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The reaction of C-alkylation of eudesmanolide (–)-α-santonin

This article is concerned with sesquiterpene γ-lactones of the eudesman structure, which is promising class of natural organic compounds and characterized by a wide spectrum of physiological activity. Stereoselective synthesis of new practically significant 4α(ethyl)-3-keto-trans-eudesm-1(2),5(6)-diene-6,12-olide(C_4-α-ethyl-santonin) was carried out at room temperature in argon atmosphere by interaction of eudesmanolide (–)-α-santonin and an organohalide in presence of a strong base: tert-butyl-potassium: dimethylsulfoxide: tert-butyl alcohol. The yield was 50 %. The spatial structure of the synthesized C_4-α-ethyl-santonin was established by ^{1}H NMR-, 2D NMR (COZY, NOESY), mass spectrometry and X-ray analysis. According to the results of X-ray analysis there has been found that the condensed six-membered C_4-α-ethyl-santonin cycles are trans-articulated (CH_3-10, β-oriented), the ethyl group at C-4 has the α-configuration, and the conformation of six-membered eudesmanolide is characterized as distorted chair-chair. Thus, combination of application in the work of modern physico-chemical and spectroscopic research methods allowed characterization of the structure and properties of the compounds obtained.

Keywords: sesquiterpene γ-lactone, cross-conjugated, eudesmanolide, α-santonin, alkylation, keto-eudesmane ester, stereoselectivity, electrophilic rearrangements.

Chemical transformations of plant metabolites, in particular eudesmane sesquiterpene γ-lactones, leading to physiologically active derivatives have become an important field in synthetic and medical chemistry [1–3]. Previously, we have shown that the interaction of natural eudesmanolide (-)-α-santonin (1) with MeOH and EtOH in the presence of sodium alkoxides and the base Me_3COK-DMCO-Me_3COH stereoselectively leads to the formation of practically significant *cis*-condensed 6-keto-eudesman esters (3) and (4) (Fig. 1). In addition, it was suggested that they were formed from enolate ions (5) and (6) with a double bond at C5-C6 [4, 5].

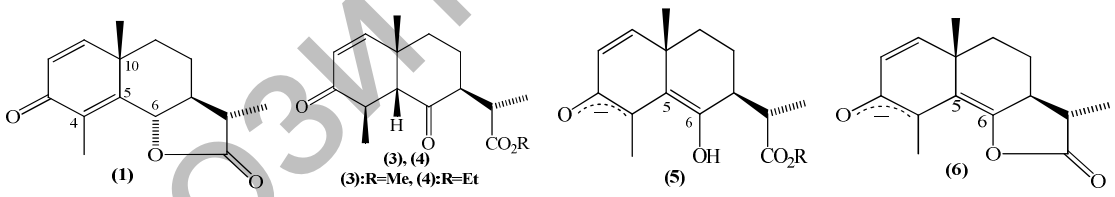


Figure 1. Structure of santonin (1), cis-eudesman esters (3), (4) and enolates (5), (6)

In further research, we studied the alkylation reaction of cross-conjugated (–)-α-santonin (1). Thus, the reaction of eudesmanolide (1) with bromoethane in the presence of base Me_3COK-DMSO-Me_3COH stereoselectively leads to the formation of a new product of C_4-alkylation, namely 4α(Et)-3-keto-trans-eudesma-1(2),5(6)-dien-6,12-olide (7). Yield was 50 % (Fig. 2).

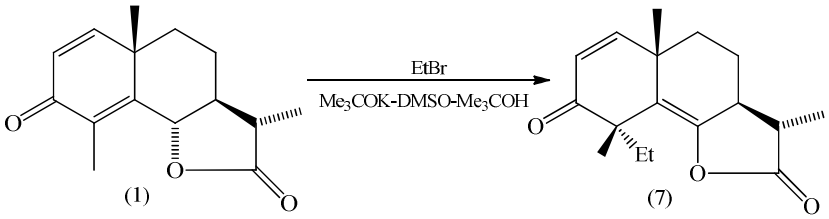


Figure 2. Synthesis of C_4-α-ethyl-eudesmanolide (7)

The spatial structure of eudesmanolide (7) was determined by X-ray analysis. It is shown in Figure 3. As shown in Figure 3, the cycles in the structure of the molecule (7) are trans-articulated (CH3-10, β-oriented), the ethyl group at C-4 has an α-configuration. The configuration of six-membered cycles is characterized as a distorted chair- chair.

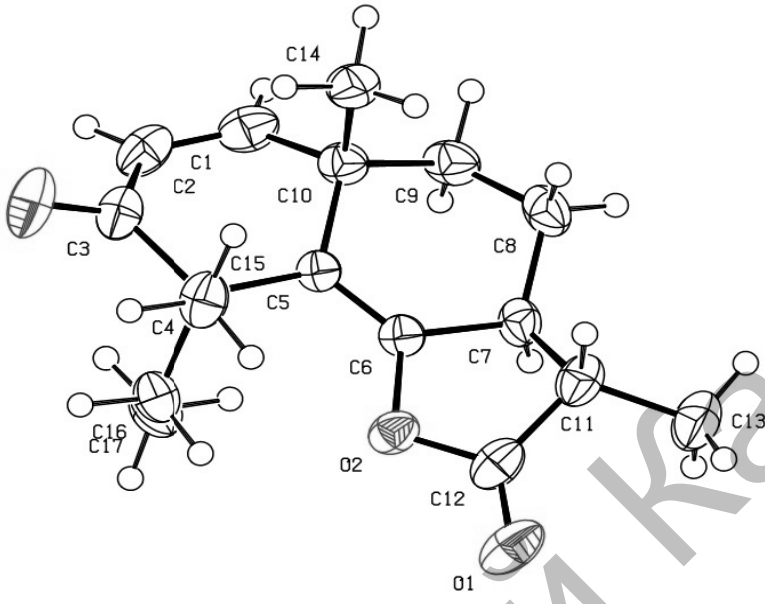


Figure 3. The spatial structure of C4-α-ethyl-eudesmanolide (7)

Two-dimensional NMR (COSY, NOESY) experiments were also carried out with C_4-ethyl eudesmanolide (7). 2D NMR spectra (COSY, NOESY) are shown in Figures 4 and 5.

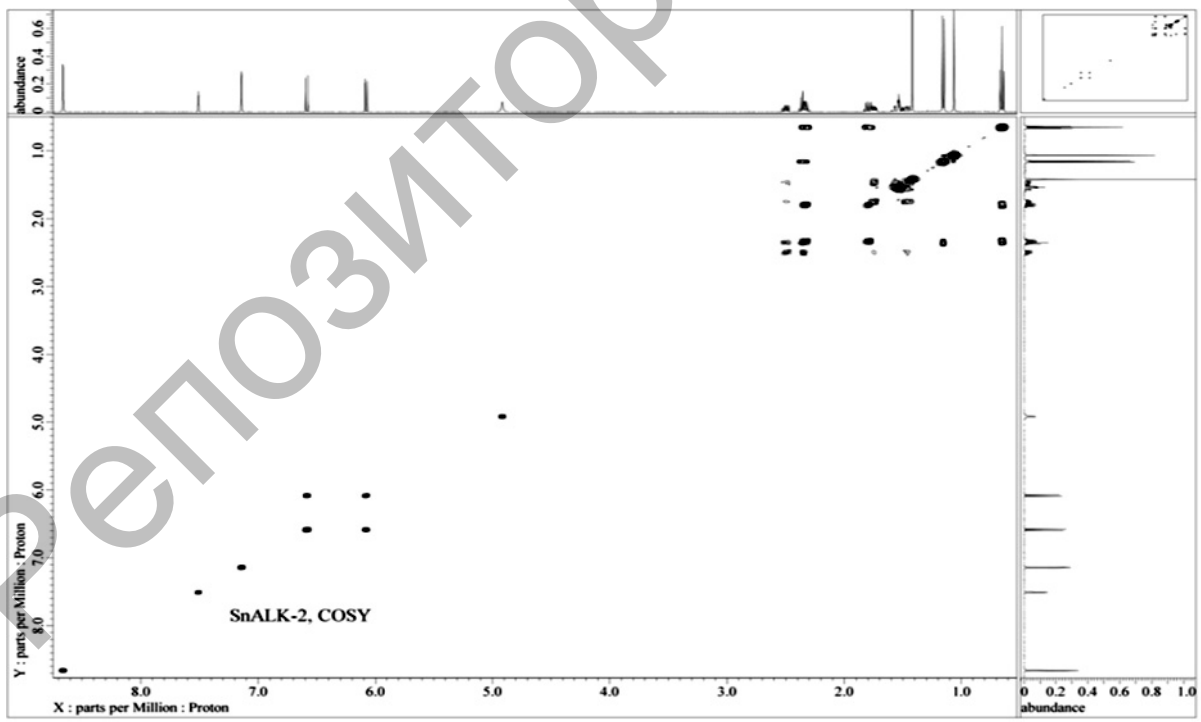


Figure 4. ^{1}H NMR (COSY) spectrum of eudesmanolide (7)

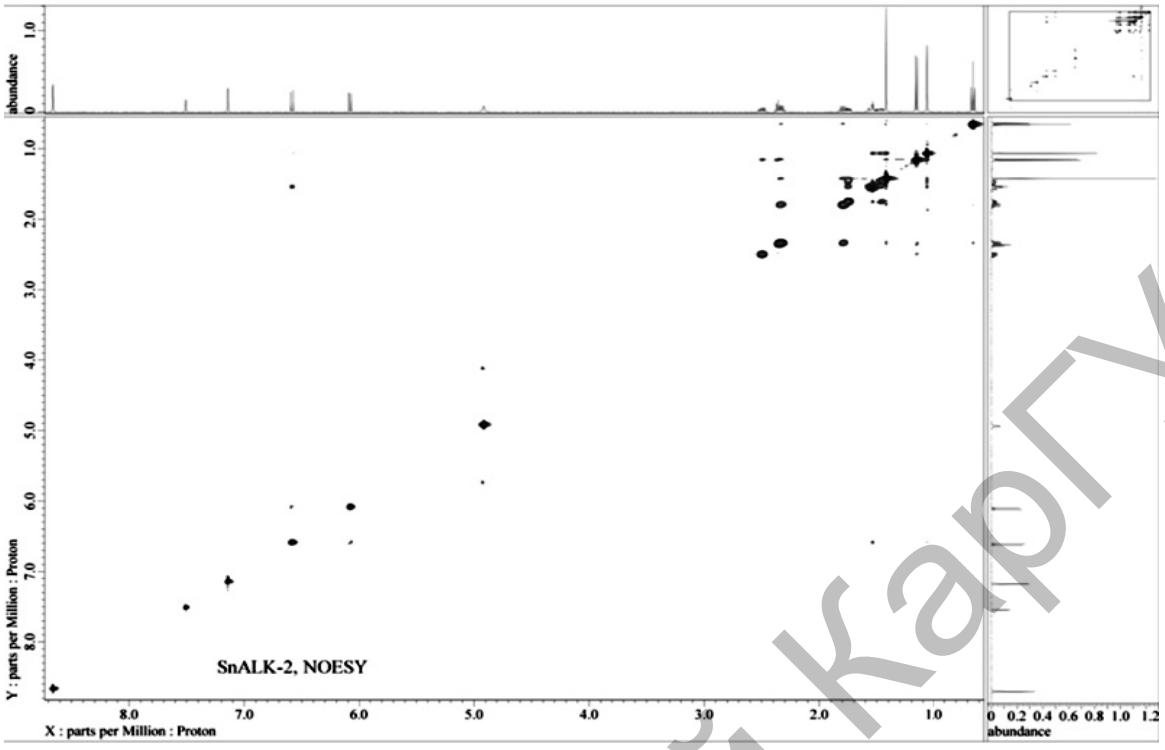
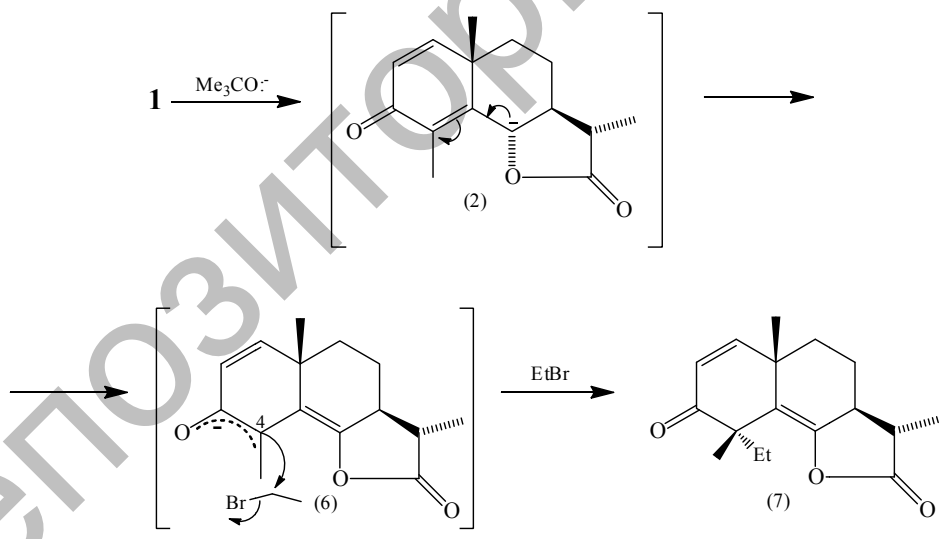


Figure 5. 2D NMR (NOESY) spectrum of eudesmanolide (7)

Considering the structure and stereochemistry of C_4-α-ethyl-eudesmanolide (7), its formation can be represented as shown in Figure 6.



1 — allyl shift; *2* — enolization

Figure 6. Mechanism of C_4-ethyl-eudesmanolide formation (7)

Probably, under the reaction conditions of α-santonin (1) initially stage of the anion (2) formation initiates the subsequent stages of intramolecular electrophilic rearrangements with the formation of enolate-ion (6), which further stereoselectively interacts with organohalide, resulting to 4α-ethyl-eudesmanolide (7) with a double bond at C5-C6. The synthesis of the compound (7) can serve as a confirmation of the proposed mechanism of formation of 6-keto-eudesman esters (3) and (4), which has been described by us in [4, 5].

Experimental

IR spectra (7) were recorded on an Avatar-360 spectrometer in KBr pellets, ^{1}H NMR spectra were registered on a Jeol, ECA-500 spectrometer (operating frequency 500.15 MHz) with a solvent — C_5D_5N. Mass spectra were measured on an Agilent 7890A. X-ray analysis was established on a Nonius Kappa CCD 4-circle automatic diffractometer (Moα, λ = 0,71073 Å, graphite monochromator) at a temperature of 150 K. Specific rotation was determined on a MCP-100 polarimeter, melting points were measured on a M-56 instrument. Sorbfil PTSX-AF-UV plates were used for thin-layer chromatography. Sorbfil PTSKh-AF-UF plates were used for thin layer chromatography.

4α(Et)-3-keto-eudesma-1(2),5(6)-dien-6,12-olide (7). To a solution of potassium tert-butoxide in Me_3COH and DMSO (prepared from 0.06 g of metallic potassium and 1.5 ml of alcohol and 2 ml of DMSO) 0.4 g (1.6 mmol) of compound (1) was added at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 5–7 minutes, and then 0.12 ml (1.62 mmol) of EtBr was added, and kept for 50 minutes. Then the alcohol was distilled off in a vacuum, the residue was dissolved in ethyl acetate, washed with water (3×10 ml), dried with $MgSO_4$. The solvent was evaporated in a vacuum; the residue (0.46 g) was chromatographed on a column with silica gel (eluent — hexane – ethyl acetate, 4:1). Yield was 0.22 g (50 %), colorless crystals, mp 105–106 ºC, R_f 0.60 (hexane – ethyl acetate, 3:2), $[\alpha]_D^{20}$ 43° (*c* 0.003; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1710 (C=O), 1778 (C=O), 1635 (C=C). ^{1}H NMR spectrum (500 MHz, C_5D_5N, δ, m.d, J/Hz): 6.08 (1H, d, J = 9.8, H-1), 6.58 (1H, d, J = 9.8, H-2), 1.42 (3H, s, CH_3-4), 1.06 (3H, s, CH_3-10), 1.15 (3H, d, J = 6.87, CH_3-11), 1.53 (2H, k, J = 5.5, J = 7.52, CH_2-16), 0.65 (3H, t, J = 7.52, CH_3-17). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 274 (M^+, 45.2).

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Эвдесманолид (–)-α-сантониннің С-алкилдеу реакциясы

Мақала физиологиялық белсенділіктің кең спектріне ие, табиғи органикалық қосылыстардың маңызды тобы болып табылатын эвдесман типті сесквитерпенді γ-лактондардың құрылысына арналған. Жаңа практикалық маңызды 4α(этил)-3-кето-транс-эвдесм-1(2),5(6)-диен-6,12-олидтің (C_4-α-этил-сантонин) стереоселективті синтезі бөлме температурасында аргон ортасында эвдесманолид (–)-α-сантониннің күшті негіз қатысында (калий трет-бутилаты – диметилсульфоксид – трет-бутил спирті) органикалық галогенидпен әрекеттестіріп жүргізілді. Оптикалық белсенді өнімнің шығымы 50 % құрайды. Синтезделіп алынған С4-α-этил-сантониннің құрылысы мен кеңістіктегі құрылымы протонды магнитті резонанс, екіөлшемді ядролы магнитті резонанс (2D NMR; COSY, NOESY), масс-спектрометрия және рентгенқұрылымдық талдау әдістерімен анықталды. Рентгенқұрылымдық анализ әдісінің нәтижесінде C_4-α-этил-сантониннің конденсирленген алтымүшелі циклдері транс-қосарланған (СН3–10, β-бағытталған), C_4 жағдайындағы этилді топ α-конфигурация күйінде, эвдесманолидтің алтымүшелі циклдерінің конформациясы бұрмаланған кресло-кресло күйінде болатындығы анықталды. Мақалада зерттеудің казіргі заманауи физика-химиялық және спектроскопиялық әдістерді қолдануы алынған заттардың құрылысы мен қасиеттерін сенімді түрде сипаттауға мүмкіндік берді.

Кілт сөздер: сесквитерпенді γ-лактон, *кросс*-қосарлану, эвдесманолид, α-сантонин, алкилдеу, кето-эвдесман эфирі, стереоселективтілік, электрофилді қайтатоптасу.

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Реакция С-алкилирования эвдесманолида (–)-α-сантонина

Статья посвящена сесквитерпеновым γ-лактонам эвдесмановой структуры, являющимся перспективным классом природных органических соединений, характеризующихся широким спектром физиологической активности. Стереоселективный синтез нового практически значимого 4α(этил)-3-кето-транс-эвдесм-1(2),5(6)-диен-6,12-олида (C_4-α-этил-сантонина) проводили при комнатной температуре в атмосфере аргона взаимодействием эвдесманолида (–)-α-сантонина с органогалогенидом в присутствии сильного основания (*трет*-бутилат-калия – диметилсульфоксид – *трет*-бутиловый спирт). Выход целевого оптически активного продукта составил 50 %. Строение и пространственная структура синтезированного C_4-α-этил-сантонина установлены методами протонного магнитного резонанса, двумерного ядерно-магнитного резонанса (2DNMR; COSY, NOESY), масс-спектрометрии и рентгеноструктурного анализа. По результатам рентгеноструктурного анализа было установлено, что конденсированные шестичленные циклы C_4-α-этил-сантонина являются транс-сочлененными (CH_3-10, β-ориентирована), этильная группа при С-4 имеет α-конфигурацию, а конформация шестичленных циклов эвдесманолида характеризуется как искаженное кресло-кресло. Таким образом, совокупность применения в работе современных физико-химических и спектроскопических методов исследования позволила надежно и однозначно охарактеризовать строение и свойства полученных соединений.

Ключевые слова: сесквитерпеновый γ-лактон, *кросс*-сопряжение, эвдесманолид, α-сантонин, алкилирование, кето-эвдесмановый эфир, стереоселективность, электрофильные перегруппировки.