Pergamon

Tetrahedron Vol. 50, No. 39, pp. 11459-11488, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00707-1

Stereochemistry of Hydrogen Peroxide - Acetic Acid Oxidation of Ursolic Acid and Related Compounds.

Alexey V. Tkachev*[a], Alexey Yu. Denisov[b], Yuri V. Gatilov[a], Irina Yu. Bagryanskaya[a], Sergey A. Shevtsov[a], Tatjana V. Rybalova[a]

[a] Novosibirsk Institute of Organic Chemistry, Novosibirsk 630090, Russia
[b] Novosibirsk Institute of Bioorganic Chemistry, Novosibirsk 630090, Russia

Abstract: Stereochemistry of a number of oxidized derivatives of ursolic acid was established using NMR data and X-ray analysis. Full signal assignments were made in ^{1}H and ^{13}C NMR spectra of 26 natural and synthetic ursane type triterpenoids. Possible mechanisms of oxidation of ursolic acid and related compounds by peracids, as well as mechanisms of secondary processes, were formulated basing on chemical behavior and molecular mechanics calculations of the starting materials and certain intermediate species.

INTRODUCTION

Many triterpenoids of vegetable origin are biologically active compounds and activate some enzymes[1] and decrease the brittleness of blood vessels[2]. Ursolic acid (**1**) is a widespread triterpenoid isolated from different extracts of plant origin individually or as conjugates with sugars. In admixture with its isomer (oleanolic acid) it is contained in pronounced quantities in many plants including those which have long been used in folk medicine[3]. Ursolic acid exhibits a wide spectrum of biological activity: antimicrobial[4], hypocholesterinemic and antiatherosclerotic[5], and antiinflammatory[6] activity; and is also believed to be an inhibitor of dental caries[7]. Biological activity has been found for some synthetic derivatives of ursolic acid[8]. Certain oxidized triterpenoids of the ursane and oleanane series possess an antimicrobial activity[9,10]. It is no wonder, therefor, that ursolic acid, being one of the most simple and easily available derivatives of the α-amirine series, is regarded as a potential substrate for the synthesis of more complex polyfunctional derivatives of the series. The oxidative transformations of ursolic and oleanolic acids as well as the oxidation reactions of the related α- and β-amirines have been studied for a long time.

Some papers were devoted to studies on the oxidation of acetylursolic acid (**2**) by hydrogen peroxide in acetic acid[11-14]. Each paper offered a correction or refinement of the results of preceding papers. It was established that the oxidation of ursolic acid derivatives by acetic peracid at an elevated temperature gives complex mixtures of products among which there are no primary products of oxidation of the 12,13-double bond. All the defined products of oxidation are the products of more extensive transformations. Though the main products of this reaction were described and the oxidation mechanisms were suggested, these results need to be investigated in more detail. The stereochemistry of the oxidation products was not proved, and the schemes of oxidative transformations suggested inadequately describe the process.

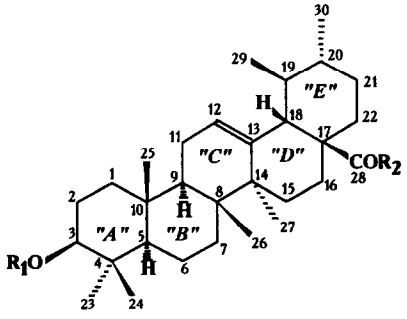
This paper gives the results of our study on stereochemistry of oxidation of ursolic acid (**1**) and some related compounds by acetic and formic peracids.

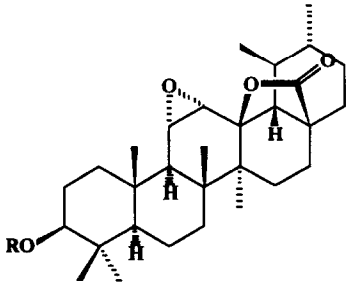
RESULTS AND DISCUSSION.

The structure and stereochemistry of the products were determined by NMR spectra together with IR and MS data. In contrast to the related oleanane derivatives whose spectral data are well-known[15], the ursane compounds were occasionally studied by NMR[16-23]. In this paper we have made full assignment of signals in the spectra of both known and newly synthesized ursane compounds. In the spectra of basic compounds in each structural series (compounds **1**, **5**, **6**, **8**, **10**, **18**, **19**, **21**, **22**, **23**, **25**), the signals were assigned using 2D NMR spectroscopy and the published data for simple derivatives of ursolic acid: methyl ether **5** and 3-acetyl derivative **2**[18-23]. Signal assignment in the spectra of the other substances was made by comparing with the spectra of basic objects using the additional information obtained by homonuclear proton double resonance and the ^{13}C NMR spectra recorded in the JMOD mode[24]. Since proton chemical shifts play an essential role in structure elucidation of new compounds by NMR[25], we also give the proton chemical shift values obtained for basic compounds by 2D spectra of CH-correlation on direct spin-spin coupling constants. NMR spectral data of the compounds studied are listed in ***Tables 1-6***. NMR spectra of acetylursolic acid (**2**) were given earlier in ref.[26].

Analysis of Stereochemistry of Main Oxidation Products.

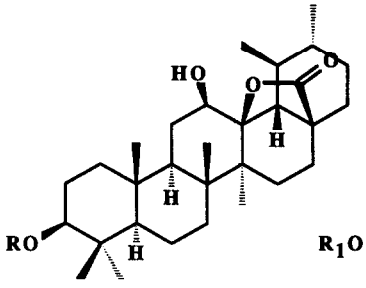
As follows from the data of the previous works, oxidation of acetylursolic acid (**2**) by hydrogen peroxide in acetic acid under heating leads to three main products referred to in ref.[11-13] as U_I, U_{II} and U_{III}. We use the same notation to facilitate comparison of our results with published data.



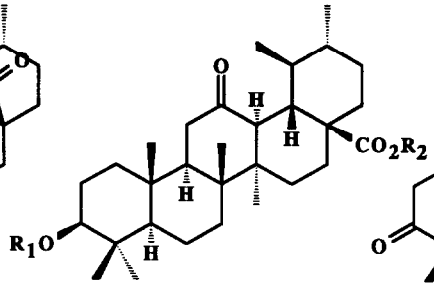


1 R_1=H, R_2=OH
2 R_1=Ac, R_2=OH
3 R_1=HCO, R_2=OH
4 R_1=Ac, R_2=OCH_3
5 R_1=H, R_2=OCH_3
6 R_1=AcO, R_2=Cl

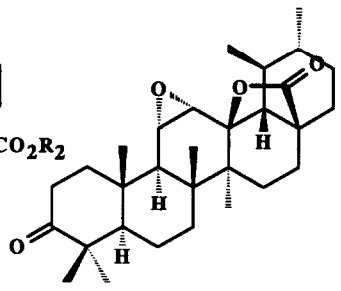
7 R=H
8 R=Ac
9 R=HCO



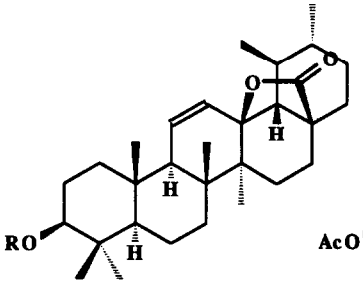
10 R=H
11 R=Ac
12 R=HCO



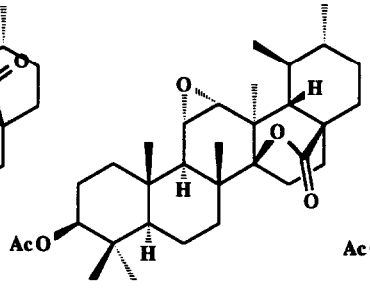
13 R_1=H, R_2=H
14 R_1=H, R_2=CH_3
15 R_1=Ac, R_2=H
16 R_1=Ac, R_2=CH_3
17 R_1=HCO, R_2=H
18 R_1=HCO, R_2=CH_3



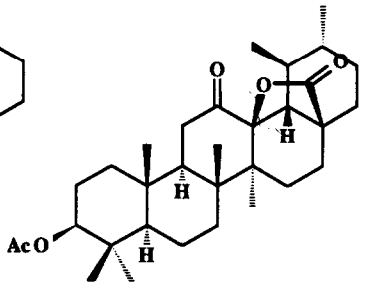
19



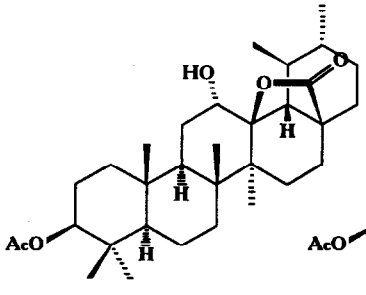
20 R=H
21 R=Ac



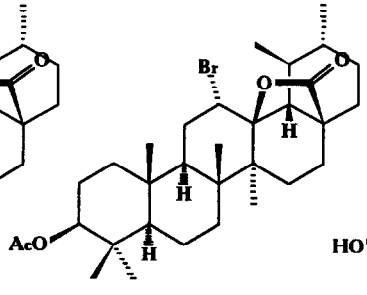
22



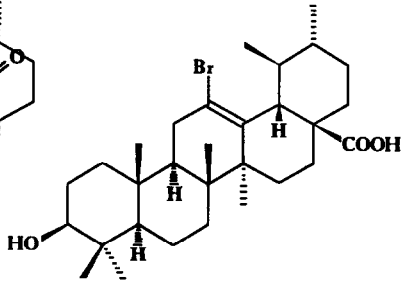
23



24



25



26

Table 1. **^{1}H and ^{13}C NMR Data for Compounds 1, 3 - 5[a,b].**

	1[c]		3[d]		4[e]		5[f]	
i	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)
1	38.37	[0.96, 1.59]	38.11		38.15		38.33	[0.85, 1.49]
2	27.02	[1.51] 2H	23.57		23.40		26.78	[1.46] 2H
3	77.00	3.05 dd, *J* 10.0, 6.0	80.95	4.60 dd, *J* 10.0, 5.8	80.74	4.45 m	78.29	3.05 dd, *J* 9.5, 5.5
4	38.41	-	37.52		37.52		38.33	-
5	54.92	0.70 d, *J* 10.0	55.17		55.16		54.90	0.58 d, *J* 10.0,
6	18.07	[1.32, 1.53]	18.05		18.05		17.94	[1.22, 1.39]
7	32.79	[1.30, 1.49]	32.70		32.75		32.60	[1.15, 1.34]
8	39.19	-	39.38		39.35		39.07	-
9	47.13	[1.51]	47.34		47.34		47.16	[1.36]
10	36.58	-	36.78		36.71		36.54	-
11	22.91	[1.89] 2H	23.15	1.90 dd (2H), *J* 8.5, 3.5	23.15	1.86 dd (2H), *J* 8.5, 3.5	22.90	1.77 dd (2H), *J* 8.5, 3.5
12	124.69	5.17 t, *J* 3.5	125.54	5.21 t, *J* 3.5	125.31	5.20 t, *J* 3.5	125.18	5.10 t, *J* 3.5
13	138.18	-	137.87		138.04		137.68	-
14	41.68	-	41.77		41.83		41.53	-
15	27.62	[1.04, 1.85]	27.86	*ax.* 1.84 ddd, *J* 13.5, 13.5, 4.0	27.86	*ax.* 1.61 ddd, *J* 13.5, 13.5, 4.5	27.63	*ax.* 1.63 ddd, *J* 13.5, 13.5, 4.5 *eq.* [0.91]
16	23.89	[1.56, 1.96]	23.90	*ax.* 1.99 ddd, *J* 13.5, 13.5, 4.2	24.07	*ax.* 1.96 ddd, *J* 13.5, 13.5, 4.2	23.81	*ax.* 1.86 ddd, *J* 13.5, 13.5, 4.0 *eq.* [1.53]
17	46.89	-	47.84		47.92		47.61	-
18	52.44	2.15 d, *J* 11.5	52.38	2.16 d, *J* 11.0	52.73	2.19 d, *J* 11.0	52.45	2.09 d, *J* 11.0
19	38.59	[1.34]	38.89		38.88		38.63	[1.19]
20	38.59	[0.98]	38.70		38.72		38.47	[0.86]
21	30.34	[1.28, 1.49]	30.47		30.49		30.26	[1.14, 1.35]
22	36.39	[1.61] 2H	36.60		36.48		36.20	[1.44, 1.53]
23	28.25	0.95 s	27.88	0.87 s	27.92	0.82 s	27.82	0.85 s
24	16.00	0.72 s	16.57	0.85 s	16.57	0.81 s	15.34	0.64 s
25	15.26	0.91 s	15.39	0.95 s	15.33	0.90 s	15.06	0.78 s
26	16.91	0.80 s	16.89	0.75 s	16.75	0.70 s	16.47	0.60 s
27	23.30	1.08 s	23.48	1.06 s	23.41	1.03 s	23.23	0.94 s
28	178.35	-	183.75		177.84		177.49	-
29	16.99	0.85 d, *J* 6.5	16.97	0.84 d, *J* 6.3	16.90	0.82 d, *J* 6.3	16.67	0.72 d, *J* 6.3
30	21.09	0.96 d, *J* 6.5[g]	21.05	0.93 d, *J* 5.8[g]	21.02	0.89 d, *J* 5.8[g]	20.82	0.81 d, *J* 6.4[g]

[a] chemical shifts are given in ppm. [b] ^{1}H chemical shifts put in square brackets were taken from the 2D heteronuclear ^{13}C-^{1}H chemical shift correlation spectra ($^{1}J_{CH}$ = 125 Hz). [c] c = 200 mg/ ml in **DMSO-d_6 - $CDCl_3$** 3:2 v/v. [d] c = 40 mg/ml in **$CDCl_3$**, formate - δ_C 161.02 *d*, δ_H 8.09 *br.s* 1H. [e] c = 130 mg/ml in **$CDCl_3$**; acetate - δ_C 21.12 *q* and 170.75 *s*, δ_H 2.00 *s* 3H; methoxy group - δ_C 51.24 *q*, δ_H 3.56 *s* 3H. [f] c = 300 mg/ ml in **$CDCl_3$**; methoxy group - δ_C 51.01 *q*, δ_H 3.46 *s* 3H. [g] appreciably distorted doublet.

Table 2. **^{1}H and ^{13}C NMR Data for Compounds 6 - 8, 10[a,b].**

	6[c]		7[d]		8[e]		10[f]	
i	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)
1	38.22	[1.05, 1.62]	38.05	*eq.* 1.88 ddd, *J* 13.4, 3.5, 3.5	37.69	*eq.* 1.87 ddd, *J* 13.5, 3.5, 3.5 *ax.* [1.27]	38.79	[0.95, 1.74]
2	23.40	[1.60] 2H	26.71		23.02	[1.68] 2H	27.09	[1.59] 2H
3	80.71	4.46 m	78.67	3.22 dd, *J* 11.2, 5.1	80.32	4.49 dd, *J* 10.5, 5.9	78.57	3.15 dd, *J* 11.0, 5.0
4	37.54	-	38.70		37.62	-	38.69	-
5	55.19	[0.80]	54.44	0.68 dd, *J* 12.0, 2.7	54.45	0.77 dd, *J* 11.7, 3.0	55.04	0.64 d, *J* 11.0,
6	18.03	[1.35, 1.50]	17.50		17.35	[1.48, 1.54]	17.55	[1.37, 1.49]
7	32.78	[1.30, 1.47]	31.21		31.12	[1.13, 1.26]	33.84	[1.22, 1.42]
8	39.45	-	41.33		41.31	-	42.26	-
9	47.32	[1.49]	51.33	1.53 d, *J* 2.2	51.19	1.55 d, *J* 2.2	49.16	[1.25]
10	36.71	-	36.30		36.18	-	36.80	-
11	23.20	1.91 m (2H)	54.69	3.10 dd, *J* 4.0, 2.2	54.57	3.08 dd, *J* 3.8, 2.2	28.91	[1.49, 1.82]
12	126.83	5.26 t, *J* 3.6	56.15	2.92 d, *J* 4.0	56.05	2.91 d, *J* 3.8	69.21	3.92 dd, *J* 11.5, 5.2
13	136.46	-	88.91		88.87	-	94.40	-
14	41.89	-	41.19		41.15	-	43.35	-
15	27.67	[1.12, 1.81]	26.71		26.67	[1.06, 1.65]	27.40	*ax.* 1.91 ddd, *J* 13.5, 13.5, 6.0 *eq.* [1.19]
16	25.22	*ax.* 2.08 ddd, *J* 13.5, 13.5, 4.8 *eq.* [1.76]	22.62	*ax.* 2.10 ddd, *J* 13.3, 13.3, 5.9	22.59	*ax.* 2.10 ddd, *J* 13.3, 13.3, 5.5 *eq.* [1.34]	22.37	*ax.* 2.07 ddd, *J* 13.5, 13.5, 6.0 *eq.* [1.31]
17	58.72	-	45.02		44.99	-	45.28	-
18	53.91	2.18 dd, *J* 11.2, 1.3	60.53		60.48	[1.74]	52.14	2.22 d, *J* 11.5
19	39.58	[1.32]	37.37		37.33	[1.71]	38.46	[1.75]
20	38.48	[0.97]	40.09		40.05	[0.89]	39.44	[0.96]
21	30.31	[1.29, 1.57]	30.43		30.40	[1.25, 1.57]	30.61	[1.24, 1.55]
22	35.22	[1.66, 1.85]	31.28	*eq.* 1.79 ddd, *J* 13.4, 3.8, 2.8	31.25	[1.48, 1.77]	31.39	[1.44, 1.75]
23	27.93	0.84 s	27.65	0.96 s	27.59	0.82 s	27.81	0.93 s
24	16.58	0.83 s	14.95	0.77s	16.07	0.83 s	15.18	0.72 s
25	15.42	0.93 s	17.10	1.00 s	17.16	1.02 s	16.31	0.83 s
26	16.78	0.79 s	20.11	1.05 s	20.10	1.04 s	18.32	1.11 s
27	23.34	1.06 s	16.23	1.08 s	16.18	1.07 s	17.00	1.15 s
28	179.22	-	179.06		179.04	-	179.64	-
29	16.85	0.85 d, *J* 6.5	17.10	1.18 d, *J* 5.8	17.09	1.18 d, *J* 5.7	16.26	1.09 d, *J* 6.3
30	20.81	0.93 d, *J* 5.5[g]	19.38	0.96 d, *J* 6.0[g]	19.38	0.95 d, *J* 5.9[g]	19.31	0.91 d, *J* 6.0[g]

[a] chemical shifts are given in ppm for $CDCl_3$ solutions. [b] ^{1}H chemical shifts put in square brackets were taken from the 2D heteronuclear ^{13}C-^{1}H chemical shift correlation spectra ($^1J_{CH}$ = 125 Hz). [c] c = 140 mg /ml; acetate - δ_C 21.13 *q* and 170.81 *s*, δ_H 2.01 *s* 3H. [d] c = 40 mg/ml. [e] c = 75 mg/ml; acetate - δ_C 21.11 *q* and 170.73 *s*, δ_H 2.02 *s* 3H. [f] c = 80 mg/ml. [g] appreciably distorted doublet.

Table 3. **^{1}H and ^{13}C NMR Data for Compounds 11 - 14[a].**

	11[b]		12[c]		13[d]		14[e]	
i	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)
1	38.50		38.43		38.35		38.26	
2	23.44		23.53		26.92		26.90	
3	80.46	4.45 dd, *J* 11.2, 6.0	80.50	4.57 m	78.57	3.20 dd, *J* 11.2, 3.9	78.33	3.14 dd, *J* 11.4, 4.2
4	37.65		37.58		38.71		38.65	
5	55.14	0.76 d, *J* 11.0	55.09	0.76 d, *J* 11.0	55.17		55.09	
6	17.45		17.44		17.50		17.40	
7	33.79		33.74		34.01		33.90	
8	42.29		42.27		40.28		40.11	
9	49.08	1.30 dd, *J* 13.0, 2.0	49.05		50.59		50.59	
10	36.75		36.71		37.15		37.03	
11	29.01		28.95		39.46	*ax.* 2.56 dd, *J* 15.0, 14.0 *eq.* 2.36 dd, *J* 15.0, 3.5	39.46	*ax.* 2.53 dd, *J* 15.3, 13.6 *eq.* 2.32 dd, *J* 15.3, 3.5
12	69.22	3.94 dd, *J* 11.5, 5.5	69.13	3.93 m	216.32		216.10	
13	94.32		94.25		59.08	1.84 d, *J* 11.0	59.05	1.79 d, *J* 11.6
14	43.38		43.36		43.06		42.87	
15	27.41	*ax.* 1.92 ddd, *J* 13.5, 13.5, 6.0	27.39	*ax.* 1.91 ddd, *J* 13.5, 13.5, 6.0	25.96		25.71	
16	22.39	*ax.* 2.09 ddd, *J* 13.5, 13.5, 5.8	22.36	*ax.* 2.08 ddd, *J* 13.5, 13.5, 6.0	31.78		31.65	
17	45.31		45.25		46.54		46.51	
18	52.21	2.23 d, *J* 11.8	52.14	2.22 d, *J* 11.8	43.03	2.71 dd., *J* 11.0, 7.5	43.30	2.75 dd., *J* 11.6, 8.3
19	38.48		38.45		36.68		36.35	
20	39.47		39.44		32.01		31.67	
21	30.63		30.60		28.99		29.00	
22	31.42		31.40		27.76		27.35	
23	27.77	0.82 s	27.67	0.84 s	27.85	0.96 s	27.78	0.93 s
24	16.40	0.81 s	16.35	0.82 s	15.32	0.77 s	15.25	0.74 s
25	16.35	0.87 s	16.29	0.87 s	15.89	0.90 s	15.81	0.87 s
26	18.35	1.13 s	18.33	1.12 s	18.06	1.29 s	17.86	1.28 s
27	16.98	1.16 s	16.97	1.15 s	24.75	0.92 s	24.53	0.87 s
28	179.61		179.49		183.78		178.81	
29	16.30	1.11 d, *J* 6.3	16.27	1.10 d, *J* 6.3	19.88	0.69 d, *J* 5.8	19.83	0.63 d, *J* 6.3
30	19.34	0.92 d, *J* 6.0[f]	19.30	0.91 d, *J* 5.8[f]	20.15	0.76 d, *J* 5.0	20.06	0.70 d, *J* 5.9

[a] chemical shifts are given in ppm for **$CDCl_3$** solutions. [b] c = 50 mg/ml; acetate - δ_C 21.14 *q* and 170.86 *s*, δ_H 2.01 *s* 3H. [c] c = 90 mg/ml, formate - δ_C 160.89 *d*, δ_H 8.06 *br.s* 1H. [d] c = 50 mg/ml. [e] c = 70 mg/ml, methoxy group - δ_C 51.86 *q*, δ_H 3.65 *s* 3H. [f] appreciably distorted doublet.

Table 4. **^{1}H and ^{13}C NMR Data for Compounds 15 - 18[a,b].**

	15[c]		16[d]		17[e]		18[f]	
i	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)
1	38.03		37.86		37.98		37.98	[1.03, 1.62]
2	23.32		23.18		23.43		23.45	[1.65] 2H
3	80.26	4.46 dd, *J* 10.8, 5.2	80.05	4.37 dd, *J* 10.5, 5.0	80.36	4.58 m	80.34	4.57 m
4	37.65		37.49		37.61		37.61	-
5	55.20		55.05		55.18		55.20	[0.81]
6	17.37		17.23		17.38		17.38	[1.45, 1.53]
7	33.85		33.74		33.85		33.86	[1.42] 2H
8	40.27		40.05		40.25		40.20	-
9	50.27		50.27		50.34		50.42	[1.63]
10	37.02		36.84		37.00		36.99	-
11	39.41	*ax.* 2.55 dd, *J* 15.3, 13.6; *eq.* 2.36 dd, *J* 15.3, 4.0	39.32	*ax.* 2.47 dd, *J* 15.1, 13.8; *eq.* 2.26 dd, *J* 15.1, 3.5	39.42	*ax.* 2.55 dd, *J* 15.2, 13.8; *eq.* 2.35 dd, *J* 15.2, 3.7	39.49	*ax.* 2.54 dd, *J* 15.3, 13.6; *eq.* 2.33 ddd, *J* 15.3, 3.5, 1.3
12	216.10		215.31		216.04		215.55	-
13	58.78	1.86 d, *J* 11.0	58.79	1.74 d, *J* 11.4	58.89	1.85 d, *J* 11.2	58.96	1.80 dd, *J* 11.6, 1.3
14	43.00		42.71		42.99		42.89	-
15	25.95		25.64		25.92		25.78	[0.85, 1.80]
16	31.54		31.45		31.65		31.61	[1.19, 1.55]
17	46.61		46.42		46.55		46.60	-
18	42.87	2.70 dd, *J* 11.0, 7.5	43.15	2.70 dd, *J* 11.4, 8.1	42.96	2.71 dd, *J* 11.2, 7.7	43.35	2.76 ddd, *J* 11.6, 8.6, 0.9
19	36.72		36.26		36.64		36.41	[1.04]
20	32.19		31.67		32.05		31.81	[0.92]
21	28.98		28.95		28.98		29.09	[0.98, 1.68]
22	28.04		27.41		27.85		27.54	[1.44, 1.77]
23	27.81	0.84 s	27.65	0.77 s	27.72	0.86 s	27.72	0.85 s
24	16.43	0.84 s	16.26	0.76 s	16.41	0.86 s	16.40	0.85 s
25	15.91	0.92 s	15.76	0.85 s	15.89	0.93 s	15.89	0.92 s
26	18.02	1.28 s	17.75	1.23 s	18.00	1.28 s	17.90	1.30 s
27	24.71	0.92 s	24.40	0.82 s	24.67	0.92 s	24.54	0.89 s
28	183.96		178.59		183.63		178.81	-
29	19.83	0.69 d, *J* 5.7	19.74	0.58 d, *J* 6.3	19.86	0.68 d, *J* 5.5	19.89	0.65 d, *J* 6.3
30	20.15	0.77 d, *J* 5.0	19.99	0.65 d, *J* 6.0	20.14	0.77 d, *J* 5.0	20.10	0.72 d, *J* 6.1

[a] chemical shifts are given in ppm for $CDCl_3$ solutions. [b] ^{1}H chemical shifts put in square brackets were taken from the 2D heteronuclear ^{13}C-^{1}H chemical shift correlation spectra ($^1J_{CH}$ = 125 Hz). [c] c = 25 mg/ml; acetate - δ_C 21.12 *q* and 170.82 *s*, δ_H 2.02 *s* 3H. [d] c = 120 mg/ml; acetate - δ_C 20.91 *q* and 170.42 *s*, δ_H 1.93 *s* 3H; methoxy group - δ_C 51.70 *q*, δ_H 3.60 *s* 3H. [e] c = 35 mg/ml; formate - δ_C 160.91 *d*, δ_H 8.07 *br.s* 1H. [f] c = 70 mg/ml; formate - δ_C 160.80 *d*, δ_H 8.06 *br.s* 1H; methoxy group - δ_C 51.88 *q*, δ_H 3.67 *s* 3H

Table 5. **^{1}H and ^{13}C NMR Data for Compounds 19 - 22[a,b].**

	19[c]		**20**[d]		**21**[e]		**22**[f]	
i	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)
1	38.51	*Ha* 2.12 ddd, *J* 13.3, 6.9, 3.3 *Hb* [1.59]	38.11	*eq.* 1.79 ddd, *J* 13.0,3.5,3.5	37.59	[0.96, 1.73]	38.19	*eq.* 1.77 ddd, *J* 13.5, 3.6, 3.6 *ax.* [1.30]
2	33.64	*Ha* 2.39 ddd, *J* 16.0, 6.2, 3.3; *Hb* 2.62 ddd, *J* 16.0, 11.9, 6.9	26.80		22.94	[1.56, 1.60]	23.18	[1.70] 2H
3	216.00	-	78.52	3.16 dd, *J* 11.2, 5.0	80.12	4.38 dd, *J* 10.5, 5.8	80.30	4.48 m
4	47.39	-	38.71		37.44	-	37.62	-
5	54.52	[1.22]	54.57	0.69 dd, *J* 11.8, 2.7	54.43	[0.74]	55.61	0.81 dd, *J* 11.5, 3.0
6	18.64	[1.49, 1.60]	17.49		17.20	[1.42, 1.49]	19.41	[1.56, 1.62]
7	30.56	[1.17, 1.30]	31.05		30.81	[1.15, 1.31]	39.00	[1.28, 1.68]
8	41.21	-	41.48		41.30	-	44.28	-
9	50.68	[1.61]	52.83	1.90 br.s	52.54	1.86 br.s	54.90	1.24 d, *J* 7.0
10	36.05	-	36.15		35.89	-	37.18	-
11	54.41	3.13 dd, *J* 3.9, 2.2	128.61	5.47 dd, *J* 10.4, 3.0	128.59	5.42 dd, *J* 10.3, 3.2	51.53	3.04 dd, *J* 7.0, 4.8
12	56.09	2.94 d, *J* 3.9	133.24	5.90 dd, *J* 10.4, 1.5	132.80	5.83 dd, *J* 10.3, 1.9	61.93	2.90 d, *J* 4.8
13	88.69	-	89.46		89.08	-	41.07	-
14	41.22	-	41.74		41.54	-	91.32	-
15	26.72	[1.08, 1.67]	25.34		25.14	[1.10, 1.60]	26.10	[1.56, 2.02]
16	22.57	*ax.* 2.10 ddd, *J* 13.5, 13.5, 5.9 *eq.* [1.35]	22.61	*ax.* 2.08 ddd, *J* 13.1, 13.1, 5.9	22.43	*ax.* 2.02 ddd, *J* 13.3, 13.3, 6.0 *eq.* [1.27]	22.51	[1.25, 2.08]
17	44.94	-	44.87		44.63	-	40.90	-
18	60.48	1.74 d, *J* 11.0	60.38	1.57 d, *J* 11.7	60.19	1.51 d, *J* 11.7	56.00	1.47 dd, *J* 10.5, 1.3
19	37.36	[1.71]	37.92		37.69	[1.67]	35.80	[1.41]
20	40.05	[0.90]	40.06		39.87	[0.77]	38.70	[1.04]
21	30.38	[1.25, 1.57]	30.62		30.44	[1.17, 1.47]	29.31	[1.02, 1.52]
22	31.24	*eq.* 1.78 ddd, *J* 13.1, 3.7, 2.8 *ax.* [1.48]	31.14		30.98	[1.39, 1.67]	31.38	*ax.* 1.90 ddd, *J* 13.8, 13.8, 3.6 *eq.* [1.61]
23	25.79	1.06 s	27.58	0.93 s	27.35	0.75 s	27.51	0.81 s
24	20.98	1.02 s	14.74	0.73 s	15.69	0.75 s	16.20	0.86 s
25	16.32	1.15 s	17.70	0.86 s	17.59	0.82 s	18.05	1.10 s
26	19.82	1.09 s	18.69	1.00 s	18.52	0.94 s	20.61	1.16 s
27	16.09	1.08 s	15.90	1.11 s	15.69	1.05 s	18.31	1.03 s
28	178.87	-	179.63		179.22	-	178.17	-
29	17.05	1.17 d, *J* 5.7	17.61	0.94 d, *J* 6.0	17.47	0.89 d, *J* 6.0	18.97	1.01 d, *J* 5.8
30	19.35	0.95 d, *J* 6.0[g]	18.95	0.88 d, *J* 6.0[g]	18.79	0.83 d, *J* 6.0[g]	19.96	0.95 d, *J* 5.3[g]

[a] chemical shifts are given in ppm for **$CDCl_3$** solutions. [b] **^{1}H** chemical shifts put in square brackets were taken from the 2D heteronuclear **^{13}C-^{1}H** chemical shift correlation spectra ($^1J_{CH}$ = 125 Hz). [c] c = 100 mg/ml. [d] c = 150 mg/ml. [e] c = 200 mg/ml; acetate - δ_C 20.87 *q* and 170.37 *s*, δ_H 1.93 *s* 3H. [f] c = 60 mg/ml; acetate - δ_C 21.10 *q* and 170.69 *s*, δ_H 2.01 *s* 3H. [g] appreciably distorted doublet.

Table 6. **^{1}H and ^{13}C NMR Data for Compounds 23 - 26[a,b].**

	23[c]		24[d]		25[e]		26[f]	
i	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)	$\delta_C{}^i$	$\delta_H{}^i$, *J* (Hz)
1	37.72	[0.99, 1.55]	38.39		37.58	[1.13, 1.64]	38.04	
2	23.12	[1.55, 1.61]	23.46		23.23	[1.64] 2H	26.67	
3	80.04	4.41 dd, *J* 11.2, 5.5	80.70	4.47 m	80.45	4.47 dd, *J* 11.0, 4.8	77.03	3.07 m
4	37.53	-	37.71		37.68	-	38.24	
5	54.82	[0.78]	55.60		55.50	[0.85]	54.45	0.67 d, *J* 11.0
6	17.26	[1.46, 1.55]	17.59		17.54	[1.50] 2H	17.72	
7	32.31	[1.28, 1.46]	35.03		35.07	[1.24, 1.47]	32.42	
8	41.36	-	42.57		42.48	-	39.82	
9	48.00	1.67 dd, *J* 13.2, 5.0	44.28		47.02	1.83 dd, *J* 10.3, 4.0	48.53	
10	36.65	-	36.49		36.97	-	36.46	
11	36.42	*ax.* 2.52 dd, *J* 18.0, 13.2 *eq.* 2.39 dd, *J* 18.0, 5.0	28.65	*ax.* 1.99 ddd, *J* 13.5, 13.5, 2.5	31.35	*ax.* 2.33 ddd, *J* 14.6, 10.3, 4.4 *eq.* [1.91]	35.94	*ax.* 2.34 dd, *J* 18.0, 11.0 *eq.* 2.42 dd, *J* 18.0, 6.5
12	205.31	-	74.16	3.71 br. *W* 7 Hz	54.48	4.35 dd, *J* 5.5, 4.4	124.43	
13	89.91	-	94.32		96.91	-	137.59	
14	43.06	-	42.96		44.43	-	44.86	
15	25.64	*ax.* 1.83 ddd, *J* 13.5, 13.5, 6.0 *eq.* [1.24]	28.45		28.47	[1.20, 1.92]	28.00	*ax.* 1.86 ddd, *J* 13.5, 13.5, 4.0
16	22.13	*ax.* 2.08 ddd, *J* 13.5, 13.5, 6.0 *eq.* [1.32]	23.20	*ax.* 2.15 ddd, *J* 13.3, 13.3, 5.9	23.13	*ax.* 2.19 ddd, *J* 13.0, 13.0, 6.0 *eq.* [1.30]	23.08	*ax.* 1.99 ddd, *J* 13.5, 13.5, 4.0
17	44.81	-	46.71		47.48	-	47.03	
18	53.04	2.32 d, *J* 11.8	62.20		61.45	1.74 d, *J* 10.5	48.87	3.15 d, *J* 11.5
19	37.82	[1.64]	39.44		39.32	[1.86]	39.99	
20	39.64	[0.99]	40.21		40.18	[0.96]	38.70	
21	30.49	[1.21, 1.54]	30.61		30.56	[1.28, 1.55]	30.20	
22	31.08	*eq.* 1.73 ddd, *J* 13.0, 4.0, 2.0 *ax.* [1.46]	31.92		31.70	*eq.* 1.79 ddd, *J* 13.0, 4.1, 2.3 *ax.* [1.47]	35.94	
23	27.65	0.81 s	27.81	0.84 s	27.71	0.82 s	27.93	0.93 s
24	16.19	0.80 s	16.39	0.83 s	16.28	0.81 s	15.58	0.72 s
25	15.36	0.86 s	16.94	0.90 s	17.21	0.91 s	14.94	0.91 s
26	17.98	1.10 s	18.88	1.19 s	20.27	1.22 s	16.71	0.82 s
27	16.53	1.12 s	18.04	1.24 s	19.08	1.29 s	22.81	1.14 s
28	177.89	-	179.52		178.13	-	178.22	
29	18.22	0.84 d, *J* 6.5	18.43	1.24 d, *J* 6.4	21.32	1.35 d, *J* 6.5	15.87	0.98 d, *J* 6.3
30	19.26	0.88 d, *J* 6.0[g]	20.26	0.97 m	20.20	0.95 m	20.54	0.92 d, *J* 6.0[g]

[a] chemical shifts are given in ppm. [b] ^{1}H chemical shifts put in square brackets were taken from the 2D heteronuclear ^{13}C-^{1}H chemical shift correlation spectra ($^1J_{CH}$ = 125 Hz). [c] c = 120 mg/ml in **$CDCl_3$**; acetate - δ_C 21.00 *q* and 170.62 *s*, δ_H 2.00 *s* 3H. [d] c = 40 mg/ml in **$CDCl_3$**; acetate - δ_C 21.17 *q* and 170.90 *s*, δ_H 2.02 *s* 3H. [e] c = 90 mg/ml in **$CDCl_3$**; acetate - δ_C 21.11 *q* and 170.75 *s*, δ_H 2.01 *s* 3H. [f] c = 40 mg/ml in **DMSO-d_6-$CDCl_3$** 1:1 v/v. [g] appreciably distorted doublet.

Epoxy derivatives **8** *and* **22**. Epoxylactone **8** described in ref.[12] as U_1 is the first product that is easily isolated from the mixture of oxidation products by ordinary crystallization from a mixture of chloroform and methanol. Chemical structure of this product is unambiguously identified by the NMR data. As to configuration of the oxide cycle, the authors of the work[12] have ascribed this compound the structure of the 11α,12α-epoxy derivative with the reference to coincident character of the epoxide proton splitting with that of the corresponding oleanane derivative. Comparison of spectral data of U_1 with published data for the oleanane epoxylactone shows there is no unambiguous coincidence. Indeed, the signals of epoxide protons have the same chemical shifts in ^{1}H NMR spectra of both synthetic and natural 11α,12α-epoxylactone of oleanolic acid: δ 2.95 s, $W_{1/2}$ = 3 Hz, 2H (100 MHz, **$CDCl_3$**)[27]; δ 3.00 s $W_{1/2}$ = 3 Hz, 2H (80 MHz, **$CDCl_3$**)[13]; δ 3.00 s 2H (60 MHz, **$CDCl_3$**)[28]. However, the authors of the work[12] have noted for U_1 that the epoxide proton signals have different chemical shifts: δ 2.95 δ J = 4 Hz, 1H and δ 3.10 br.s $W_{1/2}$ = 4 Hz (60 MHz, **$CDCl_3$**). Thus, we can hardly make any conclusion about configuration of the epoxide cycle by comparison of ^{1}H NMR spectra of U_1 with the spectrum of the corresponding oleanane derivative.

Effect of stereochemistry of the epoxide cycle on ^{13}C NMR chemical shifts for the 1,2-epoxy cyclohexane moiety was studied in detail on a wide variety of steroid compounds[29]. We have made full assignment of ^{13}C NMR signals both for the starting olefin **21** and for U_1 (**8**), but ^{13}C NMR spectra proved to be unfit to determine configuration of the epoxide cycle because the experimental values of chemical shifts did not agree with the calculated values for both 11α,12α- and 11β,12β-epoxides.

We have made an attempt to determine configuration of the epoxide ring in the U_1 molecule by comparing the experimental spin-spin coupling constant $^3J_{HH}$ values and the calculated values obtained for a pair of stereoisomers. We have refined the geometry of two epimers **8** and **33** by the molecular mechanics method. Since the available and most popular programs for molecular mechanics calculations either do not permit the calculation of molecules containing the α-epoxide fragment at all (MM2, MMP2) or permit the calculations using only generalized parameters (MMX)[30], we used additional parameterization for the epoxide cycle. In addition to the published set of parameterization[31], we have tried parameterization developed by Gatilov and Rybalova[32]. The main values of the latter one are given in ***Table 7***. The lacking parameters of our parameterization and of that described in ref.[31] were taken from the set of constants of the MM2 program in view of their analogy and semantic similarity. Because this is not an unambiguous choice, we have made up two sets of parameters in order to verify whether the results are invariant or not. These two sets of parameters are very closed and only one set is shown in ***Table 7***. The calculations were performed using the MM2 and MMX[33] programs. The refined geometry of two stereoisomeric epoxides was then used in the calculations of the $^3J_{HH}$ couplings (***Table 8***) according to the previously described procedure[34]. The results of calculations for both 11α,12α-isomer and 11β,12β-isomer are in poor agreement with the experimental values. Both molecules are considerably strained, the bond lengths and bond angles in the fragment containing the "B" and "C" rings are markedly distorted (See ***Table 8***). We believe the deviation of bond lengths and bond angles at the site of fusion of the "B" and "C" rings from normal values to be just the reason of such a great difference between the calculated and experimental spin-spin coupling constants[35].

We decided to undertake X-ray study of U_1, but it appeared that neither 3-acetoxy-derivative **8** itself nor 3-hydroxy-derivative **7** give crystals that are fit for the X-ray analysis. Only for 3-keto-derivative **19** could be grow up a suitable single crystal. ***Figure 1*** shows the structure of one of the four crystallographically

independent molecules of ketone **19** according to the X-ray structure analysis data. Thus, compound U_I was identified to be 11α,12α-epoxide.

Table 7. **Supplementary MM2 Parameters for Oxiranes[a].**

Stretching and dipole moment parameters

bond	K_S, mdyn/Å	r_o, Å	moment, D
6-22	5.36	1.427	-0.7
22-22	4.40	1.465	0.0

Torsional parameters

dihedral angle	V_1,kcal/mol	V_2,kcal/mol	V_3,kcal/mol
1-1-22-6	0.1	0.10	0.180
5-1-22-6	0.0	0.00	0.180
20-6-22-1	0.0	0.00	0.000
20-6-22-5	0.0	0.00	0.000
20-6-22-22	0.0	0.00	0.000
22-6-22-1	0.4	0.52	0.467
22-6-22-5	0.0	0.00	0.530
1-22-22-6	0.1	0.10	0.180
5-22-22-6	0.0	0.0	0.180

Bending parameters

angle	K_b, mdyn/Å·rad²	θ_o, deg.	angle type
20-6-22	0.35	105.16	1
22-6-22	0.77	60	1
6-22-22	0.45	60	0
1-22-6	0.60	117.50	0
5-22-6	0.36	116.00	0
1-22-22	0.60	121.00 122.00	1 2
5-22-22	0.36	124.00 121.00	1 2

Heat parameters

bond	increment, kcal/mol	structural feature	increment, kcal/mol
6-22	-23.673	oxirane ring	47.625
1-22	-2.333	22-methyl	-1.510
5-22	-3.205	6-sec.22	-2.355
22-22	-7.429	6-tert.22	-4.830

[a] In order to use many of the constants associated with carbon and oxygen atoms in MM2 program, we assigned type 22 to oxirane carbon and type 6 to oxirane oxygen.

Compound U_I (**8**) was prepared by the known procedure of oxidation of acetylursolic acid (**2**)[12]. Though m.p. and specific rotation of the epoxylactone sample prepared somewhat differed from the values reported in ref.[12], the spectral parameters of the product were similar to the data published (see **EXPERIMENTAL**). It appeared that in fact one more 11,12-epoxylactone **22** is formed apart from U_I, whose NMR spectra are very similar to those of U_I (**8**). The analysis of 2D NMR spectra of this compound suggests that it is a derivative of iso-ursane series. ***Figure 2*** shows the structure and configuration of this product according to the X-ray data.

12-Hydroxy-13,28-olide U_{II} (**11**). Hydroxylactone **11** is another product of oxidation of acetylursolic acid (**2**). Based on "the presence of a broad one-proton signal at δ 4.03 (W = 8 Hz)"[12,13], this compound was assigned the structure with the axial α-oriented **OH**-group at **C**-12 atom. This is just the product that would

be obtained in the ordinary trans-diaxial cleavage of 12β,13β-epoxide group. We have isolated this hydroxy lactone and it appeared to have just the same physico-chemical and spectral data as the product described in ref.[12] as compound U_{II}. However, the analysis of the ^{1}H NMR spectrum has shown this compound to have the equatorial 12β-hydroxyl group since the H-12 signal in the ^{1}H NMR spectrum is in the form of a doublet of doublets with J = 11.5 and 5.5 Hz. In addition, the OH-group absorption band is observed at 3585 cm^{-1} (the intramolecular hydrogen bond[37]) in the IR spectrum of this compound.

Table 8. **Results of Molecular Mechanics Calculations for 11,12-Epoxy Derivatives 8, 22 and 33.**

program	parameter	8	33	22
MMX	E, kcal/mol	91.8	92.0	100.2
	ΔH_f, kcal/mol	-249.4	-249.2	-242.8
MM2[a]	E, kcal/mol	100.4	100.8	104.1
	ΔH_f, kcal/mol	-262.1	-261.4	-260.2
	$l_{C^8\text{-}C^9}$ (l_o = 1.523 Å)	1.556	1.563	
	$l_{C^9\text{-}C^{10}}$ (l_o = 1.523 Å)	1.571	1.573	
	$l_{C^9\text{-}C^{11}}$ (l_o = 1.505 Å)	1.534	1.534	
	$\theta_{H^9\text{-}C^9\text{-}C^{11}}$ (θ_o = 109.4°)	104.7	100.8	
	$\theta_{H^{11}\text{-}C^{11}\text{-}C^9}$ (θ_o = 123.5°)	117.7	116.3	
	$\theta_{C^8\text{-}C^9\text{-}C^{10}}$ (θ_o = 109.5°)	118.3	117.7	
	$\theta_{C^8\text{-}C^9\text{-}C^{11}}$ (θ_o = 112.4°)	110.8	114.1	
	$\theta_{C^{10}\text{-}C^9\text{-}C^{11}}$ (θ_o = 112.4°)	115.6	116.0	
	$\phi_{H^9\text{-}C^9\text{-}C^{11}\text{-}H^{11}}$ (deg.)	124.1	58.1	151.8
	$^3J_{H^9\text{-}H^{11}}$ (Hz), calculated[b]	5.0	3.8	9.8
	$^3J_{H^9\text{-}H^{11}}$ (Hz), calculated[c]	1.6	1.4	4.0
	$^3J_{H^9\text{-}H^{11}}$ (Hz), experimental	2.2	-	7.0
MM2[d]	E, kcal/mol	97.1	98.1	100.2
	ΔH_f, kcal/mol	-263.2	-262.1	-260.9

[a] using supplementary parameters of Podlogar and Raber[31]
[b] according to the procedure described in ref.[34]
[c] according to the equation $^3J = 5.1\cos^2\phi$ [36]
[d] using supplementary parameters (see ***Table 7***).

We have synthesized α-OH derivative **24** by reduction of 12-keto-lactone **23**. This isomer really has an axial hydroxyl group, and its NMR spectra are similar to those of 12α-bromo derivative **25** whose stereochemistry was unambiguously defined (see ***Table 6***). This α-isomer **24** is not formed upon oxidation of ursolic and acetylursolic acids.

12-Keto-derivative U_{III} **(15).** One of the main products of oxidation of acetylursolic acid (**2**) is keto acid **15** defined in ref.[11,12] as U_{III}. In ref.[12] this compound was ascribed the structure of a 13αH-derivative "on the

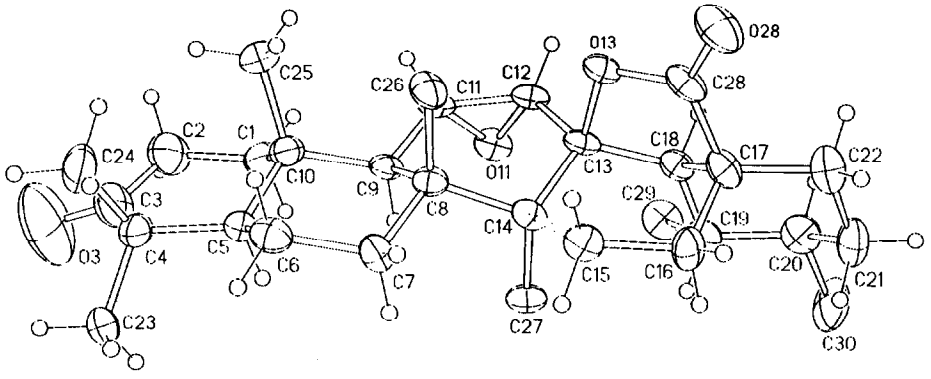


Figure 1. **Perspective veiw of one of the four crystallographically independed molecules 19 according to the X-ray analysis. Thermal ellipsoids are shown at the 40% probality level.**

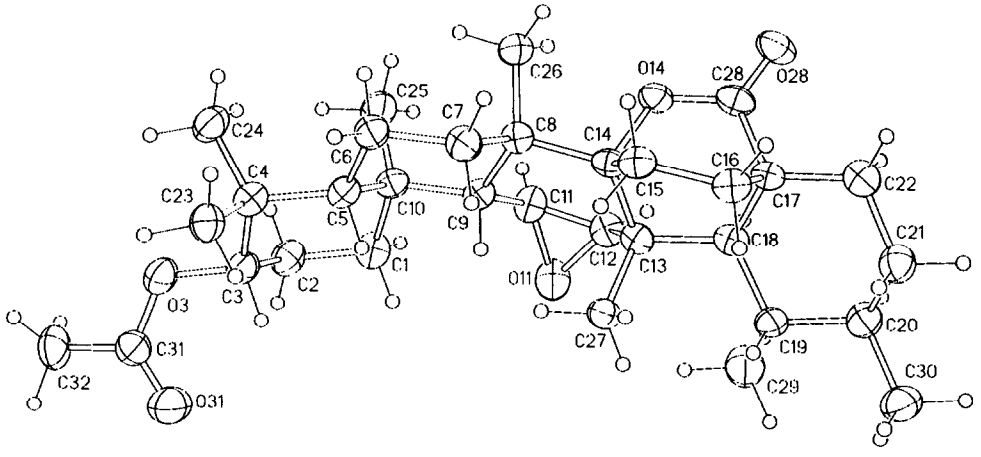


Figure 2. **Perspective veiw of molecule 22 according to the X-ray crystallographic analysis. Thermal ellipsoids are shown at the 40% probality level.**

basis of its mode of formation". Indeed, if the primary oxidation product is 12β,13β-epoxide, its isomerization to the 12-keto derivative should lead to an inverse configuration of the C-13 atom (as occurs upon isomerization of most known epoxides, though proceeding of the 1,2-hydride shift in epoxides with preserved configuration is also possible in some specific cases[38]). It was found for the oleanane 12β,13β-epoxy-derivative that under "mild" conditions (**HCl/SiO$_2$**, room temperature) its isomerization gives the 13αH-derivative, while under more rigid conditions (**HBr-AcOH**) it leads to the 13βH-derivative[39]. Since the oxidation of acetylursolic acid is conducted in acetic acid at 100-105°C for several hours, formation of any isomer would be expected "on the basis of mode of formation".

Comparison of the NMR data for compounds **13-18** testifies that molecules of all these compounds have the same stereochemistry. Because of poor solubility of U_{III}, we have examined compound **18** by NMR. The detailed analysis of the ^{1}H NMR spectrum of compound **18** shows that it is a 13αH-isomer: $^3J_{H13\_H18}$ = 11.6 Hz (antiperiplanar position of the protons) and $^3J_{H18\_H19}$ = 8.6 Hz (the twisted form of ring "E"). In all ursane type derivatives of other structural types studied by us, the cycle "E" invariably has an chair conformation with an equatorial position of both methyl groups C-29 and C-30. The distorted form of cycles "D" and "E" in **18** (as well as in compounds **13-17**) as compared to other derivatives is confirmed by the anomalous chemical shifts of signals of C-16, C-20, C-22 and H-30 in the NMR spectra (***Tables 3,4***). Further evidence is provided by the homonuclear Overhauser effect (**Figure 3**). The molecular form shown in **Figure 3** also explains the anomalous values of the H-18, H-19, H-26, and H-29 chemical shifts in terms of the anisotropy of magnetic susceptibility of the C-12carbonyl group.

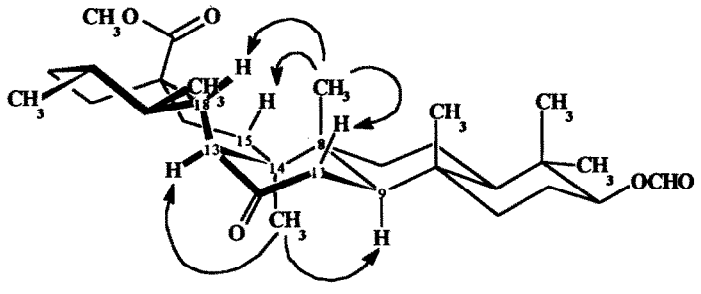


Figure 3. **Selected NOE (indicated by arrows) for compound 18.**

Probable Mechanism of Formation of the Oxidation Products.

The difficulty in interpreting the results of oxidation of ursane derivatives arises from the fact that no primary products of oxidation may be recorded, only the secondary products can be isolated whose structure and stereochemistry serve as a basis to derive the structure of intermediates.

Stereochemistry of Attack at the 12,13-double bond. The results of oxidation may be easily explained by the intermediate formation of 12β,13β-epoxide **28** but not of 12α,13α-epoxide **27** (***Scheme 1***). 12β,13β-Epoxide is just the compound that should be formed in the epoxidation of ursane type derivatives by peracids. It is known that even the less sterically hindered reagent (**O$_2$-O$_3$**) gives 12β,13β-epoxideit was shown for the oxidation of α-amirine[40]. Here the main distinction from the derivatives of oleanolic acid shows itself, i.e., the dramatic role of the C-29 methyl group completely hindering the α-attack at the 12,13-double bond in ursane derivatives (the α-attack is predominant in the oxidation of the oleanane derivatives with benzoic peracid[41]).

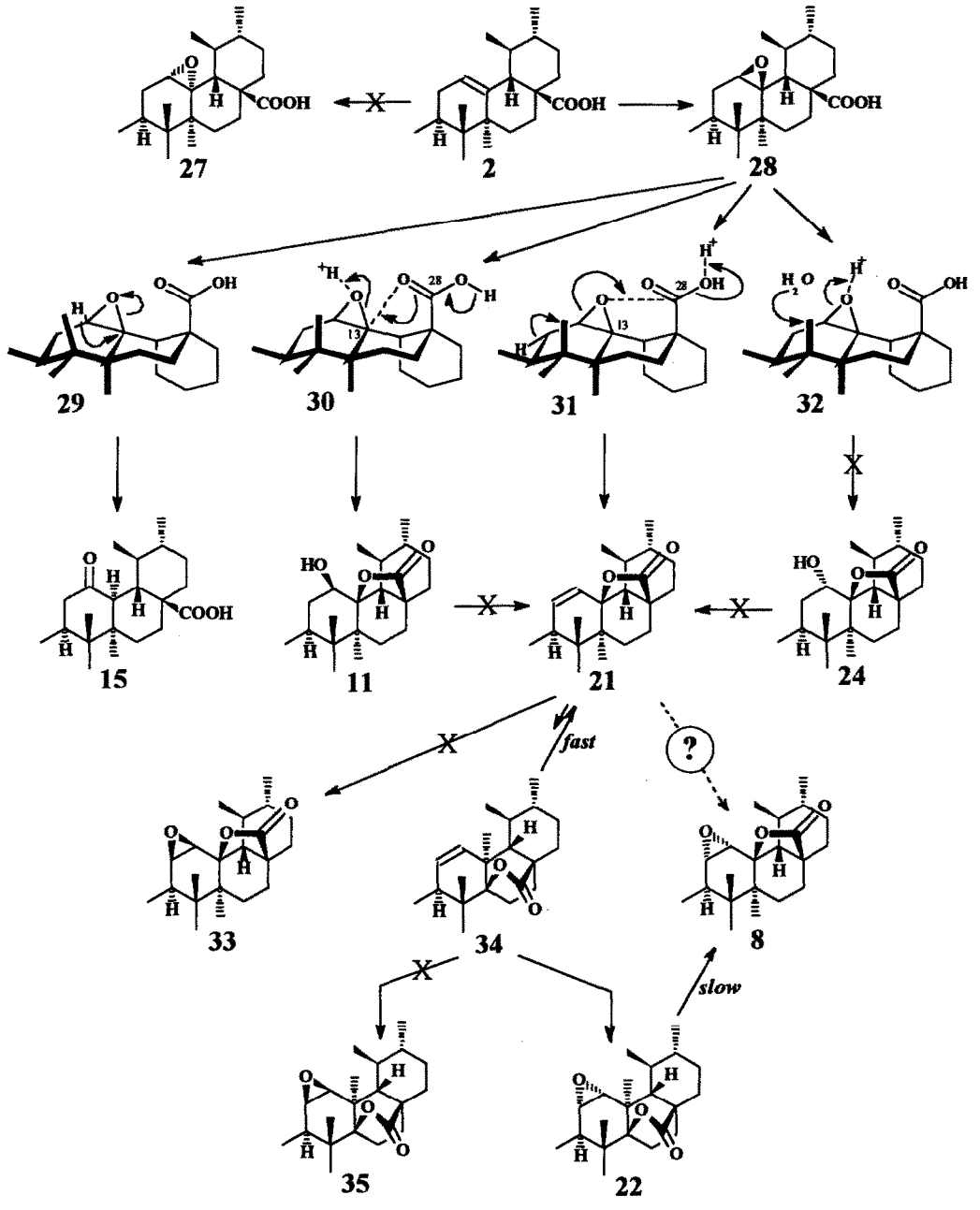
The reason for the intermediate formation of 12β,13β-epoxide **28** was discussed in ref.[12,13] and stated to be the intramolecular epoxidation of the 12,13-double bond in **2** by the 28-peroxycarboxyl group. It is argued that the presence of the 28-carboxyl group is necessary for the oxidation of the 12,13-double bond, as in this case intramolecular epoxidation can occur[13]. To prove this the authors cite the low product yields in model experiments of oxidation of acetylursolic acid (**2**) and its methyl ether **4** by hydrogen peroxide in boiling benzene. However, such experiments prove nothing because, on the one hand, formation of the 28-peroxycarboxyl group in these conditions is really impossible and, on the other hand, hydrogen peroxide "as is" is a weak epoxidizing agent (if at all). No wonder that the oxidation products are formed in low yields.

The authors of the work[13] have made an attempt to synthesized a derivative of the ursane series with the 28-peroxycarboxyl group using acetylursolyl chloride (**6**) as a starting compound. They have reported that the chloride "is one of the most stable acid chlorides, hitherto known, which remains unchanged under ordinary hydrolytic conditions and can be crystallized and chromatographed". Unfortunately, the authors gave neither the elemental analysis data nor the spectral data of the chloride (except for the IR spectrum). They have only noted that the product had been crystallized from a mixture of methanol and chloroform. We have synthesized chloride **6** by the reaction of acetylursolic acid (**2**) with $SOCl_2$ as described in ref.[42]. The physico-chemical and spectral data of this compound indicate that we obtained exactly the chloride of structure **6**. However, all our attempts to crystallize the chloride from methanol-containing mixtures always led to formation of methyl acetylursolate (**4**).

It is known that methyl ursolate (**5**) and some related methyl ethers can not be saponified under normal conditions and the hydrolysis requires some special techniques[43]. Such a behavior is typical for esters with an axial ester group and is due to the need to overcome a high barrier upon formation of the four-coordinated axial carbon atom in the addition of a nucleophilic species to carbonyl carbon. The alcoholysis of carboxyl chlorides at room temperature occurs *via* the transition state in which the carbonyl carbon has a tetrahedral configuration[44,45]. However, easy transformation of chloride **6** to methyl ether **4** indicates that the four-coordinated carbon C-28 in ursane derivatives can still be formed in rather mild conditions. The four-coordinated carbon should also be formed in the reaction of transformation of the 28-carboxyl group into the 28-peroxycarboxyl one that could be formed upon treatment of ursolic acid (**1**) or acetylursolic acid (**2**) with hydrogen peroxide on heating, so that the intermediate formation of such derivative is quite possible. Can these 28-peroxycarboxylic acid dirivatives be the intermediates in the transformations of the triterpenic acids to the oxidation products?

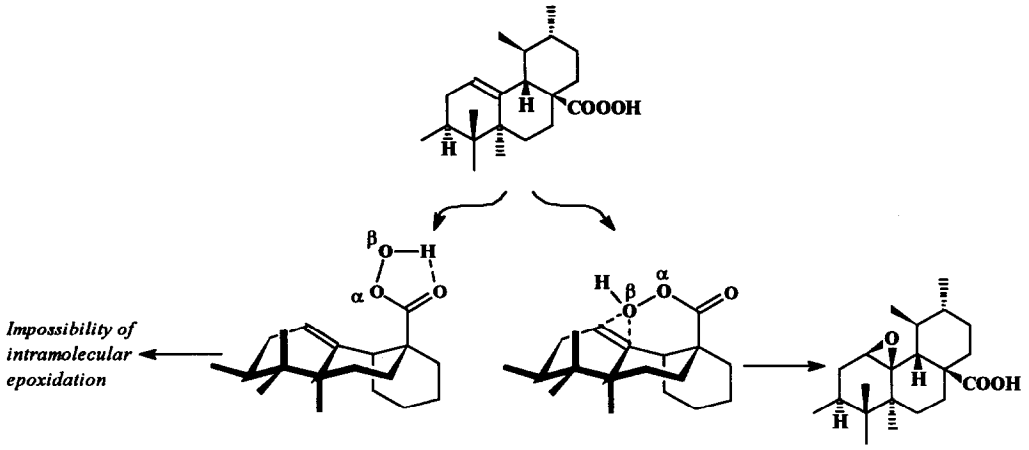
The intramolecular epoxidation of the 12,13-double bond by the 28-peroxycarboxyl group seems unlikely from the viewpoint of the epoxidation mechanism. The mechanism of epoxidation of the carbon-carbon double bond by an organic peracid suggests formation of the transition state involving an intramolecular hydrogen bond between hydrogen of the hydroperoxide fragment and the carbonyl oxygen, with the hydroperoxide b-oxygen being transferred to the olefin[46]. Steric structure of the ursolic acid molecule is such that in case of formation of the 28-peroxycarboxyl group, the presence of the above hydrogen bond makes the intramolecular epoxidation impossible. The possibility of the intramolecular epoxidation by the peroxycarboxyl group was discussed in literature[47]. However, some requirements of the transition state make it possible for this reaction to occur only when the peroxycarboxyl group is far away from the double bond being the site of addition as in the case of peroxyaraquidonic acid (16-membered transition state)[48].

Scheme 1.



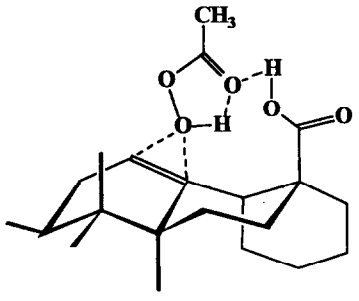
As to the mechanism of intramolecular epoxidation suggested in ref.[13] and involving a transfer of β-oxygen to the carbon-carbon double bond without intramolecular hydrogen bonding, it conflicts with the known data on the epoxidation mechanism of olefins[46] (***Scheme 2***).

Scheme 2.



Unusual mechanism of epoxidation

The authors of the work[13] have made a conclusion that the presence of the 28-carboxyl group is an absolutely necessary condition for the epoxidation at the 12,13-double bond position in ursane derivatives and that methyl ether **4** is not oxidized in contrast to acetylursolic acid (**2**). As it was shown in ref.[49], methyl ether of acetyl ursolic acid is smoothly (though rather slowly) oxidized at the 12,13-double bond under the action of hydrogen peroxide in acetic acid. Moreover, we oxidized methyl ethers **4** and **5** by hydrogen peroxide in the presence of formic acid. The main products of this reaction were the 12-keto-derivatives. Under comparable conditions the oxidation in the presence of formic acid proceeds somewhat faster than in the presence of acetic acid. Indeed, the 28-carboxyl group undoubtfully produces marked influence on the oxidation of 12,13-double bondand ursolic acid (**1**) and acetylursolic acid (**2**) are oxidized in H_2O_2-AcOH or H_2O_2-HCOOH considerably faster than the corresponding methyl ethers **5** and **4**. The differences in the oxidation rates are easily explained in terms of known schemes and it is not necessary to invoke any exotic mechanisms. In accordance with the results of investigation of the primary and secondary isotope effects and the calculated data[47], the "spiro" state is the most probable transition state in the epoxidation of olefins because it is preferable to the "parallel" transition state. However, the results of the work[46] are more in agreement with the "parallel" transition state. It is also known that some groups containing "acid" hydrogen can have a "forwarding" effect due to hydrogen bonding with the peracid molecule in the transition state[50], though in the case of the carboxyl group this effect may be absent[51]. When the peracid molecule attacks the the β-side of the 12,13-double bond of ursane derivatives, such a hydrogen bond may be formed, which stabilized the transition state and promotes oxidation of free acids as compared to methyl ethers:→



But in the case of methyl ethers the rate of oxidation may be lower due to the greater steric hindrance of the carbomethoxyl group as compared to the carboxyl one.

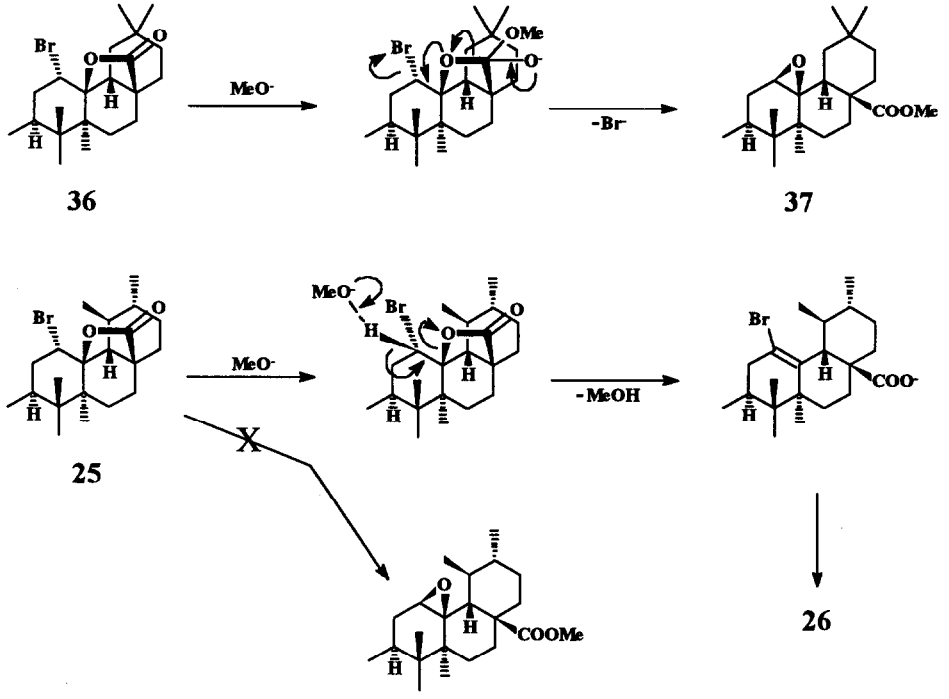
As mentioned above, 12,13-epoxides are known in the series of α-[40] and β-amirines[41]. Nevertheless, the direct synthesis of such derivatives of the ursane type triterpenoids from the corresponding compounds with the 12,13-double bond is impossible. The transformation of bromolactone **36** to epoxide **37** by sodium methoxide is known for the related compounds of the oleanolic acid series[39]. We have tried to perform a similar transformation for the bromolactone of the ursane series **25**. In contrast to bromolactone **36**, the ursane derivative **25** is not defined in literature. Moreover, it is known that acetylursolic acid (**2**) can not be brominated, unlike acetyloleanolic acid[52]. The bromination of some related derivatives of ursolic acid gives only unsaturated ethers without admixtures of bromo-derivatives[53]. We tried to synthesize bromolactone **25** in different ways. Our attempts to perform bromolactonization under the action of **Br_2-AcOH**[52] or **NBS-DMSO**[54] have failed. Slow bromination was effected using **NBS** in aqueous dioxane or **THF**. The main reaction product was unsaturated lactone **21**. The yield of bromolactone **25** strongly depends on the reaction temperature. Thus, at 60-65°C the yield of unsaturated lactone **21** was 75% while that of the bromolactone was 0.1% max. The yields were 73% and 6% respectively at 25°C. At the reaction temperature of about 10°C the 14% yield of **25** is achieved. Lactones **21** and **25** possess very similar chromatographic properties. To facilitate isolation of the target product **25**, we brominated acetylursolic acid with an excess of **NBS**. This makes it possible to convert the unsaturated lactone **21** to a number of more polar products and thus to facilitate chromatographic isolation of bromolactone **25**. It appeared, however, that lactone **25** is transformed in a high yield into the brominated ursolic acid **26** under the reaction with sodium methoxide in the conditions of the epoxide **37** formation. The different behavior of the ursane bromolactone may be caused by severe strain in the molecule due to the non-bonded interaction of axial bromine at C-12 atom and the methyl group C-29. This possibly leads to changed relative rates of the two competing reactions - bromine substitution and proton H-12 elimination (***Scheme 3***).

Suggested mechanisms of formation of oxidation products. Formation of the 13αH-12-keto-derivatives is easily explained by the stereochemically ordinary transfer of the hydride ion from the rear side of the epoxide group with the inversion of configuration of the C-13 atom (see ***Scheme 1***). Formation of compounds **8**, **11**, and **22** with intermediate formation of the 12β,13β-epoxy-derivative **28** suggests an anomalous cleavage of the epoxide cycle. Formation of the 12β-hydroxy-derivative **11** may be explained by participation of the carbonyl oxygen of the C-28 carboxyl group as nucleophile in the epoxide cleavage, this process provides preserved configuration of the C-12 atom. This is favored by spatial proximity of the carbonyl oxygen and the C-13 atom (structure **30**, the O·····C-13 distance is 2.9 Å[55]). However, one cannot exclude the possibility of nucleophilic substitution at C-12 atom with preservation of configuration as a result of an attack of a nucleophilic species (water molecule) from the β-side of the molecule with subsequent lactonization of the dihydroxy acid formed. Anyway, the normal cleavage of the epoxide cycle in **28** as a result of the α-attack of external nucleophile (structure **32**) does not occur. We have not found alcohol **24** among the reaction products and have shown it to be stable under the reaction conditions.

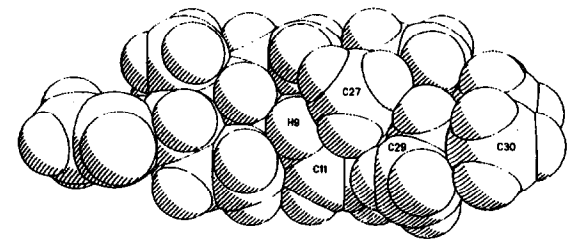
Two isomeric epoxylactones **8** and **22** are formed *via* the intermediate formation of the unsaturated lactone **21**. We have synthesized lactone **21** and oxidized it with acetic peracid under the same conditions as for oxidation of acetylursolic acid (**2**). It appeared that the main oxidation products are epoxy-derivatives **8** and **22** in the same ratio as in the oxidation of acetylursolic acid (**2**). Unsaturated lactone **21** is not formed from hydroxy-derivatives **11** and **24** in the oxidation of acetylursolic acid (**2**), as both of these compounds are stable under the reaction conditions. For the transformation of epoxide **28** to the unsaturated lactone **21** we

can suggest a scheme involving participation of the epoxide oxygen as a nucleophilic group in the attack of the electrophilic carbon atom of the protonated carboxyl group (structure **31**). This process seems probable as these atoms are sufficiently close in space (the O·····C-28 distance is 3.1 Å[55]). We cannot exclude the intermediate formation of an allyl alcohol-derivative upon isomerization of the epoxide group with its subsequent lactonization. Formation of allyl alcohol derivatives is more preferable upon isomerization of epoxides by strong bases[56]. Nevertheless allyl alcohol derivatives may also be the dominating products in isomerization of epoxides in the presence of acid catalysts under certain conditions[57].

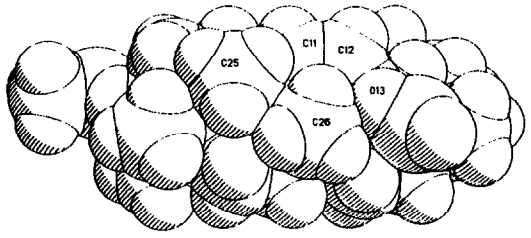
Scheme 3.



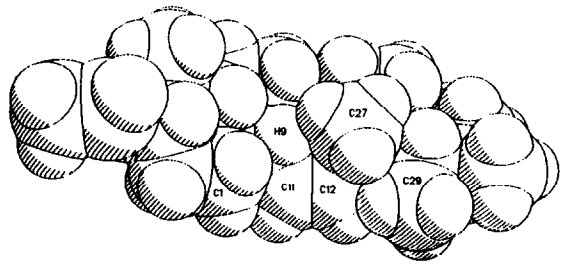
Why does oxidation form only **8** of two stereoisomeric epoxides **8** and **33**? The authors of the previous work have examined stereochemistry of compound U_1 and have stated that formation of 11α,12α-epoxide from unsaturated $\Delta^{11,12}$ lactone **21** is preferable for steric reason[12]. However, consideration of molecular models indicates that this is not quite so. ***Figure 4*** shows two projections of a molecule of **21** on the plane coinciding with that of the double bond C-11=C-12. It is obvious that the α-side of the double bond is much more hindered and is almost completely blocked by the C-29 methyl group. If spatial orientation of the electrofilic attack in this case were determined only by accessibility of the double bond, the preferable route would not be the formation of 11α,12α-epoxide **8** but, rather, of its 11β,12β-isomer **33**. At the same time, β-attack of the peracid molecule on the 11,12-double bond in lactone **21** may be hindered by the β-oxygen at the C-13 atom, which may cause additional electrostatic repulsion in the transition state. Such effects are known in the epoxidation reactions[58].



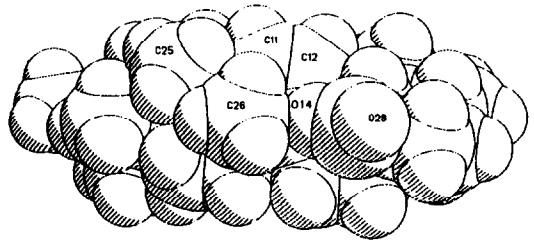
← molecule **21**, view from the α–side



← molecule **21**, view from the β–side



← molecule **34**, view from the α–side



← molecule **34**, view from the β–side

Figure 4. **Projections of molecules of ursane-type (21) and isoursane-type (34) unsaturated lactones on the plane of the double bond C^{11}-C^{12}. Geometry of the molecules is optimized by molecular mechanics method. Atoms are shown as van der Waals spheres.**

To explain the formation of the pair of epoxides **8** and **22**, the following scheme may be suggested (see ***Scheme 1***). Under the reaction conditions (acetic acid, 100-105°C), fast interconversion of unsaturated lactones **21** and **34** occurs, the content of isomer **34** in the equilibrium mixture being extremely small, and isomer **34** cannot be detected by usual methods. At the same time, the epoxidation of **34** proceeds considerably faster than of **21**. Epoxide **22** is unstable under the reaction conditions and is slowly converted to epoxide **8**. Thus, epoxide **8** is not a direct product of oxidation of the unsaturated lactone **21** but is formed *via* the intermediate isoursane epoxide **22**.

This scheme is supported by the following arguments. After lactone **21** has been stored in an acetic acid solution at 100°C, it is isolated in a virtually unchanged form and contains only small admixtures of more polar products (it is known that lactone **21** is unstable in the presence of strong acids and is transformed to unsaturated acids[59,60]). The molecular mechanics calculations for **21** and **34** shows that **21** is 4.3 kcal/mol more stable. This corresponds to the 99.6% content of **21** in the equilibrium mixture of **21** and **34** (at 100°C). As one can see from ***Figure 4***, both the α– and β–sides of the 11,12-double bond in the isomer **34** are equally accessible for the attack by peracid. Steric crowdedness around the double bond in both cases is the same as in the case of the β-attack in **21**. The α-attack at the double bond in compound **34** seems to be preferable (on the side opposite to the electronegative oxygen atom of the lactone ring). This should lead to 11α,12α-epoxide **22**, but not to the corresponding 11β,12β-epoxide **35**. Epoxide **8** is stable upon heating in an acetic acid solution at 100°C, but when epoxide **22** is heated, it is slowly transformed to epoxide **8**. Migration of the methyl group from C-13 atom to C-14 atom in ursane compounds is known[61] and leads to the compounds of the so-called isoursane series. The isomerization process **8**→**22** seems to be reversible under the reaction conditions. The absence of the isoursane type epoxide **22** upon heating of **8** may be explained by the low stability of **22**. Molecular mechanics calculations of epoxides **8** and **22** show that the heat of formation of the ursane isomer **8** is 1.9-6.6 kcal/mol lower than that of the isoursane isomer **22** (***Table 8***).

EXPERIMENTAL

General experimental procedures. All the solvents used were reagent quality. Petroleum ether refers to that fraction which boils in the range 40-70°C and was redistilled prior to use. Diethyl ether and tetrahydrofurane were freshly distilled. Removal of all solvents was carried out under reduced pressure and all commercial reagents were used without additional purification. Analytical TLC plates were **Silufol®** (Silpearl on aluminum foil, Czecho-Slovakia), R_f values of the compounds obtained are collected in ***Table 9***. Preparative column chromatography was performed on SiO_2 ("KSK", Russia, 100-200 mesh, air dried and activated at 140°C for 5h). IR spectra were obtained using a **Specord M-80** infrared spectrophotometer. A **Polamat A** polarimeter was used to measure optical rotation at 578 nm. Melting points were obtained using a **Kofler** melting point apparatus and are uncorrected. Mass spectra were obtained on a **Finnigan MAT 8200** instrument using the Electron Impact Ionization technique (100-220°C, 70eV). For all of the new compounds, precise mass determination for the molecular ion of a pure sample were obtained instead of combustion analyses. Purity was determined from constancy of melting point together with ^1H and ^{13}C NMR data.

NMR experiments. ^1H and ^{13}C NMR spectra were recorded at room temperature using a **Bruker AM-400** instrument (^1H 400.13 MHz, ^{13}C 100.61 MHz) locked to the deuterium resonance of the solvent. The chemical shifts were calculated relative to the solvent signal using as internal standard: δ_H 7.24 ppm and δ_C

76.90 ppm for **$CDCl_3$**, δ_H 2.55 ppm and δ_C 39.60 ppm for **DMSO-d_6**. 2D heteronuclear ^{13}C-^1H chemical shift correlation spectra (XHCORRD: $^1J_{CH}$ = 125 Hz, 2D memory matrix size 4K x 256 for FIDs and 2K x 2K for spectrum; COLOC: $^nJ_{CH}$ = 7.5 Hz, 2D memory matrix size 8K x 128 for FIDs and 4K x 1K for spectrum; number of scans 16-96 depending on concentration), 2D HH-COSY, 2D-NOESY, and 2D-INADEQUATE spectra were obtained using standard Bruker NMR Software System.

Table 9. **R_f values for the Ursolic Acid Derivatives.**

eluent:	1	2	3	4	5	6	7	8	9	10	11	12	13
C_6H_6-EtOAc 10:1 (v/v)		0.35	0.37	0.43	0.16	0.35		0.25	0.27				
$CHCl_3$-MeCN 20:1		0.40	0.42	0.68	0.26	0.40		0.43	0.45				
C_6H_6-EtOAc 4:1	0.28						0.15			0.05	0.16	0.22	0.08
$CHCl_3$-MeCN 10:1							0.23			0.08	0.30	0.30	010

eluent:	14	15	16	17	18	19	20	21	22	23	24	25	26
C_6H_6-EtOAc 10:1			0.26		0.30			0.30	0.20	0.27		0.40	
$CHCl_3$-MeCN 20:1			0.45		0.48			0.48	0.35	0.45		0.55	
C_6H_6-EtOAc 4:1	0.15	0.35		0.40		0.35	0.20				0.37		030
$CHCl_3$-MeCN 10:1	0.27	0.43		0.45		0.52	0.30				0.50		

X-ray crystallographic experiments. Intensity data were collected at 298°K on a **SYNTEX-$P2_1$** diffractometer using graphite monochromated CuKα radiation (λ = 1.54178 Å). After absorption correction, the structures were solved using SHELX-86, refinement was carried out using SHELX-76 by least squares procedures. Crystallographic data are collected in ***Table 10***. The structures of the compounds **19** and **22** are given in ***Figures 1*** and ***2*** respectively.

Atomic coordinates, bond length and angles, and thermal parameters have been deposited in the Cambridge Crystallographic Data Center.

Cycle *C* of epoxide **19** has the half-boat conformation, the system of the C^9-C^{11}-C^{12}-C^{13}-C^{14} atoms is nearly planar, whereas C^8 is out of this plane. The average torsion angles are ϕC^9-C^{11}-C^{12}-C^{13} = -6.0°, ϕC^{11}-C^{12}-C^{13}-C^{14} = 11.0°. The average parameters for the cycle *C* (bond length and angles) are close to the expected values.

Cycle *C* of epoxide **22** is an unusual slightly deformed boat (ϕC^8-C^{11}-C^{12}-C^{13} = -5.7(8)°, ϕC^9-C^8-C^{14}-C^{13} = -4.5(8)°), with some bond length and angles being distorted: $l_{C^8\text{-}C^{14}}$ = 1.60(1) Å (expected value 1.588(25) Å[62]), $l_{C^{13}\text{-}C^{18}}$ 1.59(1) Å (expected value 1.566(11) Å[62]), θC^9-C^{11}-C^{12} = 115.3(6)° (expected value 121°), θC^8-C^{14}-C^{13} 117.5(5)° (expected value 110°). Bicyclo[2.2.2]octyl system is appreciably twisted: ϕC^{14}-C^{13}-C^{18}-C^{17} = 12.7(7)°, ϕC^{14}-C^{15}-C^{16}-C^{17} = 16.6(6)°, ϕC^{14}-O^{14}-C^{28}-C^{17} = 8.8(7)°.

3β-Hydroxyurs-12-en-28-oic acid {ursolic acid} (**1**) was purified by crystallization from 95% aq.**EtOH**: m.p. 276-279°C (solvate with 1 mol. of **EtOH** according to ^1H NMR), $[\alpha]^{22}$ +59.8° (c 2.24, **Py**); {lit.[40]: m.p. 278-280°C (**MeOH**), $[\alpha]_D$ +76.8° (c 0.6); lit.[63]: m.p. 279-281°C}.

3β-(Acetyloxy)-urs-12-en-28-oic acid {acetylursolic acid} (**2**): m.p. 284-287°C (**MeCN**), $[\alpha]^{20}$ +69.1° (c 3.04, **$CHCl_3$**); {lit.[40]: m.p. 281-283°C (**EtOH**), $[\alpha]_D$ +62.3° (c 1.15); lit.[64]: m.p. 290-291°C (**acetone**), lit.[65]: m.p. 286°C (**MeOH**), lit.[66]: m.p. 268-269°C (**EtOH**)}.

3β-Hydroxyurs-12-en-28-oic acid methyl ester {ursolic acid methyl ester} (**5**): m.p. 171-173°C (CH_3CN), $[\alpha]^{19}$ +47.7° (c 8.25, $CHCl_3$); {lit.[64]: m.p. 172-173°C}.

Table 10. **Crystallographic Data for Compounds 19 and 22.**

	19	22		19	22
cell constants:			*mol. formula*	$C_{30}H_{44}O_4$	$C_{32}H_{48}O_5$
a, Å	12.622(5)	6.667(1)	*mol. weight*	468.68	512.73
b, Å	28.440(10)	30.847(6)	*crystal system*	monoclinic	monoclinic
c, Å,	14.297(5)	7.569(1)	*space group*	$P2_1$	$P2_1$
b, deg.	90.93(3)	113.50(2)	*μ, mm⁻¹*	0.58	0.59
Z	8	2	*F(000)*	2048	560
U, Å	5131(4)	1427.5(5)	D_C, *g×cm⁻³*	1.21	1.19
scan mode	w	2θ/θ	*unique data*	6589	1958
crystal dimensions, mm³	0.13×0.20×0.65	0.09×0.23×0.66	*observed data (I>2σ)*	4862	1534
$2\theta_{max.}$, *deg.*	110	114	*R*	0.067	0.048
transmision coefficient	0.87-0.93	0.89-0.95	*Rw*	0.073	0.054
			S	0.84	0.79

Oxidation of acetylursolic acid **(2)** ***with*** H_2O_2**-AcOH** .

Hydrogen peroxide (30%, 2 ml) was added to a solution of acetylursolic acid (**2**) (500 mg, 1.0 mmol) in a mixture of **AcOH** (10 ml) and **THF** (5 ml) and the mixture was kept at 85-90°C for 6 h. The reaction mixture was cooled to room temperature and an aqueous solution of Na_2SO_3 (5%) was added dropwise to reduce peroxides (negative reaction on a peroxide). The reaction mixture was diluted with water (50 ml) and extracted with Et_2O (3 x 20 ml). The combined ethereal extracts was washed with water (10 ml) and brine (10 ml), dried ($MgSO_4$) and concentrated to give a colorless glass (550 mg), containing three main components (according to ^1H NMR): epoxide **8** -22%, alcohol **11** - 20%, and keto acid **15** - 31%. Column chromatography of the crude product afforded 15 mg of the starting material, 110 mg of epoxide **8**, 10 mg of epoxide **22**, 100 mg of alcohol **11**, 150 mg of keto acid **15**. Methylation of **15** with CH_2N_2 gave the corresponding ester **16**.

3β-(Acetyloxy)-11α,12α-epoxy-13-hydroxyursan-28-oic acid γ-lactone (**8**): m.p. 299-302°C ($CHCl_3$-**MeOH**), 297-300°C (**EtOAc**), {lit[12]: 280°C (**MeOH**); lit[67]: 281-282°C (**MeOH-CHCl₃**)}; $[\alpha]^{20}$ +38.2° (c 10.9, $CHCl_3$) {lit[11]: $[\alpha]_D$ +51° ($CHCl_3$)}; IR (in **KBr**): 1765 (**C=O**, γ-lactone), 1730 (**C=O**, acetate) 1240 (acetate), 930 and 865 (epoxide); MS (m/z): 512.3493 {$C_{32}H_{48}O_5$ requires 512.3502} (M^+, 67%), 189 (100), mass spectrum of the compound is similar to that of the compound U_I in ref.[12]. ^1H NMR spectrum of the product coincides with that given in ref.[14], and ^{13}C chemical shifts are identical with those published

earlier[67,68]. Heating of epoxylactone **8** (5 mg) in aq.**AcOH** (1:10 v/v, 0.5 ml) at 105-110°C for 2 h recovered the starting material (5 mg).

3β-(Acetyloxy)-11α,12α-epoxy-14α-hydroxyisours-28-oic acid δ-lactone (**22**): m.p. 271-273°C (**CH_3CN**); $[\alpha]^{19}$ +27.9° (c 3.37, **$CHCl_3$**); IR (in **KBr**): 1740 (**C=O**, δ-lactone), 1725 (**C=O**, acetate) 1240 (acetate); MS (m/z): 512.3498 {**$C_{32}H_{48}O_5$** requires 512.3502} (M^+, 65%), 497 (14), 494 (12), 484 (43), 452 (29), 304 (18), 291 (30), 277 (37), 263 (51), 262 (47), 231 (33), 217 (37), 203 (100), 193 (45), 189 (76), 175 (73), 161 (49), 147 (55), 135 (65), 121 (76). Heating of epoxylactone **22** (5 mg) in aq.**AcOH** (1:10 v/v, 0.5 ml) at 105-110°C for 2 h afforded a mixture (4 mg) of the starting material and epoxylactone **8** (4:1, according to ^{1}H NMR).

3β-(Acetyloxy)-12β,13-dihydroxyursan-28-oic acid γ-lactone (**11**): m.p. 275-278°C (**$CHCl_3$-MeOH**) {lit[12]: 275°C (**MeOH-acetone**)}, $[\alpha]^{20}$ +30.6° (c 3.72, **$CHCl_3$**) {lit[11]: $[\alpha]_D$ +30° (**$CHCl_3$**)}; IR (1% in **$CHCl_3$**): 3585 (**O-H**); IR (in **KBr**): 1775 (**C=O**, γ-lactone), 1725 (**C=O**, acetate), 1245 (acetate); MS (m/z): 514.3649 {**$C_{32}H_{50}O_5$** requires 514.3658} (M^+, 32%), 189 (100%), mass spectrum of the product resembles that of the compound **U_{II}** in ref.[12]. ^{13}C chemical shifts are identical with those published earlier[68]. Heating of lactone **11** (50 mg) in acetic acid (2 ml) at 100°C for 6 h recovered the starting material (45 mg).

3β-(Acetyloxy)-12-oxo-13αH-ursan-28-oic acid (**15**): m.p. 243-246°C (**$CHCl_3$-MeOH**), $[\alpha]^{20}$ +36.2° (c 3.51, **$CHCl_3$**); IR (1% in **$CHCl_3$**): 3500-2500 (**O-H**); IR (in **KBr**): 1735 (**C=O**, acetate); 1720 and 1670 (**C=O**, acid), 1690 (**C=O**, ketone), 1250 (acetate); MS (m/z): 514.3664 {**$C_{32}H_{50}O_5$** requires 514.3658} (M^+, 53%), 499 (38), 453 (71), 333 (52), 264 (100), 218 (73), 206 (59), 189 (41), 177 (53), 154 (46), 111 (57).

3β-(Acetyloxy)-12-oxo-13αH-ursan-28-oic acid methyl ester (**16**): m.p. 247-249°C (**$CHCl_3$-MeOH**), {lit[12]: 246-250°C (**MeOH**)}; $[\alpha]^{19}$ +25.5° (c 4.24, **$CHCl_3$**); IR (in **KBr**): 1720 (**C=O**, acetate, ester), 1695 (**C=O**, ketone), 1245 (acetate); MS (m/z): 528.3816 {**$C_{33}H_{52}O_5$** requires 528.3815} (M^+, 39%), 513 (18), 333 (44), 288 (59), 220 (93), 218 (42), 176 (35), 175 (40), 174 (31), 168 (100).

3β,13-dihydroxyurs-11-en-28-oic acid γ-lactone (**20**) was prepared by the permanganate oxidation of ursolic acid (**1**) as described in ref.[69]: m.p. 246-249°C (**MeOH**) {lit[69]: m.p. 244-246°C (aq.**MeOH**), lit[70]: m.p. 270-274°C (petroleum ether)}; $[\alpha]^{21}$ +40.7° (c 11.4, **$CHCl_3$**) {lit[59]: $[\alpha]^{10}_D$ +44°}. IR (1% in **$CHCl_3$**): 3615 (**O-H**), IR (in **KBr**): 1765 (**C=O**, γ-lactone); MS (m/z): 454.3449 {**$C_{30}H_{46}O_3$** requires 454.3447} (M^+, 50%), 426 (18), 410 (100), 300 (13), 290 (12), 215 (14), 201 (18), 190 (8), 189 (12). Acetylation of (**20**) with acetic anhydride gave acetate **21**.

3β-(Acetyloxy)-13-hydroxyurs-11-en-28-oic acid γ-lactone (**21**): m.p. 260° (decomp.) {lit[68]: m.p. 230-232°C , lit[69]: m.p. 261-263°C (aq. acetone), lit[59]: m.p. 262°C (decomp.)}; $[\alpha]^{20}$ +42.7° (c 10.7, **$CHCl_3$**); {lit[59]: $[\alpha]^{26}_D$ +39° (c 0.7, **$CHCl_3$**)}; MS (m/z): 496.3554 {**$C_{32}H_{48}O_4$** requires 496.3553} (M^+, 95%), 465 (100), mass spectrum of the compound resembles that given in ref.[68].

***Oxidation of unsaturated lactone* 21 *with* H_2O_2-AcOH.**

A solution of lactone **21** (300 mg, 0.6 mmol) in a mixture of **AcOH** (30 ml) and **H_2O_2** (30%, 5 ml) was kept at 80°C for 5 h. The reaction mixture was diluted with water (200 ml) and crystalline precipitate (290 mg) was separated. Column chromatography of the crude product afforded epoxide **8** (182 mg, 59%) and epoxide **22** (32 mg, 10%).

3β,13-Dihydroxy-11α,12α-epoxyursan-28-oic acid γ-lactone (**7**). Hydrolysis of acetate **8** (240 mg, 0.47 mmol) in a solution of **KOH** (0.5 g) in a mixture of *tert*-**BuOH** (15 ml), **MeOH** (15 ml) and water (2 ml) at 40°C for 2 h followed by chromatography of the crude product afforded the *title compound* (146 mg, 67%): m.p. 316-318°C (**MeOH**) {lit[67]: m.p. 295-296°C, lit[12]: m.p. 296°C (**EtOAc**-petroleum ether)}; $[\alpha]^{21}$ +41.4° (c 3.14, $CHCl_3$); IR (1% in $CHCl_3$): 3615 (**O-H**), IR (in **KBr**): 1775 (**C=O**, γ-lactone), 930 and 860 (epoxide); MS (m/z): 470.3406 {$C_{30}H_{46}O_4$ requires 470.3396} (M^+, 38%), 455 (19), 263 (59), 235 (46), 205 (65), 204 (59), 203 (46), 189 (100), 175 (43), 147 (51), 135 (46), 119 (65), 109 (41), 107 (46), 105 (38).

11α,12α-epoxy-13-hydroxy-3-oxoursan-28-oic acid γ-lactone (**19**). Oxidation of alcohol 7 (70 mg, 0.15 mmol) with CrO_3 (18 mg, 0.18 mmol) in acetone (5 ml) at room temperature for 2 h gave the *title compound* (55 mg, 80%): m.p. 279-281°C (CH_3CN), $[\alpha]^{20}$ +41.8° (c 2.73, $CHCl_3$); IR (in **KBr**): 1765 (**C=O**, γ-lactone), 1700 (**C=O**, ketone), 940, 930 and 860 (epoxide); MS (m/z): 468.3252 {$C_{30}H_{44}O_4$ requires 468.3239} (M^+, 45%), 443 (23), 440 (17), 430 (10), 422 (15), 263 (58), 234 (100), 217 (50), 205 (45), 204 (43), 189 (65), 175 (23), 163 (18), 147 (33), 135 (15), 133 (19), 119 (35).

***Oxidation of acetylursolic acid* (2) *with* H_2O_2-HCOOH** .

Hydrogen peroxide (30%, 2 ml) was added to a solution of acetylursolic acid (**2**) (500 mg, 1.0 mmol) in a mixture of **HCOOH** (10 ml) and **THF** (10 ml) and the reaction mixture was kept at room temperature for 48 h. After the usual workup a colorless glass (600 mg) was obtained. ^{1}**H** NMR spectroscopy of the crude product indicated the presence of the starting material - 10%, traces of epoxide **8**, alcohol **11** - 31%, and keto acid **15** - 13%. Column chromatography of the crude product afforded 150 mg of alcohol **11** and 500 mg of keto acid **15**.

***Oxidation of acetylursolic acid methyl ester* (4) *with* H_2O_2-AcOH[14].**

Oxidation of methyl ester **4** (1.00 g) with hydrogen peroxide (30%, 10 ml) in a mixture of **AcOH** (40 ml) and **THF** (10 ml) at 90°C for 20 h gave the crude product which was chromatographed to give 0.28 g of the starting ester **4**.

***Oxidation of ursolic acid* (1) *with* H_2O_2-HCOOH** .

Oxidation of ursolic acid (**1**) (500 mg, 1.1 mmol) with hydrogen peroxide (30%, 2 ml) in a a mixture of **HCOOH** (10 ml) and **THF** (10 ml) at room temperature for 48 h gave a colorless glass (700 mg). Column chromatography of the crude product afforded 25 mg of formylursolic acid (**3**), 3 mg of the complex mixture containing formate **9** as the main component {^{1}**H** NMR: o 8.07 *br.s* 1**H** (formate), 4.60 *m* 1**H** (**H**-3), 3.08 dd *J* 3.8 and 2.0 Hz, 1**H** (**H**-11), 2.92 d *J* 3.8 Hz, 1**H** (**H**-12)}, 205 mg of diol monoformate **12**, 95 mg of diol **10**, 35 mg of keto acid **13**, and 125 mg of keto acid **17**. Methylation of keto acids **13** and **17** gave corresponding methyl esters **14** and **18** respectively.

3β-(Formyloxy)-urs-12-en-28-oic acid (**3**): thin plates from **EtOAc**; m.p.: in the range of 205-225°C aggregates of the plates are turned (partially melting) to needles which then melt at 239-243°C; $[\alpha]^{19}$ +55.8° (c 5.08, $CHCl_3$); IR (1% in $CHCl_3$): 3400-2400 (**O-H**); IR (in **KBr**): 1730 (**C=O**, formate), 1700 (**C=O**, acid), 1185 (formate); MS (m/z): 484.3557 {$C_{31}H_{48}O_4$ requires 484.3553} (M^+, 4%), 438 (3), 300 (3), 248 (100), 235 (26), 219 (7), 203 (30), 133 (24), 150 (8). A mixture of ursolic acid (**1**) (500 mg, 1.1 mmol) and **HCOOH** (50 ml) was stirred at 60°C for 6 h. The solvent was distilled off and the residue was dried at

reduced pressure. The crude product was taken up in benzene and percolated through a silica gel column to give formylursolic acid (**3**) (480 mg, 90%).

3β,12β,13-Trihydroxyursan-28-oic acid γ-lactone (**10**): m.p. 282-285°C (**$CHCl_3$-MeOH**), $[\alpha]^{20}$ +23.3° (c 3.83, **$CHCl_3$**); IR (1% in **$CHCl_3$**): 3615 (**O-H**), 3585 (**O-H**), 1760 (**C=O**, γ-lactone); MS (m/z): 472.3556 {**$C_{30}H_{48}O_4$** requires 472.3553} (M^+, 3%), 454 (5), 300 (4), 246 (3), 234 (4), 207 (10), 205 (12), 189 (5), 149 (5), 107 (4), 95 (4), 81 (4), 69 (4), 55 (5), 46 (50), 45 (100), 44 (9), 43 (23).

3β-(Formyloxy)-12β,13-dihydroxyursan-28-oic acid γ-lactone (**12**): m.p. 281-284°C (**$CHCl_3$-MeOH**), $[\alpha]^{20}$ +26.9° (c 5.74, **$CHCl_3$**); IR (1% in **$CHCl_3$**): 3585 (**O-H**); IR (in **KBr**): 1770 (**C=O**, γ-lactone), 1714 (**C=O**, formate), 1175 (formate); MS (m/z): 500.3500 {**$C_{31}H_{48}O_5$** requires 500.3502} (M^+, 28%), 482 (75), 300 (33), 250 (25), 246 (29), 235 (36), 234 (38), 205 (100), 189 (66), 135 (27), 121 (36), 107 (36), 105 (27), 95 (21), 81 (38), 69 (41), 55 (41), 44 (82).

3β-Hydroxy-12-oxo-13αH-ursan-28-oic acid (**13**): m.p. 237-240°C (**$CHCl_3$-MeCN**), $[\alpha]^{21}$ +25.0° (c 5.25, **$CHCl_3$**); IR (1% in **$CHCl_3$**): 3610 (**O-H**, alcohol) 3500-2400 (**O-H**, acid); IR (in **KBr**): 1715 (**C=O**, acid), 1695 (**C=O**, ketone); MS (m/z): 472.3552 {**$C_{30}H_{48}O_4$** requires 472.3553} (M^+, 44%), 457 (18), 411 (25), 291 (50), 264 (100), 249 (21), 248 (26), 246 (30), 218 (68), 207 (64), 206 (76), 191 (12), 190 (17), 189 (24), 177 (60), 161 (20), 154 (54), 135 (32), 121 (46), 111 (84).

3β-(Formyloxy)-12-oxo-13αH-ursan-28-oic acid (**17**): m.p. 253-256°C (**$CHCl_3$-MeCN**), $[\alpha]^{24}$ +22.3° (c 2.62, **$CHCl_3$**); IR (1% in **$CHCl_3$**): 3500-2400 (**O-H**, acid); IR (in **KBr**): 1720 (**C=O**, acid, formate), 1685 (**C=O**, ketone); 1175 (formate); MS (m/z): 500.3499 {**$C_{31}H_{48}O_5$** requires 500.3502} (M^+, 23%), 485 (14), 439 (22), 319 (48), 264 (100), 249 (19), 246 (31), 218 (72), 206 (81), 189 (31), 177 (71), 154 (57), 135 (36), 121 (45), 111 (79).

3β-Hydroxy-12-oxo-13αH-ursan-28-oic acid methyl ester (**14**): amorphous powder, $[\alpha]^{20}$ +24.3° (c 4.53, **$CHCl_3$**); IR (1% in **$CHCl_3$**): 3610 (**O-H**); IR (in **KBr**): 1730 (**C=O**, ester), 1695 (**C=O**, ketone); MS (m/z): 486.3714 {**$C_{31}H_{48}O_5$** requires 486.3709} (M^+, 45%), 291 (47), 278 (58), 220 (100), 218 (45), 177 (41), 176 (42), 168 (96).

3β-(Formyloxy)-12-oxo-13αH-ursan-28-oic acid methyl ester (**18**): m.p. 244-247°C (**$CHCl_3$-MeOH**), $[\alpha]^{20}$ +24.3° (c 6.59, **$CHCl_3$**); IR (in **KBr**): 1720 (**C=O**, methyl ester, formate), 1680 (**C=O**, ketone), 1180 (formate); MS (m/z): 514.3659 {**$C_{32}H_{50}O_5$** requires 514.3658} (M^+, 55%), 499 (16), 278 (68), 220 (100), 218 (46), 177 (38), 176 (46), 175 (31), 168 (94), 111 (34), 109 (34), 107 (20), 95 (20),

***Oxidation of ursolic acid methyl ester* (5) *with* H_2O_2-HCOOH .**

Oxidation of ursolic acid methyl ester (**5**) (520 mg, 1.1 mmol) with hydrogen peroxide (30%, 2 ml) in a mixture of **HCOOH** (10 ml) and **THF** (10 ml) at room temperature for 62 h gave a colorless glass (610 mg). Column chromatography of the crude product afforded 120 mg of alcohol **14** and 410 mg of formate **18**.

3β-(Acetyloxy)-13-hydroxy-12-oxoursan-28-oic acid γ-lactone (**23**). **CrO_3** (50 mg, 0.5 mmol) was added portion wise to a stirred solution of alcohol (**10**) (100 mg, 0.2 mmol) in a mixture of acetone (2.5 ml) and **THF** (2.5 ml) at room temperature. The reaction mixture was kept at stirring for 4 h, diluted with benzene (20 ml) and percolated through a silica gel column. Evaporation of solvent left a white solid which was crystallized from methanol to give the *title compound* (82 mg, 82%): m.p. 286-289°C (**MeOH**), 289-292°C (**MeCN**), {lit[12]: m.p. 274°C (**EtOAc**-petroleum ether)}; $[\alpha]^{20}$ -6.3° (c 10.2, **$CHCl_3$**); IR (in **KBr**): 1775 (**C=O**, γ-lactone), 1725 (**C=O**, acetate), 1720 (**C=O**, ketone), 1245 (acetate); MS (m/z): 512.3488

{$C_{32}H_{48}O_5$ required 512.3502} (M^+, 78%), 249 (100), mass spectrum of the compound resembles that given in ref.[12].

3β-(Acetyloxy)-12α,13-dihydroxyursan-28-oic acid γ-lactone (**24**). A cold (0°) solution of **$NaBH_4$** (5 mg) in a mixture of **DMSO-MeOH** (5 ml, 1:1 v/v) was added to a solution of ketone **23** (55 mg, 0.11 mmol) in a mixture of **DMSO-MeOH** (15 ml, 2:1 v/v) at 0° and the resulting mixture was kept at this temperature overnight. The reaction mixture was diluted with water (50 ml) and extracted with ether (25 ml). The ethereal extract was washed with water (3x25 ml), brine (10 ml), dried (**$MgSO_4$**). Evaporation of ether left a white solid (50 mg) which was chromatographed (**C_6H_6-Et_2O**) to give 5 mg of the starting ketone **23**, 25 mg of the 12β-hydroxy derivative **11**, and 15 mg of the *title compound:* m.p. 260-262°C (**MeCN**), $[\alpha]^{26}$ +25.2° (c 2.62, **$CHCl_3$**); IR (1% in **$CHCl_3$**): 3620 (**O-H**), 1760 (**C=O**, lactone), 1720 (**C=O**, acetate); MS (m/z): 514.3646 {**$C_{32}H_{50}O_5$** requires 514.3658} (M^+, 34%), 499 (39), 496 (46), 453 (100), 300 (43), 250 (45), 249 (45), 218 (50), 205 (93), 204 (66), 203 (40), 189 (96).

A solution of alcohol **24** (2 mg) in aq. **AcOH** (90%, 1 ml) was kept at 90°C for 6 h, and no changes were detected. Heating of the solution at 115°C for 15 min. resulted in formation of a number of products (TLC), no formation of unsaturated lactone **20** was detected (^{1}**H** NMR).

3β-(Acetyloxy)-urs-12-en-28-oyl chloride (**6**) was prepared from acetylursolic acid (**2**) and **$SOCl_2$** in dry benzene[42] and the crude product was crystallized from a mixture of **C_6H_6-CH_3CN** to give the *title compound* (210 mg, 68%): m.p. 215-219°C (fast heating at 10-15 deg. per minute), {lit[13]: m.p. 295°C (**$CHCl_3$-MeOH**)}; $[\alpha]^{20}$ +47.6° (c 4.87, **$CHCl_3$**); IR (in **KBr**): 1775 (**C=O**, anhydride), 1735 (**C=O**, acetate), 1245 (acetate), 770 (**C-Cl**); MS (m/z): 516.3371 {**$C_{32}H_{49}O_3Cl$** requires 516.3370} (M^+, 7%), 266 (71), 249 (38), 203 (100), 190 (62). Crystallization of chloride **6** from mixtures **C_6H_6-MeOH** or **$CHCl_3$-MeOH** resulted in formation of mixtures of the chloride and the corresponding methyl ester **4**.

3β-(Acetyloxy)-urs-12-en-28-oic acid methyl ester {acetylursolic acid methyl ester} (**4**): m.p. 245-248°C (**CH_3CN**), $[\alpha]^{20}$ +62.2° (c 9.36, **$CHCl_3$**); {lit[31]: m.p. 243-245°C}.

***Bromination of acetylursolic acid* (2)**

A solution of acetylursolic acid (**2**) (0.15 g, 0.3 mmol) and N-bromosuccinimide (0.16 g, 0.9 mmol) in a mixture of **THF** (10 ml) and water (0.5 ml) was kept in darkness at room temperature for 24 h. The reaction mixture was diluted with water (20 ml) and extracted with ether. The ethereal extract was washed with water (10 ml), 5% aq. **Na_2SO_3** (2 ml), brine (5 ml), dried (**$MgSO_4$**). Ether was distilled off and the residue was chromatographed to give bromolactone **25** (10 mg, 6%).

Bromination of acetylursolic acid (**2**) (1.10 g, 2.2 mmol) with **NBS** (0.39 g, 2.2 mmol) in a mixture of dioxane (20 ml) and water (5 ml) at 60-65°C for 30 min. gave 0.82 g (75%) of $\Delta^{11,12}$-lactone **21** and only 1 mg (0.1%) of bromolactone **25**.

Bromination of acetylursolic acid (**2**) (0.64 g, 1.28 mmol) with **NBS** (excess) in a mixture of **THF** and water at 10-12°C for 48 h gave 106 mg (14%) of bromo lactone **25**.

Bromination of acetylursolic acid (**2**) with NBS in a dimethylsulphoxide solution (as described in ref.[54]) gave unchanged starting material.

3β-(Acetyloxy)-12α-bromo-13-hydroxyursan-28-oic acid γ-lactone (**25**): m.p. 239-242°C (**MeCN**); $[\alpha]^{24}$ +54.3° (c 7.81, **$CHCl_3$**); IR (in **KBr**): 1765 (**C=O**, γ-lactone), 1730 (**C=O**, acetate), 1240 (acetate);

MS (m/z): 576.2823 {$C_{32}H_{49}O_4Br$ requires 576.2815} (M^+, 1%), 497 (M^+-**Br**, 17), 496 (18), 439 (81), 247 (100), 203 (44), 201 (26), 189 (63), 135 (28).

3β-(Acetyloxy)-12-bromoursolic acid (**26**). A solution of bromolactone (**25**) (45 mg, 0.078 mmol) and **MeONa** (2 M, 0.5 ml) in **MeOH** (5 ml) was reflux for 2 h. The solvent was evaporated and the residue was treated with water (5 ml) and extracted with ether (5 ml) to give a complex mixture (TLC) of non-acidic products (6 mg). The aqueous phase was acidified with aq. **HCl** and extracted with ether (3x10 ml) to give *the title compound* (35 mg, 78%) as white crystals: m.p. 271-274°C (aq. **EtOH**); $[\alpha]^{21}$ +69.0° (c 1.68, $CHCl_3$); IR (in **KBr**): 1700 (**C=O**); IR (1% in $CHCl_3$): 3615 (**O-H,** alcohol), 3400-2400 (**O-H,** acid); MS (m/z): 534.2712 {$C_{30}H_{47}O_3Br$ requires 534.2709} (M^+, 9%), 455 (M^+-**Br**, 5), 437 (M^+-**Br** - H_2O, 6), 247 (100), 208 (17), 207 (20), 190 (22).

Acknowledgment - This work was supported in part by grant from the International Science Foundation (Novosibirsk Office).

REFERENCES AND NOTES

1. Hirota, M.; Mori, T.; Yoshida, M.; Iriye, R. *Agric. Biol. Chem.* **1990**, *54*, 1073-1075.
2. Schimert, G.; Blomer, H. *Naunyn-Schmiedebergs Arch. exptl. Pathol. Pharmakol.* **1953**, *217*, 337-347.
3. Brieskorn, C.H. *Pharmaz. Zentralhalle* **1956**, *95*, 235-247.
4. Collins, M.-A.; Charles, H.P. *Food Microbiol.* **1987**, *4*, 311-315.
5. Vasilenko, Yu.K.; Lisevitskaya, L.I.; Frolova, L.M.; Parfentyeva, E.P.; Skulte, I.V.; Vasilenko, A.Yu.; Kozharsiy, V.V.; Voskanyan, V.L. *Farmakol. Toksikol.* **1982**, *45, No. 5*, 66-70.
6 Kowalewski, Z.; Kortus, M.; Kedria, W.; Koniar, H. *Arch. Immunol. Ther. Exp.* **1976**, *24*, 115-119.
7. Kozai, K; Miyake, Y; Kohda, H; Kametaka, S; Yamasaki, K; Suginaka, H; Nagasaka, N. *Caries Res.* . **1987**, *21*, 104-108.
8. Chaturvedi, A.K.; Parmar, S.S.; Nigam, S.K.; Bhatnagar, S.C.; Misra, G.; Sastry, B.V.K. *Pharmacol. Res. Commun.* **1976**, *8*, 199-210.
9. Hostettmann-Kaldas, M.; Nakanishi, K. *Planta Med.* **1979**, *37*, 359-360.
10. Zaletova, N.I.; Shchavlinskii, A.N.; Tolkachev, O.N.; Vichkanova, S.A.; Fateeva, T.V.; Krutikova, N.M.; Yartseva, I.V.; Klyuev, N.A. *Khim. Pharm. Zh.* **1986**, *20*, 568-571.
11. Jeger, O.; Borth, R.; Ruzicka, L. *Helv. Chim. Acta* **1946**, *29*, 1999-2006.
12. Majumder, P.L.; Chakraborty, M. *Tetrahedron* **1979**, *35*, 2397-2403.
13. Majumder, P.L.; Bagchi, A. *Tetrahedron* **1983**, *39*, 649-655.
14. Siddiqui, S.; Siddiqui, B.S.; Adil, Q.; Begum, S. *Tetrahedron* **1990**, *46*, 3569-3580.
15. Agrawal, P.K.; Jain, D.C. *Prog. Nucl. Magn. Reson. Spectrosc.* **1992**, *24*, 1-90.
16. Kojima, H.; Ogura, H. *Phytochemistry* **1989**, *28*, 1703-1710.
17. Katai, M.; Meguri, H. *Yukagaku* **1983**, *32*, 311-314.
18. Seo, S.; Tomita, Y.; Tori, K. *J. Amer. Chem. Soc.* **1981**, *103*, 2075-2080.
19. Seo, S.; Tomita, Y.; Tori, K. *J. Chem. Soc., Chem. Commun.* **1975**, 954-955.
20. Seo, S.; Yoshimura, Y.; Uomori, A.; Takeda, K.; Seto, H.; Ebizuka, Y.; Sankawa, U. *J. Amer. Chem. Soc.* **1988**, *110*, 1740-1745.

21. Talapatra, S.; Sarkar, A. *Phytochemistry*, **1981**, *20*, 1923-1925.
22. Bremser, W.; Ernst, L.; Fachinger, W.; Gerhards, R.; Lewis, P.; Hardt, A. *Carbon-13 NMR Spectral Data: a "Living" COM-Microfiche Collection of Reference Material;* Verlag Chemie: Weinheim, 1987.
23. Wehrli, F. W.; Nishida, T. *Fortschr. Chem. Org. Naturstoffe* **1979**, *36*, 1-229.
24. Seto, H.; Furihata, K. *JEOL News* **1985**, *21A*, 2-7.
25. Reynolds, W.F.; McLean, S.; Poplawski, J.; Enriques, R.G.; Escobar, L.I.; Leon, I. *Tetrahedron* **1986**, *42*, 3419-3428.
26. Tkachev, A.V.; Denisov, A.Yu. *Tetrahedron* **1994**, *50*, 2591-2598.
27. Kitagawa, I.; Kitagawa, K.; Yosioka, I. *Tetrahedron* **1972**, *28*, 907-921.
28. Hui, W.-H.,; Li, M.-M. *Phytochemistry* **1976**, *15*, 1741-1743.
29. Tori, K.; Komeno, T.; Sangare, M.; Septe, B.; Delpech, B.; Ahond, A.; Lukacs, G. *Tetrahedron Lett.* **1974**, 1157-1160.
30. Burkert, U; Allinger, N.L. *Molecular Mechanics.* ACS Monograph 177: D.C. Washington, 1982.
31. Podlogar, B.L.; Raber, D.J. *J. Org. Chem.* **1989**, *54*, 5032-5035.
32. Gatilov, Yu.V.; Rybalova, T.V. *Book of abstracts of the VIII-th All-Union Syposium on Intermolecular Interaction and Conformations of Molecules.* Novosibirsk, USSR, 1990; Part 1, p. 113.
33. Rogers, D.W. *Computational Chemistry using the P.C* VCH Publishers, Inc: New York, 1990.
34. Tkachev, A.V.; Toropov, O.V.; Salnikov, G.E.; Gatilov, Yu.V., Bagrjanskaja, I.Yu. *Zh. Org. Khim.* **1989**, *25*, 249-257.
35. Barfield, M.; Smith W.B. *J. Amer. Chem. Soc.* **1992**, *114*, 1574-1581.
36. Tori, K.; Komeno, T.; Nakagawa, T. *J. Org. Chem.* **1964**, *29*, 1136-1141.
37. Barker, S.A.; Brimacombe, J.S.; Foster, A.B.; Whiffen, D.J.; Zweifel, G. *Tetrahedron* **1959**, *7*, 10-18.
38. Tkachev, A.V.; Dubovenko, G.V.; Pentegova, V.A. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1984**, 106-110.
39. Farino, C.; Pinza, M. *Gazz. Chim. Ital.* **1987**, *117*, 561-562.
40. Boar, R.B.; Knight, D.C.; McGhie, J.F.; Barton, D.H.R. *J. Chem. Soc. (C)* **1970**, 678-682.
41. Boar, R.B.; Joukhadar, L.; de Luque, M.;, McGhie, J.F.; Barton, D.H.R.;, Arigoni, D.; Brunner, H.G.; Giger, R. *J. Chem. Soc., Perkin Trans. I* **1977**, 2104-2109.
42. Jain, S.M.; Atal, C.K. *Indian J. Chem.* **1986**, *25B*, 427-428.
43. Sengupta, P.; Sen, M.; Das, S. *Indian J. Chem.* **1980**, *19B*, 721-722.
44. Ross, S.D. *J. Amer. Chem. Soc.* **1970**, *92*, 5998-6002.
45. Kivinen, A. Mechanisms of Substitution at the COX [Acyl Halide] Group. In *The Chemistry of Acyl Halides* ;Patai, S. Ed.; Interscience: London, 1972; pp. 177-230.
46. Rebek, J., Jr.; Marshall, L., McManis, J.; Wolak, R. *J. Org. Chem.* **1986**, *51*, 1649-1653 (and references therein).
47. Rebek, J., Jr. *Heterocycles* **1981**, *15*, 517-545 (and references therein).
48. Corey, E. J.; Niwa, H.; Falck, J.R. *J. Amer. Chem. Soc.* **1979**, *101*, 1586-1587.
49. Siddiqui, S.; Begum, S.; Siddiqui, B.S.; Hafeez, F. *J. Nat. Prod.* **1989**, *52*, 57-62.
50. Henbest, H.B.; Wilson, R.A.L. *J.Chem.Soc.* **1957**, 1958-1965.
51. Kucherov, V.F.; Segal', G.M.; Nazarov, I.N. *Izvest. Akad. Nauk SSSR, Ser. Khim.* **1959**, 673-681.

52. Lewis, K.G.; Tucker, D.J. *Austr. J. Chem.* **1983**, *36*, 2297-2305.
53. Mehrotra, R.; Singh, C.; Popli, S.P. *Indian J. Chem.* **1990**, *29B*, 425-429.
54. Pradhan, B.P.; Mukherjee, M.M.; Chakrabarti, D.K.; Shoolery, J.N. *Indian J. Chem.* **1983**, *22B*, 12-16.
55. The interatomic distances were obtained on a molecule whose geometry was optimized by molecular mechanics calculations.
56. Crandall, J.K.; Apparu, M. *Org. React.(N.Y.)* **1983**, *29*, 345-443.
57. Van Zon, A.; Huis, R. *Recl.: J. R. Neth. Chem. Soc.* **1981**, *100*, 425-429.
58. Crossley, N.S.; Darby, A.C.; Henbest, H.B.; McCullough, J.J.; Nicholls, B.; Stewart, M.F. *Tetrahedron Lett.* **1961**, 398-403.
59. Horn, D.H.S.; Lamberton, J.A. *Austr. J. Chem.* **1964**, *17*, 477-480.
60. Doyal, R. *Indian J. Chem.* **1990**, *29B*, 156-157.
61. Agata, I.; Corey, E.J.; Hortmann, A.G.; Klein, J.; Proskow, S.; Ursprung, J.J. *J. Org. Chem.* **1965**, *30*, 1698-1710.
62. Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R *J. Chem. Soc., Perkin Trans. II* **1987**, N 12, S1-S19.
63. Numata, A.; Yang, P.; Takahashi, C.; Fujiki, R.; Nabae, M.; Fujita, E. *Chem. Pharm. Bull.* **1989**, *37*, 648-651.
64. Sultana, S.; Ilyas, M.; Shaida, W.A. *J. Indian. Chem. Soc.* **1986**, *63*, 1074-1075.
65. Katai, M.; Terai, T.; Meguri, H. *Chem. Pharm. Bull.* **1981**, *29*, 261-264.
66. Houghton, P.J.; Lian, L.M. *Phytochemistry* **1986**, *25*, 1939-1944.
67. Pradhan, B.P.; Chakraborty, S.; Weyerstahl, P. *Tetrahedron* **1987**, *43*, 4487-4495.
68. Katai, M.; Terai, T.; Meguri, H. *Chem. Pharm. Bull.* **1983**, *31*, 1567-1571.
69. Zaletova, N.I.; Shchavlinskii, A.N.; Tolkachev, O.N.; Vichkanova, S.A.; Fateeva, T.V.; Krutikova, N.M.; Yartseva, I.V.; Klyuev, N.A. *Khim.-Farm. Zh.* **1986**, *20*, 568-571.
70. Savina, A.A.; Sokol'skaya, T.A.; Zakharov, V.F. *Khim. Prir. Soedin.* **1988**, 295-296.

(*Received in UK* 26 *April* 1994; *revised* 8 *August* 1994; *accepted* 12 *August* 1994)