SELECTIVE OXIDATION OF BETULIN BY Cr(VI) REAGENTS

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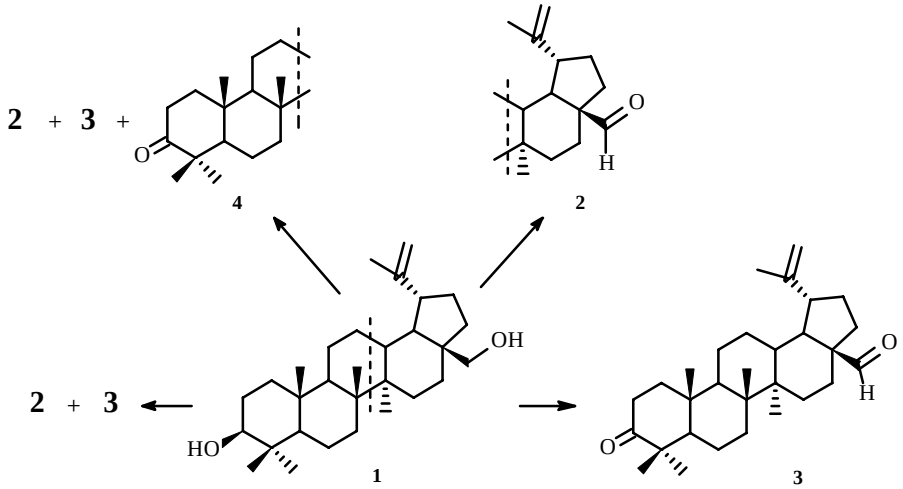
Oxidation of betulin by pyridinium dichromate, pyridinium chlorochromate, and $K_2Cr_2O_7$—H_2SO_4 in the presence of tetrabutylammonium bromide was studied. Products of regioselective C-3, C-28-, and exhaustive oxidation, 28-hydroxylup-20(29)-3-one, 3β-hydroxy- and 3-oxolup-20(29)-en-28-al were obtained.

Key words: betulin, selective oxidation, pyridinium chlorochromate, pyridinium dichromate, potassium bichromate, synthesis, 28-hydroxylup-20(29)-3-one, 3β-hydroxylup-20(29)-en-28-one, 3-oxolup-20(29)-en-28-al.

The high content of betulin (**1**) in birch bark (up to 40%) and its exceedingly simple extraction [1] have stimulated research on its use as starting material for synthesizing biologically active compounds.

We studied the selective oxidation and developed convenient methods for synthesizing functionalized derivatives of **1** that are difficultly accessible because of their low content in the plant material.

Betulin contains primary and secondary hydroxyls that are situated in different steric environments and should have fundamentally different reactivities. However, until now data on their different behavior toward oxidants have not appeared [2, 3]. It has only been stated [4] that oxidation of **1** by pyridinium dichromate (PDC) in aqueous DMF and in CH_2Cl_2 leads to a complicated mixture of hydroxyaldehyde **2**, ketoaldehyde **3**, betulinic and betulonic acids in the first instance and to ketoaldehyde **3** in 85% yield in the second. Either the traditional approach of manipulation by hydroxyl protecting groups [5] or exhaustive oxidation to betulonic acid by Jones reagent [3] or CrO_3 in AcOH [2] with subsequent reduction of the 3-ketone by $NaBH_4$ are used to prepare betulinic acid from **1**.



We tested several reagents based on Cr(VI), i.e., pyridinium dichromate (PDC) [6], pyridinium chlorochromate (PCC) [7], and $K_2Cr_2O_7$ in H_2SO_4 (9 M) in the presence of tetrabutylammonium bromide (TBAB) [8]. We noted the effect of the type of oxidant, solvent, and mole ratio of reactants on the selectivity of the process. It has been found that the reaction of **1** and PDC (2 equivalents) in benzene occurs regioselectively with oxidation of the primary C-28 OH.

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TABLE 1. Oxidation of Betulin (**1**) by Cr(VI) Reagents

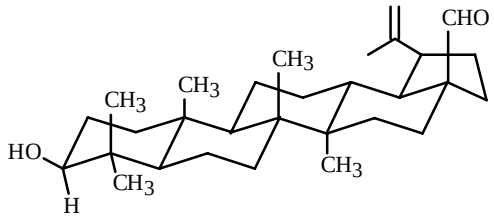
Reagent	Solvent	Ratio **1**:reagent, mol	Time*	Product (yield, %), **1** conversion, %
PDC	C_6H_6	1:2	3 h	**2** (68), 50
	$CHCl_3$	1:1.5	1h 15 min	**2** (86), 37
				3 (4)
PCC	CH_2Cl_2	1:1.5	45 min	**2** (74)**, 50
	C_6H_6	1:2	3 h	**2** (62), 58
				3 (23)
K_2CrO_7—9M H_2SO_4—TBAB	CH_2Cl_2	1:6	45 min	**3** (85), 100
	C_6H_6	1:1.05	12 h	**2** (37), 70
				3 (8)
				4 (12)
	$CHCl_3$	1:1.5	2.5 h	**2** (60), 50
				3 (13)

*Reaction monitored by TLC with benzene—EA (5:1) eluent.

Isolated as oxime of **2.

Incomplete conversion of the starting material under strictly controlled conditions (Table 1) produced hydroxyaldehyde **2** (68%). In $CHCl_3$, another minor ketoaldehyde **3** was isolated in addition to **2**. The **2**:**3** ratio was ~20:1. The product obtained in CH_2Cl_2 was boiled without purification with $NH_2OH \cdot HCl$—Py in EtOH to give the oxime of **2** (**2a**) in 74% yield calculated for reacted **1**. The reaction of **1** and PCC (2 equiv.) in benzene produced after 3 h a mixture of **2** and **3**. The effect of PCC (6 equiv.) in CH_2Cl_2 gave after 45 min the product of exhaustive oxidation, ketoaldehyde **3**. Thus, using benzene, in which the reaction is much slower than in $CHCl_3$ or CH_2Cl_2, increases the selectivity. Oxidation of **1** under phase-transfer conditions in benzene or $CHCl_3$ by $K_2Cr_2O_7$ (1.05-1.5 equiv.) in H_2SO_4 (9 M) can stop the reaction at the C-28 aldehyde stage, in contrast with the effect of $Na_2Cr_2O_7$—H_2SO_4 [9], which forms betulonic acid. The product of oxidation of the secondary hydroxyl without affecting the primary one, ketoalcohol **4**, was observed along with **2** and **3** in benzene.

The structures of the products were confirmed by ^1H and ^{13}C NMR spectra (Table 2). Two-dimensional heteronuclear correlation of direct spin—spin coupling constants enabled a determination of the chemical shifts of H atoms and their assignment to the corresponding C atoms and confirmed the chair conformation for rings A, B, C, and D in **2**-**4**.



Thus, we have developed a convenient route for synthesizing previously difficultly accessible derivatives of **1** with aldehyde and ketone groups that possess biological activity [10] and are interesting as intermediates in the synthesis of natural compounds.

TABLE 2. ^{13}C and ^{1}H Chemical Shifts of **2-4**

C_i	**2**		**2a**		**3**		**4**	
	δC	δH	δC	δH	δC	δH	δC	δH
1	38.73	0.90, 1.68	38.93	0.90,1.83	39.57	1.43, 1.80	39.76	1.48, 1.89
2	27.39	1.60	27.46		34.08	2.45	34.08	2.43
3	78.99	3.20 dd, J 11.0, 5.3	79.07	3.20 dd, J 11.0, 5.3	218.04		218.38	
4	38.85		38.79		47.28		47.52	
5	55.31	0.68 d, J 10.0	55.38	0.72 d, J 10.0	54.87	1.31	55.07	1.33
6	18.26	1.42, 1.55	18.37	1.36, 1.52	19.55	1.45	19.83	1.49
7	34.33	1.37	34.38	1.40	33.55	1.40	34.13	1.46
8	40.82		40.97		40.69		41.02	
9	50.40	1.27	50.47	1.24	49.75	1.36	49.90	1.33
10	37.17		37.09		36.82		37.01	
11	20.74	1.40, H*e*	20.87	1.42, H*e*	21.20	1.40, H*e*	21.51	1.10, 1.42
12	25.53	1.05, 1.76	25.29	1.07, 1.70	25.45	1.05, 1.77	25.36	1.00, H*a*
13	38.69	2.02 ddd, J 12.2, 12.2, 3.7	38.66	1.83	38.67	2.02 ddd, J 12.2, 12.2, 3.7	37.57	1.68
14	42.55		42.43		42.54		42.93	
15	28.80	1.20, 1.42	27.95	1.15, 1.82	28.73	1.20, 1.47	27.20	1.20, 1.73
16	29.25	1.46, He 2.05 dd, J 11.0, 2.9	32.48	1.45, 1.98	29.06	1.42 2.05 dd, J 11.0,	29.88	1.50
17	59.31		49.84		59.26	2.9	47.93	
18	47.52	1.75	49.44	1.64	47.42	1.75	48.83	1.60
19	48.06	2.88 ddd, J 11.0, 11.6, 5.6	47.96	2.55 ddd, J 11.0, 11.0, 5.4	47.86	2.90 ddd, J 11.0, 11.0, 5.6	49.90	2.44
20	149.72		149.89		149.59		150.55	
21	29.89	1.54, 1.87	29.82	1.50, 1.95, H*e*	29.77	1.50, 1.84	29.27	1.23, 1.92
22	33.22	1.33, H*e*	37.24		33.10	1.37, 1.75	33.67	1.81, H*e*
23	27.97	0.97 s	28.07	0.99 s	26.54	1.07 s	26.79	1.10
24	15.33	0.75 s	15.44	0.77 s	20.97	1.00 s	21.27	1.03 s
25	15.89	0.92	16.13	0.98 s	15.64	0.94 s	15.26	1.07 s
26	16.13	0.83 s	16.13	0.83 s	15.94	0.92 s	16.13	0.95 s
27	14.26	0.98 s	14.82	0.99 s	14.12	0.98 s	14.86	1.00 s
28	206.67	9.7 d, J 1.5	155.69	7.52 s	206.49	9.7 d, J 1.4	60.67	3.35 d, J 10.0
29	18.99	1.7 s	19.26	1.70 s	18.94	1.7 s	19.26	1.7 s
30	110.15	4.65 d, J 2.0 4.78 s	110.11	4.60 s 4.70 s	110.19	4.62 s 4.75 s	109.94	4.6 s 4.73 s
N-OH				7.70 br s				

EXPERIMENTAL

IR spectra were recorded on a Specord-M80 spectrophotometer in vaseline oil. ^{1}H and ^{13}C NMR spectra were recorded at room temperature in a Bruker-AM-300 spectrometer at working frequencies 300 and 75 MHz, respectively, in $CDCl_3$ without a standard. Chemical shifts are given in ppm relative to the solvent signal at 7.27 (δ_H) and 77.1 (δ_C). The multiplicity of the ^{13}C signals was found from ^{13}C spectra with C–H decoupling. Heteronuclear 2D spectra were obtained by the standard C–H correlation technique using direct spin—spin coupling constants (J = 140 Hz). Rotation angles were measured on a Perkin—Elmer 141 instrument. Mass spectra were measured using direct sample introduction into the ion source of Varian MAT CH-5 (**2**) and MX-1320 mass spectrometers.

TLC used Sorbfil (Russia) plates. Column chromatography was performed over Al_2O_3 (Brockman neutral) or SiO_2. Melting points were determined on a Kofler block. Anhydrous solvents were prepared by standard methods [11]. Acetone was

distilled over $KMnO_4$. Compound **1** was extracted from birch bark by the literature method [12] and recrystallized from ethylacetate, mp 258-260°C, $[\alpha]_D^{25}$ +20° (*c* 2, Py) {lit. mp 256-257°C, $[\alpha]_D^{25}$ +19° (*c* 2, Py)} [13].

Oxidation of 1 by PCC and PDC. A solution of **1** (0.226 mmole) in the appropriate anhydrous solvent (12 mL) was poured under a N_2 atmosphere at room temperature into stirred suspension of the corresponding number of millimoles of PDC or PCC in the same solvent (5 mL). When the reaction was finished, the mixture was diluted with absolute ether (12 mL), stirred for 10 min, and filtered through a thin layer of Al_2O_3. The solvent was evaporated. The solid was chromatographed over Al_2O_3 (petroleum ether—ethylacetate, 5:1). Depending on the reaction conditions, **2** and unreacted **1** or **2** and **3** were isolated. The solvent, reagent ratio, and yields of the products are listed in Table 1.

Compound 2. Mp 170-173°C, $[\alpha]_D^{25}$ (*c* 8.7, C_6H_6) {lit. mp 190-193°C (subl.), $[\alpha]_D^{25}$ +19° (*c* 1.06, $CHCl_3$) [14]}. IR spectrum (ν, cm^{-1}): 870, 1660, 1705, 2700, 3600. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 440 [M^+] (20), 425 [M - CH_3]$^+$ (3), 422 [M - H_2O] (7), 407 [M - CH_3 - H_2O]$^+$ (4), 412 [M - CO]$^+$ (14), 411 [M - CHO]$^+$ (10), 232 [$C_{16}H_{24}O$]$^+$ (9), 207 [$C_{14}H_{23}O$]$^+$ (30), 189 [$C_{14}H_{21}$]$^+$ (34), 43 [C_2H_3O + C_3H_7]$^+$ (100), 41 [C_3H_5]$^+$ (84).

Compound 3. Mp 121-123°C, $[\alpha]_D^{25}$ +53.8° (*c* 1.77, $CHCl_3$) (lit. [15]). IR spectrum (ν, cm^{-1}): 870, 1645, 1705, 1730, 2700, 3600.

3*β*-Hydroxylup-20(29)-en-28-al Oxime (2a). Compound **1** (0.226 mmole) and PDC (0.128 g, 0.339 mmole) in absolute CH_2Cl_2 (10 mL) were stirred at room temperature under an N_2 atmosphere for 25 min and diluted with absolute ether (3 mL). The reaction mixture was filtered through a thin layer of SiO_2. The filtrate was evaporated. The solid was dissolved in absolute EtOH (1.3 mL), treated with absolute pyridine (0.5 mL) and $NH_2OH \cdot HCl$ (0.15 g, 2.16 mmole), and boiled for 15 h. The solvent was evaporated. The solid was chromatographed over SiO_2 with elution by benzene—*t*-butylmethylether (5:1) to give **1** (0.045 g) and **2a** (0.043 g, 74%), mp 188-190°C, $[\alpha]_D^{25}$ +6° (*c* 8.0, C_6H_6). IR spectrum (ν, cm^{-1}): 870, 1645, 1660, 1705, 2700, 3600. Mass spectrum (EI, 70 eV, 50-100°C), *m*/*z* (I_{rel}, %): 455 [$M]^+$ (12), 438 [M - OH]$^+$ (14), 207 [$C_{14}H_{23}O$]$^+$ (25), 189 [$C_{14}H_{21}$]$^+$ (46), 107 [C_8H_{13}]$^+$ (58), 81 (50), 43 [C_2H_3O]$^+$, [C_3H_7]$^+$, [CNOH]$^+$, (100), 41 (92).

Phase-Transfer Oxidation of 1 by $K_2Cr_2O_7$. A solution of **1** (0.10 g, 0.226 mmole) in the appropriate solvent (20 mL) containing TBAB (6.4 mg, 0.0226 mmole) was stirred vigorously and treated with the corresponding amount of $K_2Cr_2O_7$ (Table 1) in H_2SO_4 (9 M, 0.57 mL). After the reaction was finished (TLC monitoring), the mixture was treated with $FeSO_4$ (10 mL, 10%). The organic layer was separated, washed with NaOH (10 mL, 10%), dried over Na_2SO_4, and evaporated. The solid was chromatographed over Al_2O_3 (petroleum ether—ethylacetate, 5:1). Depending on the reaction conditions, **1**, **2**, **3**, **4** or **1**, **2**, **3** were isolated (Table 1).

28-Hydroxylup-20(29)-en-3-one (4). Amorphous solid, $[\alpha]_D^{25}$ +17.8° (*c* 1.52, CH_2Cl_2). IR spectrum (ν, cm^{-1}): 870, 164, 1740, 3600.

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