ОРГАНИКАЛЫҚ ХИМИЯ
ОРГАНИЧЕСКАЯ ХИМИЯ

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Stereocontrolled synthesis of trans-eudesmanolides from (+)-hanphilline

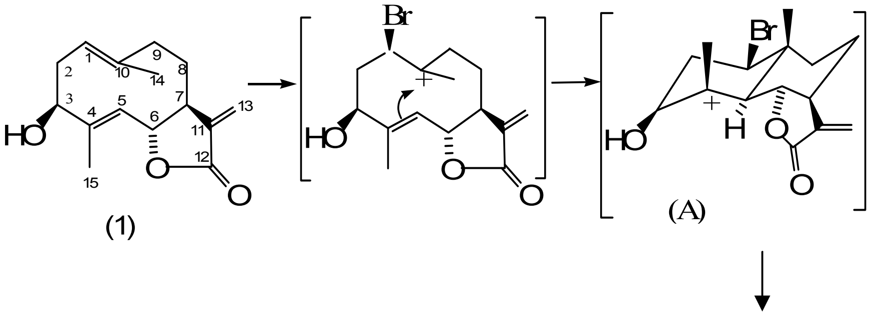
Directed synthesis methods of practically significant eudesmanolides on the basis of germacranolide E,E-hanphilline were presented in this article. Synthesis of obtained trans-eudesmanolides was carried out with stereocontrolled 5,10-cyclization of E,E-germacranolide (+)-hanphilline. The considered mechanism of 5,10-carbocyclization of the E,E-germacranolide (+)-hanphilline consistent with the results of quantum-chemical calculations of the total energies of all cationic intermediates formed during the reaction. It was shown that electrophilic reagents led to different eudesmanolide sesquiterpenoids. The one-step synthetic method of functionalized at C-1 and C-3 trans-eudesmanolides was developed.

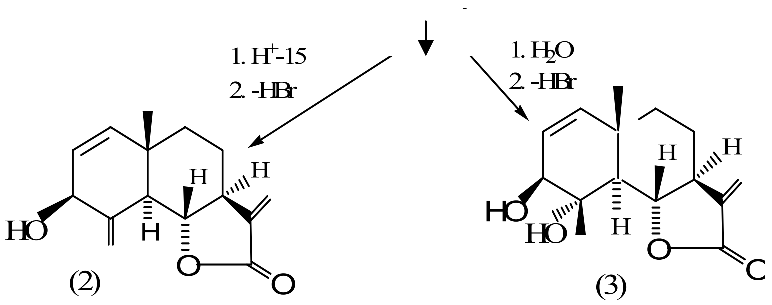
Key words: sesquiterpene lactones, eudesmanolides, germacranolides, stereocontrolled synthesis, hanphilline, cyclization, electrophilic reagents, quantum-chemical calculations.

Sesquiterpene γ-lactones, in particular trans-eudesmanolides and E,E-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 [1–3].

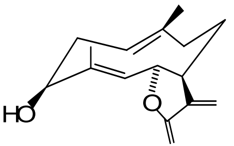
Stereocontrolled synthesis methods of eudesmanolides on the basis of germacranolide E,E-hanphilline were presented in this work. Hanphilline is a characteristic component of the Noble Yarrow (*Achillea nobilis L.*), which is widespread in Central Kazakhstan [4].

Interaction of hanphilline (1) with N-bromosuccinimide in aqueous acetone at temperature 25–30 ºC led to formation of trans-condensed 5(α),10(β)-eudesmanolides (2) and (3) with 30 and 40 % yields. Synthesized eudesmanolides are chiral diastereomers. Specific rotation of (2) is $[\alpha]_D^{18}$+ 50º (c 0,02; $CHCl_3$) and specific rotation of (3) is $[\alpha]_D^{18}$ + 46º (c 0,01; $CHCl_3$). Apparently, reaction started with regiospesific electrophilic bromation of the most electron-donor and space available double bond at C_1–C_{10} in molecule of hanphilline (1). And then intramolecular 5,10-carbocyclization (Markovnikov's rule) with the assistance of second skeletal $\Delta^{4,5}$-double bond (in the capacity of nucleophile) was initiated. In the end, an intermediate 1-bromeudesman cation (A) was formed:





Further stabilization occurred through ejection of protons from the C-15 (Hofmann's rule) and cleavage of HBr from the C_1-C_2. It gave eudesman allyl alcohol (2). Nucleophilic attack of hydroxyl ion (or water) with simultaneous β-dehydrobromation formed diol (3). Moreover, the cyclization was realized through low-energy conformation of hanphilline (4) — chair–chair (Fig.1) with configuration $_1D^{14}$and $^{15}D_5$ leading to the formation of trans-condensed eudesmanolides. ^{1}H-NMR spectrum data of obtained compounds are shown in Table 1.



(4)

Figure 1. The conformation of hanphilline — chair–chair

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	–	1,26 singlet
Me-10	1,43 singlet	0,9 singlet	0,94 singlet
H-1	5,24 broad doublet (3)	5,28 doublet (11)	5,29 doublet (11)
H-2	–	5,40 quartet (11;9)	5,41 quartet (11;9)
H-3	4,90 broad doublet of doublets (10;5)	4,40 broad doublet (9)	4,45 doublet (9)
H-5	4,86 broad doublet (8,5)	2,24 broad doublet (11)	2,18 doublet (11)
H-6	4,12 quartet (10;8,5)	3,98 triplet (11)	4,21 triplet (11)
H-13a	5,52 doublet (3,5)	5,40 doublet (3)	5,35 doublet (3)
H-13b	6,26 doublet (3,5)	6,06 doublet (3)	6,14 doublet (3)
H-15a	–	5,25 doublet (1)	–
H-15b	–	5,90 doublet (1)	–

^{1}H NMR spectra of all obtained compounds were registered on a spectrometer Bruker Avance-400 (operating frequency 400,13 MHz), solvent $CDCl_3$, internal reference TMS.

Treatment of hanphilline (1) with formic acid at room temperature led to stereocontrolled products of 5,10-carbocyclization — optically active keto,hydroxy-5(α),10(β)-trans-eudesmanolides (5) and (6) with 68 and 20 % yields (Fig. 2). Reaction occurred more rapidly than with N-bromosuccinimide. Apparently, acid-catalyzed 5,10-carbocyclization occurred by the same mechanism as with NBS through regiospesific protonation of the most electron-donor and space available $\Delta^{1,10}$-double bond of hanphilline (1) with configuration $_1D^{14}$ and $^{15}D_5$. Following nucleophilic attack of $\Delta^{4,5}$-double bond (Markovnikov's rule) led to only trans-condensed eudesmanolides (5) and (6). ^{1}H-NMR spectrum data of obtained compounds are shown in Table 2.

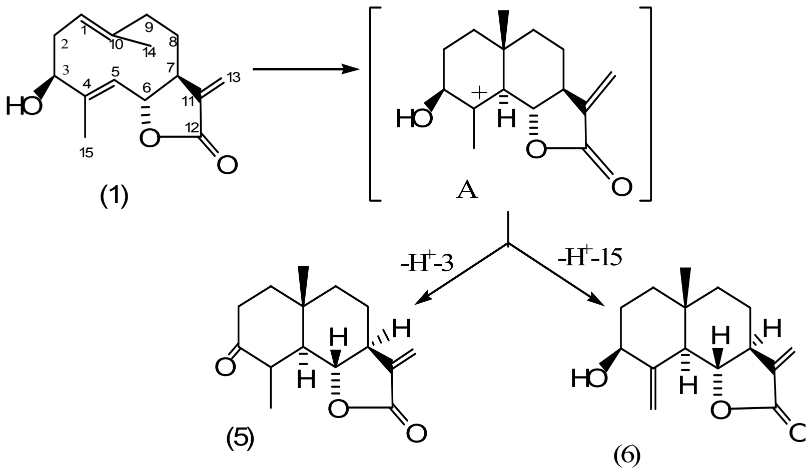


Figure 2. The obtaining of eudesmanolides (5) and (6)

Table 2

Chemical shifts (δ, ppm), spin-spin interaction constants (in Hz) of hanphilline and its derivatives (5) and (6)

Protons	Compounds		
	(1)	(5)	(6)
Me-4	1,68 broad singlet	1,22 doublet (7,5)	–
Me-10	1,43 singlet	0,63 singlet	0,63 singlet
H-1	5,24 broad doublet (3)	–	–
H-3	4,90 broad doublet of doublets (10;5)	–	4,0 broad doublet of doublets (10;6)
H-5	4,86 broad doublet (8,5)	–	–
H-6	4,12 quartet (10;8,5)	4,04 broad triplet (10,5)	3,98 broad triplet (11)
H-13a	5,52 doublet (3,5)	5,43 doublet (3)	5,43 doublet (3)
H-13b	6,26 doublet (3,5)	6,10 doublet (3)	6,10 doublet (3)
H-15a	–	–	4,95 broad singlet
H-15b	–	–	5,24 broad singlet

^{1}H NMR spectra of all obtained compounds were registered on a spectrometer Bruker Avance-400 (operating frequency 400,13 MHz), solvent $CDCl_3$, internal reference TMS.

Treatment of hanphilline (1) with perbenzoic acid in chloroform at room temperature led to trans-condensed β-hydroxyleudesmanolides: 4-epiartekalin (7) andridentin B (8) with 42–45 and 51–53 % yields (Fig. 3). These eudesmanolides were isolated from plant sources. ^{1}H-NMR spectrum data of obtained compounds are shown in Table 3.

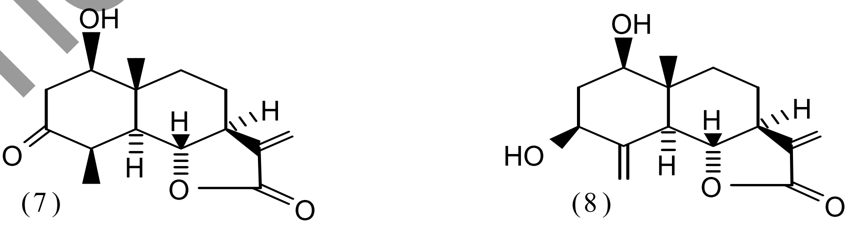


Figure 3. 4-epiartekalin (7) and andridentin B (8)

Quantum-chemical (semiempirical methods AM1, PM3, MINDO-3 by MOPAC-7) calculations of the total energies of all cationic intermediates formed during the reaction were carried out in order to confirmation the proposed mechanism of electrophilic 5,10-carbocyclization of hanphilline [5].

Table 3

Chemical shifts (δ, ppm), spin-spin interaction constants (in Hz) of hanphilline and its derivatives (7) and (8)

Protons	Compounds		
	(1)	(7)	(8)
Me-4	1,68 broad singlet	1,26 doublet (7,5)	–
Me-10	1,43 singlet	1,14 singlet	1,05 singlet
H-1	5,24 broad doublet (3)	3,71 broad triplet (8,5)	3,79 broad doublet of doublets (11,5;4)
H-2a	–	2,65 broad doublet (8,5)	2,32 multiplet
H-2b	–	2,74 broad triplet (7,5)	2,68 multiplet
H-3	4,90 broad doublet of doublets (10;5)	–	4,40 broad doublet of doublets (11;5)
H-4	–	2,10 multiplet	–
H-5	4,86 broad doublet (8,5)	2,10 multiplet	2,23 broad doublet
H-6	4,12 quartet (10;8,5)	4,04 triplet (10,5)	4,23 triplet (11)
H-13a	5,52 doublet (3,5)	5,43 doublet (3)	5,35 doublet (3)
H-13b	6,26 doublet (3,5)	6,09 doublet (3)	6,14 doublet (3)
H-15a	–	–	5,26 doublet (1)
H-15b	–	–	5,92 doublet (1)

^{1}H NMR spectra of all obtained compounds were registered on a spectrometer Bruker Avance-400 (operating frequency 400.13 MHz), solvent $CDCl_3$, internal reference TMS.

The acid-catalyzed cyclization of hanphilline was investigated (Fig. 4). According to generally accepted ideas, acid-addition to unsymmetrical alkene (for example to $\Delta^{1,10}$-double bond of hanphilline) could form two carbocation: secondary (A) and tertiary (B). Calculations showed an energy preference for carbocation (A) (E_{tot} = –68566 kcal/mol) than (B) (E_{tot} = –68555 kcal/mol) — the difference in energy was 11 kcal/mol. Subsequent cyclization of carbocation (B) by nucleophilic attack of $\Delta^{4,5}$-bond could lead to two bicyclic cations (C) and (D). Calculations (particularly by PM3 method) showed a greater energy stability for the carbocation (C) (E_{tot} = –68584 kcal/mol) than (D) (E_{tot} = –68570 kcal/mol). The energy difference was 14 kcal/mol. Carbocation (C) was identical to the intended tertiary cation (A) (see scheme of cyclization with formic acid). In this case, stabilization of this cation by deprotonation could form eudesmanolides (5) and (6). In this way, quantum-chemical calculations confirmed the proposed mechanism of trans-eudesmanolides formation.

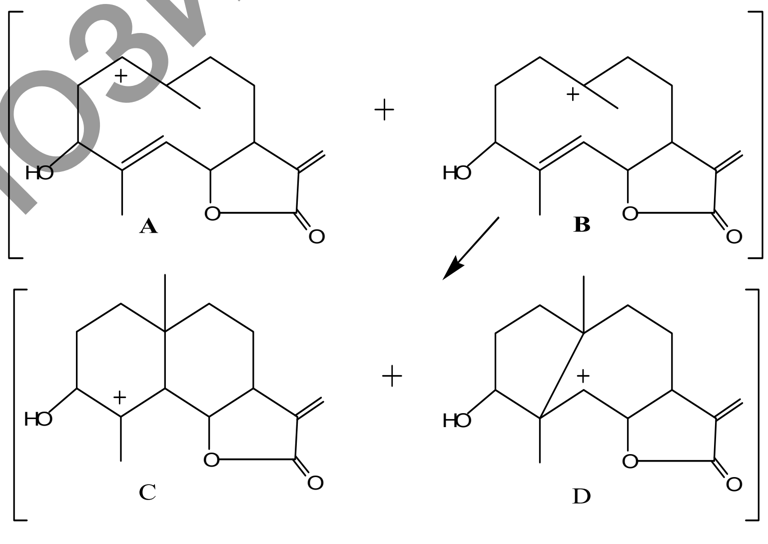


Figure 4. Basic carbocations of acid cyclization of hanphilline

Practically significant eudesmanolides were synthesized with hanphilline electrophilic carbocyclization reactions. It was found that double bond at C_4-C_5 did not react in the electrophilic addition reaction. Obviously, this was in consequence of steric difficulty or electronic factors (otherwise, we would have other types of skeletal sesquiterpenoids). It was shown that the variation of electrophilic reagents led to synthesis of different functionalized at C-1 and C-3 trans-eudesmanolides and well-known natural trans-eudesman sesquiterpenoids. It allowed for us to develop the one-step method for the synthesis of practically significant heteroatomic trans-eudesmanolides.

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(+)-Ханфиллиннің транс-эвдесманолидтерінің стереобақыланған синтезі

Мақалада ханфиллин Е,Е-гермакранолидтердің тәжірибелік маңызды транс-конденсацияланған эвдесманолидтерінің бағытталған синтезі қарастырылды. Алынған транс-эвдесманолидтердің синтезі (+)-ханфиллин Е,Е-гермакранолидтің стереобақыланған 5,10-карбоциклденуімен жүргізілді. Ол 5,10-карбоциклдену механизмдері кванттыхимиялық есептеулер нәтижелерімен сәйкес келді. Электрофильді реагенттерді қолданып, әр түрлі эвдесманды сесквитерпеноидтарды синтездеп алуға болатыны көрсетілді. Транс-эвдесманолидтердің С-1 және С-3 бойынша бірсатылы синтездеп алу әдісі ұсынылды.

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Стереоконтролируемый синтез транс-эвдесманолидов из (+)-ханфиллина

В статье рассмотрены подходы к направленному синтезу практически значимых эвдесманолидов из гермакранолида Е,Е-ханфиллина. Синтез полученных транс-эвдесманолидов был осуществлен стереоконтролируемой 5,10-циклизацией Е,Е-гермакранолида (+)-ханфиллина. Рассмотренные механизмы 5,10-карбоциклизации ханфиллина согласуются с результатами квантовохимических расчетов величин полных энергий всех образующихся в ходе реакции катионных интермедиатов. Показано, что электрофильные реагенты могут синтезировать различные эвдесмановые сесквитерпеноиды. Разработан одностадийный метод синтеза функционализированных при С-1 и С-3 транс-эвдесманолидов.

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