(-)-SCLAREOL CONVERSION IN THE RITTER'S REACTION CONDITIONS

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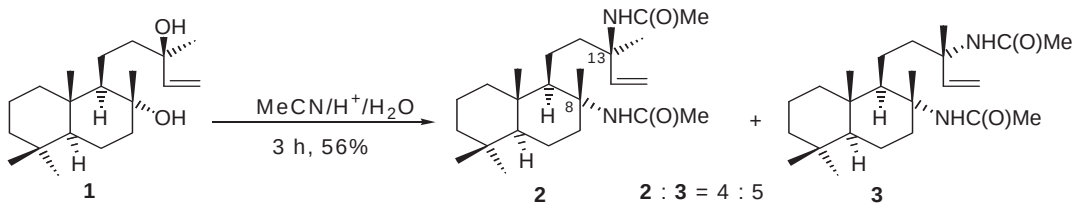
Abstract. The main products of sclareol (**1**) Ritter's reaction in mild conditions are (8*R*,13*R*)-Labd-14(15)-en-8,13-diacetamide (**2**) (8*R*,13*S*)-Labd-14(15)-en-8,13-diacetamide (**3**) stereoisomeric on C13 atom and having unrearranged native diol skeleton.

Keywords: diterpenoids, Ritter's reaction, diamide, sclareol.

Labdanoids represent one of the numerous and important diterpenoids sub-class and a lot of them posess a broad biological activity spectrum [1-3]. Different natural sources provided an array of nitrogen-containing labdanoids with different biological activities [4-9]. Due to this properties, an encreased interest towards nitrogen-containing labdanoids synthesis has been wittnessed in recent years [10-16].

We present in the current communication the results of sclareol converting (**1**) into nitrogen-containing labdanes in the Ritter's reaction conditions.



Scheme 1

Our first expectations have been connected to the posibility of obtaining chiral amides of labdane series, with a potential biological activity. Provided the fact that sclareol (**1**) (Scheme 1) molecule contains three potential reaction centers, namely two hydroxyl groups and an allylic double bond, a non-selective course of Ritter reaction was expected. Accordingly, investigation of the corresponding reaction products has revealed formation of two labdanic diamides (**2**) and (**3**), diastereomeric on C-13 chiral center, along with a minor amount of polymeric material. The double bond integrity is kept in the products and no allylic rearrangements occur. It is noteworthy mentioning that obtaining of amides from tertiarry alcohols by Ritter reaction has been recently described [17].

The structure of the synthesized diamides (**2**) and (**3**) was revealed on the basis of spectral data (IR, ^{1}H and ^{13}C NMR). The IR spectra of both compounds contain NH-characteristic bands (~3270 and 1550 cm^{-1}) and those corresponding to amidic carbonyl (1650 cm^{-1}). The ^{1}H NMR spectrum of both diamides (**2**) [18] and (**3**) [19] contains three signals of tertiarry methyl groups (δ = 0.78 - 0.90 ppm), as well as the signals of two methyl groups, geminally disposed versus amidic groups (δ = 1.20 ppm) along with two acetyl groups (δ = 1.80 ppm). There are also signals of three olefinic protons, corresponding to the terminal double bond. The position and shape of other signals are similar to that of sclareol (**1**). The ^{13}C NMR data are in full agreament with the suggested structures for diamides (**2**) and (**3**). Each diamide spectrum shows the presence of three shelded methyls (δ = 16, 18 and 21 ppm), two methyls of the acetyl group (δ = 23 ppm) and two low shelded methyl groups (δ = 33 ppm) corresponding to methyls geminally disposed versus amide group. The signals corresponding to quaternary carbons at C-8 and C-13 both linked to amide groups are detected at δ = 60 ppm and δ = 61 ppm, while the signals of terminal double bond apear at δ = 108 ppm and δ = 131 ppm. The carbonyl signals are detected at δ = 169 ppm. Besides, the ^{13}C NMR spectra contain other two signals of quaternary carbons, two CH- signals and seven CH_2- signals with chemical shifts being quite similar to those of sclareol (**1**), showing conservation of the bicyclic framework during the reaction. In such a way the Ritter reaction performed with sclareol (**1**) occurs stereoselectively at C-8 atom with less stereocontrol at C-13 (**2** and **3** isomers ratio is ~4:5) and without allylic rearrangement.

The high stereoselectivity at C-8 center is due to the concerted actions of both steric and thermodinamic factors: formation of equatorial amide isomer is preponderent, which takes place via adition of the acetonitrile molecule to a *trans*- stereochemistry versus the bulky hydroxyalkenyl (or amidoalkenyl) at C-9. The moderate reaction selectivity

at C-13 seems to be logic, provided the advanced flexibility of the lateral chain and its less interaction with the rigid bicyclic framework. In the same time, the fact that Ritter reaction of allylic alcohol **1** is not acompanied by a allylic rearrangement is quite surprising, since interaction of the tertiarry hydroxyl with a week nucleophile (acetonitrile) shall lead to elimination and the resulting carbonium ion would be inevitably acompanied by an allyl rearrangement, providing the isomeric allylic cation more accessible at C-15.

In conclusion, it was realized a single step synthesis of diterpenic diamides epimeric at C-13 chiral center from commercially available sclareol. The obtained products represent interest as substances with potential biological activity.

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[18]. Data of (8*R*,13*R*)-Labd-14(15)-en-8,13-diacetamide (**2**) as an oil: IR (liquid film): 3270, 3080, 2925, 2865, 2845, 1650, 1550 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, selected): δ_H = 0.74 (s, 3H, 10-CH_3), 0.77 (s, 3H, 4-CH_3), 0.82 (s, 3H, 4-CH_3-*e*), 0.92 (m, 2H), 1.08 (m, 2H), 1.19 (dt, 1H, $^2J = {}^3J_{a,a}$ = 12 Hz, $^3J_{a,e}$ = 3 Hz, 1-H*a*), 1.22 (s, 3H, 13-CH_3), 1.28 (s, 3H, 8-CH_3), 1.35 (m, 4H), 1.61 (m, 6H), 1.78 (s, 3H, $COCH_3$), 1.84 (s, 3H, $COCH_3$), 1.87 (dd, (1H, ^1J = 12 Hz, and ^2J = 2 Hz, 9-H), 4.88 (d, 1H, $^3J_{cis}$ = 11 Hz, 15-H-*cis*), 5.17 (d, 1H, $^3J_{trans}$ = 17 Hz, 15-H-*trans*), 5.81 (dd, 1H, $^3J_{trans}$ 17, $^3J_{cis}$ = 11 Hz, 14-H), 6.35 (br s, 1H, NH), 6.50 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 15.7 (q, 10-CH_3), 18.4 (t, C-3), 18.7 (t, C-2), 20.4 (q, 4-CH_3-*a*), 22.8 (t, C-1), 23.1 (q, 4-CH_3-*e*), 24.4 (q, CO$\underline{CH_3}$), 24.5 (q, CO$\underline{CH_3}$), 28.1 (q, 13-CH_3), 33.0 (s, C-4), 33.3 (q, 8-CH_3), 38.9 (s, C-10), 39.6 (t, C-6), 41.6 (t, C-7), 42.1 (t, C-11), 43.2 (t, C-12), 53.7 (t, C-5), 60.8 (d, C-9), 63.8 (s, C-13), 64.7 (s, C-8), 109.3 (t, C-15), 146.0 (d, C-14), 169.3 (s, C=O), 169.8 (s, C=O).
[19]. Data of (8*R*,13*S*)-Labd-14(15)-en-8,13-diacetamide (**3**) as an oil: IR (liquid film): 3270, 3080, 2925, 2865, 2845, 1650, 1550 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, selected): δ_H = 0.74 (s, 3H, 10-CH_3), 0.76 (s, 3H, 4-CH_3), 0.83 (s, 3H, 4-CH_3-*e*), 0.91 (m, 2H), 1.10 (m, 2H), 1.17 (dt, 1H, $^2J = {}^3J_{a,a}$ = 12 Hz, $^3J_{a,e}$ = 3 Hz, 1-H*a*), 1.21 (s, 3H, 13-CH_3), 1.26 (s, 3H, 8-CH_3), 1.37 (m, 4H), 1.64 (m, 6H), 1.81 (s, 3H, $COCH_3$), 1.83 (s, 3H, $COCH_3$), 1.91 (dd, (1H, ^1J = 12 Hz, and ^2J = 2 Hz, 9-H), 4.87 (d, 1H, $^3J_{cis}$ = 15 Hz, 15-H-*cis*), 5.19 (d, 1H, $^3J_{trans}$ = 17 Hz, 15-H-*trans*), 5.84 (dd, 1H, $^3J_{trans}$ 17 Hz, $^3J_{cis}$ = 11 Hz, 14-H), 6.40 (br s, 1H, NH), 6.60 (br s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 15.6 (q, 10-CH_3), 18.5 (t, C-3), 18.8 (t, C-2), 20.7 (q, 4-CH_3-*a*), 22.4 (t, C-1), 22.9 (q, 4-CH_3-*e*), 24.2 (q, CO$\underline{CH_3}$), 24.4 (q, CO$\underline{CH_3}$), 31.2 (q, 13-CH_3), 32.9 (s, C-4), 33.3 (q, 8-CH_3), 38.7 (s, C-10), 39.5 (t, C-6), 41.6 (t, C-7), 42.0 (t, C-11), 43.4 (t, C-12), 53.4 (t, C-5), 60.9 (d, C-9), 64.1 (s, C-13), 64.4 (s, C-8), 109.9 (t, C-15), 145.1 (d, C-14), 169.6 (s, C=O), 169.9 (s, C=O).