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Synthesis of Vinyl Chloride Derivatives on the Basis of Betulin

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Abstract

Triterpenoids with a chlorovinyl fragment were synthesized through the interaction of diacetoxy-29-nor-20-oxobetulin and 2-cyano-3,4-seco-23-nor-4,28-dioxo-19β,28-epoxyoleane with phosphorus pentoxide *via* boiling in chloroform.

Keywords: triterpenoids, betulin, methyl ketones, chlorovinyl derivatives, synthesis, ozonolysis

INTRODUCTION

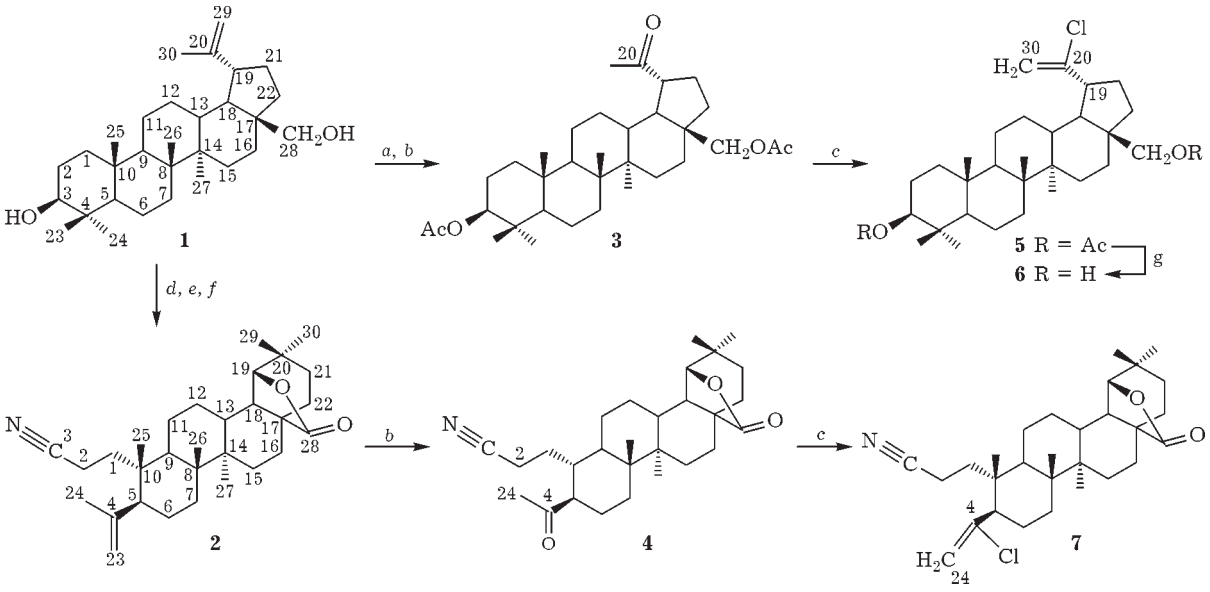
The main direction of using of easily accessible triterpenoid betulin consists in obtaining biologically active supplements and in the development of promising pharmaceutical preparations with antiviral and anticancer activity [1–3]. Another important direction could be presented by obtaining oligomeric derivatives with practically valuable properties. So, *via* the condensation of betulin with adipic acid, polyester was obtained with the molecular mass equal to 18 000–20 000 [4, 5]. There are examples in the literature concerning the synthesis of diglycidyl esters of betulin and phthalic anhydride derivatives for further obtaining epoxy polymers [6].

Polyvinyl chloride is one of the most widely used and worldwide produced polymers owing to its cheapness, the ability of chemical and physical modification and a diversity of other valuable properties. Modified analogues of polyvinyl chloride could exhibit another set of characteristics.

This paper describes the synthesis of possible monomers for the synthesis of copolymers based on betulin derivatives with chlorovinyl fragment.

RESULTS AND DISCUSSION

The general approach to the obtaining of chlorovinyl triterpenoids consisted in the interaction of methyl ketones **3** and **4** with phosphorus pentachloride in boiling chloroform (Scheme 1). In turn, methyl ketones **3** and **4** represent products available from the ozonolysis of betulin **1** and its derivative 2-cyano-3,4-seco-4(23)-ene-28-oxoallobetulin **2**. To all appearance, the formation of vinyl chloride triterpenoids **5**, **7** proceeds *via* the stage of *gem*-dichloro derivatives with further dehydrochlorination, in this case the dehydrohalogenation of *gem*-dichloride occurs with thermal elimination of only one HCl molecule to be stopped at the stage of vinyl chloride formation. Perhaps this is connected with a reduced reactivity of an intermediate precision derivative of betulin with a chlorovinyl fragment, since the further elimination of the second HCl molecule is difficult requiring for the presence of a basic eliminating agent. We obtained vinyl chloride **6** from compound **5** after unblocking the acetyl shielding.



Conditions: *a* – Ac_2O, pyridine; *b* – O_3, CH_2Cl_2; *c* – $PCl_5/CHCl_3$; *d* – Jones reagent/acetone; *e* – HCOOH; *f* – NH_2OH HCl/EtOH, *p*-TsCl/pyridine; *g* – 5 % KOH/EtOH.

Scheme 1.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were registered on a Bruker AM-300 NMR spectrometer (75.47 and 300.13 MHz, respectively) in deuterochloroform, internal standard tetramethylsilane was used as the internal standard. Melting point values were determined on the Boethius microheating plate. Absorbance was measured on a Perkin-Elmer MC 241 polarimeter using a 1 dm long tube. The TLC analysis was performed using Sorbfil plates (Sorbpolymer Co., Russia) using solvent system chloroform–ethyl acetate at a ratio of 40 : 1. The elemental analysis was performed using an EuruEA-3000 CHNS analyzer, with acetanilide as the basic standard. The substances were revealed with the help of 10 % H_2SO_4 solution and further heating at 100–120 °C for 2–3 min. Diacetoxy-29-nor-20-oxobetulin 3 was prepared *via* the procedure described in paper [7], 28-oxoallobetulon oxime was synthesized according to the procedure described by the authors of [8].

2-Cyano-3,4-seco-4(23)-ene-19β,28-epoxy-28-oxooleane 2. To a solution of 0.45 g (1.00 mmol) of 28-oxoallobetulon oxime in 15 mL of dry pyridine was added 0.88 g (4.62 mmol) of *p*-toluenesulphochloride and boiled for 6 h under reflux with a backflow condenser. The reaction mixture was poured into 100 mL of 5 % HCl solution, a precipitate was filtered, washed with water and dried. The product obtained was chromatographed on a column with Al_2O_3, with eluents petroleum ether and benzene. Yield: 0.39 g (86 %), m. p. 221–222 °C. $[\alpha]_D^{20}$ +60° (*c* 0.50, $CHCl_3$). Found, %: C 79.75, H 10.06, N 3.08. $C_{30}H_{45}NO_2$ (*M* 451.681). Calculated, %: %: C 79.77, H 10.04, N 3.10. ^1H NMR spectrum ($CDCl_3$, δ, ppm): 0.75 s (3H, H^{25}), 0.81 s (3H, H^{26}), 0.86 s (3H, H^{29}), 0.86 s (3H, H^{27}), 0.93 s (1H, H^{30}), 0.93–2.25 m (26H, CH, CH_2), 1.61 s (3H, H^{24}), 3.84 s (1H, H^{19}), 4.53 and 4.78, both br. s (2H, H^{23}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 11.1 (C^2), 13.3 (C^{27}), 15.3 (C^{26}), 19.5 (C^{22}), 21.4 (C^{11}), 22.5 (C^{25}), 23.7 (C^{24}), 23.8 (C^{29}), 25.2 (C^{12}), 25.6 (C^6), 27.5 (C^{30}), 28.5 (C^{15}), 31.6 (C^{16}), 31.8 (C^1), 32.1 (C^{21}), 33.3 (C^7), 34.1 (C^{13}), 35.8 (C^5), 39.8 (C^8), 39.8 (C^{14}), 40.5 (C^{10}), 40.7 (C^{20}), 46.3 (C^{17}), 47.3 (C^{18}), 47.5 (C^9), 85.6 (C^{19}), 113.9 (C^{23}), 119.9 (C^3), 146.6 (C^4), 179.4 (C^{28}).

2-Cyano-3,4-seco-23-nor-4,28-dioxo-19β,28-epoxyoleane 4. A solution of 0.45 g (1.01 mmol) of compound **2** in 50 mL of CH_2C1_2 was bubbled with ozone at about –60 °C until disappearing the initial substance used (TLC monitoring), to hold then for 24 h at a room

temperature. The solvent was evaporated under vacuum using a water-jet air pump, the product obtained was chromatographed on a column packed with Al_2O_3, using benzene as the eluent. Yield: 0.35 g (78 %), m. p. 181–182 °C. $[\alpha]_D^{20}$ +74° (*c* 0.50, $CHCl_3$). Found, %: C 76.77, H 9.56, N 3.11. $C_{29}H_{43}NO_3$ (*M* 453.663). Calculated, %: C 76.78, H 9.55, N 3.09. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.83 s (3H, H^{25}), 0.89 s (3H, H^{26}), 0.91 s (3H, H^{29}), 0.95 s (3H, H^{27}), 0.97 s (3H, H^{30}), 1.01–2.47 m (23H, CH, CH_2), 2.06 s (3H, H^{24}), 2.31 t (1H, H^5, *J* 7.8 Hz), 3.88 s (1H, H^{19}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 11.4 (C^2), 13.4 (C^{27}), 15.5 (C^{26}), 19.8 (C^{22}), 21.1 (C^{11}), 21.5 (C^{25}), 23.9 (C^{24}), 25.4 (C^{29}), 25.6 (C^{12}), 27.7 (C^6), 28.6 (C^{30}), 30.3 (C^{15}), 31.2 (C^{16}), 31.8 (C^1), 32.2 (C^{21}), 33.5 (C^7), 34.3 (C^{13}), 35.9 (C^{10}), 39.1 (C^{20}), 40.1 (C^8), 40.3 (C^{14}), 41.1 (C^{17}), 45.9 (C^{18}), 46.5 (C^9), 56.3 (C^5), 85.8 (C^{19}), 121.1 (C^3), 179.5 (C^{28}), 211.5 (C^4).

3β,28-Di-*O*-acetyl-20-chloro-29-norlup-20(30)-ene 5. To a solution of 0.51 g (1.00 mmol) of compound **3** in 50 mL of $CHCl_3$ was added 0.51 g (2.43 mmol) PCl_5 and boiled with a backflow condenser for 8 h. The reaction mixture was washed with water, dried over $CaCl_2$ and evaporated under vacuum using a water-jet air pump. The product was chromatographed on a column with Al_2O_3, using benzene as the eluent. Yield: 0.45 g (83 %), m. p. 200–201 °C. $[\alpha]_D^{20}$ +9° (*c* 2.60, $CHCl_3$). Found, %: C 72.45, H 9.37, Cl 6.46. $C_{33}H_{51}ClO_4$ (*M* 547.216). Calculated, %: C 72.43, H 9.39, Cl 6.48. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.82 s (3H, H^{24}), 0.83 s (3H, H^{23}), 0.97 s (3H, H^{25}), 1.01 s (3H, H^{26}), 1.02 s (3H, H^{27}), 1.14–1.98 m (24H, CH, CH_2), 2.03 and 2.06, both s (6H, 2OAc), 2.67–2.75 m (1H, H^{19}), 3.81 and 4.21, both d (2H, H^{28}, *J* 11.2 Hz), 4.44–4.49 m (1H, H^3), 5.03 and 5.14, both d (2H, H^{30}, *J* 1.3 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.5 (C^{27}), 15.9 (C^{25}), 16.1 (C^{26}), 16.4 (C^{24}), 17.9 (C^6), 20.5 (C^{34}), 20.9 (C^{33}), 23.6 (C^2), 24.8 (C^{12}), 26.8 (C^{21}), 27.8 (C^{15}), 27.8 (C^{23}), 29.6 (C^{16}), 33.2 (C^{22}), 34.0 (C^7), 36.9 (C^{13}), 37.1 (C^{10}), 37.7 (C^4), 38.3 (C^1), 40.7 (C^8), 42.7 (C^{14}), 46.1 (C^{17}), 48.2 (C^{18}), 49.8 (C^9), 50.4 (C^{11}), 53.1 (C^{19}), 55.2 (C^5), 62.8 (C^{28}), 80.7 (C^3), 111.5 (C^{30}), 148.7 (C^{20}), 170.8 (C^{31}), 171.3 (C^{32}).

3β,28-dihydroxy-20-chloro-29-norlup-20(30)-ene 6. To a solution of 0.58 g (1.00 mmol) of compound 5 in 50 mL of methanol was added 0.17 g (3.00 mmol) of KOH and stirred for 3 h (TLC monitoring). The reaction mixture was poured into 100 mL of cooled water; a precipitate was filtered, washed with water and dried. The product was crystallized from chloroform–methanol mixture. Yield: 0.41 g (89 %). m. p. 211–212 °C. $[\alpha]_D^{20}$ −2° (*c* 2.60, $CHCl_3$). Found, %: C 75.21, H 10.23, Cl 7.65. $C_{29}H_{47}ClO_2$ (*M* 463.143). Calculated, %: C 75.25, H 10.22, Cl 6.94. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.83 s (3H, H^{24}), 0.98 s (3H, H^{23}), 1.01 s (3H, H^{25}), 1.02 s (3H, H^{26}), 1.02 s (3H, H^{27}), 1.08–2.07 m (26H, CH, CH_2), 2.62–2.72 m (1H, H^{19}), 3.31 and 3.82, both d (2H, H^{28}, *J* 10.8 Hz), 3.17–3.27 m (1H, H^3), 5.03 and 5.14, both d (2H, H^{30}, *J* 1.2 Hz). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.7 (C^{27}), 15.4 (C^{24}), 15.9 (C^{25}), 16.1 (C^{26}), 18.3 (C^6), 20.7 (C^{11}), 25.0 (C^{12}), 26.5 (C^{21}), 27.3 (C^{15}), 27.3 (C^2), 28.0 (C^{23}), 29.1 (C^{16}), 33.1 (C^{22}), 34.5 (C^7), 36.1 (C^{13}), 37.1 (C^{10}), 38.7 (C^1), 38.9 (C^4), 40.9 (C^8), 42.8 (C^{14}), 48.4 (C^{17}), 49.3 (C^{18}), 50.2 (C^9), 53.3 (C^{19}), 55.3 (C^5), 60.9 (C^{28}), 78.9 (C^3), 111.3 (C^{30}), 149.2 (C^{20}).

2-Cyano-3,4-seco-23-nor-4-chloro-4(24)-ene-28-oxo-19β,28-epoxyoleane 7 was prepared from 0.47 g (1.00 mmol) of compound **4** in a similar manner as compound **5**. Yield: 0.42 g (88 %). m. p. 208 °C. $[\alpha]_D^{20}$ +154° (*c* 0.10, $CHCl_3$). Found, %: C 73.77, H 8.97, Cl 7.49, N 2.95. $C_{29}H_{42}ClNO_2$ (*M* 472.108). Calculated, %: C 73.78, H 8.97, Cl 7.51, N 2.97. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.87 s (3H, H^{25}), 0.91 s (3H, H^{26}), 0.94 s (3H, H^{29}), 0.97 s (3H, H^{27}), 1.04 s (3H, H^{30}), 1.08–2.41 m (24H, CH, CH_2), 3.95 s (1H, H^{19}), 5.12 and 5.36, both br. s (2H, H^{24}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 11.5 (C^2), 13.4 (C^{27}), 15.5 (C^{26}), 19.5 (C^{25}), 21.6 (C^{22}), 23.9 (C^{11}), 24.6 (C^6), 25.4 (C^{29}), 25.8 (C^{12}), 27.7 (C^{30}), 28.7 (C^{15}), 31.9 (C^{16}), 31.9 (C^{21}), 32.3 (C^7), 33.5 (C^1), 34.2 (C^{13}), 35.9 (C^{20}), 39.7 (C^8), 40.2 (C^{10}), 40.3 (C^{14}), 40.9 (C^{17}), 46.1 (C^9), 46.5 (C^{18}), 51.9 (C^5), 85.9 (C^{19}), 115.1 (C^{24}), 119.9 (C^3), 143.4 (C^4), 179.6 (C^{28}).

CONCLUSION

Thus, basing on betulin, a synthesis of practically important triterpenoids with vinyl chloride fragment was proposed consisting in the interaction between triterpene methyl ketones and phosphorus pentachloride in boiling chloroform.

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