Cyclopropanation of betulonic acid and its methyl ester with dichlorocarbene generated under phase transfer catalysis conditions

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The addition of dichlorocarbene generated under phase transfer catalysis conditions to the double bond of betulonic acid occurs stereoselectively and is accompanied by transformation of the carboxy group leading to the dichloromethyl ester and chloride of 3-oxo-20,29-(dichloromethano)lupan-28-oic acid. Together these products, the chloride of the starting betulonic acid is formed depending on the reaction conditions. The reaction of dichlorocarbene with methyl betulonate leads to the corresponding cyclopropane adduct in a quantitative yield.

Key words: betulonic acid, methyl betulonate, dichlorocarbene, phase transfer catalysis, cyclopropanation, acid chlorides, triterpenoids

A cyclopropane fragment present in natural products is combined most often with a carboxylic acid or ester function. Among compounds of this type, potent natural insecticides (pyrethroids), fungicides, analgesics, and compounds with antiinflammatory, antiviral, and other types of biological activities have been found.[1,2] In the series of lupane triterpenoids possessing a broad range of biological activities, two compounds containing both of these fragments are known. The synthesis of 3-*O*-permethrate- and 3-*O*-tetramethylcyclopropylcarbamate of 3β-hydroxylup-20(29)-en-28-oic (betulinic) acid by acylation with the chlorides of the corresponding cyclopropanecarboxylic acids has been reported.[3] *O*-Acyl derivatives of betulin and allobetulin have been prepared by a similar way; the antiinflammatory activities of these compounds have been studied. A high antituberculous activities of 20,29-(dichloromethano)lupane-3β,28-diol has been reported.[4]

In order to synthesize new biologically active compounds based on lupane triterpenoids, here we attempted to introduce a cyclopropane fragment into the betulonic acid **1a**. This was done through the Makosza addition of dichlorocarbene, generated from $CHCl_3$, to a C(19)-isopropenyl group. Previously,[5] we reported a stereoselective cyclopropanation of the isopropenyl group of the most readily available representative of this series, betulin and its diacetate, with dihalocarbenes under phase transfer catalysis conditions, resulting in *gem*-dichloro- or *gem*-dibromocyclopropanated derivatives in high yields. In the case of betulin, cyclopropanation of the double bond was accompanied by the attack by dichlorocarbene on the primary hydroxy group to give the corresponding chloride and formate.

The phase transfer catalyzed addition of dichlorocarbene to some 3-alkenoic acids and 2-methylbut-2-enoic acid is known[6] to smoothly give cyclopropanated derivatives. However, the reactions of acids such as acrylic, *trans*-crotonic, and 3-butenoic with dichlorocarbene generated from $PhHgCCl_2Br$ by heating in benzene involves primary attack of dichlorocarbene by the carboxy group to give dichloromethyl esters.[7]

The reaction of acid **1a** with dichlorocarbene generated from $CHCl_3$ on treatment with 50% NaOH in the presence of triethylbenzylammonium chloride (TEBAC) at room temperature proceeded as [1+2]-cycloaddition at the double bond but was accompanied by the attack of dichlorocarbene on the carboxy group. The major reaction products were cyclopropanated dichloromethyl ester **2** and chloride **3** (Scheme 1). The composition of the products was found to depend on the reaction conditions.

Treatment of acid **1a** dissolved in chloroform (10% solution) with 50% aqueous NaOH (1 mL) for 5 h (run *A*) resulted in dichloromethyl ester **2** and chloride **3**. When the reaction time was reduced to 3 h (run *B*), the reaction was noted to give betulonic acid chloride **4**, together with compounds **2** and **3**. This product was separated by column chromatography as a mixture with chloride **3** and identified by ^1H and ^{13}C NMR spectra. The predominant formation of chloride **3** (yield 73%) was observed in the reaction of dichlorocarbene with pre-synthesized sodium salt of acid **1a** (run *C*).

The addition of dichlorocarbene to the C(20)—C(29) double bond of methyl ester **1b** was diastereoselective and gave *gem*-dichlorocyclopropane derivative **5** in a quantitative yield.

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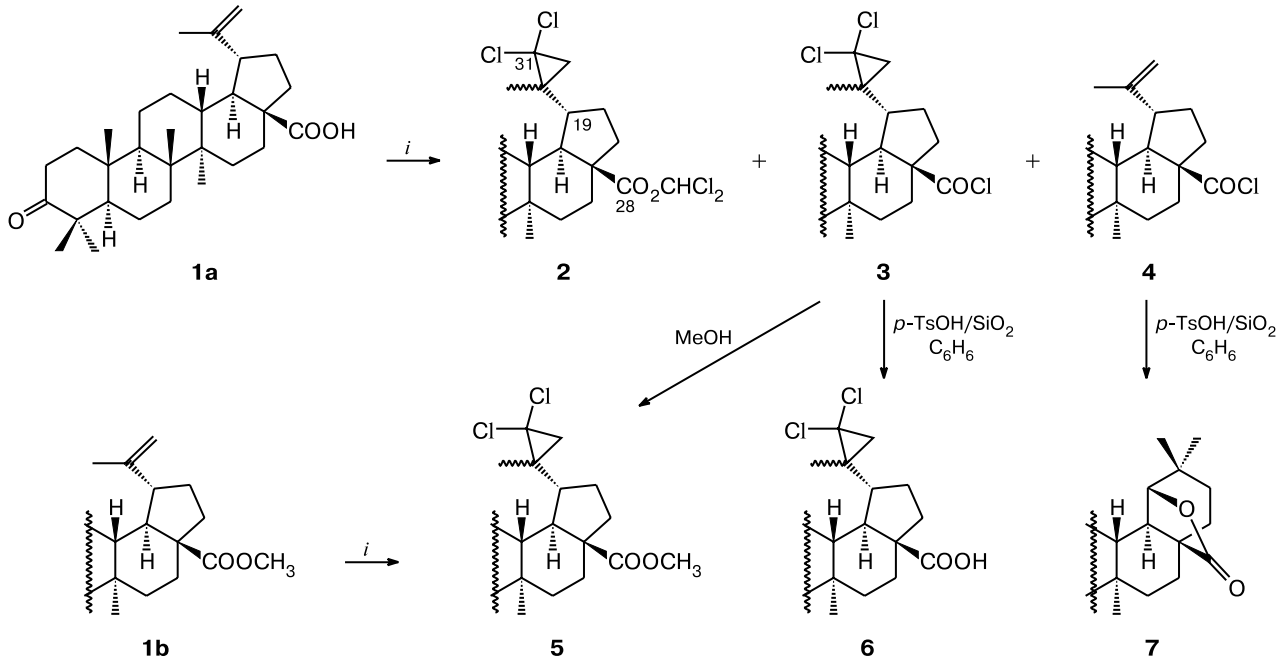
Scheme 1



1a **2** **3** **4**

1b **5** **6** **7**

i. $CHCl_3$, 50% NaOH, TEBAC

For determining the structures of the synthesized *gem*-dichlorocyclopropane derivatives, their ^{13}C NMR spectra are most informative. For example, in the spectra of compounds **2**, **3**, and **5**, the number and the multiplicity of signals corresponded to the presumed structures. The signals for the carbon atoms of the double bond were missing from all spectra, but the singlets typical of the carbon atom of the cyclopropane fragment bonded to two chlorine atoms ($\delta_{C(31)}$ 69.27—69.57) were observed. The signals of the carbonyl atoms of dichloromethyl ester **2**, chloride **3**, and methyl ester **5** were observed at $\delta_{C(28)}$ 171.51, 171.77, and 176.40, respectively. The spectrum of ester **2** contained a doublet for the $OCHCl_2$ carbon with δ_C 89.31. The molecular weights of compounds determined by high-resolution mass spectrometry corresponded to the calculated values.

The formation of chlorides **3** and **4** was confirmed by some chemical transformations. For instance, hydrolysis of chloride **3** carried out in benzene for 20 h and catalyzed by SiO_2-supported *p*-toluenesulfonic acid[8] has given acid **6** in a quantitative yield. Treatment of a mixture of chlorides **3** and **4** under the same conditions yielded a mixture of acid **6** and lactone **7**. The lactone results from hydrolysis of chloride **4** followed by the acid-catalyzed Wagner—Meerwein rearrangement of acid **1a** proceeding under the same conditions.[9] The acylation of methanol with chloride **3** gave methyl ester **5** in a high yield.

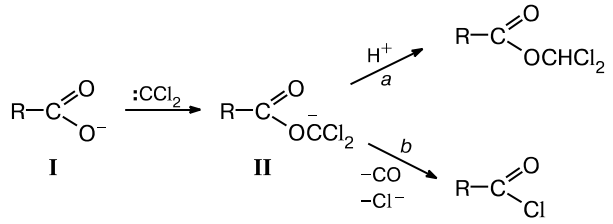
Unlike chloride **3**, dichloromethyl ester **2** did not undergo any changes on treatment with a 50% aqueous solution of NaOH in $CHCl_3$ in the presence of TEBAC for 12 h. A similar stability against hydrolysis has been noted previously[6] for dichloromethyl acrylate and *trans*-crotonate. Presumably, dichloromethyl ester **2** is not an intermediate in the formation of chloride **3**.

Compounds **2—4** are apparently formed according to the following route. The primary attack by dichlorocarbene on the carboxylate anion **I** results in carbanion **II** whose stabilization upon protonation (Scheme 2, path *a*) or loss of CO with chloride ion (path *b*) furnishes the dichloromethoxy derivative or chloride, respectively. The yields of the reaction products are determined by the relationship of the transformation rates of carbanion **II** according to pathways *a* and *b*.

Note that the formation of acid chlorides with participation of dichlorocarbene under phase transfer catalysis conditions has not been reported previously.

The reason for this phenomenon is apparently in the structural features of the chlorides **3** and **4** formed. Due to the steric hindrance at the C(28) carbonyl carbon atom, these products are rather stable against hydrolysis possible under the reaction conditions and do not undergo changes on treatment of the reaction mixture during chromatography or on storage; hence, they can be isolated and reliably identified. Presumably, acid chlorides are also formed as intermediates in the phase transfer reactions of dichlorocarbene with unsaturated carboxylic acids with simpler structures; however, due to the lability under the reaction condi-

Scheme 2



tions, they are rapidly converted into the corresponding acids.

Previously,[5] it was shown that the addition of dichlorocarbene to the C(20)—C(29) double bond of betulin diacetate affords two diastereomers (95 : 5 ratio); one of these was isolated in a pure state by recrystallization, while the second was obtained as a 1 : 1 mixture with the first one. In this study, compounds **2**, **3**, and **5** are formed as individual diastereomers.

Thus, in a study of the phase transfer catalyzed reaction of betulonic acid with dichlorocarbene, we found a reaction of dichlorocarbene with the carboxy group to give rise to acid chloride. As a result of the study, we synthesized lupane derivatives that may be of interest as potential biologically active compounds.

Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature on a Bruker-AM 300 spectrometer operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C; the chemical shifts were referred to the solvent signal: δ_H 7.27 (residual protons) and δ_C 77.0. The ^{13}C NMR signals were assigned using C—H coupling constant modulation mode and heteronuclear correlation; the ^{1}H NMR signals were taken from the {CH}-correlation spectrum. Mass spectra were obtained on a Thermo Finnigan MAT 95XP spectrometer (EI, 70 eV, direct injection), with temperature programming from 50 to 270 °C at a heating rate of 25 K min^{-1}. The rotation angles were measured on a Perkin—Elmer-241 instrument. Column chromatography was performed using SiO_2, KSM, 100/160 mesh (Russia). The reaction was monitored by TLC on Silufol plates (Czechia). Acid **1a** (yield 55%) was prepared from betulin, isolated from the birch bark,[10] by the Jones oxidation,[11] transformation into the sodium salt,[12] acidification, and chromatography on SiO_2 (benzene). The melting point (253—254 °C) and the spectroscopic data corresponded to those reported in the literature.[13] Methyl betulonate **1b** was prepared in 98% yield by treatment of acid **1a** with diazomethane in ether followed by chromatography on SiO_2 (benzene), m.p. 168 °C (*cf.* Ref. 14: 164 °C). The ^{13}C and ^{1}H NMR spectra of compounds **2—6** are reported in Table 1.

The reaction of acid 1a with dichlorocarbene. Run *A*. To a solution of acid **1a** (0.10 g, 0.22 mmol) in $CHCl_3$ (1.0 mL), TEBAC (0.005 g, 0.022 mmol) and 50% NaOH (1.0 mL) were added and the reaction mixture was stirred for 5 h at 20 °C. The mixture was diluted with water, the organic layer was separated, washed with water to pH ~7, and dried with Na_2SO_4, the solvent was evaporated, and the residue was chromatographed on SiO_2 (elution with benzene, and then benzene—ethyl acetate) to give 0.030 g (22%) of ester **2**, 0.045 g (37%) of chloride **3**, and 0.017 g of a mixture of **2** and **3**.

Dichloromethyl 3-oxo-20,29-(dichloromethano)lupan-28-oate (2), oil, $[\alpha]_D^{20}$ +9 (*c* 0.80, $CHCl_3$). Found *m/z* 618.2198 $[M]^+$. $C_{32}H_{46}{}^{35}Cl_4O_3$. Calculated M = 618.2196.

3-Oxo-20,29-(dichloromethano)lupan-28-oic acid chloride (3), m.p. 228 °C, $[\alpha]_D^{20}$ +7 (*c* 0.70, $CHCl_3$).

Run *B*. To a solution of acid **1a** (0.20 g, 0.44 mmol) in $CHCl_3$ (2.0 mL), TEBAC (0.010 g, 0.044 mmol) and 50% NaOH (2.0 mL) were added and the mixture was stirred for 3 h at 20 °C. Then it was treated as described in run *A*, and chromatographed on SiO_2 (elution with benzene, then benzene : ethyl acetate, 25 : 1) to give 0.030 g (13%) of dichloromethyl ester **2**, 0.135 g of a mixture of chloride **3** and 3-oxolup-20(29)-en-28-oic acid chloride (**4**), together with 0.025 g of the initial acid **1a**.

Run *C*. To a solution of acid **1a** (0.050 g, 0.11 mmol) in benzene (1.5 mL), 50% NaOH (0.20 mL) was added, and the mixture was stirred for 2 h and left for 16 h. Chloroform (1.0 mL) and TEBAC (0.0025 g. 0.011 mmol) were added to the suspension of the sodium salt of acid **1a** in benzene. The reaction mixture was stirred for 12 h at 20 °C, diluted with chloroform, treated as described in run *A*, and chromatographed in SiO_2 (elution with benzene) to give 0.007 g (10%) of ester **2** and 0.045 g (73%) of chloride **3**.

Methyl 3-oxo-20,29-(dichloromethano)lupan-28-oate (5). A solution of methyl ester **1b** (0.050 g, 0.11 mmol) in $CHCl_3$ (2 mL), 50% NaOH (0.5 mL), and TEBAC (0.0025 g, 0.011 mmol), the mixture was stirred for 3 h at 20 °C, treated as described in run *A*, and chromatographed on SiO_2 (benzene as the eluent) to give 0.057 g (97%) of ester **5**, amorphous, $[\alpha]_D^{20}$ +6.8 (*c* 2.45, $CHCl_3$). Found: *m/z* 550.2979 $[M]^+$. $C_{32}H_{48}O_3{}^{35}Cl_2$. Calculated: M = 550.2975.

3-Oxo-20,29-(dichloromethano)lupan-28-oic acid (6). A TsOH—SiO_2 mixture (1.5 g) was added to a solution of chloride **2** (0.05 g, 0.09 mmol) in benzene (3 mL). The suspension was stirred for 20 h at 20 °C, the solid phase was filtered through a thin layer of SiO_2, and the solvent was evaporated to give 0.046 g (96%) of acid **6**, amorphous, $[\alpha]_D^{20}$ +14 (*c* 0.85, $CHCl_3$).

Hydrolysis of a mixture of chlorides 3 and 4. A TsOH—SiO_2 mixture (3.0 g) was added to a solution of a mixture of **3** and **4** (0.10 g) in benzene (6 mL). The suspension was stirred for 20 h at 20 °C, the solid phase was filtered off, the solvent was evaporated, and the residue was chromatographed on SiO_2 (benzene—EtOAc, 50 : 1) to give 0.068 g of acid **6**, 0.026 g of lactone **7**, and 0.015 g of an unidentified product. Lactone **7**, $[\alpha]^{20}$ +65 (*c* 0.7, CH_2Cl_2), m.p. >300 °C, the ^{1}H and ^{13}C NMR spectra corresponded to published data.[15]

Acylation of methanol with chloride 3. A solution of acid **1a** (0.050 g, 0.11 mmol) in $CHCl_3$ (1.0 mL), TEBAC (2.5 mg), and 50% NaOH (0.5 mL) were stirred for additional 6 h, MeOH (4.5 mL) was added, and the mixture was stirred for 6 h. Methanol was evaporated from the reaction mixture, water (3 mL) was added, the product was extracted with $CHCl_3$ (5×3 mL), the organic layer was separated, washed with water, dried with Na_2SO_4, the solvent was evaporated, and the residue was chromatographed on SiO_2 (benzene as the eluent) to give 0.009 g (13%) of dichloromethyl ester **2**, 0.040 g (66%) of methyl ester **5**, and 0.004 g of a complex mixture of products.

Table 1. ^{13}C and ^{1}H NMR spectra (δ, *J*/Hz) of compounds **2—6**

Atom C	**2**		**3**		**4**		**5**		**6**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	39.71	1.45 (H_{ax}); 1.94 (ddd, H_{eq}, J = 14.3, 7.6, 4.4)	39.81	1.90, 1.40	39.69		39.70	1.40, 1.90	39.59	1.40, 1.95
2	34.17	2.42 (ddd, H_{eq}, J = 15.7, 7.5, 4.4); 2.53 (ddd, H_{ax}, J = 15.7, 10.0. 7.6)	34.26	2.43, 2.50	34.15		34.18	2.45	34.08	2.55, 2.45
3	217.99		218.02		217.82		218.08		216.07	
4	47.41		47.51		47.37		47.41		47.34	
5	55.01	1.34	55.15	1.30	55.00		55.00	1.30	54.90	1.35
6	19.63	1.44	19.72	1.45	19.63		19.68	1.50	19.57	1.45
7	33.60	1.40	33.77	1.40	33.65		33.66	1.40	33.56	1.40
8	40.79		40.68		40.75		40.70		40.63	
9	50.32	1.70	50.35	1.70	49.94		50.46	1.60	50.11	1.70
10	36.92		37.02		36.92		36.92		36.65	
11	21.39	1.50 (2 H)	21.50	1.50	21.40		21.44	1.50	21.33	1.45
12	26.83	1.65, 1.20	27.00	1.60, 1.20	26.90		26.91	1.22, 1.60	26.80	1.25, 1.65
13	37.58	2.15 (td, J = 12.2, 3.5)	37.57	2.20	38.25		37.50	2.20	37.54	2.22
14	42.72		42.96		42.58		42.73		42.67	
15	28.67	1.28, 1.50	29.12	1.45, 1.20	29.75		29.19	1.17, 1.45	29.10	1.20, 1.45
16	31.44	2.28 (td, H_{ax}, J = 14.0; 3.8); 2.40 (H_{eq})	31.95	1.20, 1.65	31.67		32.22	1.28, 1.40	32.22	1.45, 2.30
17	57.20		58.35		58.00		56.83		56.67	
18	46.05	2.22	46.12	2.20	46.62		46.22	2.25	46.09	2.30
19	49.70	1.45	49.61	1.40	49.15		49.72	1.40	49.58	1.40
20	34.76		34.91		147.76		34.95		34.65	
21	29.27	1.28, 1.70	29.53	1.70, 1.25	30.32		29.42	1.25, 1.75	29.37	1.20, 1.70
22	36.39	1.35, 1.95	36.49	1.90, 1.35	36.32		36.92	1.30, 1.90	36.97	1.35, 2.05
23	26.61	1.08 (s)	26.67	1.08 (s)	26.60	1.08 (s)	26.61	1.07 (s)	26.56	1.08 (s)
24	21.09	1.03 (s)	21.20	1.04 (s)	21.09	1.04 (s)	21.10	1.02 (s)	21.00	1.03 (s)
25	15.69	0.94 (s)	16.01	0.95 (s)	15.90	0.95 (s)	15.75	0.94 (s)	15.74	0.94 (s)
26	15.98	0.95 (s)	16.01	1.00 (s)	15.90	1.00 (s)	15.96	0.93 (s)	15.88	0.94 (s)
27	14.66	1.01 (s)	14.72	1.01 (s)	14.62	0.97 (s)	14.76	0.99 (s)	14.58	1.01 (s)
28	171.51		171.77		171.54		176.40		182.04	
29	36.27	1.35	36.28	1.35	109.99	4.53 (br.s); 4.68 (br.s)	36.40	1.35	36.30	1.35
30	17.34	1.24 (s)	17.49	1.25 (s)	19.43	1.70 (s)	17.42	1.23 (s)	17.33	1.24 (s)
31	69.27		69.38				69.56		69.46	
32	89.31 ($OCHCl_2$	7.80 ($OCHCl_2$)					55.01 (OMe)	3.65		

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