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SYNTHESIS OF LUPANE AND 19β,28-EPOXY-18α-OLEANANE 2,3-*seco*-DERIVATIVES BASED ON BETULIN

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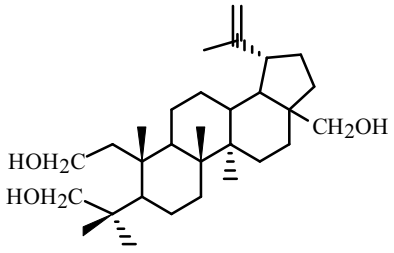
*The α-hydroxyoximes of methyl betulonate and allobetulone were synthesized. Beckmann fragmentation of them produced the lupane and 19β,28-epoxy-18α-oleanane 2,3-*seco*-derivatives.*

Key words: 2,3-*seco*-triterpenoids, betulin, allobetulin, Beckmann fragmentation.

Many polycyclic terpenoids of plant origin, including the lupane triterpenoid betulin, the principal component of bark extracts of *Betula* species, exhibit biological activity [1]. Preparative methods have been developed for synthesizing from betulin -betulinic acid [2-4], which selectively suppresses development of tumor cells and possesses anti-HIV activity. A preparation based on betulinic acid is included in the list of the RAID Program of the US National Cancer Institute and is at present being tested in human clinical trials [4]. Compounds with high antiviral and antitumor activity have been found among the many semisynthetic conjugates of betulin and betulinic acid [1, 5, 6]. However, the search for new ways of modifying betulin is critical despite the success that has been achieved. Recently Urban et al. [7] prepared a lupane 2,3-*seco*-triol that had cytotoxic activity from betulinic acid through the corresponding diosphenol:



Herein we describe the synthesis of 2,3-*seco*-aldehydonitriles of the lupane and 19β,28-epoxy-18α-oleanane types that are promising as starting materials for preparing heterocyclic and open heteroatomic derivatives.

We used the scheme that includes Beckmann fragmentation of α-hydroxyoximes and is well known in the chemistry of steroidal ketones [8-10]. The starting materials were the methyl ester of betulonic acid **1** and allobetulone **2**, the oximes of which were prepared using isoamylnitrite in the presence of potassium *t*-butoxide. This produced the corresponding hydroxyiminoketones **3** and **4** [8], reduction of which with $NaBH_4$ [2] gave 3β-hydroxy derivatives **5** and **6**. The presence of the hydroxyimine substituent on C-2 in **3**-**6** was confirmed by IR absorption bands in the ranges 1640-1648 and 3220-3250 cm^{-1}. The PMR spectra in DMSO-d_6 that were recorded for **3**-**6** showed a resonance for the oxime proton at 12.17-12.21 ppm (**3**, **4**) or 10.57-10.61 ppm (**5**, **6**).

Beckmann cleavage of ring A of the triterpenoids was carried out by treatment of **5** and **6** with tosylchloride in pyridine [8]. The structures of the resulting 2,3-*seco*-aldehydonitriles **7** and **8** were obvious and were confirmed by spectral data. The IR spectra of **7** and **8** contained a band at 2236-2244 cm^{-1} that corresponded to vibrations of the nitrile group. PMR spectra showed the aldehyde proton on C-3 as a singlet with chemical shift 9.61 ppm. ^{13}C NMR spectra had characteristic resonances for the nitrile (117.97-118.08 ppm) and aldehyde (206.01-206.15 ppm) C atoms. Resonances of H and C atoms in PMR and ^{13}C NMR spectra of **8** were completely assigned using 2D ^1H—^1H and ^{13}C—^1H NMR methods (Table 1).

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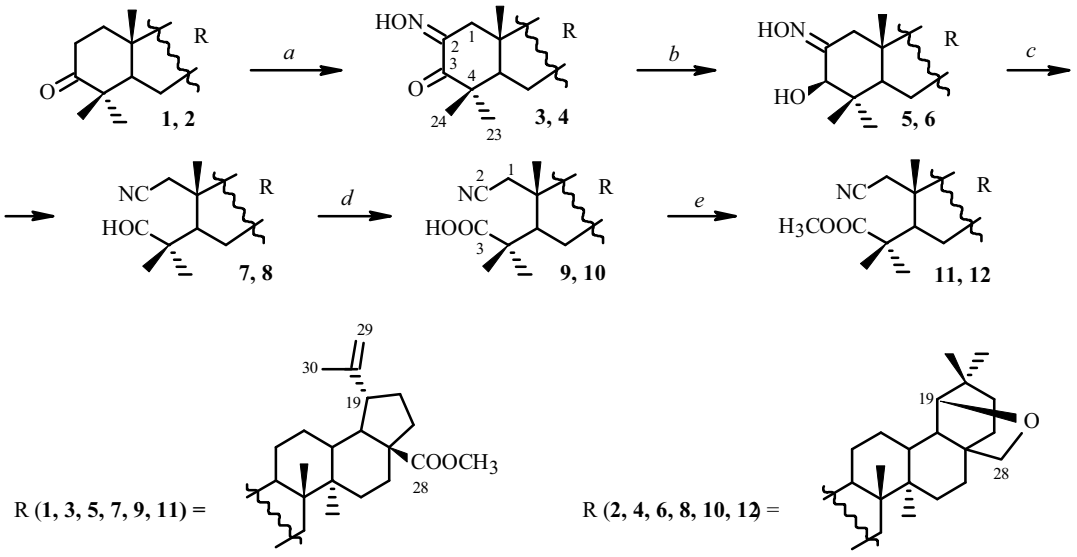
TABLE 1. ^{13}C NMR and PMR Spectra of **8** and **9** (300 MHz, $CDCl_3$, δ, ppm, J/Hz)

C atom	**8**		**9**	
	δ_C	δ_H	δ_C	δ_H
1	29.81	2.25 (1H, d, J = 18.5); 2.62 (1H, d, J = 18.5)	28.84	2.48 (2H, s)
2	117.97	-	118.24	-
3	206.01	9.61 (1H, s)	184.60	-
4	50.76	-	45.90	-
5	49.18	1.86-2.00 (1H, m)	50.61	1.96-2.05 (1H, m)
6	20.09	1.48-1.62 (2H, m)	20.24	1.50-1.64 (2H, m)
7	32.75	1.15-1.28 (2H, m)	33.28	1.38-1.42 (1H, m) 1.49-1.54 (1H, m)
8	41.14	-	40.53	-
9	45.07	1.91-2.06 (1H, m)	45.01	1.90-1.98 (1H, m)
10	42.27	-	42.25	
11	21.92	1.23-1.31 (1H, m) 1.38-1.51 (1H, m)	25.32	1.72-1.80 (2H, m)
12	26.42	1.38-1.55 (1H, m) 1.71 (1H, dm, J = 12.2)	21.55	1.18-1.26 (1H, m); 1.32-1.40 (1H, m)
13	34.29	1.43-1.56 (1H, m)	38.13	2.21 (1H, dm, J = 11.4)
14	40.47	-	42.80	-
15	26.29	1.27-1.40 (2H, m)	29.61	1.18-1.28 (2H, m)
16	26.13	0.98-1.17 (2H, m)	31.91	2.17-2.28 (2H, m)
17	41.44	-	56.49	-
18	46.59	1.46-1.60 (1H, m)	49.18	1.56-1.64 (1H, m)
19	87.82	3.51 (1H, s)	46.91	2.97 (1H, td, J = 5.4, 9.3)
20	36.25	-	150.19	-
21	32.66	1.37-1.58 (2H, m)	30.42	1.35-1.43 (1H, m) 1.84-1.92 (1H, m)
22	36.63	1.26-1.50 (2H, m)	36.83	1.36-1.42 (1H, m) 1.82-1.94 (1H, m)
23	23.51	1.15 (3H, s)	27.89*	1.28 (3H, s)
24	19.55	1.09 (3H, s)	21.55*	1.22 (3H, s)
25	19.03	0.91 (3H, s)	18.68	0.94 (3H, s)
26	15.60	0.96 (3H, s)	15.63	0.91 (3H, s)
27	13.45	0.96 (3H, s)	14.65	1.02 (3H, s)
28	71.22	3.44 (1H, d, J = 7.5); 3.75 (1H, d, J = 7.5)	176.61	-
29	24.51*	0.79 (3H, s)	109.90	4.72 and 4.59 (2H, 2s)
30	28.76*	0.92 (3H, s)	19.17	1.66 (3H, s)
31			51.28	3.65 (3H, s)

*Values may be interchanged.

2,3-*seco*-Derivatives **7** and **8** were oxidized by standard Jones reagent [11] to carboxy derivatives **9** and **10**, which were then converted to the corresponding methyl esters **11** and **12** under classical alkylation conditions by methyliodide [12]. A distinguishing feature of the PMR spectra of **7**-**12** was the nature of the resonances for the methylene protons on C-1 that appeared in **7**, **8** and **11**, **12** as two doublets in the ranges 2.15-2.30 and 2.42-2.62 ppm; in spectra of acids **9** and **10**, as a singlet at 2.48 or 2.45 ppm, respectively. The 1D PMR and ^{13}C NMR spectra of **9** were interpreted using data from 2D ^{1}H—^{1}H and ^{13}C—^{1}H NMR spectra (Table 1).

Thus, the research produced lupane and 19β,28-epoxy-18α-oleanane 2,3-*seco*-triterpenoids **7**-**12** that can be used to synthesize new biologically active compounds.



a. i-$C_6H_{11}NO_2$/t-C_4H_9OH/t-C_4H_9OK; *b.* $NaBH_4/CH_3OH$; *c*. $TsCl/C_5H_5N$; *d.* $Cr_2O_3/H_2SO_4/(CH_3)_2CO$; *e.* $CH_3I/K_2CO_3/(CH_3)_2CO$

EXPERIMENTAL

IR spectra in mineral oil were recorded on a Specord M80 spectrophotometer (Germany). PMR, ^{13}C NMR, ^1H—^1H (COSY), and ^{13}C—^1H (TOCSY, ROESY, HSQC, HMQC, HMBC) spectra in $CDCl_3$ or DMSO-d_6 solutions were recorded on a Varian Mercury+ spectrometer (USA) at operating frequency of 300 or 75.5 MHz with HMDS internal standard. Melting points were measured on a PTP apparatus (Russia). Specific optical rotation was recorded for $CHCl_3$ solutions on a Perkin—Elmer Model 341 polarimeter (USA) at 589 nm. Elemental analyses (C, H, N) were performed using a Leco CHNS-9321 P (Netherlands) elemental analyzer and agreed with those calculated.

Column chromatography was performed over Merck (60-200 μm) silica gel at a compound:sorbent ratio of 1:50. The eluent was selected individually for each comound. TLC used Sorbfil (Russia) plates. Compounds **7** and **8** were chromatographed using hexane:ethylacetate (5:1); the others, $CHCl_3$:ethylacetate (10:1). Compounds were detected by spraying plates with phosphomolybdic acid in EtOH (20%) and subsequent heating at 100-120°C for 2-3 min. Anhydrous solvents were prepared by standard methods [13]. Oxidation of betulin by Jones reagent [11] produced betulonic acid [2], which was methylated by methyliodide in acetone [12] to the corresponding methyl ester **1**. Allobetulone **2** was prepared by oxidation of allobetulin [14] by Jones reagent [11] in acetone.

Synthesis of Lupane (3) and 19β,28-Epoxy-18α-oleanane (4) α-hydroxyiminoketones. Betulonic acid methyl ester (**1**, 6 mmol) or allobetulone (**2**, 6 mmol) was dissolved in t-BuOH (100 mL) in the presence of t-BuOK (46 mmol), stirred at room temperature for 30 min, treated dropwise with freshly prepared isoamylnitrite (18 mmol), and stirred for 2 h. Formation of products was monitored by TLC. The reaction mixture was treated with aqueous KOH (50 mL, 1%). The products were extracted with ethylacetate (50 mL × 2). The combined ethylacetate extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo using a water aspirator. The solid was crystallized from EtOH.

Methyl Ester of 2-Hydroxyimino-3-oxolup-20(29)-en-28-oic Acid (3). Yield 2.3 g (77%), R_f 0.55, mp 160-162°C (EtOH), $[\alpha]_D^{21}$ +90.3° (*c* 0.6, $CHCl_3$). $C_{31}H_{47}NO_4$.

IR spectrum (ν, cm^{-1}): 3232 (OH), 1728 ($COOCH_3$), 1672 (C=O), 1648 (C=N).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.77, 0.90, 0.93, 1.05, 1.11 (5 × 3H, 5s, $5CH_3$), 1.63 (3H, s, CH_3-30), 2.04 and 2.90 (2H, 2d, J_{AB} = 18.5, 2H-1, AB system), 2.93 (1H, m, H-19), 3.61 (3H, s, CH_3-31), 4.55 and 4.68 (2H, 2s, 2H-29). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 12.17 (1H, s, NOH).

^{13}C NMR spectrum: 14.69, 15.37, 16.93, 19.49, 20.38, 21.67, 21.91, 25.68, 29.11, 29.76, 30.73, 32.21, 33.10, 35.81, 37.04, 38.54, 40.57, 41.89, 42.62, 46.05, 47.05, 48.61, 49.57, 51.32, 52.65, 56.67, 109.86 (C-29), 150.37 (C-20), 154.12 (C-2), 176.66 (C-28), 203.53 (C-3).

2-Hydroxyimino-19β,28-epoxy-18α-olean-3-one (4). Yield 2.25 g (80%), R_f 0.4, mp 236-238°C (EtOH), $[\alpha]_D^{21}$ +151.0° (*c* 0.5, $CDCl_3$). $C_{30}H_{47}NO_3$.

IR spectrum (ν, cm^{-1}): 3244 (OH), 1700 (C=O), 1640 (C=N).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.75, 0.80, 0.88, 0.95, 1.06, 1.12 (7 × 3H, 6s, $7CH_3$), 2.08 and 2.96 (2H, 2d, J_{AB} = 18.3, 2H-1, AB system), 3.40 and 3.72 (2H, 2d, J_{AB} = 7.8, 2H-28, AB system), 3.48 (1H, m, H-19). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 12.21 (1H, s, NOH).

^{13}C NMR spectrum: 13.43, 15.15, 17.24, 20.25, 21.66, 21.86, 24.62, 26.26, 26.37, 26.40, 28.84, 29.11, 32.53, 32.76, 34.35, 35.76, 36.32, 36.76, 40.36, 40.82, 41.52, 41.95, 45.91, 46.79, 48.87, 52.53, 71.30 (C-28), 87.99 (C-19), 153.96 (C-2), 203.97 (C-3).

Synthesis of Lupane (5) and 19β,28-Epoxy-18α-oleanane (6) α-hydroxyiminoalcohols. Compound **3** or **4** (3.6 mmol) was dissolved in CH_3OH (140 mL), stirred, treated in portions with $NaBH_4$ (37 mmol), stirred for 40 min at room temperature, and refluxed for 5 min. Solvent was evaporated. The resulting solid was dissolved in HCl (100 mL, 10%). The products were extracted with ethylacetate (50 mL × 2). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated. The solid was purified by column chromatography with elution by $CHCl_3$:ethylacetate (10:1).

Methyl Ester of 3β-Hydroxy-2-hydroxyiminolup-20(29)-en-28-oic Acid (5). Yield 1.23 g (68%), R_f 0.34, mp 163-167°C ($CHCl_3$:ethylacetate), $[\alpha]_D^{21}$ +19.66° (*c* 0.6, $CHCl_3$). $C_{31}H_{49}NO_4$.

IR spectrum (ν, cm^{-1}): 3408 (OH), br. 3250 (OH), 1728 ($COOCH_3$), 1644 (C=N).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.68, 0.73, 0.88, 0.97, 1.08 (5 × 3H, 5s, $5CH_3$), 1.66 (3H, s, CH_3-30), 2.22 and 3.39 (2H, 2d, J_{AB} = 12.5, 2H-1, AB system), 2.98 (1H, td, J = 10.3, 5.0, H-19), 3.66 (3H, s, CH_3-31), 3.79 (1H, s, H-3), 4.58 and 4.71 (2H, 2s, 2H-29). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 10.57 (1H, s, NOH).

^{13}C NMR spectrum: 14.68, 15.58 (2q), 16.53, 18.20, 19.35, 21.21, 25.35, 28.32, 29.69, 30.52, 32.10, 33.98, 36.92, 38.04 (C-1), 38.16, 40.96, 41.17, 42.42, 42.92 (C-1), 46.84, 49.42, 49.85, 51.32, 54.93 (C-5), 56.54, 78.54 (C-3), 109.69 (C-29), 150.35 (C-20), 158.20 (C-2), 176.74 (C-28).

3β-Hydroxy-2-hydroxyimino-19β,28-epoxy-18α-oleanane (6). Yield 0.81 g (50%), R_f 0.24, mp 229-233°C (EtOH), $[\alpha]_D^{21}$ +47.2° (*c* 0.6, $CHCl_3$). $C_{30}H_{49}NO_3$.

IR spectrum (ν, cm^{-1}): 3475 (OH), 3220 (OH), 1648 (C=N).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.70, 0.78, 0.79, 0.94, 1.10 (5 × 3H, 5s, $5CH_3$), 0.92 (2 × 3H, s, $2CH_3$), 1.67 and 3.45 (2H, 2d, J_{AB} = 12.3, 2H-1, AB system), 3.46 and 3.79 (2H, 2d, J_{AB} = 7.4, 2H-28, AB system), 3.54 (1H, s, H-19), 3.80 (1H, s, H-3). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm): 10.61 (1H, s, NOH).

^{13}C NMR spectrum: 13.51, 15.42, 15.65, 17.03, 18.23, 21.43, 24.56, 26.26, 26.30, 26.51, 28.40, 28.80, 32.75, 33.66, 34.17, 36.25, 36.74, 38.22, 40.81, 41.00, 41.26, 41.56, 42.98, 46.81, 50.49, 55.10, 71.28 (C-28), 78.54 (C-3), 87.93 (C-19), 158.10 (C-2).

Synthesis of Lupane (7) and 19β,28-Epoxy-18α-oleanane (8) 2,3-*seco*-aldehydonitriles. A mixture of **5** or **6** (3 mmol) and *p*-toluenesulfonic acid chloride (6 mmol) in C_5H_5N (20 mL) was refluxed for 4-5 h. The course of the reaction was monitored by TLC. The reaction mixture was treated with aqueous HCl until weakly acidic. The resulting precipitate was filtered off, washed with water, and purified by column chromatography with elution by hexane:ethylacetate (5:1).

Methyl Ester of 2-Cyano-2,3-*seco*-lup-20(29)-en-3-al-28-oic Acid (7). Yield 0.94 g (65%), R_f 0.36, mp 125-128°C (hexane:ethylacetate), $[\alpha]_D^{21}$ +22.08° (*c* 0.5, $CHCl_3$). $C_{31}H_{47}NO_3$.

IR spectrum (ν, cm^{-1}): 2244 (C=N), 1728 ($OOCH_3$), 1720 (CHO).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.83, 0.87, 0.97, 1.03, 1.08 (5 × 3H, 5s, $5CH_3$), 1.62 (3H, s, CH_3-30), 2.16 and 2.53 (2H, 2d, J_{AB} = 18.3, 2H-1, AB system), 2.92 (1H, td, J = 10.4, 5.1, H-19), 3.60 (3H, s, CH_3-31), 4.54 and 4.67 (2H, 2s, 2H-29), 9.61 (1H, s, H-3).

^{13}C NMR spectrum: 14.69, 15.80, 18.82, 19.29, 19.58, 20.18, 21.92, 23.61, 25.50, 29.69, 29.73, 30.52, 31.97, 33.30, 36.89, 38.28, 40.65, 42.31, 42.89, 44.67, 46.96, 49.18, 49.26, 50.85, 51.36, 56.55, 109.97 (C-29), 118.08 (C-2), 150.26 (C-20), 176.61 (C-28), 206.15 (C-3).

2-Cyano-2,3-*seco*-19β,28-epoxy-18α-oleanan-3-al′ (8). Yield 0.91 g (67%), R_f 0.22, mp 220-223°C (hexane:ethylacetate), $[\alpha]_D^{21}$ +75.2° (*c* 0.5, $CHCl_3$). $C_{30}H_{47}NO_2$.

IR spectrum (ν, cm^{-1}): 2236 (C=N), 1712 (CHO).

Table 1 gives the PMR and ^{13}C NMR spectra.

Synthesis of Lupane (9) and 19β,28-Epoxy-18α-oleanane (10) 2,3-*seco*-carboxynitriles. A solution of **7** or **8** (1.4 mmol) in acetone (50 mL) was stirred and treated with Jones reagent (3.5 mL) [11]. The course of the reaction was monitored by TLC. The solvent was evaporated. The solid was treated with a large volume of water. The resulting precipitate was filtered off and washed with water. The product was purified by column chromatography with elution by $CHCl_3$:ethylacetate (10:1).

28-Methoxycarbonyl-2-cyano-2,3-*seco*-lup-20(29)-en-3-oic Acid (9). Yield 0.43 g (62%), R_f 0.25, mp 123-126°C (hexane:ethylacetate), $[\alpha]_D^{21}$ +6.7° (*c* 0.7, $CHCl_3$). $C_{31}H_{47}NO_4$.

IR spectrum (ν, cm^{-1}): 2246 (C=N), 1728 ($COOCH_3$), 1704 (COOH).

Table 1 gives the PMR and ^{13}C NMR spectra.

2-Cyano-2,3-*seco*-19β,28-epoxy-18α-oleanan-3-oic Acid (10). Yield 0.42 g (63%), R_f 0.36, mp 139-141°C (hexane:ethylacetate), $[\alpha]_D^{21}$ +42.4° (*c* 0.6, $CHCl_3$). $C_{30}H_{47}NO_3$.

IR spectrum (ν, cm^{-1}): 2250 (C=N), 1732 ($COOCH_3$), 1722 (COOH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.73, 0.87, 0.91, 0.92, 1.17, 1.24 (7 × 3H, 6s, $7CH_3$), 2.45 (2H, s, 2H-1), 3.40 and 3.73 (2H, 2d, J_{AB} = 7.8, 2H-28, AB system), 3.50 (1H, s, H-19).

^{13}C NMR spectrum: 13.62, 15.58, 19.01, 20.25, 21.79, 22.85, 24.58, 26.19, 26.35, 26.49, 28.16, 28.80, 29.09, 32.75, 32.94, 34.28, 36.32, 36.70, 40.57, 41.24, 41.53, 42.39, 45.56, 45.88, 46.65, 50.78, 71.20 (C-28), 88.00 (C-19), 118.28 (C-2), 184.13 (C-3).

Synthesis of Lupane (11) and 19β,28-Epoxy-18α-oleanane (12) 2,3-*seco*-methoxycarbonylnitriles. Methyl esters of **9** and **10** were prepared by the standard method [12].

Dimethyl Ester of 2-Cyano-2,3-*seco*-lup-20(29)-en-3,28-dioic Acid (11). Yield 0.16 g (82%), R_f 0.25, mp 194-195°C (hexane:ethylacetate), $[\alpha]_D^{21}$ +26.9° (*c* 0.6, $CHCl_3$). $C_{32}H_{48}NO_4$.

IR spectrum (ν, cm^{-1}): 2240 (C=N), 1724 ($COOCH_3$).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90, 0.91, 1.02, 1.17, 1.24 (5 × 3H, 5s, $5CH_3$), 1.67 (3H, s, CH_3-30), 2.15 and 2.42 (2H, 2d, J_{AB} = 18.3, 2H-1, AB system), 2.97 (1H, td, J = 9.5, 5.0, H-19), 3.65 and 3.72 (2 × 3H, 2s, $2COOCH_3$), 4.59 and 4.71 (2H, 2s, 2H-29).

^{13}C NMR spectrum: 14.67, 15.62, 18.55, 19.21, 19.91, 21.64, 22.32, 25.36, 28.36, 28.82, 29.64, 30.47, 31.92, 33.24, 36.83, 38.17, 40.57, 42.16, 42.83, 44.81, 45.57, 46.94, 49.23, 50.77, 51.25, 51.88, 56.52, 109.88 (C-29), 118.07 (C-2), 150.21 (C-20), 176.56 (C-31), 179.80 (C-32).

Methyl Ester of 2-Cyano-2,3-*seco*-19β,28-epoxy-18α-oleanan-3-oic Acid (12). Yield 0.16 g (70%), R_f 0.25, mp 172-173°C (hexane:ethylacetate), $[\alpha]_D^{21}$ +29.0° (*c* 0.8, $CHCl_3$). $C_{31}H_{49}NO_3$.

IR spectrum (ν, cm^{-1}): 2252 (C=N), 1732 ($COOCH_3$).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.91, 1.04, 1.05, 1.09, 1.10, 1.30, 1.38 (7 × 3H, 7s, $7CH_3$), 2.30 and 2.59 (2H, 2d, J_{AB} = 18.2, 2H-1, AB system), 3.56 and 3.87 (2H, 2d, J_{AB} = 8.0, 2H-28, AB system), 3.64 (1H, s, H-19), 3.85 (3H, s, $COOCH_3$).

^{13}C NMR spectrum: 13.53, 15.47, 18.85, 19.81, 21.70, 22.22, 24.50, 26.12, 26.26, 26.42, 28.49, 28.75, 28.86, 32.66, 32.77, 34.23, 36.25, 36.63, 40.46, 41.14, 41.44, 42.18, 45.28, 45.52, 46.59, 50.85, 51.88, 71.24 (C-28), 87.86 (C-19), 118.10 (C-2), 179.81 (C-3).

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