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Synthesis of guaian sesquiterpene γ -lactones from hanphilline

Synthetic methods of guaianolides on the basis of germacranolide E,E-hanphilline were presented in this article. Hanphilline is a characteristic component of the Noble Yarrow (*Achillea nobilis* L.), which is widespread in Central Kazakhstan. Synthesis of obtained guaianolides were carried out with stereocontrolled 1,5-cyclization of E,E-germacranolide (+)-hanphilline. The one-step stereospecific syntheses of guaianolides on the basis of available germacradienolide E,E-hanphilline were developed and carried out. The mechanism of 1,5-carbocyclization was considered. Scheme of biogenetic interdependence of guaianolides in *Achillea nobilis* L. was offered. It allowed a deeper understanding of a very complex process of biosynthesis of sesquiterpene lactones in the plant body.

Key words: sesquiterpene lactones, guaianolides, germacranolides, stereocontrolled synthesis, hanphilline, carbocyclization, biogenetic interdependence, quantum-chemical calculations.

Sesquiterpene γ -lactones, in particular guaianolides and germacranolides, are widespread in flowering plants of the family Asteraceae (Acteraceae). They are valuable natural compounds for studying various reactions and synthesis of new biologically active derivatives [1].

Synthesis methods of guaianolides on the basis of germacranolide E,E-hanphilline were presented in this work. Hanphilline is a characteristic component of the Noble Yarrow (*Achillea nobilis* L.), which is widespread in Central Kazakhstan [2].

Reaction of electrophilic cyclization of hanphilline (1) occurred through $\Delta^{1,10}$ -double bond. Investigation of cyclization by activation of second $\Delta^{4,5}$ -double bond arouse interest for us (because other skeletal types of sesquiterpenoids could be formed) [3, 4]. It was necessary to induce allyl cation (in the molecule, namely the carbon C₃-C₄-C₅) by cleavage of the hydroxyl group at C₃.

In connection with it, reactions of hanphilline with dehydrating reagents were investigated. Selective and widespread in chemistry of natural compounds p-toluenesulfonyl chloride (TsCl) and methyl sulfochloride (MsCl) were used in the capacity of dehydrating reagents.

Treatment of hanphilline (1) with tosyl chloride in pyridine at 80 °C gave chiral cis-condensed 5(α),10(α)-guaianolides — (2) and (3) with 55 and 30 % yields (Fig. 1). ¹H-NMR spectrum data of obtained compounds are shown in Table 1.

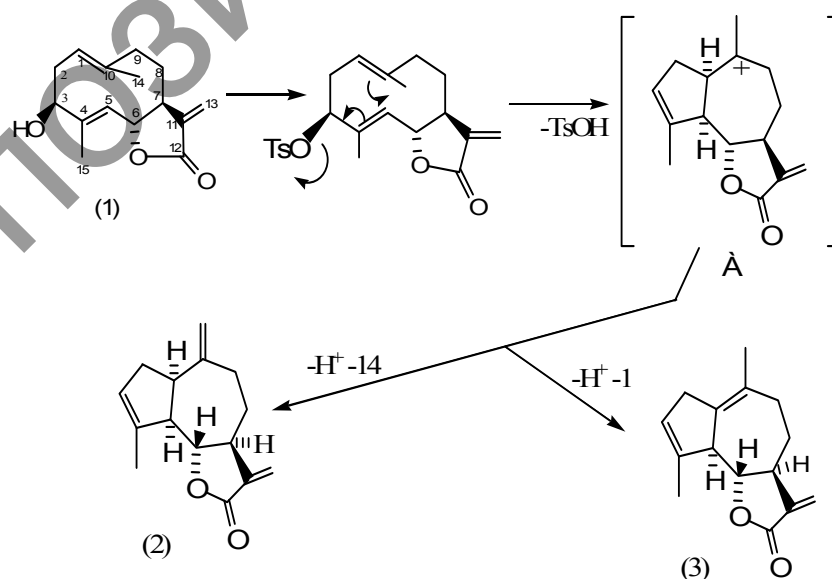


Figure 1. The obtaining of guaianolides (2) and (3)

Table 1

**Chemical shifts (δ , ppm), spin-spin interaction constants (in Hz)
of hanphilline and its derivatives (2) and (3)**

Protons	Compounds		
	(1)	(2)	(3)
Me-4	1,68 broad singlet	1,61 broad singlet	1,60 broad singlet
Me-10	1,43 singlet	–	1,81 singlet
H-1	5,24 broad doublet (3)	–	–
H-3	4,90 broad doublet of doublets (10;5)	4,87 broad doublet (3)	4,87 broad doublet (3)
H-5	4,86 broad doublet (8,5)	2,15 multiplet	2,15 multiplet
H-6	4,12 quartet (10;8,5)	3,97 triplet (10, 5)	4,10 triplet (10, 4)
H-13a	5,52 doublet (3,5)	5,44 doublet (3)	5,44 doublet (3)
H-13b	6,26 doublet (3,5)	6,15 doublet (3)	6,15 doublet (3)
H-14a	–	4,78 broad singlet	–
H-14b	–	4,78 broad singlet	–

¹H NMR spectra of all obtained compounds were registered on a spectrometer Bruker Avance-400 (operating frequency 400,13 MHz), solvent CDCl₃, internal reference TMS.

As we can see from the scheme, cleavage of intermediate sulfoester C₃-OH group initiated stereocontrolled electrophilic rearrangement (a resonantly stabilized allyl cation could be formed). It led to 1,5-cyclization by Markovnikov's rule and formation of the most stable guaian carbocation (A). Further stabilization of carbocation (A) through regioselective deprotonation (Hofmann's rule) led to final guaianolides (2) and (3). A similar result was obtained by treatment (1) with mesyl chloride in pyridine under reflux, which also led to the stereocontrolled formation of isomeric cis-guaianolides (2) and (3) with 54 and 31 % yields.

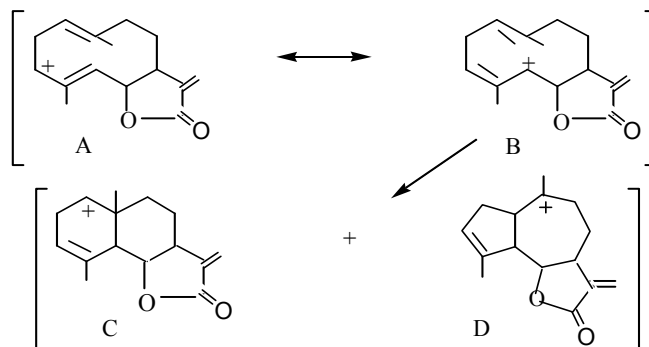
Quantum-chemical calculations (Table 2) of the total energies of all cationic intermediates formed during by cleavage of hydroxyl group did not reveal an energy preferableness of one of the two resonant structure of allyl cation (A, B). It was found that they had the same total energy ($E_{\text{tot}} = -61057$ kcal/mol) [5].

Table 2

Quantum-chemical calculations of the total energies of all cationic intermediates

Compound	E_{tot} , kcal/mol				
	1	A	B	C	D
PM3	-68400,984	-61056,932	-61056,965	-61062,342	-61081,231

Further cyclization of the most preferable (from the viewpoint of structure) allyl cation (B) could lead to bicyclic cation (C) and (D). The guaian cation (D) (identical to carbocation (A)) was the most energetically stable than (C). The difference in energy was 19 kcal/mol. Therefore the further cyclization by deprotonation led to guaianolides (2) and (3). Thus, quantum-chemical calculations of the total energies of all cationic intermediates confirmed the proposed mechanism of cis-guaianolides formation.



Thus, it was found that the cleavage of the C₃-OH group of hanphilline activated $\Delta^{4,5}$ -double bond and initiated intramolecular 1,5-carbocyclization which led to only cis-condensed guaian structures. The cyclization was stereospecific and completely controlled by conformation of chiral hanphilline.

Namely the stereocontrolled synthesis of cis-guaianolides (2) and (3) allowed us to develop a scheme of biogenetic interdependence of guaian sesquiterpene γ -lactones in Noble Yarrow (*Achillea nobilis* L.), (Fig. 2).

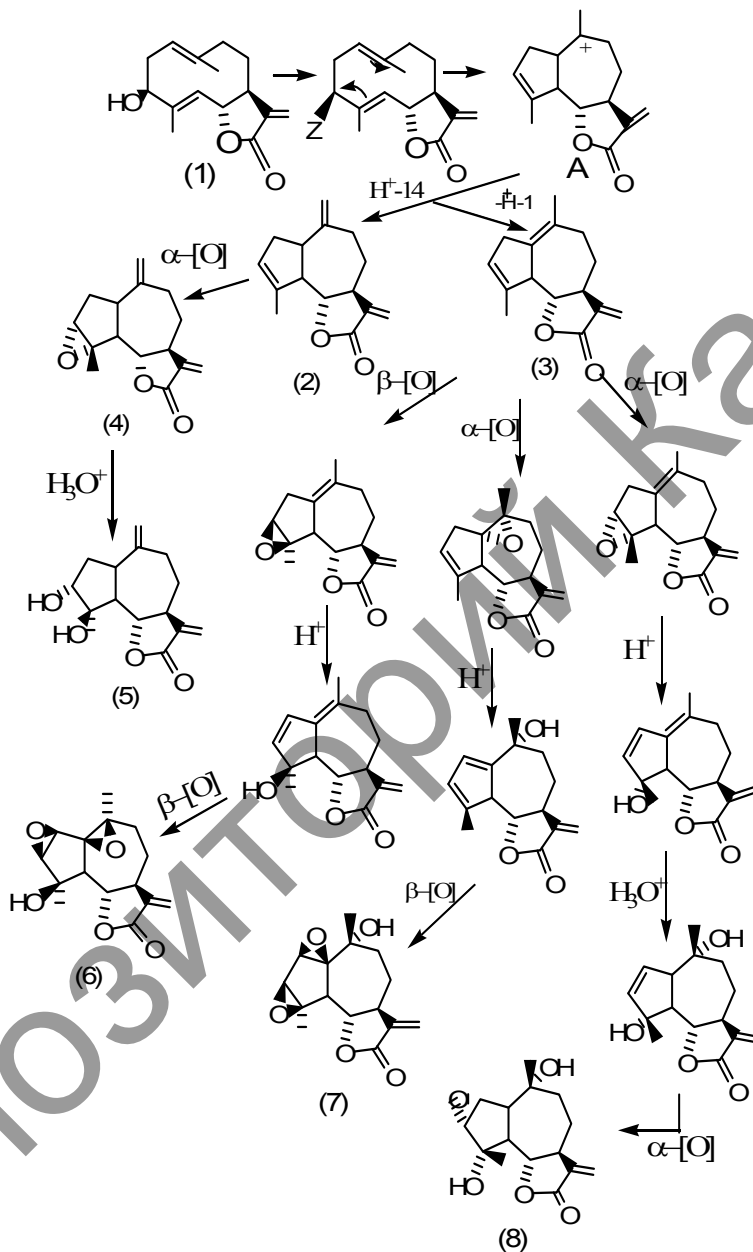


Figure 2. Scheme of biogenetic interdependence of guaianolides in *Achillea nobilis* L.

As we can see, reaction of 1,5-carbocyclization of hanphilline (key stage) led through bicyclic cation (A) to guaianolides (2) and (3). In further successive regio- and stereoselective reaction of epoxidation, isomerization and hydrolysis led to guaianolides: estafiatin (4), anolide (5), anobin (6), canin (7) and khризартемин A (8). The epoxidation reaction was an important step for the introduction of the oxygen atom in the molecular structure. Proposed way of biogenetic interdependence confirmed fact that guaianolides (4), (5), (6), (7) and (8) were isolated from the aboveground part of Yarrow Noble. Furthermore, it became apparent that hanphilline was a biogenetic predecessor of these guaianolides in the plant organism. Because, it was isolated from the Noble Yarrow by water extraction method, too [2].

Thus, the one-step stereospecific syntheses of cis-guaianolides were carried out and developed. We chose germacradienolide hanphilline, easily available sesquiterpene, as the starting material. The key stage was the dehydration reaction. In addition the scheme of biogenetic interdependence of guaianolides in *Achillea nobilis* L. was developed. It allowed a deeper understanding of a very complex process of biosynthesis of sesquiterpene lactones in the plant body.

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Ханфиллиннен гваянды сесквитерпенді γ -лактондарды синтездеп алу

Мақалада сесквитерпенді γ -лактон E,E-ханфиллиннен гваянолидтерді синтездеп алу әдістері қарастырылды. Бұл қосылыс Орталық Қазақстанда кенінен таралған асыл мыңжапырақтан (*Achillea nobilis* L.) бөлініп алынды. Алынған гваянолидтердің синтезі (+)-ханфиллиннің E,E-гермакранолидінің стереобакыланған 1,5-циклденуімен жүргізілді. Ханфиллиннен цис-гваянолидтердің бірсағылы стереоспецификалық синтездеп алу әдістері ұсынылып, жүргізілді. 1,5-карбоциклденудің механизмі зерттеліп, *Achillea nobilis* L. өсімдігінде гваянолидтердің биогенетикалық өзара байланысының сызбасы ұсынылды.

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Синтез гваяновых сесквитерпеновых γ -лактонов из ханфиллина

В статье представлены методы синтеза гваянолидов из сесквитерпенового γ -лактона E,E-ханфиллина. Ханфиллин является характерным компонентом широко распространенного в Центральном Казахстане растительного сырья тысячелистника благородного (*Achillea nobilis* L.). Синтез полученных гваянолидов был осуществлен стереоконтролируемой 1,5-циклизацией E,E-гермакранолида (+)-ханфиллина. Были разработаны и осуществлены одностадийные стереоспецифичные синтезы цис-гваянолидов, исходя из доступного гермакраниолида ханфиллина. Рассмотрен механизм 1,5-карбоциклизации и предложена схема биогенетической взаимосвязи гваянолидов в *Achillea nobilis* L., которая позволяет глубже понять весьма сложные процессы биосинтеза сесквитерпеновых лактонов в растительном организме.

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