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SYNTHESIS OF 2-AMINOETHANESULFONAMIDES OF BETULINIC AND BETULONIC ACIDS

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New potentially biologically active sulfonamide derivatives of pentacyclic lupane-type triterpenoids, the sulfonamide group of which was bonded to C-17 of the triterpene skeleton through an amidoethane spacer, were synthesized via conjugation of 2-aminoethanesulfonamides to betulinic and betulonic acids in the presence of Mukaiyama reagent (2-bromo-1-methylpyridinium iodide).

Keywords: betulinic acid, betulonic acid, 2-aminoethanesulfonic acid, 2-aminoethanesulfonamides.

Betulinic and betulonic acids are lupane-type triterpene acids with broad spectra of inherent biological activity, synthetic modification of which led to a series of compounds with activities surpassing those of the natural precursors [1, 2].

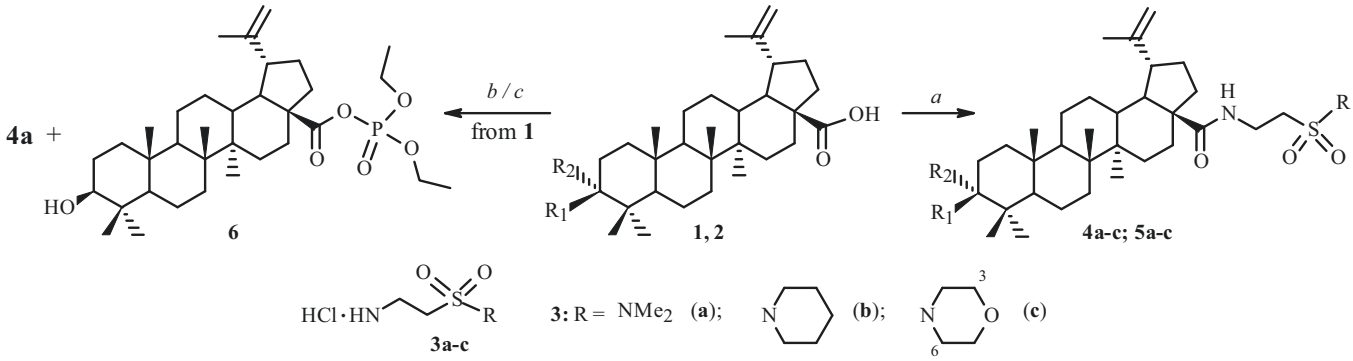
In continuation of work on the modification of lupane-type triterpenoids, sulfonamide derivatives of betulinic and betulonic acids were synthesized by us.

The sulfonamide motif was introduced into the structures of drugs [3, 4] and various biologically active compounds with a broad range of activity including antibacterial, anti-inflammatory, antitumor, and antiviral [5, 6] against important viral infections (HIV-1, HCV, SARS-CoV, DENV2) [7–9].

Derivatives of lupane triterpenoids containing a sulfonamide in the C-17 side chain or in the C-3 position with antitumor [10] and antiviral activity against HIV-1 virus have been reported [11, 12].

Herein, we report the synthesis of sulfonamides of lupane triterpenoids, the sulfonamide fragment of which is bonded to C-17 of the triterpene skeleton through an amidoethane spacer.

The starting compounds were betulinic (**1**) and betulonic acids (**2**) and 2-aminoethanesulfonamides **3a**–**c**, the combination of which in the presence of Mukaiyama reagent (2-bromo-1-methylpyridinium iodide) synthesized the target 2-amidoethanesulfonamides **4a**–**c** and **5a**–**c**.



1, 4a–c: R_1 = OH, R_2 = H; **2, 5a–c:** $R_1 + R_2$ = O

a. **3a–c,** Mukaiyama reagent, CH_2Cl_2, Et_3N (for **5a**, **5c**), Bu_3N (for **4a, 4b, 4c),** *i*-Pr_2EtN (for **5b**); *b.* DEPC, $NH_2CH_2CH_2SO_3H$, DMF, Et_3N (only **6** was isolated); *c.* **3a,** DEPC, DMF, Et_3N

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2-Aminoethanesulfonamides **3a**–**c** (as the hydrochlorides) were prepared by reacting phthalic anhydride with 2-aminoethanesulfonic acid (taurine) in the presence of NaOAc–AcOH by the literature method [13] followed by treatment of the obtained Na-salt of 2-phthalimidoethanesulfonic acid with PCl_5 and combination of the resulting chloride with amines ($NHMe_2$, piperidine, morpholine). The phthalyl protection was removed using NH_2NH_2 in EtOH to give the corresponding 2-aminoethanesulfonamides [14, 15].

Mukaiyama reagent (2-bromo-1-methylpyridinium iodide) was prepared by treating 2-bromopyridine with MeI [16, 17]. 2-Amidoethanesulfonamides **4a**–**c** and **5a**–**c** were synthesized via conjugation of 2-aminoethanesulfonamides **3a**–**c** (as the hydrochlorides) with acids **1** and **2**, the carboxylic group of which was activated by Mukaiyama reagent [18]. The reaction was carried out in refluxing CH_2Cl_2 for 1 h in the presence of Et_3N, Bu_3N, or *i*-Pr_2EtN. Target compounds **4a**–**c** and **5a**–**c** were isolated by chromatography over silica gel in 28–67% yields.

The structures of sulfonamides **4a**–**c** and **5a**–**c** were confirmed by IR, PMR, and ^{13}C NMR spectroscopy and mass spectrometry. Resonances in PMR and ^{13}C NMR spectra of sulfonamide **4a** were completely assigned using 1D and 2D experiments.

The combination of acids **1** and **2** with taurine in the presence of various condensing agents, conversion of the obtained 2-amidoethanesulfonic acids into the chlorides, and reaction of them with amines could serve as an alternative synthesis of sulfonamides **4a**–**c** and **5a**–**c**. Combination of the carboxylic acids with the amines through the action of diethyl phosphorocyanidate (DEPC) in the presence of Et_3N was an effective method for preparing the amides [19]. However, compound **6**, the mixed anhydride of **1** and diethyl phosphoric acid that did not subsequently react with taurine, was obtained by us in 85% yield upon reaction of **1** with taurine in DMF in the presence of DEPC–Et_3N. Replacing **1** by sulfonamide **3a** under the same conditions led to the formation of anhydride **6** (93%) together with **4a**, which was isolated in 5% yield.

The structure of mixed anhydride **6** was confirmed using 1D and 2D PMR, ^{13}C NMR, and ^{31}P NMR spectra. The PMR spectrum contained characteristic resonances for the ethyls of the diethyl phosphate group as a triplet at 1.35 ppm (6H, J = 7 Hz, $2OCH_2C\underline{H}_3$) and a multiplet at 4.27 ppm (4H, $OC\underline{H}_2CH_3$) that correlated with the ^{31}P resonance at –7.51 ppm in the 2D ^1H–^{31}P HMBC spectrum. The ^{31}P resonance in the ^{31}P NMR spectrum appeared as a pentet with J_{H-P} = 7.5 Hz.

Thus, a series of 2-amidoethanesulfonamides, new potentially biologically active derivatives of lupane-type triterpenoids, were synthesized from betulinic and betulonic acids.

EXPERIMENTAL

IR spectra were recorded in Vaseline oil on an IR Prestige-21 spectrophotometer (Shimadzu). PMR, ^{13}C NMR, and ^{31}P NMR spectra were taken at 295 K on an AMXIII-300 (Bruker, Germany) at operating frequency 300.13 MHz for ^1H and 75.47 MHz for ^{13}C or an Avance III-500 spectrometer (Bruker, Germany) at operating frequency 500.13 and 125.47 MHz, respectively, and 202.46 MHz (^{31}P). Chemical shifts in ^{13}C NMR and PMR spectra were given in ppm vs. $CD(H)Cl_3$ resonances (δ_H 7.27 ppm, δ_C 77.1 ppm) or TMS internal standard. Chemical shifts of ^{31}P resonances were determined vs. phosphoric acid (85%). Mass spectra of positive and negative ions were recorded using APCI or ESI method in an LCMS-2010EV liquid chromatograph (Shimadzu). Rotation angles were measured on a Perkin-Elmer 341C polarimeter. Column chromatography used SiO_2 (L brand, 40/60 μm, Russia); TLC, Sorbfil plates (Imid LLC, Russia). Chromatograms were visualized using anisic detector. Melting points were measured on a Boetius apparatus (Germany).

Preparation of 2-Amidoethanesulfonamides (4a–c, 5a–c). General Method. A suspension of 2-bromo-1-methylpyridinium iodide (0.53 mmol) in CH_2Cl_2 (2 mL) was treated dropwise with acid **1** or **2** (0.44 mmol), the appropriate sulfonamide chloride **3a**–**c** (0.44 mmol), and amine (1.49 mmol) (Et_3N, for **5a** and **5c**; Bu_3N, for **4a**, **4b**, and **4c**; *i*-Pr_2EtN, for **5b**) in CH_2Cl_2 (10 mL). The mixture was refluxed for 1 h, cooled, diluted with methyl-*tert*-butylether (MTBE) (50 mL), and washed with HCl solution (5%, 3 × 10 mL). The organic layer was separated, washed with H_2O, dried over Na_2SO_4, and evaporated. The solid was chromatographed over SiO_2 (C_6H_6, C_6H_6–MTBE, 8:1).

***N*-[2-(*N*,*N*-Dimethylsulfamoyl)ethyl]-3β-hydroxylup-20(29)-en-17β-carboxamide (4a).** Yield 67%, mp 140–143°C; $[\alpha]_D^{20}$ –0.3° (*c* 0.559, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1140, 1334, 1517, 1597, 1640, 1686, 3387. ^1H NMR spectrum (500 MHz, $CDCl_3$, TMS, δ, ppm, J/Hz): 0.67 (1H, d, J = 9.8, H-5), 0.75, 0.81, 0.93 (3H each, s, CH_3-24, 25, 26), 0.96 (8H, s, CH_3-23, 27, H_a-12, 15), 1.25 (3H, m, H-9, H_a-11, 16), 1.35 (2H, m, 2H-7), 1.38 (1H, m, H_a-21), 1.42 (3H, m, H-13, H_b-11, H_a-6), 1.56 (4H, m, 2H-2, H_b-6, H-18, H_a-22), 1.67 (1H, m, H_b-1), 1.71 (4H, m, H_b-15, CH_3-30), 1.79 (1H, m, H_b-22), 1.92 (1H, m, H_b-21), 1.98 (1H, m, H_b-16), 2.42 (1H, td, J = 13.0, 4.5, H-13), 2.89 (6H, s, $N(CH_3)_2$), 3.00 (2H, m,

$NCH_2C\underline{H}_2SO_3$), 3.08 (1H, td, J = 10.7, 4.4, H-19), 3.19 (1H, dd, J = 11.1, 5.6, H-3), 3.73 (2H, m, $NC\underline{H}_2CH_2SO_3$), 4.59, 4.74 (1H each, s, both H-29), 6.50 (1H, br.s, NH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, TMS, δ, ppm): 14.63 (C-27), 15.39 (C-24), 16.15 (C-25), 16.15 (C-26), 18.29 (C-6), 19.42 (C-30), 20.16 (C-11), 25.09 (C-12), 25.57 (C-15), 27.37 (C-2), 27.99 (C-23), 29.40 (C-16), 30.81 (C-21), 33.40 (C-22), 33.45 ($NHCH_2$), 34.37 (C-7), 37.18 (C-10), 37.44 (NMe_2), 37.72 (C-13), 38.70 (C-1), 38.85 (C-4), 40.75 (C-8), 42.44 (C-14), 46.72 (C-19), 47.17 (CH_2SO_2), 49.96 (C-18), 50.59 (C-9), 55.33 (C-5), 55.73 (C-17), 78.93 (C-3), 109.44 (C-29), 150.84 (C-20), 176.66 (C-28). ESI-MS, *m/z* 591 $[M + H]^+$ (100%) (calcd for $C_{34}H_{58}N_2O_4S$, 590).

***N*-[2-(Piperidin-1-ylsulfonyl)ethyl]-3β-hydroxylup-20(29)-en-17β-carboxamide (4b).** Yield 40%, mp 218–220°C; [α] +8.5° (*c* 0.33, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1139, 1335, 1514, 1641, 1685, 3422. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS, δ, ppm, J/Hz): 0.68 (1H, d, J = 9.8, H-5), 0.75, 0.80, 0.93, 1.67 (3H each, s, CH_3-24, 25, 26, 30), 0.96 (6H, s, CH_3-23, 27), 1.97 (3H, m, H_b-16, 21, 22), 2.42 (1H, m, H-13), 3.01 (2H, m, $NCH_2C\underline{H}_2SO_3$), 3.08 (1H, m, H-19), 3.21 (5H, m, H-3, piperidine: 2H-2, 6), 3.71 (2H, br.s, $NC\underline{H}_2CH_2SO_3$), 4.59, 4.73 (1H each, s, both H-29), 6.46 (1H, br.s, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS, δ, ppm): 14.64 (C-27), 15.38 (C-24), 16.13 (C-25), 16.16 (C-26), 18.29 (C-6), 19.42 (CH_3-30), 20.80 (C-11), 23.68 (piperidine: C-4), 25.57 (C-15), 25.57 (C-12), 25.57 (piperidine: C-3, 5), 27.40 (C-2), 27.99 (C-23), 29.43 (C-16), 30.84 (C-21), 33.47 (C-22), 33.47 ($NH\underline{C}H_2CH_2SO_3$), 34.40 (C-7), 37.21 (C-10), 37.76 (C-13), 38.72 (C-1), 38.87 (C-4), 40.87 (C-8), 42.47 (C-14), 46.60 (piperidine: C-2, 6), 46.75 (C-19), 48.42 ($NHCH_2\underline{C}H_2SO_3$), 49.98 (C-18), 50.61 (C-9), 55.37 (C-5), 55.76 (C-17), 78.98 (C-3), 109.47 (C-29), 150.87 (C-20), 176.61 (C-28). APCI-MS, *m/z*: 631 $[M + H]^+$ (100%), 613 $[M + H - H_2O]^+$ (13.3%), 546 $[M - NC_5H_{10}]^+$ (2.2%) (calcd for $C_{37}H_{62}N_2O_4S$, 630).

***N*-[2-(Morpholinosulfonyl)ethyl]-3β-hydroxylup-20(29)-en-17β-carboxamide (4c).** Yield 30%, mp 115–117°C; $[\alpha]_D^{20}$ +10° (*c* 0.128, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1115, 1152, 1641, 3400. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS, δ, ppm, J/Hz): 0.66 (1H, d, J = 9.4, H-5), 0.73, 0.79, 0.89, 1.66 (3H each, s, CH_3-24, 25, 26, 30), 0.91 (6H, s, CH_3-23, 27), 2.45 (1H, m, H-13), 3.04 (3H, m, $NCH_2C\underline{H}_2SO_3$, H-19), 3.15 (1H, dd, J = 10.5, 5.4, H-3), 3.23 (2H, m, morpholine: H-2, 6), 3.75 (6H, m, $NC\underline{H}_2CH_2SO_3$, morpholine: 2H-3, 5), 4.57, 4.72 (1H each, s, both H-29), 6.39 (1H, t, J = 5.5, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS, δ, ppm): 14.60 (C-27), 15.40 (C-24), 16.15 (C-25), 16.15 (C-26), 18.30 (C-6), 19.40 (CH_3-30), 20.74 (C-11), 25.10 (C-12), 25.60 (C-15), 27.40 (C-2), 28.00 (C-23), 29.40 (C-16), 30.85 (C-21), 33.38 (C-22), 33.42 ($NH\underline{C}H_2CH_2SO_3$), 34.40 (C-7), 37.20 (C-10), 37.73 (C-13), 38.75 (C-1), 38.86 (C-4), 40.78 (C-8), 42.46 (C-14), 45.70 (morpholine: C-2, 6), 46.72 (C-19), 47.90 ($NHCH_2\underline{C}H_2SO_3$), 49.98 (C-18), 50.60 (C-9), 55.37 (C-5), 55.73 (C-17), 66.43 (morpholine: C-3, 5), 78.92 (C-3), 109.48 (C-29), 150.75 (C-20), 176.67 (C-28). APCI-MS, *m/z*: 633 $[M + H]^+$ (100%), 615 $[M + H - H_2O]^+$ (15.5%), 546 $[M - NC_4H_8O]^+$ (5.3%) (calcd for $C_{36}H_{60}N_2O_5S$, 632).

***N*-[2-(*N*,*N*-Dimethylsulfamoyl)ethyl]-3-oxolup-20(29)-en-17β-carboxamide (5a).** Yield 30%, amorphous, $[\alpha]_D^{20}$ +19.2° (*c* 0.54, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1145, 1333, 1523, 1629, 1700, 3343. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS, δ, ppm, J/Hz): 0.92, 1.01, 1.07, 1.68 (3H each, s, CH_3-25, 24, 23, 30), 0.94 (6H, s, CH_3-26, H-27), 2.47 (3H, m, 2H-2, H-13), 2.89 (6H, s, $N(CH_3)_2$), 3.07 (3H, m, H-19, $NCH_2C\underline{H}_2SO_3$), 3.74 (2H, m, $NC\underline{H}_2CH_2SO_3$), 4.60, 4.74 (1H each, s, both H-29), 6.40 (1H, t, J = 5.5, C(O)NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS, δ, ppm): 14.54 (C-27), 15.97 (C-25), 15.97 (C-26), 19.44 (C-30), 19.64 (C-6), 21.05 (C-24), 21.46 (C-11), 25.58 (C-12), 26.62 (C-23), 29.38 (C-15), 30.79 (C-16), 33.33 (C-21), 33.51 ($N\underline{C}H_2CH_2SO_3$), 33.51 (C-7), 34.13 (C-2), 36.89 (C-10), 36.89 (C-22), 37.42 (NMe_2), 37.78 (C-13), 39.61 (C-1), 40.69 (C-8), 42.49 (C-14), 46.67 (C-19), 47.15 ($NCH_2\underline{C}H_2SO_2$), 47.32 (C-4), 49.94 (C-18), 49.94 (C-9), 54.92 (C-5), 55.68 (C-17), 109.51 (C-29), 150.76 (C-20), 176.62 (C-28), 218.22 (C-3). APCI-MS, *m/z* 589 $[M + H]^+$ (100%), 544 $[M - N(CH_3)_2]^+$ (6.3%) (calcd for $C_{34}H_{56}N_2O_4S$, 588).

***N*-[2-(Piperidin-1-ylsulfonyl)ethyl]-3-oxolup-20(29)-en-17β-carboxamide (5b).** Yield 32%, mp 160–161°C; $[\alpha]_D^{20}$ +24° (*c* 0.192, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1139, 1335, 1507, 1640, 1662, 1705, 3300. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, TMS, δ, ppm, J/Hz): 0.88, 1.02, 1.06, 1.68 (3H each, s, CH_3-25, 24, 23, 30), 0.97 (6H, s, CH_3-26, 27), 2.48 (3H, m, 2H-2, H-13), 3.03 (2H, m, $NCH_2C\underline{H}_2SO_3$), 3.09 (1H, m, H-19), 3.21 (4H, m, piperidine: 2H-2, 6), 3.75 (2H, m, $NC\underline{H}_2CH_2SO_3$), 4.60, 4.74 (1H each, s, both H-29), 6.42 (1H, t, J = 4.8, C(O)NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS, δ, ppm): 14.55 (C-27), 16.00 (C-25), 16.00 (C-26), 19.43 (C-30), 19.64 (C-6), 21.05 (C-24), 21.47 (C-11), 25.68 (piperidine: C-4), 25.57 (piperidine: C-3, 5), 25.57 (C-12), 26.63 (C-23), 29.40 (C-15), 30.80 (C-16), 33.26 (C-21), 33.51 (C-7), 33.70 ($N\underline{C}H_2CH_2SO_3$), 34.17 (C-2), 36.92 (C-10), 36.92 (C-22), 37.80 (C-13), 39.62 (C-1), 40.70 (C-8), 42.52 (C-14), 46.62 (C-19), 46.62 (piperidine: C-2, 6), 47.35 (C-4), 48.35 ($NCH_2\underline{C}H_2SO_2$), 49.96 (C-18), 50.00 (C-9), 54.95 (C-5), 55.73 (C-17), 109.53 (C-29), 150.81 (C-20), 176.57 (C-28), 218.29 (C-3). APCI-MS, *m/z*: 629 $[M + H]^+$ (100%), 544 $[M - NC_5H_{10}]^+$ (2.8%) (calcd for $C_{37}H_{60}N_2O_4S$, 628).

***N*-[2-(Morpholinosulfonyl)ethyl]-3-oxolup-20(29)-en-17-carboxamide (5c).** Yield 28%, amorphous, [α] +17° (*c* 0.371, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1109, 1157, 1641, 1662, 1703. ^1H NMR spectrum (300 MHz, $CDCl_3$, TMS, δ, ppm, J/Hz): 0.89, 0.99, 1.04, 1.66 (3H, s, CH_3-25, 24, 23, 30), 0.95 (6H, s, CH_3-26, 27), 2.45 (2H, m, H-2), 3.07 (3H, m, H-19, $NCH_2C\underline{H}_2SO_3$), 3.22 (4H, m, morpholine: 2H-2, 6), 3.74 (6H, m, $NC\underline{H}_2CH_2SO_3$, morpholine: 2H-3, 5), 4.57, 4.71 (1H each, s, both H-29), 6.40 (1H, t, J = 5.3, C(O)NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, TMS, δ, ppm): 14.54 (C-27), 15.97 (C-25), 15.97 (C-26), 19.42 (C-30), 19.64 (C-6), 21.02 (C-24), 21.45 (C-11), 25.56 (C-12), 26.61 (C-23), 29.37 (C-15), 30.76 (C-16), 33.34 (C-21), 33.49 (C-7), 33.68 ($N\underline{C}H_2CH_2SO_3$), 34.13 (C-2), 36.90 (C-10), 36.90 (C-22), 37.76 (C-13), 39.61 (C-1), 40.69 (C-8), 42.49 (C-14), 45.70 (morpholine: C-2, 6), 46.65 (C-19), 47.31 (C-4), 47.85 ($NCH_2\underline{C}H_2SO_2$), 49.90 (C-18), 49.94 (C-9), 54.95 (C-5), 55.67 (C-17), 66.43 (morpholine: C-3, 5), 109.55 (C-29), 150.69 (C-20), 176.67 (C-28), 218.16 (C-3). ESI-MS, *m/z*: 631 $[M + H]^+$ (100%), 544 $[M - NC_4H_8O]^+$ (3.5%) (calcd for $C_{36}H_{58}N_2O_5S$, 630).

Reaction of Acid 1 with Taurine. A solution of **1** (0.20 g, 0.44 mmol) in DMF (5 mL) at 0°C was treated sequentially with DEPC (0.1 mL, 0.53 mmol), taurine (0.11 g, 0.88 mmol), and Et_3N (0.73 mL, 5.25 mmol), stirred at 20°C for 10 h, and diluted at 0°C with saturated $NaHCO_3$ solution (10 mL). The resulting precipitate was filtered off and chromatographed over SiO_2 (C_6H_6–MTBE, 4:1) to afford mixed anhydride **6** (0.22 g, 85%).

Mixed Anhydride of Diethyl Phosphoric and Betulinic Acid (6). Mp 108–110°C; $[\alpha]_D^{20}$ –5.5° (*c* 0.35, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1019, 1377, 1641, 1763, 3460. ^1H NMR spectrum (500 MHz, $CDCl_3$, TMS, δ, ppm, J/Hz): 0.67 (1H, d, J = 9.1, H-5), 0.75, 0.82, 0.95, 1.67 (3H each, s, CH_3-24, 25, 23, 30), 0.96 (6H, s, CH_3-26, 27), 1.35 (6H, t, J = 7.0, $OCH_2C\underline{H}_3$), 1.97 (2H, m, H_b-21, 22), 2.22 (2H, m, H_b-16, H-13), 2.97 (1H, td, J = 10.7, 4.8, H-19), 3.18 (1H, dd, J = 11.2, 4.8, H-3), 4.27 (4H, m, $OC\underline{H}_2CH_3$), 4.61, 4.73 (1H each, s, both H-29). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, TMS, δ, ppm): 14.67 (C-27), 15.36 ($OCH_2\underline{C}H_3$), 15.87 (C-26), 16.15 (C-24, 25, $OCH_2\underline{C}H_3$), 18.26 (C-6), 19.35 (C-30), 20.83 (C-11), 25.45 (C-12), 27.36 (C-2), 27.97 (C-23), 28.03 (C-13), 29.73 (C-15), 30.16 (C-21), 31.68 (C-16), 34.29 (C-7), 36.16 (C-22), 37.19 (C-10), 38.72 (C-1), 38.84 (C-4), 40.73 (C-8), 42.44 (C-14), 46.45 (C-19), 49.14 (C-18), 50.55 (C-9), 55.35 (C-5), 58.00 (d, $^3J_{C-P}$ = 5.1, C-17), 64.87 (d, $^2J_{C-P}$ = 5.2, $O\underline{C}H_2CH_3$), 65.17 (d, $^2J_{C-P}$ = 5.2, $O\underline{C}H_2CH_3$), 78.93 (C-3), 109.96 (C-29), 149.85 (C-20), 170.17 (d, $^2J_{C-P}$ = 10.6, C-28). ^{31}P NMR spectrum (202 MHz, $CDCl_3$, TMS, δ, ppm, J/Hz): –7.51 (pentet, $^3J_{H-P}$ = 7.5). ESI-MS, *m/z* 563 $[M - C_2H_5]^-$ (calcd for $C_{34}H_{57}O_6P$, 592).

Reaction of Acid 1 with 3a in the Presence of DEPC. A solution of **1** (0.20 g, 0.438 mmol) in anhydrous DMF (5 mL) at 0°C was treated with **3a** (0.153 g, 0.876 mmol), DEPC (0.1 mL, 0.525 mmol), and Et_3N (0.85 mL, 6.132 mmol), stirred for 10 h at 20°C, and diluted with saturated $NaHCO_3$ solution (3 mL). The resulting precipitate was filtered off, rinsed with H_2O (3 × 5 mL), dried, and chromatographed over SiO_2 (C_6H_6, C_6H_6–MTBE, 8:1) to afford **4a** (0.012 g, 5%) and mixed anhydride **6** (0.20 g, 93%).

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