compound **37** reversed the resistance of colchicine against KB-C2 cells to almost sensitive cells (KB cells) level, since the IC_{50} value of colchicine against KB cells was 0.013 μM. The 17-fold recovery of colchicine resistance was also observed at 1 μg/mL of **37**. By contrast, 5 μg/mL of compounds **26**–**28**, **38**, and **39** increased sensitivity of colchicine by ranging from 87- to 49-fold, which were comparable to or slightly more potent than methyl papyriferate (5 μg/mL) and verapamil (5 μM), while compounds **4** and **36** only showed moderate reversal effect even at highest concentration.

Several important physico-chemical properties were calculated to consider structure–activity relationships (SARs) in our derivatives. All the compounds shown in Table 2 are lipophilic with the octanol/water partition coefficient (log *P*) in the range of 6.5–8.5, strong H-bond acceptors (6–11 H-bond acceptors), and possess a molecular weight in the range of 560–759. Their physico-chemical properties are in good agreement with those previously reported MDR-reversing agents.[13,17–20] The log *P* value was shown to be increased according to the chain length of the alkyl group in both ester and amide derivatives (data not shown), which was well correlated with the potency of their reversing activity. In contrast, the acetoxy group at C-12 in papyriferic acid was found to be functionalized as two hydrogen acceptors by comparison of the properties between **3** and **4**. The lack of this group led to increasing the log *P* value, which was also correlated with the decrease of the reversing activity. However, the other correlations between the MDR-reversing effect and calculated physico-chemical properties were complex and multifunctional similar to those observed in other SAR studies of P-gp modulators.[19–21]

3. Conclusions

Based on our previous finding that methyl papyriferate (**3**) showed potent reversing effect on cytotoxicity of colchicine against MDR human cancer cells (KB-C2), forty-one analogues of papyriferic acid were prepared and evaluated their cytotoxicity and MDR-reversing effect against cancer cell lines. All the investigated compounds showed little or no antiproliferative effect, and the cytotoxicity of several analogues was enhanced in the presence of non-toxic concentration of colchicine. Among the alkyl papyriferate derivatives, methyl papyriferate (**3**) showed the most enhanced cytotoxicity in the presence of 2.5 μM colchicine, and the enhancement of the cytotoxicity was decreased according to the chain length of the alkyl group. Removal of 12-acetoxy group of the alkyl papyriferate derivatives reduced their reversal effect. The amide derivatives of papyriferic acid demonstrated more potent activity than the alkyl papyriferate. However, the 25-*O*-alkylcarbamoyl formate of the amide derivatives were less potent. Furthermore, the recovery of the cytotoxicity of colchicine against KB-C2 cells by compounds **3**, **4**, **26**–**28**, and **36**–**39** were assessed. Compound **37** significantly reversed the resistance of colchicine against KB-C2 cells at 5 μg/mL. It increased the sensitivity of colchicine against KB-C2 cells by 185-fold, and thus the cytotoxicity of colchicine was recovered to nearly that of sensitive cells. These analogues appear to be potential candidates of MDR-reversing agents in cancer cells and, studies of the effect of these analogues on P-gp functions are in progress.

4. Experimental section

4.1. General procedures

Unless otherwise indicated, all reagents were purchased from commercial suppliers and are used without further purification. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. NMR (400 MHz for ^{1}H, 100 MHz for ^{13}C, using TMS as internal standard) was recorded on a Bruker AVANCE 400 spectrometer. HRESIMS was obtained on a Waters LCT Premier. Column chromatography was performed with silica gel 60 N (63–210 nm, Merck); Preparative HPLC was carried out on Mightysil Si 60 (250 × 20 mm id).

4.2. Chemical preparation

Papyriferic acid (3-*O*-malonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane **1**) and **12-deacetoxy papyriferic acid** (3-*O*-malonyl-epiocotillol-II **2**).

These triterpenes used in this work were separated from the floral spikes of *B. platyphylla* var. *japonica* by reported procedures.[16] The ^{1}H and ^{13}C spectral data correspond with that previously reported.[22,23]

4.2.1. General procedure for preparation of ester analogues (5–16, 17–25)

Method A: A solution of **1** or **2** (50–60 mg, 1 equiv), an appropriate bromide (1.1–5 equiv, but 30 equiv for **13**) and K_2CO_3 (2–3 equiv, but 16 equiv for **13**) in anhydrous acetone (3 mL) was refluxed at 60 °C overnight with stirring. After removal of the inorganic salts by filtration, the filtrate was concentrated under reduced pressure to dryness. The oily residue was chromatographed over a silica gel column (hexane/ethyl acetate 10:1) and further purified by semi-preparative HPLC (hexane/acetone/2-propanol 4:1:0.01) to afford the desired compounds.

Method B: To a solution of **1** or **2** (50–60 mg, 1 equiv) in CH_2Cl_2 (2 mL), oxalyl dichloride (2.0 M solution in CH_2Cl_2, 2.5 equiv) was added with stirring. The mixture was stirred at room temperature for 3 h, and then CH_2Cl_2 was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (3 mL) and then isopropanol or isobutanol (3 equiv) and NEt_3 (2.5 equiv) were added. The reaction mixture was left standing overnight at room temperature. The reaction mixture was diluted with $CHCl_3$ and washed three times with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give an oily residue. The residue was subjected to silica gel column chromatography and semi-preparative HPLC to yield pure product.

4.2.1.1. 3-*O*-Ethylmalonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (5). Yield 29.1% (starting with 50 mg of **1** by method A); colorless oil; $[\alpha]_D^{29}$ −18.5 (*c* 0.83, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.96 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.24 (3H, s, CH_3-26), 1.27 (3H, t, *J* = 6.8, CH_3-Et), 2.01 (3H, s, CH_3-Ac), 3.40 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, *J* = 6.8, 7.2 Hz, H-24), 4.21 (2H, q, *J* = 6.8, CH_2-Et), 4.68 (1H, br s, H-3), 4.83 (1H, dt, *J* = 5.2, 10.4 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2(CH_3-Et), 15.5 (C-18), 15.8 (C-19), 17.6 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.6 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.6 (C-26), 27.9 (C-28), 28.2 (C-11),31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.1 (malonyl –CH_2–), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.7 (C-5), 52.3 (C-14), 61.5 (COO-CH_2), 71.0 (C-25), 75.5 (C-12), 79.7 (C-3), 83.3 (C-24), 85.7 (C-20), 166.1 (malonyl –CO–), 169.7 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) *m*/*z* 655.4165 $[M+Na]^+$ (calcd for $C_{37}H_{60}O_8Na$, 655.4186).

4.2.1.2. 3-*O*-Propylmalonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*, 24*R*)-epoxydammarane (6). Yield 65.1% (starting with 55 mg of **1** by method A); colorless oil; $[\alpha]_D^{29}$ −16.0 (*c* 3.53, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19),

0.88 (3H, s, CH_3-29), 0.96 (3H, s, CH_3-30), 0.96 (3H, t, J = 6.8, CH_3-3′), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.18 (3H, s, CH_3-26), 1.67 (2H, hex, J = 6.8, CH_2-2′), 2.00 (3H, s, CH_3-Ac), 3.40 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 6.4, 6.8 Hz, H-24), 4.21 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.4 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.3 (C-3′), 15.5 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.9 (Ac, –CH_3), 21.9 (C-2′), 22.2 (C-21), 22.6 (C-2), 24.2 (C-27), 26.1 (C-23), 26.7 (C-16), 27.5 (C-26), 27.8 (C-28), 28.2 (C-11),31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.0 (malonyl –CH_2–), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.2 (C-14), 67.0 (C-1′), 71.0 (C-25), 75.4 (C-12), 79.6 (C-3), 83.3 (C-24), 85.7 (C-20), 166.1 (malonyl –CO–), 166.7 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 669.4333 $[M+Na]^+$ (calcd for $C_{38}H_{62}O_8Na$, 669.4342).

4.2.1.3. 3-*O*-Butylmalonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (7). Yield 40.7% (starting with 54 mg of **1** by method A); colorless oil; $[\alpha]_D^{29}$ −16.2 (*c* 2.20, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.93 (3H, t, J = 7.2, CH_3-4′), 0.96 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 1.40 (2H, m, CH_2-3′), 1.63 (2H, m, CH_2-2′), 2.00 (3H, s, CH_3-Ac), 3.40 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 6.8, 7.2 Hz, H-24), 4.16 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.8 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6 (C-4′), 15.5 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 19.0 (C-3′), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.6 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.8 (C-28), 28.2 (C-11), 30.5 (C-2′), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.0 (malonyl –CH_2–), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.7 (C-5), 52.3 (C-14), 65.3 (C-1′), 71.0 (C-25), 75.4 (C-12), 79.6 (C-3), 83.3 (C-24), 85.7 (C-20), 166.1 (malonyl –CO–), 166.7 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 683.4485 $[M+Na]^+$ (calcd for $C_{39}H_{64}O_8Na$, 683.4499).

4.2.1.4. 3-*O*-Pentylmalonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (8). Yield 27.7% (starting with 55 mg of **1** by method A); colorless oil; $[\alpha]_D^{28}$ −14.6 (*c* 5.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.88 (3H, t, J = 6.8, CH_3-5′), 0.96 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.19 (3H, s, CH_3-26), 1.33 (2H, m, CH_2-4′), 1.64 (4H, m, CH_2-3′, 2′), 2.00 (3H, s, CH_3-Ac), 3.40 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 6.0, 6.4 Hz, H-24), 4.14 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.8 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (C-5′), 15.6 (C-18), 15.9 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.3 (C-4′), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.6 (C-26), 27.9 (C-28), 28.3 (C-11), 27.9 (C-3′), 28.2 (C-2′), 31.2 (C-15), 34.0 (C-1), 34.4 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.0 (malonyl –CH_2–), 46.3 (C-13), 49.6 (C-9), 50.5 (C-17), 50.7 (C-5), 52.3 (C-14), 69.2 (C-1′), 71.0 (C-25), 75.5 (C-12), 79.7 (C-3), 83.4 (C-24), 85.8 (C-20), 166.1 (malonyl –CO–), 166.8 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 697.4629 $[M+Na]^+$ (calcd for $C_{40}H_{66}O_8Na$, 697.4655).

4.2.1.5. 3-*O*-Hextylmalonyl-12β-acetoxy-3α,25-dihydroxy-(17*S*,20*S*,24*R*)-epoxydammarane (9). Yield 51.2% (starting with 55 mg of **1** by method A); colorless oil; $[\alpha]_D^{28}$ −15.1 (*c* 3.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.88 (3H, t, J = 6.8, CH_3-6′), 0.96 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.18 (3H, s, CH_3-26), 1.29 (4H, m, CH_2-4′, 5′), 1.65 (4H, m, CH_2-2′, 3′), 2.00 (3H, s, CH_3-Ac), 3.40 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 6.4, 6.8 Hz, H-24), 4.11 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.8 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (C-6′), 15.6 (C-18), 15.9 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.5 (C-5′), 22.7 (C-2), 24.2 (C-27), 25.5 (C-4′), 26.1 (C-23), 26.8 (C-16), 27.6 (C-26), 27.9 (C-28), 28.3 (C-11), 28.5 (C-3′), 31.3 (C-15), 31.4 (C-2′), 34.0 (C-1), 34.4 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.0 (malonyl –CH_2–), 46.3 (C-13), 49.6 (C-9), 50.5 (C-17), 50.7 (C-5), 52.3 (C-14), 65.7 (C-1′), 71.0 (C-25), 75.5 (C-12), 79.6 (C-3), 83.4 (C-24), 85.7 (C-20), 166.1 (malonyl –CO–), 166.8 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 711.4794 $[M+Na]^+$ (calcd for $C_{41}H_{68}O_8Na$, 711.4812).

4.2.1.6. 3-*O*-Heptylmalonyl-12β-acetoxy-3α,25-hydroxy-(20*S*,24*R*)-epoxydammarane (10). Yield 64.7% (starting with 59 mg of **1** by method A); colorless oil; $[\alpha]_D^{28}$ −17.3 (*c* 4.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.87 (3H, t, J = 6.8, CH_3-7′), 0.96 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.18 (3H, s, CH_3-26), 1.25–1.30 (6H, m, CH_2-4′, 5′, 6′), 1.64 (4H, m, CH_2-2′, 3′), 2.00 (3H, s, CH_3-Ac), 3.40 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 6.8, 7.2 Hz, H-24), 4.14 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.4 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (C-7′), 15.5 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.2 (C-21), 22.5 (C-6′), 22.6 (C-2), 24.2 (C-27), 25.7 (C-5′), 26.0 (C-23), 26.7 (C-16), 27.5 (C-26), 27.8 (C-28), 28.2 (C-11), 28.4 (C-4′), 28.8 (C-3′), 31.2 (C-15), 31.6 (C-2′), 34.0 (C-1), 34.4 (C-7), 36.7 (C-4), 37.0 (C-10), 38.8 (C-22), 39.7 (C-8), 42.0 (malonyl –CH_2–), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.2 (C-14), 65.6 (C-1′), 71.0 (C-25), 75.4 (C-12), 79.6 (C-3), 83.4 (C-24), 85.7 (C-20), 166.1 (malonyl –CO–), 166.7 (malonyl –CO–), 170.4 (Ac, –CO–). HRESIMS (positive) m/z 725.4953 $[M+Na]^+$ (calcd for $C_{42}H_{70}O_8Na$, 725.4968).

4.2.1.7. 3-*O*-Octylmalonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (11). Yield 65.1% (starting with 55 mg of **1** by method A); colorless oil; $[\alpha]_D^{28}$ −12.1 (*c* 4.09, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.87 (3H, t, J = 6.8, CH_3-8′), 0.96 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.18 (3H, s, CH_3-26), 1.27–1.30 (8H, m, CH_2-4′, 5′,6′,7′), 1.64 (4H, m, CH_2-2′, 3′), 2.00 (3H, s, CH_3-Ac), 3.40 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 6.8, 7.2 Hz, H-24), 4.14 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.8 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (C-8′), 15.5 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.6 (C-7′), 22.6 (C-2), 24.2 (C-27), 25.8 (C-6′), 26.1 (C-23), 26.7 (C-16), 27.5 (C-26), 27.8 (C-28), 28.2 (C-11), 28.5 (C-5′), 29.1 (C-3′, 4′), 31.2 (C-15), 31.7 (C-2′), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.0 (malonyl –CH_2–), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.2 (C-14), 65.7 (C-1′), 71.0 (C-25), 75.4 (C-12), 79.6 (C-3), 83.4 (C-24), 85.7 (C-20), 166.1 (malonyl –CO–), 166.7 (malonyl –CO–), 170.4 (Ac, –CO–). HRESIMS (positive) m/z 739.5125 $[M+Na]^+$ (calcd for $C_{43}H_{72}O_8Na$, 739.5125).

4.2.1.8. 3-*O*-Allylmalonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (12). Yield 85.0% (starting with 60 mg of **1** by method A); colorless oil; $[\alpha]_D^{28}$ −16.4 (*c* 4.65, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.96 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.18 (3H, s, CH_3-26), 2.01 (3H, s, CH_3-Ac), 3.44 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 7.6, 6.4 Hz, H-24), 4.65 (2H, d, J = 6.0, CH_2-1′), 4.68 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.8 Hz, H-12), 5.29 (1H, dd, J = 1.2, 10.4, CH_2-3′), 5.36 (1H, dd, J = 1.2, 15.2, CH_2-3′), 5.93 (1H, ddt,

J = 6.0, 10.4, 15.2, CH-2′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (C-18), 15.8 (C-19), 17.6 (C-30), 17.9 (C-6), 21.5 (C-29), 21.8 (Ac, –CH_3), 22.2 (C-21), 22.6 (C-2), 24.2 (C-27), 26.0 (C-23), 26.7 (C-16), 27.5 (C-26), 27.8 (C-28), 28.2 (C-11), 31.2 (C-15), 33.9 (C-1), 34.3 (C-7), 36.7 (C-4), 37.1 (C-10), 38.8 (C-22), 39.7 (C-8), 42.0 (malonyl –CH_2–), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.2 (C-14), 66.0 (C-1′), 71.0 (C-25), 75.4 (C-12), 79.7 (C-3), 83.3 (C-24), 85.7 (C-20), 118.9 (C-3′), 131.4 (C-2′), 165.9 (malonyl –CO–), 166.3 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 667.4175 [M+Na]$^+$ (calcd for $C_{38}H_{60}O_8Na$, 667.4186).

4.2.1.9. 3-*O*-tert-Butylmalonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (13).

Yield 22.3% (starting with 53 mg of **1** by method A); colorless oil; $[\alpha]_D^{28}$ −15.6 (c 0.98, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.95 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.18 (3H, s, CH_3-26), 1.49 (9H, s, $CH_3 \times 3$), 2.00 (3H, s, CH_3-Ac), 3.31 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 6.8, 7.2 Hz, H-24), 4.67 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.8 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.7 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.6 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.0 (C × 3-*t*Bu), 28.3 (C-11), 31.2 (C-15), 34.1 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.9 (C-22), 39.8 (C-8), 43.4 (malonyl –CH_2–), 46.3 (C-13), 49.6 (C-9), 50.5 (C-17), 50.6 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 79.5 (C-3), 83.4 (C-24), 82.0 (C-*t*Bu), 85.7 (C-20), 165.8 (malonyl –CO–), 166.5 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 683.4490 [M+Na]$^+$ (calcd for $C_{39}H_{64}O_8Na$, 683.4499).

4.2.1.10. 3-*O*-Benzylmalonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (14).

Yield 75.0% (starting with 38 mg of **1** by method A); colorless oil; $[\alpha]_D^{28}$ −10.9 (c 3.36, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.95 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.19 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 2.03 (3H, s, CH_3-Ac), 3.47 (2H, s, malonyl –CH_2–), 3.66 (1H, dd, J = 6.8, 7.6 Hz, H-24), 4.70 (1H, br s, H-3), 4.85 (1H, dt, J = 5.2, 10.4 Hz, H-12), 5.20 (2H, s, CH_2-Benzyl), 7.33-7.39 (5H, m, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.6 (C-26), 27.9 (C-28), 28.3 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.0 (malonyl –CH_2–), 46.3 (C-13), 49.6 (C-9), 50.5 (C-17), 50.7 (C-5), 52.3 (C-14), 67.2 (CH_2-Benzyl), 71.0 (C-25), 75.5 (C-12), 79.7 (C-3), 83.3 (C-24), 85.7 (C-20), 128.4 (×2, C2′,6′-Ph), 128.6 (×2, C3′,5′-Ph), 128.5 (C4′-Ph), 135.2 (C1′-Ph), 165.9 (malonyl –CO–), 166.5 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 717.4333 [M+Na]$^+$ (calcd for $C_{42}H_{64}O_8Na$, 717.4342).

4.2.1.11. 3-*O*-(2-Propyl)malonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (15).

Yield 13.6% (starting with 50 mg of **1** by method B); colorless oil; $[\alpha]_D^{28}$ −14.1 (c 0.64, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.96 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.18 (3H, s, CH_3-26), 1.27, 1.28 (each 3H, d, J = 6.4, $CH_3 \times$ 2-*i*Pr), 2.00 (3H, s, CH_3-Ac), 3.37 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 6.4, 6.8 Hz, H-24), 4.68 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.8 Hz, H-12), 5.06 (1H, sept, J = 6.4, CH-*i*Pr); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.9 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 21.8 $CH_3 \times$ 2-*i*Pr), 22.23 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.6 (C-26), 27.9 (C-28), 28.3 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.4 (malonyl –CH_2–), 46.3 (C-13), 49.6 (C-9), 50.5 (C-17), 50.7 (C-5), 52.3 (C-14), 69.2 (CH-*i*Pr), 71.0 (C-25), 75.4 (C-12), 79.7 (C-3), 83.4 (C-24), 85.8 (C-20), 166.2 (malonyl –CO–), 166.2 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 669.4319 [M+Na]$^+$ (calcd for $C_{38}H_{62}O_8Na$, 669.4342).

4.2.1.12. 3-*O*-iso-Butylmalonyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (16).

Yield 40.3% (starting with 50 mg of **1** by method A); colorless oil; $[\alpha]_D^{28}$ −16.5 (c 0.64, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.95 (3H, s, CH_3-30), 0.95 (6H, d, J = 7.2 Hz, $CH_3 \times$ 2-*i*Bu), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.18 (3H, s, CH_3-26), 1.91–2.00 (1H, m, CH-*i*Bu), 2.00 (3H, s, CH_3-Ac), 3.37 (2H, s, malonyl –CH_2–), 3.65 (1H, dd, J = 6.4, 6.8 Hz, H-24), 3.94 (2H, d, J = 6.4, CH_2-*i*Bu), 4.68 (1H, br s, H-3), 4.83 (1H, dt, J = 5.2, 10.8 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 19.0 ($CH_3 \times$ 2-*i*Bu), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.23 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.6 (C-26), 27.7 (CH-*i*Bu), 27.9 (C-28), 28.3 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.0 (malonyl –CH_2–), 46.3 (C-13), 49.6 (C-9), 50.5 (C-17), 50.7 (C-5), 52.3 (C-14), 71.0 (C-25), 71.5 (CH_2-*i*Bu), 75.5 (C-12), 79.7 (C-3), 83.4 (C-24), 85.7 (C-20), 166.1 (malonyl –CO–), 166.7 (malonyl –CO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 683.4502 [M+Na]$^+$ (calcd for $C_{39}H_{64}O_8Na$, 683.4499).

4.2.1.13. 3-*O*-Ethylmalonyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (17).

Yield 23.8% (starting with 49 mg of **2** by method A); colorless oil; $[\alpha]_D^{29}$ −3.1(c 1.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.85 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.89 (3H, s, CH_3-30), 0.95 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.12 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 1.29 (3H, t, J = 7.2, CH_3-Et), 3.39 (2H, s, malonyl –CH_2–), 3.72 (1H, t, J = 7.2 Hz, H-24), 4.21 (2H, q, J = 7.2, CH_2-Et), 4.67 (1H, t, J = 2.6, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2(CH_3-Et), 15.5 (C-18), 16.0 (C-19), 16.6 (C-30), 18.1 (C-6), 21.4 (C-11), 21.7 (C-29), 22.8 (C-2), 23.6 (C-21), 24.3 (C-27), 25.7 (C-16), 26.1 (C-23), 27.4 (C-12), 27.5 (C-26), 27.9 (C-28), 31.5 (C-15), 34.2 (C-1), 35.1 (C-7), 35.7 (C-22), 36.9 (C-4), 37.2 (C-10), 40.6 (C-8), 42.2 (malonyl –CH_2–), 42.9 (C-13), 49.5 (C-17), 50.1 (C-14), 50.6 (C-9), 50.8 (C-5), 61.5 (CH_2-Et), 71.4 (C-25), 80.0 (C-3), 83.3 (C-24), 86.4 (C-20), 166.1 (malonyl –CO–), 166.8 (malonyl –CO–). HRESIMS (positive) m/z 597.4131 [M+Na]$^+$ (calcd for $C_{35}H_{58}O_6Na$, 597.4131).

4.2.1.14. 3-*O*-Propylmalonyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (18).

Yield 41.9% (starting with 65 mg of **2** by method A); colorless oil; $[\alpha]_D^{29}$ −3.9 (c 2.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.90 (3H, s, CH_3-30), 0.96 (3H, s, CH_3-18), 0.96 (3H, t, J = 6.8, CH_3-3′), 1.12 (3H, s, CH_3-27), 1.13 (3H, s, CH_3-21), 1.21 (3H, s, CH_3-26), 1.69 (2H, hex, J = 6.8, CH_2-2′), 3.41 (2H, s, malonyl –CH_2–), 3.73 (1H, t, J = 7.2 Hz, H-24), 4.12 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.3 (CH_3-3′), 15.4 (C-18), 16.0 (C-19), 16.6 (C-30), 18.0 (C-6), 21.4 (C-11), 21.6 (C-29), 21.8 (C-2′), 22.8 (C-2), 23.6 (C-21), 24.3 (C-27), 25.7 (C-16), 26.1 (C-23), 27.3 (C-12), 27.5 (C-26), 27.9 (C-28), 31.4 (C-15), 34.2 (C-1), 35.1 (C-7), 35.6 (C-22), 36.8 (C-4), 37.1 (C-10), 40.5 (C-8), 42.1 (malonyl –CH_2–), 42.8 (C-13), 49.5 (C-17), 50.1 (C-14), 50.6 (C-9), 50.7 (C-5), 67.0 (C-1′), 71.4 (C-25), 80.0 (C-3), 83.3 (C-24), 86.4 (C-20), 166.1 (malonyl –CO–), 166.8 (malonyl –CO–). HRESIMS (positive) m/z 611.4267 [M+Na]$^+$ (calcd for $C_{36}H_{60}O_6Na$, 611.4288).

4.2.1.15. 3-*O*-Butylmalonyl-3α,25-hydroxy-(20*S*,24*R*)-epoxydammarane (19).

Yield 16.9% (starting with 45 mg of **2** by method A); colorless oil; $[\alpha]_D^{30}$ −2.6 (c 0.86, $CHCl_3$). ^{1}H NMR ($CDCl_3$,

400 MHz) δ 0.86 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.90 (3H, s, CH_3-30), 0.96 (3H, s, CH_3-18), 1.03 (3H, t, J = 6.8, CH_3-4′), 1.12 (3H, s, CH_3-27), 1.14 (3H, s, CH_3-21), 1.21 (3H, s, CH_3-26), 1.37-1.44 (2H, m, CH_2-3′), 1.61–1.66 (2H, m, CH_2-2′), 3.41 (2H, s, malonyl –CH_2–), 3.73 (1H, t, J = 7.2 Hz, H-24), 4.16 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (CH_3-4′), 15.5 (C-18), 16.0 (C-19), 16.6 (C-30), 18.1 (C-6), 19.1 (C-3′), 21.4 (C-11), 21.7 (C-29), 22.8 (C-2), 23.6 (C-21), 24.3 (C-27), 25.7 (C-16), 26.1 (C-23), 27.4 (C-12), 27.5 (C-26), 27.9 (C-28), 30.5 (C-2′), 31.5 (C-15), 34.2 (C-1), 35.1 (C-7), 35.6 (C-22), 36.8 (C-4), 37.1 (C-10), 40.5 (C-8), 42.1 (malonyl –CH_2–), 42.9 (C-13), 49.5 (C-17), 50.1 (C-14), 50.6 (C-9), 50.8 (C-5), 65.4 (C-1′), 71.4 (C-25), 80.0 (C-3), 83.3 (C-24), 86.4 (C-20), 166.1 (malonyl –CO–), 166.9 (malonyl –CO–). HRESIMS (positive) m/z 625.4427 $[M+Na]^+$ (calcd for $C_{37}H_{62}O_6Na$, 625.4444).

4.2.1.16. 3-*O*-Pentylmalonyl-3α,25-hydroxy-(20*S*,24*R*)-epoxydammarane (20). Yield 32.0% (starting with 62 mg of **2** by method A); colorless oil; $[\alpha]_D^{30}$ −3.0 (c 2.43, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.91 (3H, s, CH_3-30), 0.91 (3H, t, J = 6.8, CH_3-5′), 0.96 (3H, s, CH_3-18), 1.12 (3H, s, CH_3-27), 1.13 (3H, s, CH_3-21), 1.21 (3H, s, CH_3-26), 1.33 (2H, m, CH_2-4′), 1.34 (2H, m, CH_2-3′), 1.66 (2H, m, CH_2-2′), 3.41 (2H, s, malonyl –CH_2–), 3.73 (1H, dd, J = 7.6, 6.8 Hz, H-24), 4.15 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (CH_3-5′), 15.4 (C-18), 16.0 (C-19), 16.6 (C-30), 18.0 (C-6), 21.4 (C-11), 21.6 (C-29), 22.3 (C-4′), 22.8 (C-2), 23.6 (C-21), 24.3 (C-27), 25.7 (C-16), 26.1 (C-23), 27.3 (C-12), 27.5 (C-26), 27.9 (C-28), 28.0 (C-3′), 28.2 (C-2′), 31.4 (C-15), 34.2 (C-1), 35.1 (C-7), 35.6 (C-22), 36.8 (C-4), 37.1 (C-10), 40.6 (C-8), 42.1 (malonyl –CH_2–), 42.9 (C-13), 49.5 (C-17), 50.1 (C-14), 50.6 (C-9), 50.7 (C-5), 65.6 (C-1′), 71.4 (C-25), 80.0 (C-3), 83.3 (C-24), 86.4 (C-20), 166.1 (malonyl –CO–), 166.8 (malonyl –CO–). HRESIMS (positive) m/z 639.4582 $[M+Na]^+$ (calcd for $C_{38}H_{64}O_6Na$, 639.4601).

4.2.1.17. 3-*O*-Hexylmalonyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (21). Yield 31.1% (starting with 61 mg of **2** by method A); colorless oil; $[\alpha]_D^{30}$ −3.1 (c 2.32, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.89 (3H, t, J = 6.8, CH_3-6′), 0.91 (3H, s, CH_3-30), 0.96 (3H, s, CH_3-18), 1.12 (3H, s, CH_3-27), 1.14 (3H, s, CH_3-21), 1.21 (3H, s, CH_3-26), 1.29–1.31 (4H, m, CH_2-4′, 5′), 1.62–1.67 (4H, m, CH_2-2′, 3′), 3.41 (2H, s, malonyl –CH_2–), 3.73 (1H, dd, J = 7.6, 6.8 Hz, H-24), 4.15 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (CH_3-6′), 15.4 (C-18), 16.0 (C-19), 16.6 (C-30), 18.0 (C-6), 21.4 (C-11), 21.6 (C-29), 22.5 (C-5′), 22.8 (C-2), 23.6 (C-21), 24.3 (C-27), 25.5 (C-4′), 25.7 (C-16), 26.1 (C-23), 27.3 (C-12), 27.5 (C-26), 27.9 (C-28), 28.5 (C-3′), 31.4 (C-2′), 31.4 (C-15), 34.2 (C-1), 35.1 (C-7), 35.6 (C-22), 36.8 (C-4), 37.1 (C-10), 40.6 (C-8), 42.1 (malonyl –CH_2–), 42.9 (C-13), 49.5 (C-17), 50.1 (C-14), 50.6 (C-9), 50.7 (C-5), 65.7 (C-1′), 71.4 (C-25), 80.0 (C-3), 83.3 (C-24), 86.4 (C-20), 166.1 (malonyl –CO–), 166.8 (malonyl –CO–). HRESIMS (positive) m/z 653.4736 $[M+Na]^+$ (calcd for $C_{39}H_{66}O_6Na$, 653.4757).

4.2.1.18. 3-*O*-Heptylmalonyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (22). Yield 38.7% (starting with 57 mg of **2** by method A); colorless oil; $[\alpha]_D^{30}$ −3.8 (c 2.77, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.89 (3H, t, J = 6.8, CH_3-7′), 0.91 (3H, s, CH_3-30), 0.96 (3H, s, CH_3-18), 1.12 (3H, s, CH_3-27), 1.13 (3H, s, CH_3-21), 1.21 (3H, s, CH_3-26), 1.26–1.32 (6H, m, CH_2-4′, 5′, 6′), 1.62–1.67 (4H, m, CH_2-2′, 3′), 3.41 (2H, s, malonyl –CH_2–), 3.73 (1H, t, J = 7.2 Hz, H-24), 4.15 (2H, t, J = 6.8, CH_2-1′), 4.68 (1H, br s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (CH_3-7′), 15.4 (C-18), 16.0 (C-19), 16.6 (C-30), 18.0 (C-6), 21.4 (C-11), 21.6 (C-29), 22.5 (C-6′), 22.8 (C-2), 23.6 (C-21), 24.3 (C-27), 25.8 (C-5′), 25.7 (C-16), 26.1 (C-23), 27.3 (C-12), 27.5 (C-26), 27.9 (C-28), 28.5 (C-4′), 28.9 (C-3′), 31.4 (C-15), 31.7 (C-2′), 34.2 (C-1), 35.1 (C-7), 35.6 (C-22), 36.8 (C-4), 37.1 (C-10), 40.5 (C-8), 42.1 (malonyl –CH_2–), 42.9 (C-13), 49.5 (C-17), 50.1 (C-14), 50.6 (C-9), 50.7 (C-5), 65.7 (C-1′), 71.4 (C-25), 80.0 (C-3), 83.3 (C-24), 86.4 (C-20), 166.1 (malonyl –CO–), 166.8 (malonyl –CO–). HRESIMS (positive) m/z 667.4929 $[M+Na]^+$ (calcd for $C_{40}H_{68}O_6Na$, 667.4914).

4.2.1.19. 3-*O*-Oxtylmalonyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (23). Yield 55.4% (starting with 57 mg of **2** by method A); colorless oil; $[\alpha]_D^{30}$ −2.3 (c 4.12, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.85 (3H, s, CH_3-19), 0.88 (3H, s, CH_3-29), 0.88 (3H, t, J = 6.8, CH_3-8′), 0.90 (3H, s, CH_3-30), 0.96 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.13 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 1.27 (8H, m, CH_2-4′, 5′, 6′, 7′), 1.61–1.65 (4H, m, CH_2-2′, 3′), 3.40 (2H, s, malonyl –CH_2–), 3.72 (1H, t, J = 7.2 Hz, H-24), 4.14 (2H, t, J = 6.8, CH_2-1′), 4.67 (1H, br s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (CH_3-8′), 15.4 (C-18), 16.0 (C-19), 16.6 (C-30), 18.0 (C-6), 21.4 (C-11), 21.6 (C-29), 22.6 (C-7′), 22.7 (C-2), 23.5 (C-21), 24.3 (C-27), 25.8 (C-6′), 25.7 (C-16), 26.1 (C-23), 27.3 (C-12), 27.4 (C-26), 27.9 (C-28), 28.5 (C-5′), 29.1 (C-4′), 29.1 (C-3′), 31.4 (C-15), 31.7 (C-2′), 34.2 (C-1), 35.1 (C-7), 35.6 (C-22), 36.8 (C-4), 37.1 (C-10), 40.5 (C-8), 42.1 (malonyl –CH_2–), 42.8 (C-13), 49.5 (C-17), 50.1 (C-14), 50.6 (C-9), 50.7 (C-5), 65.6 (C-1′), 71.4 (C-25), 79.9 (C-3), 83.3 (C-24), 86.4 (C-20), 166.1 (malonyl –CO–), 166.8 (malonyl –CO–). HRESIMS (positive) m/z 681.5055 $[M+Na]^+$ (calcd for $C_{41}H_{70}O_6Na$, 681.5070).

4.2.1.20. 3-*O*-(2-Propyl)malonyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (24). Yield 23.2% (starting with 60 mg of **2** by method B); colorless oil; $[\alpha]_D^{30}$ −4.1 (c 1.43, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.90 (3H, s, CH_3-29), 0.90 (3H, s, CH_3-30), 0.97 (3H, s, CH_3-18), 1.13 (3H, s, CH_3-27), 1.14 (3H, s, CH_3-21), 1.22 (3H, s, CH_3-26), 1.29 (6H, d, J = 6.4, 2 × CH_3-*i*Pr), 3.38 (2H, s, malonyl –CH_2–), 3.74 (1H, dd, J = 6.8, 7.2 Hz, H-24), 4.69 (1H, br s, H-3), 5.07 (H, sept, J = 6.4, CH-*i*Pr); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (C-18), 16.0 (C-19), 16.6 (C-30), 18.1 (C-6), 21.4 (C-11), 21.7 (C-29), 21.8 (2 × CH_3-*i*Pr), 22.8 (C-2), 23.6 (C-21), 24.3 (C-27), 25.7 (C-16), 26.1 (C-23), 27.3 (C-12), 27.5 (C-26), 27.9 (C-28), 31.4 (C-15), 34.2 (C-1), 35.0 (C-7), 35.6 (C-22), 36.8 (C-4), 37.1 (C-10), 40.5 (C-8), 42.5 (malonyl –CH_2–), 42.9 (C-13), 49.5 (C-17), 50.1 (C-14), 50.5 (C-9), 50.7 (C-5), 69.1 (CH- *i*Pr), 71.4 (C-25), 79.9 (C-3), 83.3 (C-24), 86.4 (C-20), 166.2 (malonyl –CO–), 166.2 (malonyl –CO–). HRESIMS (positive) m/z 611.4283 $[M+Na]^+$ (calcd for $C_{36}H_{60}O_6Na$, 611.4288).

4.2.1.21. 3-*O*-iso-Butylmalonyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (25). Yield 26.6% (starting with 61 mg of **2** by method B); colorless oil; $[\alpha]_D^{30}$ −4.7 (c 1.84, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.91 (3H, s, CH_3-30), 0.95 (6H, d, J = 7.2, 2 × CH_3-*i*Bu), 0.96 (3H, s, CH_3-18), 1.13 (3H, s, CH_3-27), 1.14 (3H, s, CH_3-21), 1.22 (3H, s, CH_3-26), 1.97 (1H, m, CH-*i*Bu), 3.42 (2H, s, malonyl –CH_2–), 3.74 (1H, dd, J = 6.8, 7.6 Hz, H-24), 3.95 (H, d, J = 6.4, CH_2-*i*Pr), 4.69 (1H, br s, H-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (C-18), 16.0 (C-19), 16.7 (C-30), 18.1 (C-6), 19.1 (2 × CH_3-*i*Bu), 21.4 (C-11), 21.7 (C-29), 22.8 (C-2), 23.6 (C-21), 24.3 (C-27), 25.7 (C-16), 26.1 (C-23), 27.4 (C-12), 27.5 (C-26), 27.7 (CH-*i*Bu), 27.9 (C-28), 31.5 (C-15), 34.2 (C-1), 35.1 (C-7), 35.6 (C-22), 36.8 (C-4), 37.1 (C-10), 40.6 (C-8), 42.1 (malonyl –CH_2–), 42.9 (C-13), 49.5 (C-17), 50.1 (C-14), 50.6 (C-9), 50.8 (C-5), 71.4 (C-25), 71.5 (CH_2-*i*Bu), 80.0 (C-3), 83.3 (C-24), 86.4 (C-20), 166.1 (malonyl –CO–), 166.8 (malonyl –CO–). HRESIMS m/z (positive) 625.4427 $[M+Na]^+$ (calcd for $C_{37}H_{62}O_6Na$, 625.4444).

4.2.2. General procedure for preparation of amide analogues (29–38, 39–45)

Method C: To a solution of **1** (40–60 mg, 1 equiv) in CH_2Cl_2 (2 mL), oxalyl dichloride (2.0 M solution in CH_2Cl_2, 3 equiv) was added dropwise, and the mixture was refluxed for 4 h with stirring. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in CH_2Cl_2 (3 mL), and then an appropriate amine (3 equiv) was added. The mixture was refluxed for 4 h with stirring. After cooled down to room temperature, the reaction solution was diluted with $CHCl_3$ and washed by water, 2 M HCl solution, brine, sat. $NaHCO_3$ solution and brine in turn. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue. The residue was chromatographed over a silica gel column and then purified by semi-preparative HPLC to afford the desired products **29**, **31**–**36**, together with compound**s 39**–**45** in each case.

Method D: To a solution of **1** (40–60 mg, 1 equiv), DCC (3 equiv) and HOBt (3 equiv) in CH_2Cl_2 (3 mL), excessive amount of an appropriate amine was added. The reaction mixture was stirred at room temperature overnight. After filtration of insolubles, the filtrate was concentrated to dryness, and the residue was subjected to silica gel chromatography and then repurified by semi-preparative HPLC to yield the products (**26**–**28**, **30**, **37**, and **38**).

4.2.2.1. 3-*O*-Malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (26). Yield 30% (starting with 42 mg of **1** by method D); colorless oil; $[\alpha]_D^{29}$ −12.7 (*c* 2.46, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.88 (3H, s, CH_3-19), 0.91 (3H, s, CH_3-29), 0.99 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.19 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 2.02 (3H, s, CH_3-Ac), 3.38 (2H, s, malonamoyl $-CH_2-$), 3.66 (1H, dd, *J* = 6.8, 7.6 Hz, H-24), 4.71 (1H, br s, H-3), 4.84 (1H, dt, *J* = 5.2, 10.4 Hz, H-12), 5.64, 7.09 (each 1H, br s, NH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.8 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.3 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.3 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 41.3 (malonamoyl $-CH_2-$), 46.3 (C-13), 49.5 (C-9), 50.5 (C-17), 50.7 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 80.0 (C-3), 83.4 (C-24), 85.7 (C-20), 167.4 (malonamoyl –COO–), 168.9 (malonamoyl $-CONH_2$), 170.5 (Ac, –CO–). HRESIMS (positive) *m*/*z* 626.4037 $[M+Na]^+$ (calcd for $C_{35}H_{57}NO_7$ Na, 626.4033).

4.2.2.2. 3-*O*-(*N*-Methyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (27). Yield 46.4% (starting with 53 mg of **1** by method D); colorless oil; $[\alpha]_D^{29}$ −14.6 (*c* 2.97, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (3H, s, CH_3-28), 0.86 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.97 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.09 (3H, s, CH_3-27), 1.17 (3H, s, CH_3-21), 1.18 (3H, s, CH_3-26), 2.00 (3H, s, CH_3-Ac), 2.85 (3H, d, *J* = 4.8 Hz, NCH_3), 3.35 (2H, s, malonamoyl $-CH_2-$), 3.65 (1H, dd, *J* = 6.4, 7.6 Hz, H-24), 4.67 (1H, br s, H-3), 4.83 (1H, dt, *J* = 5.2, 10.4 Hz, H-12), 7.10 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (C-18), 15.8 (C-19), 17.7 (C-30), 17.9 (C-6), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.2 (C-21), 22.6 (C-2), 24.2 (C-27), 26.0 (C-23), 26.3 (NCH_3), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.0 (C-10), 38.8 (C-22), 39.7 (C-8), 41.3 (malonamoyl $-CH_2-$), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.2 (C-14), 71.0 (C-25), 75.5 (C-12), 79.8 (C-3), 83.3 (C-24), 85.7 (C-20), 165.7 (malonamoyl –CONH), 169.2 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) *m*/*z* 640.4190 $[M+Na]^+$ (calcd for $C_{36}H_{59}NO_7$ Na, 640.4189).

4.2.2.3. 3-*O*-(*N*-Ethyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (28). Yield 22.7% (starting with 42 mg of **1** by method D); colorless oil; $[\alpha]_D^{29}$ −14.0 (*c* 2.10, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.90 (3H, s, CH_3-29), 0.98 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.18 (3H, s, CH_3-21), 1.18 (3H, t, *J* = 7.2 Hz, CH_3-Et), 1.19 (3H, s, CH_3-26), 2.01 (3H, s, CH_3-Ac), 3.34 (2H, m, *N*-CH_2), 3.35 (2H, s, malonamoyl $-CH_2-$), 3.66 (1H, dd, *J* = 6.4, 6.8 Hz, H-24), 4.69 (1H, br s, H-3), 4.84 (1H, dt, *J* = 5.2, 10.4 Hz, H-12), 7.02 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (CH_3-Et), 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.3 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 34.4 (NCH_2), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 41.5 (malonamoyl $-CH_2-$), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 79.8 (C-3), 83.3 (C-24), 85.7 (C-20), 164.9 (malonamoyl –CONH), 169.2 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) *m*/*z* 654.4346 $[M+Na]^+$ (calcd for $C_{37}H_{61}NO_7$ Na, 654.4346).

4.2.2.4. 3-*O*-(*N*-Propyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (29). Yield 21.7% (starting with 52 mg of **1** by method C); colorless oil; $[\alpha]_D^{28}$ −12.7 (*c* 1.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.90 (3H, s, CH_3-29), 0.94 (3H, t, *J* = 7.2 Hz, CH_3-3′), 0.98 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.18 (3H, s, CH_3-21), 1.56 (2H, m, CH_2-2′), 1.20 (3H, s, CH_3-26), 2.01 (3H, s, CH_3-Ac), 3.27(2H, q, *J* = 6.8 Hz, *N*-CH_2), 3.36 (2H, s, malonamoyl $-CH_2-$), 3.66 (1H, t, *J* = 7.2 Hz, H-24), 4.69 (1H, br s, H-3), 4.84 (1H, dt, *J* = 5.2, 10.8 Hz, H-12), 7.08 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.3 (CH_3-3′), 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.3 (C-21), 22.6 (C-2), 22.7 (C-2′), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 41.3 (NCH_2), 41.5 (malonamoyl $-CH_2-$), 46.3 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 79.8 (C-3), 83.4 (C-24), 85.7 (C-20), 165.0 (malonamoyl –CONH), 169.3 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) *m*/*z* 668.4515 $[M+Na]^+$ (calcd for $C_{38}H_{63}NO_7Na$, 668.4502).

4.2.2.5. 3-*O*-(*N*-Butyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (30). Yield 28.1% (starting with 60 mg of **1** by method D); colorless oil; $[\alpha]_D^{17}$ −12.7 (*c* 1.84, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.90 (3H, s, CH_3-29), 0.93 (3H, t, *J* = 7.2 Hz, CH_3-4′), 0.98 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.18 (3H, s, CH_3-21), 1.19 (3H, s, CH_3-26), 1.36 (2H, m, CH_2-3′), 1.51 (2H, m, CH_2-2′), 2.01 (3H, s, CH_3-Ac), 3.30(2H, q, *J* = 6.4 Hz, NCH_2), 3.35 (2H, s, malonamoyl $-CH_2-$), 3.66 (1H, dd, *J* = 6.4, 8.0 Hz, H-24), 4.69 (1H, br s, H-3), 4.84 (1H, dt, *J* = 5.2, 10.8 Hz, H-12), 7.07 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7 (CH_3-4′), 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 20.0 (C-3′), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.3 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 31.2 (C-15), 31.4 (C-2′), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.3 (NCH_2), 39.8 (C-8), 41.5 (malonamoyl $-CH_2-$), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 79.8 (C-3), 83.3 (C-24), 85.7 (C-20), 164.9 (malonamoyl –CONH), 169.4 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) *m*/*z* 682.4677 $[M+Na]^+$ (calcd for $C_{39}H_{65}NO_7Na$, 682.4659).

4.2.2.6. 3-*O*-(*N*-Pentyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (31). Yield 26.6% (starting with 50 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −12.6 (*c* 1.43, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 (3H, s, CH_3-28), 0.87

(3H, s, CH_3-19), 0.90 (3H, s, CH_3-29), 0.90 (3H, t, J = 6.8 Hz, CH_3-5′), 0.98 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.18 (3H, s, CH_3-21), 1.19 (3H, s, CH_3-26), 1.32 (4H, m, CH_2-3′, 4′), 1.58 (2H, m, CH_2-2′), 2.01 (3H, s, CH_3-Ac), 3.29 (2H, q, J = 6.8 Hz, N-CH_2), 3.35 (2H, s, malonamoyl –CH_2–), 3.66 (1H, dd, J = 6.4, 8.0 Hz, H-24), 4.69 (1H, br s, H-3), 4.84 (1H, dt, J = 5.2, 10.8 Hz, H-12), 7.09 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (CH_3-5′), 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-4′), 22.3 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 29.0 × 2 (C-2′, 3′), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.6 (NCH_2), 39.8 (C-8), 41.5 (malonamoyl –CH_2–), 46.3 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 79.8 (C-3), 83.3 (C-24), 85.7 (C-20), 164.9 (malonamoyl –CONH), 169.4 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 696.4822 [M+Na]$^+$ (calcd for $C_{40}H_{67}NO_7Na$, 696.4815).

4.2.2.7. 3-*O*-(*N*-Nonyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (32). Yield 20.6% (starting with 51 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −11.2 (c 1.32, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.87 (3H, t, J = 7.2 Hz, CH_3-9′), 0.90 (3H, s, CH_3-29), 0.98 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.10 (3H, s, CH_3-27), 1.18 (3H, s, CH_3-21), 1.19 (3H, s, CH_3-26), 1.26 (12H, m, CH_2-3′- CH_2-8′), 1.55 (2H, m, CH_2-2′), 2.01 (3H, s, CH_3-Ac), 3.27(2H, m, NCH_2), 3.35 (2H, s, malonamoyl –CH_2–), 3.66 (1H, dd, J = 6.4, 7.2 Hz, H-24), 4.69 (1H, br s, H-3), 4.84 (1H, dt, J = 5.2, 10.8 Hz, H-12), 7.08 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3-9′), 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.6 (C-8′), 22.6 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 26.9 (C-7′), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 29.2 × 2 (C-5′, 6′), 29.4 (C-4′), 29.5 (C-3′), 31.2 (C-15), 31.8 (C-2′), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.6 (N-CH_2), 39.8 (C-8), 41.5 (malonamoyl –CH_2–), 46.3 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 79.8 (C-3), 83.4 (C-24), 85.7 (C-20), 164.9 (malonamoyl –CONH), 169.4 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 752.5468 [M+Na]$^+$ (calcd for $C_{44}H_{75}NO_7Na$, 752.5441).

4.2.2.8. 3-*O*-(*N*-Benzyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (33). Yield 20.9% (starting with 38 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −13.5 (c 1.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.98 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.19 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 2.02 (3H, s, CH_3-Ac), 3.42 (2H, s, malonamoyl –CH_2–), 3.66 (1H, dd, J = 6, 6.8 Hz, H-24), 4.49, 4.50 (each d, J = 5.6 Hz, NCH_2), 4.69 (1H, br s, H-3), 4.85 (1H, dt, J = 5.2, 10.8 Hz, H-12), 7.29–7.36 (5H, m, Ph), 7.42 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 41.4 (malonamoyl –CH_2–), 43.6 (NCH_2), 46.3 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 79.9 (C-3), 83.3 (C-24), 85.7 (C-20), 127.5 ($C_{4'}$-Ph), 127.7 × 2 ($C_{2',6'}$-Ph), 128.7 × 2 ($C_{3',5'}$-Ph), 137.9 ($C_{1'}$-Ph),165.0 (malonamoyl –CONH), 169.2 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 716.4473 [M+Na]$^+$ (calcd for $C_{42}H_{63}NO_7Na$, 716.4502).

4.2.2.9. 3-*O*-(*N*-Phenyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (34). Yield 25.8% (starting with 38 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −8.2 (c 1.29, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (3H, s, CH_3-28), 0.89 (3H, s, CH_3-19), 0.92 (3H, s, CH_3-29), 0.96 (3H, s, CH_3-30), 1.01 (3H, s, CH_3-18), 1.12 (3H, s, CH_3-27), 1.19 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 2.02 (3H, s, CH_3-Ac), 3.53 (2H, d, J = 2.8 Hz, malonamoyl –CH_2–), 3.66 (1H, dd, J = 6.8, 7.2 Hz, H-24), 4.77 (1H, br s, H-3), 4.85 (1H, dt, J = 5.2, 10.8 Hz, H-12), 7.13 (1H, t, J = 8 Hz, –CH–, 4′-Ph), 7.34 (2H, t, J = 8 Hz, –CH–, 3′,5′-Ph), 7.57 (2H, d, J = 8 Hz, –CH–, 2′,6′-Ph), 9.16 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.9 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.3 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.9 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.0 (malonamoyl –CH_2–), 46.3 (C-13), 49.6 (C-9), 50.5 (C-17), 50.7 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 80.4 (C-3), 83.4 (C-24), 85.7 (C-20), 120.0 × 2 ($C_{2',6'}$-Ph), 124.5 ($C_{4'}$-Ph), 129.0 × 2 ($C_{3',5'}$-Ph), 137.5 ($C_{1'}$-Ph), 163.0 (malonamoyl –CONH), 169.5 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 702.4334 [M+Na]$^+$ (calcd for $C_{41}H_{61}NO_7Na$, 702.4346).

4.2.2.10. 3-*O*-(*N*-2,5-Dimethoxyphenyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (35). Yield 16.8% (starting with 50 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −6.3 (c 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (3H, s, CH_3-28), 0.88 (3H, s, CH_3-19), 0.91 (3H, s, CH_3-29), 0.94 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.12 (3H, s, CH_3-27), 1.19 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 2.02 (3H, s, CH_3-Ac), 3.53 (2H, d, J = 2.8 Hz, malonamoyl –CH_2–), 3.67 (1H, dd, J = 6.8, 7.2 Hz, H-24), 3.79 (3H, s, CH_3O-5′-Ph), 3.88 (3H, s, CH_3O-2′-Ph), 4.78 (1H, br s, H-3), 4.84 (1H, dt, J = 5.2, 10.8 Hz, H-12), 6.59 (1H, dd, J = 2.4, 8.8 Hz, –CH–, 4′-Ph), 6.82 (1H, d, J = 8.8 Hz, –CH–, 3′-Ph), 8.11 (1H, d, J = 2.8 Hz, –CH–, 6′-Ph), 9.39 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.8 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.3 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.9 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.8 (malonamoyl –CH_2–), 46.3 (C-13), 49.5 (C-9), 50.5 (C-17), 50.6 (C-5), 52.3 (C-14), 55.8 (CH_3O-5′-Ph), 56.5 (CH_3O-2′-Ph), 71.0 (C-25), 75.5 (C-12), 80.0 (C-3), 83.4 (C-24), 85.7 (C-20), 106.39 ($C_{6'}$-Ph), 108.9 ($C_{3'}$-Ph), 111.1 ($C_{4'}$-Ph), 128.1 ($C_{1'}$-Ph), 142.6 ($C_{2'}$-Ph), 153.9 ($C_{5'}$-Ph), 163.0 (malonamoyl –CONH), 168.8 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 762.4526 [M+Na]$^+$ (calcd for $C_{43}H_{65}NO_9Na$, 762.4557).

4.2.2.11. 3-*O*-(*N*-tert-Butyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (36). Yield 11.9% (starting with 40 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −13.1 (c 1.52, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.90 (3H, s, CH_3-29), 0.99 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.11 (3H, s, CH_3-27), 1.18 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 1.38 (9H, s, CH_3 × 3-*tert*-butyl), 2.00 (3H, s, CH_3-Ac), 3.27 (2H, d, J = 2.8 Hz, malonamoyl –CH_2–), 3.66 (1H, dd, J = 6.4, 6.8 Hz, H-24), 4.69 (1H, br s, H-3), 4.84 (1H, dt, J = 5.2, 10.8 Hz, H-12), 6.79 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.8 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.3 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 28.7 × 3 (CH_3-*tert*-butyl), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 42.8 (malonamoyl –CH_2–), 46.2 (C-13), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 51.3 (NHC), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 79.7 (C-3), 83.3 (C-24), 85.7 (C-20), 164.1 (malonamoyl –CONH), 169.5 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) m/z 682.4658 [M+Na]$^+$ (calcd for $C_{39}H_{65}NO_7Na$, 682.4569).

4.2.2.12. 3-*O*-(Morpholino-β-oxopropanoyl)-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (37). Yield 85.8% (starting with 43 mg of **1** by method D); colorless oil; $[\alpha]_D^{27}$ −12.3

(*c* 4.60, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (3H, s, CH_3-28), 0.85 (3H, s, CH_3-19), 0.87 (3H, s, CH_3-29), 0.96 (3H, s, CH_3-30), 0.98 (3H, s, CH_3-18), 1.08 (3H, s, CH_3-27), 1.16 (3H, s, CH_3-21), 1.17 (3H, s, CH_3-26), 2.00 (3H, s, CH_3-Ac), 3.43-3.49 (2H, m, CH_2-mor), 3.49 (2H, s, β-oxopropanoyl $-CH_2-$), 3.58-3.64 (2H, m, CH_2-mor), 3.66 (1H, t, *J* = 6.8 Hz, H-24), 3.68–3.71 (4H, m, CH_2-mor), 4.67 (1H, br s, H-3), 4.82 (1H, dt, *J* = 5.2, 10.8 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (C-18), 15.8 (C-19), 17.7 (C-30), 17.9 (C-6), 21.5 (C-29), 21.8 (Ac, $-CH_3$), 22.2 (C-21), 22.7 (C-2), 24.1 (C-27), 26.0 (C-23), 26.7 (C-16), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 35.5, 36.7 (C-4), 37.0 (C-10), 38.7 (C-22), 39.7 (C-8), 41.2 (β-oxopropanoyl $-CH_2-$), 42.2 (CH_2-mor), 46.2 (C-13), 46.8 (CH_2-mor), 49.6 (C-9), 50.4 (C-17), 50.6 (C-5), 52.2 (C-14), 66.4 (CH_2-mor), 66.7 (CH_2-mor), 70.9 (C-25), 75.4 (C-12), 79.9 (C-3), 83.3 (C-24), 85.7 (C-20), 164.6 (β-oxopropanoyl, –CONH), 167.0 (β-oxopropanoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) *m*/*z* 696.4438 $[M+Na]^+$ (calcd for $C_{39}H_{63}NO_8Na$, 696.4451).

4.2.2.13. 3-*O*-(*N*-Dimethyl)malonamoyl-12β-acetoxy-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (38).

Yield 45.4% (starting with 42 mg of **1** by method D); colorless oil; $[\alpha]_D^{27}$ −14.7 (*c* 2.92, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.83 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.98 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.10 (3H, s, CH_3-27), 1.18 (3H, s, CH_3-21), 1.20 (3H, s, CH_3-26), 2.02 (3H, s, CH_3-Ac), 3.01, 3.06 (each 3H, s, $(CH_3)_2N$), 3.50 (2H, s, malonamoyl $-CH_2-$), 3.65 (1H, dd, *J* = 6.8, 7.2 Hz, H-24), 4.69 (1H, br s, H-3), 4.84 (1H, dt, *J* = 5.2, 10.4 Hz, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5(C-18), 15.9 (C-19), 17.7 (C-30), 18.0 (C-6), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.3 (C-21), 22.7 (C-2), 24.2 (C-27), 26.1 (C-23), 26.8 (C-16), 27.5 (C-26), 27.9 (C-28), 28.2 (C-11), 31.2 (C-15), 34.0 (C-1), 34.3 (C-7), 35.5, 38.0 ($(CH_3)_2N$), 36.8 (C-4), 37.1 (C-10), 38.8 (C-22), 39.8 (C-8), 41.7 (malonamoyl $-CH_2-$), 46.2 (C-13), 49.7 (C-9), 50.4 (C-17), 50.7 (C-5), 52.3 (C-14), 71.0 (C-25), 75.5 (C-12), 79.5 (C-3), 83.3 (C-24), 85.7 (C-20), 166.1 (malonamoyl –CONH), 167.2 (malonamoyl –COO–), 170.6 (Ac, –CO–). HRESIMS (positive) *m*/*z* 654.4343 $[M+Na]^+$ (calcd for $C_{37}H_{61}NO_7Na$, 654.4346).

4.2.2.14. 3-*O*-(*N*-Propyl)malonamoyl-12β-acetoxy-25-*O*-(*N*-propyl)oxamoyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (39).

Yield 19.0% (starting with 41 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −20.6 (*c* 0.98, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.90 (3H, s, CH_3-29), 0.94 (3H, t, *J* = 7.2 Hz, CH_3-3′), 0.95 (3H, t, *J* = 7.2 Hz, CH_3-3″), 0.98 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.17 (3H, s, CH_3-21), 1.51 (6H, s, CH_3-27, 26), 1.57 (4H, m, CH_2-2′, CH_2-2″), 2.00 (3H, s, CH_3-Ac), 3.28 (4H, q, *J* = 6.8 Hz, CH_2-1′, CH_2-1″), 3.36 (2H, s, malonamoyl $-CH_2-$), 4.02 (1H, t, *J* = 7.2 Hz, H-24), 4.69 (1H, br s, H-3), 4.84 (1H, dt, *J* = 5.2, 10.8 Hz, H-12), 7.02 (1H, br s, oxamoyl -NH), 7.09 (1H, br s, -NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.3 (CH_3-3″), 11.4 (CH_3-3′), 15.6 (C-18), 15.8 (C-19), 17.5 (C-30), 18.0 (C-6), 21.1 (C-27), 21.5 (C-21), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.3 (C-26), 22.5 (C-2″), 22.6 (C-2), 22.6 (C-2′), 25.9 (C-23), 27.2 (C-16), 27.9 (C-28), 28.2 (C-11), 31.0 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.9 (C-22), 39.7 (C-8), 41.3 (C-1′), 41.5 (C-1″),41.5 (malonamoyl $-CH_2-$), 46.2 (C-13), 49.5 (C-9), 50.6 (C-17), 50.6 (C-5), 52.3 (C-14), 75.6 (C-12), 79.9 (C-3), 81.4 (C-24), 86.4 (C-20), 86.9 (C-25), 157.2 (oxamoyl, –CONH), 159.7 (oxamoyl, –COO–), 165.0 (malonamoyl –CONH), 169.4 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) *m*/*z* 781.4949 $[M+Na]^+$ (calcd for $C_{43}H_{70}N_2O_9Na$, 781.4979).

4.2.2.15. 3-*O*-(*N*-Pentyl)malonamoyl-12β-acetoxy-25-*O*-(*N*-pentyl)oxamoyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (40).

Yield 23.4% (starting with 51 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −19.3 (*c* 2.18, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.83 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-29), 0.89 (6H, m, CH_3-5′, CH_3-5″), 0.97 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.17 (3H, s, CH_3-21), 1.32 (8H, m, CH_2-3′, 4′, CH_2-3″, 4″), 1.50 (6H, s, CH_3-26, 27), 1.54 (4H, m, CH_2-2′, CH_2-2″), 2.00 (3H, s, CH_3-Ac), 3.29 (4H, q, *J* = 6.8 Hz, CH_2-1′, CH_2-1″), 3.35 (2H, s, malonamoyl $-CH_2-$), 4.03 (1H, t, *J* = 7.2 Hz, H-24), 4.69 (1H, br s, H-3), 4.84 (1H, dt, *J* = 5.2, 10.8 Hz, H-12), 7.01 (1H, br s, oxamoyl -NH), 7.10 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (CH_3-5″), 13.9 (CH_3-5′), 15.6 (C-18), 15.8 (C-19), 17.5 (C-30), 18.0 (C-6), 21.1 (C-27), 21.5 (C-21), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.2 (CH_2-4″), 22.3 (C-26), 22.3 (C-4′), 22.7 (C-2), 25.9 (C-23), 27.2 (C-16), 27.9 (C-28), 28.2 (C-11), 28.8 (CH_2-3″), 28.9 (CH_2-2″), 29.0 × 2 (C-2′, 3′), 31.0 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.9 (C-22), 39.6 (C-1′), 39.8 (C-8), 39.7 (CH_2-1″), 41.4 (malonamoyl $-CH_2-$), 46.2 (C-13), 49.5 (C-9), 50.6 (C-17), 50.6 (C-5), 52.3 (C-14), 75.6 (C-12), 79.8 (C-3), 81.4 (C-24), 86.4 (C-20), 86.9 (C-25), 157.2 (oxamoyl, –CONH), 159.7 (oxamoyl, –COO–), 164.9 (malonamoyl –CONH), 169.4 (malonamoyl –COO-), 170.4 (Ac, –CO–). HRESIMS (positive) *m*/*z* 837.5610 $[M+Na]^+$ (calcd for $C_{47}H_{78}N_2O_9Na$, 837.5605).

4.2.2.16. 3-*O*-(*N*-Nonyl)malonamoyl-12β-acetoxy-25-*O*-(*N*-nonyl)oxamoyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (41).

Yield 25.8% (starting with 51 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −9.4 (*c* 1.12, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.87 (6H, t, *J* = 7.2 Hz, CH_3-9′, oxamyl, $-CH_3$), 0.90 (3H, s, CH_3-29), 0.98 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.17 (3H, s, CH_3-21), 1.27 (24H, m, CH_2-3′- CH_2-8′, CH_2-3″-CH_2-8″), 1.51 (6H, s, CH_3-26, 27), 1.54 (4H, m, CH_2-2′, CH_2-2″), 2.00 (3H, s, CH_3-Ac), 3.29 (4H, q, *J* = 6.8 Hz, CH_2-1′, CH_2-1″), 3.36 (2H, s, malonamoyl $-CH_2-$), 4.04 (1H, t, *J* = 7.2 Hz, H-24), 4.69 (1H, br s, H-3), 4.85 (1H, dt, *J* = 5.2, 10.8 Hz, H-12), 7.00 (1H, br s, oxamoyl-NH), 7.09 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 × 2 (CH_3-9″, CH_3-9′), 15.6 (C-18), 15.8 (C-19), 17.5 (C-30), 18.0 (C-6), 21.1 (C-27), 21.5 (C-21), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.2 (C-26), 22.6 × 3 (C-2, C-8′, C-8″), 25.9 (C-23), 26.8 (C-7″), 26.9 (C-7′), 27.2 (C-16), 27.9 (C-28), 28.2 (C-11), 29.2 × 4 (C-5′, 6′, C-5″, 6″), 29.2 (C-4″), 29.4 (C-4′), 29.4 × 2 (C-3′, C-3″), 31.8 × 3 (C-15, C-2′, C-2″), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.9 (C-22), 39.6 (C-1′), 39.8 (C-8), 39.7 (C-1″), 41.4 (malonamoyl $-CH_2-$), 46.2 (C-13), 49.5 (C-9), 50.6 (C-17), 50.6 (C-5), 52.3 (C-14), 75.6 (C-12), 79.8 (C-3), 81.3 (C-24), 86.4 (C-20), 86.9 (C-25), 157.2 (oxamoyl, –CONH), 159.7 (oxamoyl, –COO–), 164.9 (malonamoyl –CONH), 169.4 (malonamoyl –COO–), 170.4 (Ac, –CO–). HRESIMS (negative) *m*/*z* 971.6942 $[M+HCOO]^-$ (calcd for $C_{56}H_{95}N_2O_{11}$, 971.6936).

4.2.2.17. 3-*O*-(*N*-Benzyl)malonamoyl-12β-acetoxy-25-*O*-(*N*-benzyl)oxamoyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (42).

Yield 9.5% (starting with 38 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −19.1 (*c* 1.06, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.83 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.90 (3H, s, CH_3-29), 0.96 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.17 (3H, s, CH_3-21), 1.52 (6H, s, CH_3-27, 26), 2.01 (3H, s, CH_3-Ac), 3.42 (2H, s, malonamoyl $-CH_2-$), 4.03 (1H, t, *J* = 7.2 Hz, H-24), 4.49(2H, d, *J* = 6.0 Hz, oxamoyl-NCH_2), 4.49, 4.50 (2H, each d, *J* = 6.4 Hz, NCH_2), 4.69 (1H, br s, H-3), 4.85 (1H, dt, *J* = 5.2, 10.8 Hz, H-12), 7.28-7.34 (10H, m, Ph, oxamoyl-Ph), 7.35 (1H, br s, oxamoyl-NH), 7.36 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.5 (C-30), 18.0 (C-6), 21.2 (C-27), 21.5 (C-21), 21.6 (C-29), 21.8 (Ac, $-CH_3$), 22.1 (C-26), 22.7 (C-2), 25.9 (C-23), 27.2 (C-16), 27.9 (C-28), 28.2 (C-11), 31.0 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.9 (C-22), 39.7 (C-8), 41.4 (malonamoyl $-CH_2-$), 43.6 (NCH_2), 43.9 (oxamoyl-NCH_2), 46.2 (C-13), 49.5 (C-9), 50.6 (C-17), 50.6 (C-5), 52.3 (C-14), 75.6 (C-12), 80.0 (C-3), 81.4 (C-24), 86.4 (C-20), 87.2 (C-25), 127.5 ($C_{4'}$-Ph), 127.7 × 2 ($C_{2',6'}$-Ph),

127.8 (oxamoyl-$C_{4'}$-Ph), 128.0 × 2 (oxamoyl-$C_{2',6'}$-Ph), 128.7 × 2 ($C_{3',5'}$-Ph), 137.0 × 2 (oxamoyl-$C_{3',5'}$-Ph), 137.0 (oxamoyl-$C_{1'}$-Ph), 137.9 ($C_{1'}$-Ph), 157.2 (oxamoyl –CONH), 159.5 (oxamoyl –COO–), 165.0 (malonamoyl –CONH), 169.2 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (positive) *m*/*z* 877.4991 $[M+Na]^+$ ($C_{51}H_{70}N_2O_9Na$, 877.4979).

4.2.2.18. 3-*O*-(*N*-Phenyl)malonamoyl-12β-acetoxy-25-*O*-(*N*-phenyl)oxamoyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (43).

Yield 3.9% (starting with 38 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −17.6 (*c* 1.08, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (3H, s, CH_3-28), 0.89 (3H, s, CH_3-19), 0.92 (3H, s, CH_3-29), 0.97 (3H, s, CH_3-30), 1.00 (3H, s, CH_3-18), 1.20 (3H, s, CH_3-21), 1.56 (6H, s, CH_3-27, 26), 2.02 (3H, s, CH_3-Ac), 3.54 (2H, d, *J* = 2.8 Hz, malonamoyl –CH_2–), 4.05 (1H, t, *J* = 7.2 Hz, H-24), 4.77 (1H, br s, H-3), 4.87 (1H, dt, *J* = 5.2, 10.8 Hz, H-12), 7.13 (1H, t, *J* = 8 Hz, –CH–, 4′-Ph), 7.18 (1H, t, *J* = 8 Hz, –CH–, oxamoyl-Ph-4′), 7.34 (2H, t, *J* = 8 Hz, –CH–, 3′,5′-Ph), 7.38 (2H, t, *J* = 8 Hz, –CH–, oxamoyl-Ph-3′,5′), 7.57 (2H, d, *J* = 8 Hz, –CH–, 2′,6′-Ph), 7.63 (2H, d, *J* = 8 Hz, –CH–, oxamoyl-Ph-2′,6′), 8.84 (1H, br s, oxamoyl-NH), 9.19 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.5 (C-30), 18.0 (C-6), 21.3 (C-27), 21.6 × 2 (C-21, 29), 21.8 (Ac, –CH_3), 22.1 (C-26), 22.8 (C-2), 25.9 (C-23), 27.2 (C-16), 28.0 (C-28), 28.2 (C-11), 31.1 (C-15), 34.0 (C-1), 34.3 (C-7), 36.9 (C-4), 37.1 (C-10), 38.9 (C-22), 39.8 (C-8), 41.9 (malonamoyl –CH_2–), 46.2 (C-13), 49.5 (C-9), 50.6 (C-17), 50.7 (C-5), 52.3 (C-14), 75.6 (C-12), 80.4 (C-3), 81.7 (C-24), 86.5 (C-20), 87.5 (C-25), 119.6 × 2 (oxamoyl-$C_{2',6'}$-Ph), 120.7 × 2 ($C_{2',6'}$-Ph), 124.5 ($C_{4'}$-Ph), 125.2 (oxamoyl-$C_{4'}$-Ph), 129.0 × 2 ($C_{3',5'}$-Ph), 129.2 × 2 (oxamoyl-$C_{3',5'}$-Ph), 136.6 (oxamoyl-$C_{1'}$-Ph), 137.5 ($C_{1'}$-Ph), 154.5 (oxamoyl, –CONH), 159.8 (oxamoyl –COO–), 163.0 (malonamoyl –CONH), 169.5 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (negative) *m*/*z* 871.4780 $[M+HCOO]^-$ (calcd for $C_{50}H_{67}N_2O_{11}Na$, 871.4745).

4.2.2.19. 3-*O*-(*N*-2,5-Dimethoxyphenyl)malonamoyl-12β-acetoxy-25-*O*-(*N*-2,5-dimethoxyphenyl)oxamoyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (44).

Yield 25.3% (starting with 51 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −11.5 (*c* 1.86, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.91 (3H, s, CH_3-29), 0.94 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.19 (3H, s, CH_3-21), 1.57 (6H, s, CH_3-26, 27), 2.02 (3H, s, CH_3-Ac), 3.54 (2H, d, *J* = 2.8 Hz, malonamoyl –CH_2–), 3.78 (3H, s, oxamoyl CH_3O-5′-Ph), 3.80 (3H, s, CH_3O-5′-Ph), 3.87 (3H, s, CH_3O-2′-Ph), 3.87 (3H, s, oxamoyl CH_3O-2′-Ph), 4.05 (1H, t, *J* = 7.2 Hz, H-24), 4.77 (1H, br s, H-3), 4.87 (1H, dt, *J* = 5.2, 10.8 Hz, H-12), 6.59 (1H, dd, *J* = 2.8, 8.8 Hz, –CH–, 4′-Ph), 6.66 (1H, dd, *J* = 2.8, 8.8 Hz, –CH–, oxamoyl 4′-Ph), 6.82 (1H, d, *J* = 8.8 Hz, –CH–, 3′-Ph), 6.83 (1H, d, *J* = 8.8 Hz, –CH–, oxamoyl 3′-Ph), 8.11 (1H, d, *J* = 2.8 Hz, –CH–, 6′-Ph), 8.15 (1H, d, *J* = 2.8 Hz, –CH–, oxamoyl 6′-Ph), 9.43 (1H, br s, NH), 9.47 (1H, br s, oxamoyl-NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.5 (C-18), 15.8 (C-19), 17.4 (C-30), 18.0 (C-6), 21.1 (C-27), 21.6 × 2 (C-21, C-29), 21.8 (Ac, –CH_3), 22.4 (C-26), 22.8 (C-2), 25.9 (C-23), 27.2 (C-16), 27.9 (C-28), 28.2 (C-11), 31.0 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.9 (C-22), 39.7 (C-8), 42.7 (malonamoyl –CH_2–), 46.2 (C-13), 49.4 (C-9), 50.5 (C-17), 50.6 (C-5), 52.2 (C-14), 75.6 (C-12), 80.0 (C-3), 81.6 (C-24), 86.5 (C-20), 87.3 (C-25), 105.6 (oxamyl $C_{6'}$-Ph), 106.4 ($C_{6'}$-Ph), 108.9 ($C_{3'}$-Ph), 110.2 (oxamoyl $C_{3'}$-Ph), 110.9 (oxamoyl $C_{4'}$-Ph), 111.0 ($C_{4'}$-Ph), 126.9 (oxamoyl $C_{1'}$-Ph), 128.1 ($C_{1'}$-Ph), 142.5 (oxamoyl $C_{2'}$-Ph), 142.6 ($C_{2'}$-Ph), 153.8 × 2 ($C_{5'}$-Ph, oxamoyl $C_{5'}$-Ph), 154.3 (oxamoyl, –CONH), 159.2 (oxamoyl –COO–), 163.0 (malonamoyl –CONH), 168.9 (malonamoyl –COO–), 170.4 (Ac, –CO–). HRESIMS (negative) *m*/*z* 945.5109 $[M-H]^-$ (calcd for $C_{53}H_{73}N_2O_{13}$, 945.5113).

4.2.2.20. 3-*O*-(*N*-*tert*-Butyl)malonamoyl-12β-acetoxy-25-*O*-(*N*-tert-butyl)oxamoyl-3α,25-dihydroxy-(20*S*,24*R*)-epoxydammarane (45).

Yield 22.1% (starting with 40 mg of **1** by method C); colorless oil; $[\alpha]_D^{27}$ −19.6 (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (3H, s, CH_3-28), 0.87 (3H, s, CH_3-19), 0.90 (3H, s, CH_3-29), 0.98 (3H, s, CH_3-30), 0.99 (3H, s, CH_3-18), 1.18 (3H, s, CH_3-21), 1.50 (6H, s, CH_3-26, 27), 1.38 (18H, s, CH_3 × 3-*t*Bu, oxamoyl CH_3 × 3-*t*Bu), 2.02 (3H, s, CH_3-Ac), 3.28 (2H,d, *J* = 3.6 Hz, malonamoyl –CH_2–), 4.00 (1H, t, *J* = 7.2 Hz, H-24), 4.68 (1H, br s, H-3), 4.84 (1H, dt, *J* = 5.2, 10.8 Hz, H-12), 6.80 (1H, br s, NH), 6.92 (1H, br s, oxamoyl-NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.6 (C-18), 15.8 (C-19), 17.5 (C-30), 18.0 (C-6), 21.0 (C-27), 21.6 (C-21), 21.6 (C-29), 21.8 (Ac, –CH_3), 22.1 (C-26), 22.7 (C-2), 25.9 (C-23), 27.2 (C-16), 27.9 (C-28), 28.2 (C-11), 28.2 × 3 (oxamoyl CH_3-*t*Bu), 28.7 × 3 (CH_3-*t*Bu), 31.0 (C-15), 34.0 (C-1), 34.3 (C-7), 36.8 (C-4), 37.1 (C-10), 38.9 (C-22), 39.7 (C-8), 42.8 (malonamoyl –CH_2–), 46.2 (C-13), 49.4 (C-9), 50.6 × 2 (C-17, C-5), 51.3 (C-*t*Bu), 51.6 (oxamoyl C-*t*Bu), 52.3 (C-14), 75.6 (C-12), 79.8 (C-3), 81.7 (C-24), 86.5 (C-20), 86.7 (C-25), 156.2 (oxamoyl, –CONH), 160.3 (oxamoyl –COO–), 164.1 (malonamoyl –CONH), 169.5 (malonamoyl –COO–), 170.5 (Ac, –CO–). HRESIMS (negative) *m*/*z* 831.5391 $[M+HCOO]^-$ (calcd for $C_{46}H_{75}N_2O_{11}$, 831.5371).

4.3. Biological activity

4.3.1. Cell lines and cell culture

KB cell line (human epidermoid carcinoma of the nasopharynx) was obtained from the Cell Resource Center for Biomedical Research (Tohoku University). Multidrug-resistant human epidermoid carcinoma KB-C2 cells were kindly provided by Professor Shin-ichi Akiyama (Kagoshima University, Japan). KB cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS). KB-C2 cells were maintained in DEME medium in the presence of 10% FBS and 2 μg/mL colchicine. All cells were incubated at 37 °C in a humidified atmosphere with 5% CO_2–95% air.

4.3.2. Assay for cytotoxicity effect

Cells in exponential growth were trypsinized, dispersed in a single cell suspension, and dispensed in 100 μL volumes into 96-well plates. For each assay, 5×10^3 cells/well were inoculated in 100 μL of medium containing 10% FBS and incubated for 24 h. Test samples were dissolved in small amounts of DMSO and diluted in appropriate culture medium (0.5% DMSO final concentration). After removal of preincubated culture medium, 100 μL of medium containing various concentrations (2, 10, 50, 100 μg/mL) of each test compound was added, and the plates were further incubated for 48 h. Followed by removal of the mixture, 100 μL of fresh medium containing 0.5 mg/mL MTT (thiazoil blue) was added to each well.[24,25] After incubation at 37 °C for another 4 h, medium was discarded carefully and 100 μL DMSO was added to dissolve the purple formazan. The cell growth was determined by measuring the optical density (OD) at 540 nm with Sunrise microplate reader (Tecan, Switzerland). IC_{50} values are defined as the concentration of each test sample that reduced absorbance to 50% of vehicle-treated controls. Daunorubicin was used as a positive control.

4.3.3. Assay for MDR-reversing activity in KB-C2 cells

Cells were seeded at a density of 5×10^3 per well in 96-well plates and incubated for 24 h. After preincubated medium was removed, 100 μL of medium containing various concentration of colchicine in the presence of each test sample (1 or 5 μg/mL) was added to each well. The negative control group was prepared by adding colchicine without any reversing compounds, while verapamil was used as a positive control. After incubated for 48 h, cells were stained using MTT method described in Section 4.3.2. IC_{50}

values of colchicine in the presence of each test compound were calculated using the concentration–inhibition curve.

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