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SYNTHESIS OF SULFOBETAINES BASED ON BETULINIC ACID AND ITS ESTERS

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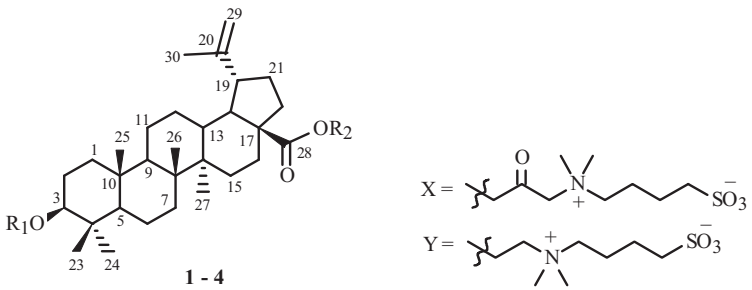
Methods for preparing sulfobetaines of betulinic acid that contained N,N-*(dimethylammonium)butane-1-sulfonate, a new type of Zwitter-ion in a series of lupane-type pentacyclic triterpenoids, were developed in order to prepare new betulinic acid derivatives and to study the structure–biological-activity relationship.*

Keywords: betulinic acid, 1,4-butane sultone, sulfobetaine.

Betulinic acid is the lead compound among lupane-type pentacyclic triterpenoids and is interesting as a platform for developing drugs with antitumor, antiviral, antimicrobial, and other types of pharmacological activity [1–5]. Recently, a series of ionic betulinic-acid derivatives such as ammonium and triphenylphosphonium salts were synthesized. They exhibited significantly higher antitumor and antimicrobial activity than the acid itself [6–13]. Sulfobetaine derivatives of betulinic acid and other lupane-type pentacyclic triterpenoids have not been reported despite the frequent use of the biomimetic sulfobetaine group to design biologically active compounds with antibacterial, antiviral, and antiproliferative properties; to increase the solubility of hydrophobic compounds; and also to construct nanocarriers for targeted drug delivery [14–21].

New derivatives of betulinic acid (**1**) were prepared and their structure–biological-activity relationship was studied using the synthetic method developed by us for betulinic-acid sulfobetaines **2**–**4**, a new class of lupane-type pentacyclic triterpenoids containing *N*,*N*-(dimethylammonium)butane-1-sulfonate bonded to the C-3 or C-28 position of the triterpene backbone.



1 - 4

1: $R_1 = R_2 = H$; **2:** $R_1 = X$, $R_2 = H$
3: $R_1 = X$, $R_2 = Me$; **4:** $R_1 = H$, $R_2 = Y$

Sulfobetaines **2**–**4** were prepared by treating the corresponding triterpene C-3 or C-28 tertiary amine of **5–7** with commercially available 1,4-butane sultone [22, 23]. Betulinic acid C-3 tertiary amine **5** was synthesized by acylating the C-3-OH of betulin 28-*O*-vinyl ether with chloroacetic acid (DCC, DMAP) and oxidizing in two steps the resulting betulin 3β-chloroacetate (**9**) with pyridinium chlorochromate (PCC) to give the corresponding aldehyde, which was reacted immediately after flash chromatography with $NaClO_2$ to obtain the 3β-chloroacetate of acid **10**. Amination of **10** with an excess of *N*,*N*-dimethylamine (40% aqueous) gave tertiary amine **5** in 93% yield. C-28-*O*-Vinyl ether **8**, which was prepared by us earlier via vinylation of betulin with acetylene in KOH–DMSO superbase [24], turned out to be a convenient intermediate for synthesizing betulinic acid 3β-chloroacetate **10**.

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TABLE 1. ^{13}C NMR Spectra of **2**–**4**, **5**–**7**, **9**–**11**, and **13** (δ, ppm)*

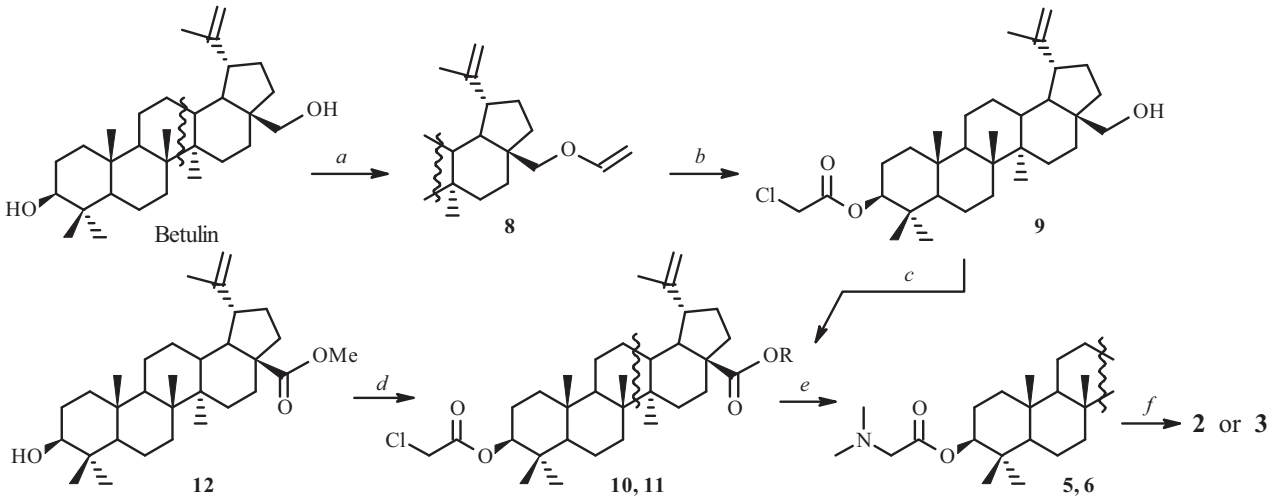
C atom	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10**	**11**	**13**
1	38.04	38.08	39.62	37.90	38.36	38.84	38.26	38.29	38.28	38.72
2	23.28	23.30	27.42	23.69	23.81	27.40	23.49	23.55	23.52	27.40
3	84.06	84.06	80.18	81.35	81.28	78.93	83.30	83.36	83.35	78.97
4	37.66	37.70	39.62	37.72	37.83	38.70	37.95	38.01	37.97	38.86
5	55.30	55.35	56.49	55.32	55.38	55.35	55.30	55.35	55.35	55.34
6	17.94	17.99	19.23	18.06	18.16	18.27	18.09	18.10	18.10	18.29
7	33.99	34.02	35.31	34.71	34.22	34.32	34.09	34.19	34.17	34.31
8	40.56	40.58	41.71	40.62	40.67	40.70	40.89	40.69	40.65	40.73
9	50.33	50.38	51.62	50.33	50.43	50.56	50.24	50.37	50.40	50.55
10	36.88	36.93	38.06	37.00	37.07	37.17	37.01	37.10	37.06	37.19
11	20.72	20.77	21.86	20.85	20.88	20.87	20.83	20.84	20.86	20.88
12	25.40	25.45	26.56	25.39	25.44	25.52	25.10	25.41	25.41	25.53
13	38.28	38.22	39.21	38.21	38.21	38.18	37.24	38.41	38.18	38.33
14	42.26	42.25	43.46	42.37	42.37	42.38	42.68	42.43	42.37	42.40
15	29.46	29.52	30.70	29.68	29.65	29.59	27.00	29.67	29.63	29.68
16	31.78	31.86	32.71	32.43	32.16	32.09	29.71	32.14	32.12	32.06
17	56.24	56.50	57.57	56.46	56.54	56.47	47.70	56.41	56.51	56.69
18	49.02	49.31	50.40	49.16	51.25	49.40	48.71	49.24	51.26	49.41
19	46.95	47.01	48.01	47.00	49.44	46.90	47.74	46.95	49.41	46.95
20	150.25	150.41	151.23	150.80	150.55	150.62	150.38	150.36	150.52	150.44
21	30.27	30.35	31.28	30.67	30.57	30.57	29.12	30.55	30.55	30.59
22	36.73	36.62	37.46	36.81	36.95	36.96	33.91	37.10	36.92	37.00
23	27.30	27.35	28.45	27.91	27.99	27.97	27.86	27.93	27.88	27.99
24	15.80	15.86	16.09	15.98	15.92	15.33	15.94	16.04	15.92	15.37
25	15.35	15.36	16.62	16.10	16.16	15.97	16.08	16.16	16.13	16.01
26	15.55	15.61	16.70	16.48	16.59	16.11	16.35	16.40	16.40	16.13
27	13.97	14.06	15.09	14.56	14.65	14.67	14.68	14.66	14.64	14.72
28	182.04	176.89	176.34	181.21	176.67	175.95	60.45	182.38	176.64	175.72
29	109.36	109.33	110.67	109.38	109.63	109.52	109.67	109.78	109.62	109.68
30	18.43	18.51	19.41	19.26	19.33	19.35	19.02	19.36	19.31	19.37
$CH_2\underline{C}(O)OC$	164.58	164.62	–	169.90	170.46	–	167.01	167.19	167.14	–
$\underline{C}H_2C(O)OC$	61.24	61.29		59.66	60.43	–	41.16	41.26	41.23	–
$C(O)O\underline{C}H_2CH_2$			58.53			61.77				63.34
$C(O)OCH_2\underline{C}H_2$			64.00			57.85				29.17
$N\underline{C}H_2CH_2CH_2CH_2SO_3$	65.77	65.79	66.24							
$NCH_2CH_2CH_2CH_2SO_3$	20.82	20.92	21.95							
$NCH_2CH_2CH_2CH_2SO_3$	21.04	21.14	22.28							
$NCH_2CH_2CH_2\underline{C}H_2SO_3$	49.78	49.93	51.01							
$N(CH_3)_2$	51.29	51.22	52.22	44.46	45.17	45.72				
	51.19	51.31								
$CO_2\underline{C}H_3$		50.97			46.98				46.95	

*__2__–__4__ (125.75 MHz, CD_3CO_2D, TMS); others (75.47 MHz, $CDCl_3$, TMS).

Protection of the primary hydroxyl in betulin by a vinyl group, its removal by treating the reaction mixture with HCl (10%), and subsequent purification of the product by flash chromatography gave the target compound in a satisfactory yield of 65% and was a good alternative to tetrahydropyranyl or dimethyl-*t*-butylsilyl protecting groups that are usually used for this [25–29].

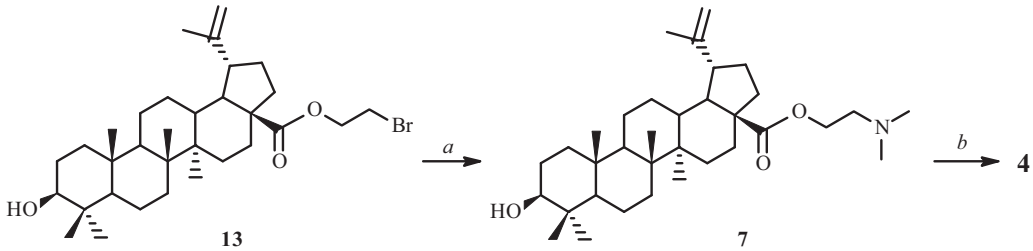
3*β*-(2-Dimethylamino)acetate **6** was prepared via *O*-chloroacylation of betulinic acid methyl ester **12** with chloroacetic acid (DCC, DMAP) followed by amination of the resulting chloroacetate **11** with *N*,*N*-dimethylamine. C-28-Tertiary amine **7** was synthesized via amination of bromomethylate **13** [8] analogously to that for amines **5** and **6**.

Sulfobetaines **2**–**4** were obtained after refluxing the corresponding tertiary amines **5**–**7** with an excess of 1,4-butane sultone under Ar in anhydrous MeCN. The precipitate of sulfobetaine that formed during the reaction was filtered off, rinsed several times with MeCN, and dried *in vacuo*. The structures of **2**–**4** were confirmed by mass, PMR, and ^{13}C NMR spectral data (Table 1).



5, 10: R = H; **6, 11:** R = Me

a. [24]; *b*. 1. $ClCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, 30 min; 2. HCl (10%); *c*. 1. PCC, CH_2Cl_2, 1 h; 2. $NaClO_2$–NaH_2PO_4–2-methyl-2-butene, *t*-BuOH, 40 min; *d*. $ClCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, 20 min; *e*. Me_2NH (40% aq.), EtOH (reflux 5 h for **5**; 1 h, 20°C for **6**); *f*. 1,4-butane sultone, MeCN, reflux 20 h



a. Me_2NH (40% aq.), EtOH, 1 h; *b*. 1,4-butane sultone, MeCN, reflux 20 h

EXPERIMENTAL

IR spectra were recorded in mineral oil on a Prestige-21 IR spectrophotometer (Shimadzu). PMR and ^{13}C NMR spectra were recorded on an Avance III pulsed spectrometer (Bruker) at operating frequency 500.13 MHz for ^1H and 125.47 MHz for ^{13}C using a Z-gradient PABBO probe at constant sample temperature 298 K or on an AM-300 spectrometer (Bruker) at operating frequency 300.13 and 75.47 MHz, respectively. Chemical shifts δ in PMR and ^{13}C NMR spectra were measured in ppm vs. TMS internal standard. Spin–spin coupling constants were measured in Hz. PMR and ^{13}C NMR spectra of **2**–**4** were assigned using standard 1D and 2D programs embedded in the Avance III spectrometer. Positive- and negative-ion mass spectra were recorded using electrospray ionization (ESI) on an LCMS-2010EV GC-MS (Shimadzu) (heater temperature 200°C, vaporizer temperature 230°C, sprayer flow rate 1.5 L/min, ion-source potential 3.5 kV, injected sample volume 2.5 μL, MeCN–H_2O eluent). Rotation angles were measured on a PerkinElmer 341C instrument. Column chromatography used SiO_2 (L grade, 40/60 μm, Russia). TLC was performed on Sorbfil plates (PTSKh-AF-A, ZAO Sorbpolimer, Krasnodar, Russia). Melting points were determined on a Kofler apparatus. Betulin was isolated from *Betula pendula* bark by the literature method [30]. Betulin *O*-vinyl ether **8** was prepared as before [24]; bromomethyl ester **13**, by the literature method [8]; betulinic acid methyl ester, by the literature method [31]. Anhydrous MeCN was prepared by distillation over P_2O_5 and then over CaH_2.

3β-(2-Chloroacetoxy)-28-hydroxylup-20(29)-ene (9). A solution of vinyl ether **8** (0.78 g, 1.667 mmol) and chloroacetic acid (0.32 g, 3.333 mmol) in anhydrous CH_2Cl_2 (30 mL) was treated under Ar with DMAP (0.41 g, 3.333 mmol), stirred for 5 min, treated in one portion with DCC (0.69 g, 3.333 mmol), and stirred for 30 min. The precipitate of *N*,*N*-dicyclohexylurea was filtered off. The filtrate was washed with HCl (10%, 10 mL) and water and dried over Na_2SO_4.

The solvent was evaporated. The residue was purified by flash chromatography over SiO_2 (C_6H_6–MTBE, 4:1) to afford **9** (0.56 h, 65%) [32]. Amorphous, $[\alpha]_D^{20}$ +4.8° (*c* 0.37, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3400, 1758, 1645. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hzц): 0.79 (1H, d, J = 9.4, H-5), 0.84 (6H, s, CH_3-24, 25), 0.86 (3H, s, CH_3-23), 0.96 (3H, s, CH_3-26), 1.01 (3H, s, CH_3-27), 1.67 (3H, s, CH_3-30), 1.80–2.00 (3H, m, H_b-16, 21, 22), 2.37 (1H, dt, J = 5.7, 11.0, H-19), 3.30 (1H, d, J = 10.8, H_a-28), 3.79 (1H, d, J = 10.8, H_b-28), 4.04 (2H, s, CH_2Cl), 4.55 (1H, m, H-3), 4.57 (1H, s, H_a-29), 4.67 (1H, s, H_b-29). ESI-MS, *m/z* 425 $[M - ClCH_2CO_2]^+$ (calcd 518 for $C_{32}H_{51}ClO_3$).

3β-(2-Chloroacetoxy)lup-20(29)-en-28-oic Acid (10). A solution of **9** (0.56 g, 1.088 mmol) in anhydrous CH_2Cl_2 (30 mL) was stirred under Ar, treated in one portion with PCC (0.70 g, 3.263 mmol), stirred for 1 h, diluted with MTBE (30 mL), stirred for 15 min, and filtered through a layer of Al_2O_3. The solvent was evaporated. The residue was purified by flash chromatography over SiO_2 (C_6H_6–MTBE, 4:1) to afford the aldehyde (0.56 g, 98%), which was dissolved in *t*-BuOH (33 mL), treated with 2-methyl-2-butene (0.5 mL) and then simultaneously dropwise with solutions of $NaClO_2$ (0.74 g, 6.505 mmol) in H_2O (5 mL) and NaH_2PO_4 (0.78 g, 6.505 mmol) in H_2O (3 mL), stirred for 40 min, diluted with H_2O (100 mL), and extracted with $CHCl_3$ (5 × 30 mL). The organic layer was dried over Na_2SO_4. The solvent was evaporated. The residue was chromatographed over SiO_2 (C_6H_6, C_6H_6–MTBE, 4:1) to afford **10** (0.40 g, 70%) [32]. Amorphous, $[\alpha]_D^{20}$ +2.5° (*c* 0.6, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1728 (C=C, C=O), 1693, 1638. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.79 (1H, d, J = 9.4, H-5), 0.85 (6H, s, CH_3-24, 25), 0.86 (3H, s, H-23), 0.92 (3H, s, CH_3-27), 0.96 (3H, s, CH_3-26), 1.68 (3H, s, CH_3-30), 1.96 (2H, m, H_b-21, 22), 2.17 (1H, t, J = 10.0, H-13), 2.27 (1H, d, J = 12.0, H_b-16), 3.02 (1H, dt, J = 5.5, 10.5, H-19), 4.05 (2H, s, CH_2Cl), 4.54 (1H, dd, J = 6.4, 10.0, H-3), 4.61 (1H, s, H_a-29), 4.74 (1H, s, H_b-29). ESI-MS, *m/z* 531 $[M - H]^-$ (calcd 532 for $C_{32}H_{49}ClO_4$).

Methyl 3β-(2-Chloroacetoxy)lup-20(29)-en-28-oate (11). A solution of methyl ester **12** (0.50 g, 1.064 mmol) in anhydrous CH_2Cl_2 (60 mL) was treated with chloroacetic acid (0.20 g, 2.128 mmol) and DMAP (0.26 g, 2.128 mmol), stirred for 5 min, treated with DCC (0.44 g, 2.128 mmol), and stirred under Ar for 20 min. The precipitate of *N*,*N*-dicyclohexylurea was filtered off. The organic layer was washed with HCl (10%, 20 mL) and water and dried over Na_2SO_4. The solvent was evaporated. The residue was purified by flash chromatography over SiO_2 (C_6H_6–MTBE, 4:1) to afford **11** (0.55 g, 94%). Amorphous, $[\alpha]_D^{20}$ +4° (*c* 0.15, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1734, 1650. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.68 (1H, d, J = 10.0, H-5), 0.84 (3H, s, CH_3-24), 0.85 (3H, s, CH_3-25), 0.86 (3H, s, CH_3-23), 0.91 (3H, s, CH_3-27), 0.95 (3H, s, CH_3-26), 1.68 (3H, s, CH_3-30), 1.87 (2H, m, H_b-21, 22), 2.19 (1H, m, H-13), 2.22 (1H, m, H_b-16), 3.00 (1H, dt, J = 4.5, 11.0, H-19), 3.66 (3H, s, $COOCH_3$), 4.05 (2H, s, CH_2Cl), 4.56 (1H, dd, J = 6.0, 10.0, H-3), 4.60 (1H, s, H_a-29), 4.73 (1H, s, H_b-29). ESI-MS, *m/z* 453 $[M - ClCH_2CO_2]^+$ (calcd 546 for $C_{33}H_{51}ClO_4$).

3β-[2-(Dimethylamino)acetoxy]lup-20(29)-en-28-oic Acid (5). A suspension of **10** (0.30 g, 0.498 mmol) in EtOH (15 mL) was treated with dimethylamine (0.6 mL, 4.975 mmol, 40% aq.) and refluxed for 4 h. The solvent was evaporated. The residue was purified by flash chromatography over SiO_2 ($CHCl_3$–MeOH, 10:1) to afford **5** (0.25 g, 93%). Amorphous, $[\alpha]_D^{20}$ +8.6° (*c* 0.33, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3389, 1734, 1707, 1641. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.80 (1H, m, H-5), 0.82 (3H, s, CH_3-24), 0.83 (3H, s, CH_3-23), 0.85 (3H, s, CH_3-25), 0.92 (3H, s, CH_3-27), 0.97 (3H, s, CH_3-26), 1.68 (3H, s, CH_3-30), 1.90 (2H, m, H_b-21, 22), 2.21 (2H, m, H-13, H_b-16), 2.38 (6H, s, $N(CH_3)_2$), 2.98 (1H, dt, J = 5.6, 11.0, H-19), 3.21 (2H, s, $OC(O)CH_2N$), 4.56 (1H, dd, J = 5.3, 11.0, H-3), 4.58 (1H, s, H_a-29), 4.71 (1H, s, H_b-29). ESI-MS, *m/z* 542 $[M + H]^+$ (calcd 541 for $C_{34}H_{55}NO_4$).

Methyl 3β-[2-(Dimethylamino)acetoxy]lup-20(29)-en-28-oate (6). A solution of **11** (0.20 g, 0.338 mmol) in EtOH (10 mL) was treated with dimethylamine (1.0 mL, 3.384 mmol, 40% aq.) and stirred for 1 h at 20°C. The solvent was evaporated. The residue was purified by flash chromatography over SiO_2 (C_6H_6–MTBE, 4:1) to afford **6** (0.11 g, 60%) amine **6**. Mp 147–148°C, $[\alpha]_D^{20}$ + 4° (*c* 0.39, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1732, 1708, 1641. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.83 (10H, s, H-5, CH_3-23, 24, 25), 0.91 (3H, s, CH_3-27), 0.95 (3H, s, CH_3-26), 1.68 (3H, s, CH_3-30), 1.88 (2H, m, H_b-21, 22), 2.22 (2H, m, H-13, H_b-16), 2.36 (6H, s, $N(CH_3)_2$), 2.97 (1H, dt, J = 5.3, 11.0, H-19), 3.16 (2H, s, $OC(O)CH_2N$), 3.66 (3H, s, $COOCH_3$), 4.57 (1H, dd, J = 5.3, 10.5, H-3), 4.59 (1H, s, H_a-29), 4.73 (1H, s, H_b-29). ESI-MS, *m/z* 556 $[M + H]^+$ (calcd 555 for $C_{35}H_{57}NO_4$).

2-Bromoethyl 3β-Hydroxylup-20(29)-en-28-oate (13). A suspension of **1** (1.0 g, 2.193 mmol) in anhydrous DMF (24 mL) under Ar was treated with calcined K_2CO_3 (0.30 g, 2.13 mmol), stirred for 20 min, treated dropwise with dibromoethane (0.2 mL, 2.193 mmol) in DMF (1 mL), and stirred at 20°C for 5 h. The K_2CO_3 was filtered off. The filtrate was evaporated. The residue was chromatographed over SiO_2 (C_6H_6, C_6H_6–MTBE, 16:1) to afford **13** (0.57 g, 50%). Mp 182–183°C (lit. [8] 185°C (MeOH)). ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.68 (1H, d, J = 8.0, H-5), 0.75 (3H, s, CH_3-24), 0.81 (3H, s, CH_3-25), 0.91 (3H, s, CH_3-26), 0.95 (6H, s, CH_3-23, 27), 1.68 (3H, s, CH_3-30), 1.92 (2H, m, H_b-21, 22), 2.17 (1H, dt,

J = 5.5, 11.0, H-13), 2.29 (1H, dd, J = 8.8, 1.8, H_b-6), 3.01 (1H, dt, J = 5.5, 10.5, H_b-19), 3.18 (1H, dd, J = 5.2, 11.0, H-3), 3.53 (2H, t, J = 6.0, CH_2Br), 4.39 (1H, dt, J = 15.0, 6.0, $COOCH_2$: H_a), 4.41 (1H, dt, J = 15.0, 6.0, $COOCH_2$: H_b), 4.60 (1H, s, H_a-29), 4.73 (1H, s, H_b-29).

2-(Dimethylamino)ethyl 3β-Hydroxylup-20(29)-en-28-oate (7). A solution of **13** (0.26 g, 0.443 mmol) in EtOH (15 mL) was treated with dimethylamine (0.2 mL, 4.434 mmol, 40% aq.) and stirred for 1 h at 20°C. The solvent was evaporated. The residue was purified by flash chromatography over SiO_2 (C_6H_6–MTBE, 4:1) to afford **7** (0.24 g, 98%). Mp 181–182°C, $[\alpha]_D^{20}$ –2.4° (*c* 0.3, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3440, 1726, 1650. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.69 (1H, m, H-5), 0.75 (3H, s, CH_3-24), 0.81 (3H, s, CH_3-25), 0.91 (3H, s, CH_3-26), 0.95 (6H, s, CH_3-23, 27), 1.67 (3H, s, CH_3-30), 1.91 (2H, m, H_b-21, 22), 2.23 (1H, m, H_b-6), 2.28 (7H, s, H-13, $N(CH_3)_2$), 2.56 (2H, t, J = 6, CH_2N), 3.01 (1H, m, H-19), 3.17 (1H, dd, J = 5.2, 10.5, H-3), 4.20 (2H, m, $COOCH_2$), 4.59 (1H, s, H_a-29), 4.72 (1H, s, H_b-29). ESI-MS, *m/z* 529 $[M + H]^+$ (calcd 528 for $C_{34}H_{57}NO_3$).

4-({2-[17β-Carboxylup-20(29)-en-3β-yloxy]-2-oxoethyl}dimethylammonium)butane-1-sulfonate (2). A suspension of **5** (0.10 g, 0.185 mmol) in anhydrous MeCN (3 mL) under Ar was treated dropwise with a solution of 1,4-butane sultone (0.17 mL, 1.661 mmol) in anhydrous MeCN (1.0 mL) (three equal portions every hour), and refluxed for 30 h. The precipitate of **5** was filtered off, rinsed with MeCN (5 × 5 mL), and dried *in vacuo* (KOH, 80°C) to afford **2** (0.06 g, 48%, white powder). Mp 288–290°C, $[\alpha]_D^{20}$ +11° (*c* 0.31, HCOOH). IR spectrum (ν, cm^{-1}): 3440, 1743, 1725, 1640, 1204, 1193, 1151, 1307, 794. ^1H NMR spectrum (500 MHz, CD_3COOD, δ, ppm, J/Hz): 0.86 (1H, m, H-5), 0.89 (3H, s, CH_3-24), 0.91 (6H, s, CH_3-23, 25), 0.99 (3H, s, CH_3-26), 1.04 (3H, s, CH_3-27), 1.06 (1H, m, H_a-1), 1.10 (1H, m, H_a-12), 1.20 (1H, d, J = 12.0, H_a-15), 1.31 (1H, m, H_a-11), 1.40 (1H, m, H-9), 1.42 (1H, m, H_a-21), 1.45 (2H, m, 2H-7), 1.48 (3H, m, H_a-6, H_b-11, H_a-16), 1.51 (1H, m, H_a-22), 1.56 (2H, m, H_b-6, 15), 1.65 (1H, m, H-18), 1.72 (5H, s, 2H-2, CH_3-30), 1.75 (2H, m, H_b-1, 12), 1.90 (2H, m, $NCH_2CH_2C\underline{H}_2CH_2SO_3$), 2.00 (2H, m, H_b-21, 22), 2.07 (2H, m, $NCH_2C\underline{H}_2CH_2CH_2SO_3$), 2.30 (2H, m, H-13, H_b-16), 3.06 (3H, m, H-19, $NCH_2CH_2CH_2C\underline{H}_2SO_3$), 3.37 (6H, s, $N(CH_3)_2$), 3.65 (2H, m, $NC\underline{H}_2CH_2CH_2CH_2SO_3$), 4.36 (1H, d, J = 17.0, $OC(O)CH_2N$: H_a), 4.42 (1H, d, J = 17.0, $OC(O)CH_2N$: H_b), 4.63 (1H, s, H_a-29), 4.68 (1H, dd, J = 5.3, 10.5, H-3), 4.77 (1H, s, H_b-29). ESI-MS, *m/z* 678 $[M + H]^+$ (calcd 677 for $C_{38}H_{63}NO_7S$).

4-({2-[17β-Methoxycarbonyllup-20(29)-en-3β-yloxy]-2-oxoethyl}dimethylammonium)butane-1-sulfonate (3) was prepared analogously to **2** from **6** (0.11 g, 0.202 mmol) and 1,4-butane sultone (0.20 mL, 2.02 mmol). Yield 0.054 g (39%) (white powder). Mp 283–286°C, $[\alpha]_D^{20}$ +13° (*c* 0.28, HCOOH). IR spectrum (ν, cm^{-1}): 1729, 1650, 1203, 1166, 1136, 1040. ^1H NMR spectrum (500 MHz, CD_3CO_2D, δ, ppm, J/Hz): 0.86 (1H, d, J = 10, H-5), 0.88 (3H, s, CH_3-24), 0.90 (6H, s, CH_3-23, 25), 0.95 (3H, s, CH_3-26), 1.02 (3H, s, CH_3-27), 1.05 (1H, m, H_a-1), 1.10 (1H, m, H_a-12), 1.20 (1H, m, H_a-15), 1.30 (1H, m, H_a-11), 1.39 (2H, m, H-9, H_a-21), 1.45 (7H, m, H_a-6, 2H-7, H_b-11, H_b-15, H_a-16, H_a-22), 1.52 (1H, m, H_b-6), 1.65 (1H, m, H-18), 1.71 (3H, s, CH_3-30), 1.73 (4H, m, H_b-1, 2H-2, H_b-12), 1.90 (4H, m, $NCH_2CH_2C\underline{H}_2CH_2SO_3$, H_b-21, 22), 2.06 (2H, m, $NCH_2C\underline{H}_2CH_2CH_2SO_3$), 2.24 (2H, m, H-13, H_b-16), 3.03 (3H, m, H-19, $NCH_2CH_2CH_2C\underline{H}_2SO_3$), 3.34 (6H, s, $N(CH_3)_2$), 3.64 (2H, m, $NC\underline{H}_2CH_2CH_2CH_2SO_3$), 3.68 (3H, s, $COOCH_3$), 4.36 (1H, d, J = 17.0, $OC(O)CH_2N$: H_a), 4.39 (1H, d, J = 17.0, $OC(O)CH_2N$: H_b), 4.61 (1H, s, H_a-29), 4.66 (1H, dd, J = 5.3, 10.5, H-3), 4.73 (1H, s, H_b-29). ESI-MS, *m/z* 714 $[M + Na]^+$ (calcd 691 for $C_{39}H_{65}NO_7S$).

4-({2-[3β-Hydroxylup-20(29)-en-17β-carbonyloxy]ethyl}dimethylammonium)butane-1-sulfonate (4) was prepared analogously to **2** from **7** (0.12 g, 0.224 mmol) and 1,4-butane sultone (0.20 mL, 2.02 mmol). Yield 0.04 g (27%) (white powder). Mp 265–267°C, $[\alpha]_D^{20}$ +9.5° (*c* 0.4, HCOOH). IR spectrum (ν, cm^{-1}): 3414, 1726, 1650, 1212, 1166, 1037, 1036. ^1H NMR spectrum (500 MHz, CD_3CO_2D, δ, ppm, J/Hz): 0.68 (1H, d, J = 10.0, H-5), 0.78 (3H, s, CH_3-24), 0.86 (3H, s, CH_3-25), 0.95 (4H, s, CH_3-26, m, H_a-1), 0.96 (3H, s, CH_3-23), 1.02 (3H, s, CH_3-27), 1.08 (1H, m, H_a-12), 1.25 (2H, m, H_a-11, 15), 1.40 (1H, m, H-9), 1.43 (6H, m, H_a-6, 2H-7, H_b-15, H_b-11, H_a-21), 1.54 (3H, m, H_b-6, H_a-16, H_a-22), 1.65 (1H, m, H-18), 1.68 (2H, m, H-2), 1.70 (4H, m, H_b-1, s, CH_3-30), 1.74 (1H, m, H_b-12), 1.92 (4H, m, H_b-21, 22, $NCH_2C\underline{H}_2CH_2CH_2SO_3$), 2.05 (2H, m, $NCH_2CH_2C\underline{H}_2CH_2SO_3$), 2.23 (1H, d, J = 13.7, H_b-16), 2.28 (1H, dt, J = 3.5, 12.5, H-13), 3.02 (1H, dt, J = 5.5, 11.5, H-19), 3.07 (2H, t, J = 7.5, $NCH_2CH_2CH_2C\underline{H}_2SO_3$), 3.23 (6H, s, $N(CH_3)_2$), 3.26 (1H, dd, J = 5.5, 10.5, H-3), 3.54 (2H, m, $NC\underline{H}_2CH_2CH_2CH_2SO$), 3.78 (2H, br.s, $C(O)OCH_2C\underline{H}_2N$), 4.59 (1H, d, J = 14.0, $C(O)OC\underline{H}_2CH_2N$: H_a), 4.63 (1H, s, H_a-29), 4.65 (1H, d, J = 14.0, $C(O)OC\underline{H}_2CH_2N$: H_b), 4.76 (1H, s, H_b-29). ESI-MS, *m/z* 664 $[M + H]^+$ (calcd 663 for $C_{38}H_{65}NO_6S$).

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