

SYNTHESIS OF NEW DI- AND TRI-NORLABDANE COMPOUNDS WITH 2-AMINO-1,3-THIAZOLE UNITS

Svetlana Blaja

*Institute of Chemistry, 3, Academiei str., Chisinau MD-2028, Republic of Moldova
e-mail: svetlana-blaja@mail.ru*

Abstract. The present paper reports the synthesis of new hybrid terpeno-heterocyclic compounds belonging to di- and tri-norlabdane series. Starting from natural labdane diterpenoide (-)-sclareol, *via* its intermediates 8 α -hydroxy-15,16-dinorlabd-13-one and sclareolide, two di-norlabdane and three tri-norlabdane, previously unreported compounds possessing 2-amino-1,3-thiazole structural units were obtained in three and four steps, respectively, with acceptable to good overall yields. The structures of newly obtained compounds were confirmed by means of spectral IR, ¹H and ¹³C NMR analyses. It can be assumed that the synthesized compounds possess potential biological activity due to the presence of the heterocyclic unit. Additionally, the mechanism of 2-amino-1,3-thiazole ring formation is proposed.

Keywords: synthesis, di-norlabdane, tri-norlabdane, 2-amino-1,3-thiazole, cyclization reaction.

Received: 24 July 2019/ Revised final: 29 August 2019/ Accepted: 30 August 2019

Introduction

Terpenoids represent one of the most numerous and important classes of natural compounds from both, theoretical and practical points of view. Terpenic compounds possess a strong biological activity and influence vital processes in vegetal and animal worlds [1-4].

From the diversity of terpenic compounds, labdanes, belonging to the bicyclic diterpenoids group, have been found as secondary metabolites in tissues of fungi, insects, marine organisms, and in essential oils, resins and tissues of higher plants. Diterpenes of labdane type reportedly showed a broad spectrum of biological activities such as cytotoxic, antifungal, anti-inflammatory, antiparasitic, analgesic activities, *etc.* [5-11]. In recent years, a special attention was drawn to the isolation of biologically active compounds with terpenic and heterocyclic structural units from various natural sources [12-15].

Thiazoles are the most important class of heterocyclic compounds. According to published data, these compounds are highlighted by a broad spectrum of pharmacological properties such as anticancer, antitubercular, antimicrobial, anti-inflammatory, analgesic and anticonvulsant activities [16,17]. Based on these data, a remarkable progress has been made lately in the development of new thiazole compounds. Moreover, much interest has also been focused on the antihelminthic, diuretic, and antimalarial

activities displayed by compounds incorporating this heterocyclic system [18,19].

In the scientific literature, there are just a few mentions related to the syntheses of hybrid compounds with terpenic and heterocyclic skeleton. According to some authors, such compounds possess a potent biological activity [12-15]. Therefore, the use of terpenic derivatives as chiral synthones in condensation reactions with heterocycles is expected to give some new biologically active compounds containing both terpenic and heterocyclic units.

The main goal of the research presented here was the synthesis of new di- and tri-norlabdane compounds containing 1,3-thiazole structural units. The key strengths of this research are: accessible starting material, a natural labdane diterpenoide (-)-sclareol, extracted from renewable resources, and high probability of biological activities combined with low toxicity of the mentioned compounds, due to their natural origin.

Experimental

Generalities

Optical rotations were measured on a Jasco DIP 370 polarimeter with a 1 dm microcell, in CHCl₃. The *IR spectra* were registered on a Spectrum-100FT-IR spectrometer (Perkin-Elmer) by the ATR technique. ¹H and ¹³C *NMR spectra* were acquired on a Bruker Avance DRX 400 spectrometer (400, 100 MHz). CDCl₃ was used as

solvent. The following abbreviations were used to designate chemical shift multiplicities: s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet. All chemical shifts are quoted on the δ -scale in ppm and referred to residual CHCl_3 (δ_{H} at 7.26 ppm) and as CDCl_3 (δ_{C} 77.00 ppm). The coupling constants (J) are given in Hz. The two-dimensional H, H-COSY; H, C-HSQC and H, C-HMBC experiments were recorded using standard pulse sequences, in the version with z -gradients, as delivered by the Bruker Corporation. Carbon substitution degrees were established by the DEPT pulse sequence. For the analytical TLC, Merck silica gel plates 60G in 0.25 mm layers were used. Visualization of the plates was achieved using UV lamp (λ_{max} = 254 or 365 nm) and/or by spraying with acidic aqueous cerium(III) sulphate solution, or 20% KMnO_4 solution. The column chromatography was carried out on the Acros Organics silica gel (60–200 mesh) using dichloromethane and the gradient mixture of CH_2Cl_2 and MeOH.

All solvents were purified and dried by standard techniques before use. Solutions in organic solvents were dried over anhydrous Na_2SO_4 , then filtered and evaporated under reduced pressure.

Classic procedure for the synthesis of di- and tri-norlabdane compounds with 2-amino-1,3-thiazole fragment

One of ketones **2** (0.280 g, 1 mmol), **3** (0.262 g, 1 mmol), **4** (0.262 g, 1 mmol), **8** (0.266 g, 1 mmol), **9** (0.248 g, 1 mmol) or **10** (0.248 g, 1 mmol) was treated with iodine (0.14 g, 1.1 mmol) and thiourea (0.23 g, 3.0 mmol) in ethanol (10 mL) and heated under reflux for 12 h. Further, the reaction mixture was quenched with NaOH (aq.) (0.08 g, 2 mmol) and the ethanol was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and the solvent was removed under reduced pressure. Crude reaction products were purified by flash column chromatography on SiO_2 (10 g, eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 1→5%) to give products **5**, **6** and **11-13**.

4-(2-((8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethyl)thiazol-2-amine 5. Yield 0.165 g (52%, condition *c*, Scheme 1), 0.270 g (85%, condition *d*, Scheme 1), yellow oil; $[\alpha]_{\text{D}}^{26} = 49.1^\circ$ (c 2.5, CHCl_3). IR (ATR) ν 3284, 3116, 2920, 1610, 1527, 1510, 1470, 1336, 1047, 970 cm^{-1} . ^1H NMR: δ 6.08 (1H, s, H-5'); 5.21 (2H, br. s, NH_2); 1.59 (3H, s, H-17); 0.94 (3H, s, H-20); 0.88 (3H, s, H-18); 0.82 (3H,

s, H-19). ^{13}C NMR: δ 167.4 (C-2'); 153.7 (C-4'); 139.9 (C-9); 126.5 (C-8); 101.6 (C-5'); 51.9 (C-5); 41.8 (C-3); 39.0 (C-10); 37.0 (C-1); 33.6 (C-7); 33.3 (C-12); 33.3 (C-4); 32.4 (C-19); 27.3 (C-11); 21.7 (C-18); 20.1 (C-20); 19.6 (C-17); 19.0 (C-6); 19.0 (C-2).

4-(2-((8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)ethyl)thiazol-2-amine 6. Yield 0.111 g (35%, condition *c*, Scheme 1), 0.254 g (80%, condition *d*, Scheme 1), yellow oil; $[\alpha]_{\text{D}}^{26} = 26.7^\circ$ (c 2.4, CHCl_3). IR (ATR) ν 3308, 3131, 2928, 1620, 1521, 1458, 1375, 1334, 1040, 970 cm^{-1} . ^1H NMR: δ 6.15 (1H, s, H-5'); 5.33 (1H, s, H-7); 5.16 (2H, br. s, NH_2); 1.81 (3H, s, H-17); 1.10 (3H, s, H-20); 0.93 (3H, s, H-18); 0.90 (3H, s, H-19). ^{13}C NMR: δ 167.5 (C-2'); 152.3 (C-4'); 130.3 (C-8); 122.1 (C-7); 102.5 (C-5'); 53.9 (C-9); 50.3 (C-5); 41.3 (C-3); 41.0 (C-10); 35.9 (C-1); 30.8 (C-12); 33.1 (C-4); 32.5 (C-19); 28.9 (C-11); 21.3 (C-18); 18.0 (C-20); 19.3 (C-6); 18.6 (C-2); 11.5 (C-17).

(1R,2R,8aS)-1-((2-aminothiazol-4-yl)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol 11. Yield 0.055 g (17%, condition *d*, Scheme 2), yellow oil; $[\alpha]_{\text{D}}^{26} = -70.1^\circ$ (c 3.1, CHCl_3). IR (ATR) ν 3305, 3191, 2923, 1618, 1522, 1387, 1084, 937, 752 cm^{-1} . ^1H NMR: δ 6.02 (1H, s, H-5'); 5.41 (2H, br. s, NH_2); 2.65 (1H, dd, J 15.1, 4.7 Hz, H-11); 2.53 (1H, dd, J 15.3, 3.0 Hz, H-11); 1.22 (3H, s, H-17); 0.86 (3H, s, H-18); 0.85 (3H, s, H-19); 0.80 (3H, s, H-20). ^{13}C NMR: δ 167.4 (C-2'), 153.1 (C-4'), 101.3 (C-5'), 72.8 (C-8); 60.7 (C-9); 55.9 (C-5); 44.1 (C-7); 41.8 (C-3); 39.4 (C-1); 39.4 (C-10); 33.3 (C-19); 33.2 (C-4); 26.7 (C-11); 24.3 (C-17); 21.4 (C-18); 20.3 (C-6); 18.4 (C-2); 15.4 (C-20).

4-(((8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)thiazol-2-amine 12. Yield 0.076 g (25%, condition *d*, Scheme 2), 0.249 g (82%, *e*, Scheme 2), yellow oil; $[\alpha]_{\text{D}}^{26} = 4.8^\circ$ (c 3.4, CHCl_3). IR (ATR) ν 3298, 3136, 2925, 1615, 1519, 1457, 1363, 1087, 754, 699 cm^{-1} . ^1H NMR: δ 5.92 (1H, s, H-5'); 5.05 (2H, br. s, NH_2); 3.26 (2H, dd, J 31.1, 16.9 Hz, H-11); 1.54 (3H, s, H-17); 0.95 (3H, s, H-20); 0.88 (3H, s, H-18); 0.82 (3H, s, H-19). ^{13}C NMR: δ 167.1 (C-2'); 151.9 (C-4'); 137.0 (C-9); 128.7 (C-8); 102.9 (C-5'); 52.1 (C-5); 41.7 (C-3); 38.5 (C-10); 36.2 (C-1); 33.5 (C-7); 33.3 (C-4); 33.2 (C-19); 29.9 (C-11); 21.7 (C-18); 20.2 (C-20); 19.9 (C-17); 19.1 (C-6); 18.9 (C-2).

4-(((8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)thiazol-2-amine 13. Yield 0.130 g (43%, condition *d*, Scheme 2), 0.243 g (80%, condition *e*, Scheme 2), yellow oil; $[\alpha]_{\text{D}}^{26} = -2.9^\circ$ (c 5.4, CHCl_3). IR (ATR) ν 3299,

3120, 2922, 1615, 1519, 1455, 1365, 754 cm^{-1} . ^1H NMR: δ 6.05 (1H, s, H-5'); 5.39 (1H, s, H-7); 5.14 (2H, br. s, NH_2); 1.52 (3H, s, H-17); 0.87 (3H, s, H-18); 0.85 (3H, s, H-19); 0.80 (3H, s, H-20). ^{13}C NMR: δ 167.7 (C-2'); 154.5 (C-4'); 135.1 (C-8); 122.5 (C-7); 101.9 (C-5'); 53.1 (C-9); 50.1 (C-5); 42.2 (C-3); 39.2 (C-1); 36.6 (C-10); 33.2 (C-19); 33.0 (C-4); 29.5 (C-11); 23.8 (C-6); 22.5 (C-17); 21.8 (C-18); 18.8 (C-2); 13.7 (C-20).

Results and discussion

The starting material for the synthesis of the above compounds was a natural labdane diterpenoid (-)-sclareol **1**, which was oxidatively degraded with potassium permanganate in acetone, to afford 8 α -hydroxy-15,16-dinorlabd-13-one **2** in 90% yield, according to procedure [20]. The treatment of hydroxyketone **2** with trimethylsilylmethanesulphonate ($\text{MeSO}_3\text{SiMe}_3$) in acetonitrile, under the conditions described in [21], led to the mixture of known 15,16-dinorlabd-8(9)-en-13-one **3** and 15,16-dinorlabd-7(8)-en-13-one **4** (Scheme 1), obtained in a ratio 8.5:1.5, with a 95% overall yield, which were successfully separated *via* column chromatography on silica gel.

Further, ketones **2-4** underwent a condensation-cyclization reaction with thiourea and iodine in ethanol, to afford di-norlabdane compounds with 2-amino-1,3-thiazole fragment **5** and **6** [22].

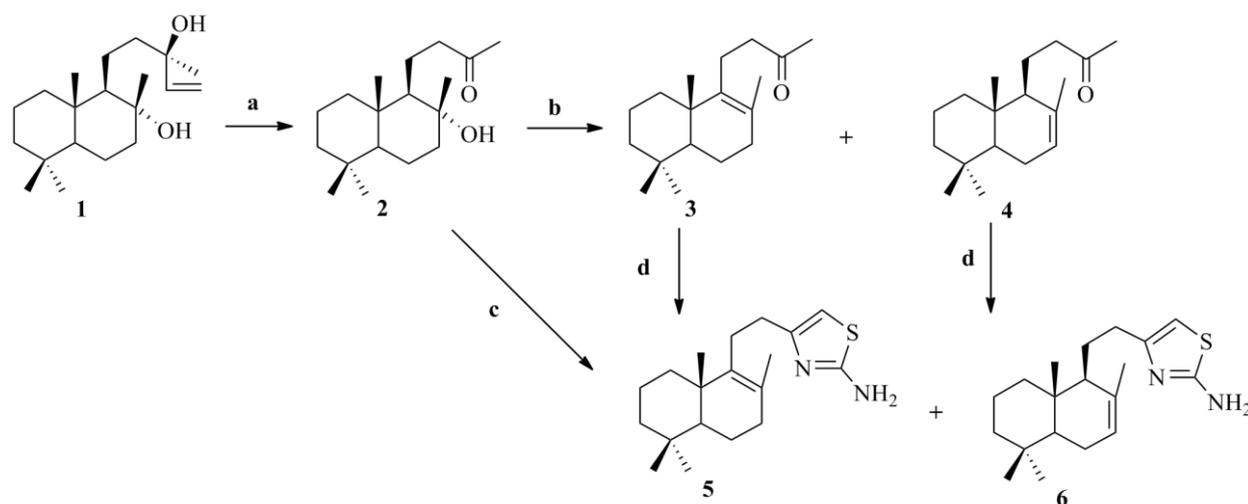
Hydroxyketone **2** forms a mixture of two compounds under the described conditions: 2-amino-4-(15,16-dinorlabd-8(9)-en-13-on)-1,3-

thiazole **5** and 2-amino-4-(15,16-dinorlabd-7(8)-en-13-on)-1,3-thiazole **6** in a 1.5:1 ratio, with 87% overall yield. The formation of this mixture can be explained as follows: the presence of molecular iodine favours the dehydration of the hydroxy group in the initial compound and leads to thiazole **5** and thiazole **6**, obtained in 52% and 35% yields, respectively.

The unsaturated ketones **3** and **4**, under the same conditions, gave only the mentioned 2-amino-4-(15,16-dinorlabd-8(9)-en-13-on)-1,3-thiazole **5** and 2-amino-4-(15,16-dinorlabd-7(8)-en-13-on)-1,3-thiazole **6**, within 85% and 80% overall yields, respectively.

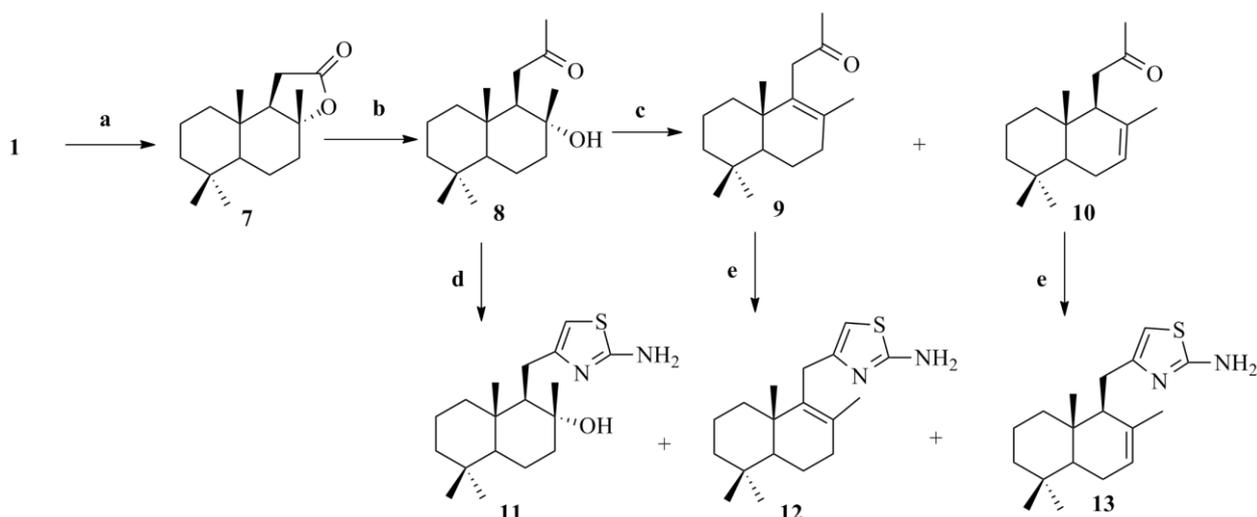
As previously stated, the target trinorlabdane compounds with 2-amino-1,3-thiazole fragment were synthesized from commercially available sclareolide **7**, which can be easily prepared from natural labdane diterpenoid (-)-sclareol **1** [23]. For this, sclareolide **7** was treated with methyl lithium, in a molar ratio 1:2, in diethyl ether to afford 8 α -hydroxy-14,15,16-trinorlab-12-one **8**, in 65% yield, according to the described method [24] (Scheme 2).

Hydroxyketone **8** was then treated with $\text{MeSO}_3\text{SiMe}_3$ in acetonitrile under the aforementioned conditions [21], and gave a mixture of unsaturated ketones: 14,15,16-trinorlab-8(9)-en-12-one **9** and 14,15,16-trinorlab-7(8)-en-12-one **10** (ratio 8:2), with 91% overall yield, which were successfully separated *via* column chromatography on silica gel.



Reagents and conditions: *a.* KMnO_4 , acetone, 0°C , 4h, 90%; *b.* $\text{MeSO}_3\text{SiMe}_3$, MeCN, r.t., 15 min, 95%; *c.* $\text{SC}(\text{NH}_2)_2$, I_2 , EtOH, 12 h, Δ , **5** (35%), **6** (52%); *d.* $\text{SC}(\text{NH}_2)_2$, I_2 , EtOH, 12 h, Δ , **5** (85%), **6** (80%).

Scheme 1. Synthesis of di-norlabdane compounds with 2-amino-1,3-thiazole fragment.



Reagents and conditions: *a.* $\text{Na}_2\text{Cr}_2\text{O}_7$, H_2SO_4 , H_2O , 6h, r.t. 65%; *b.* $\text{MeLi}/\text{Et}_2\text{O}$, r.t., 15 min, 65%; *c.* $\text{MeSO}_3\text{SiMe}_3$, MeCN , r.t., 15 min, 91%; *d.* $\text{SC}(\text{NH}_2)_2$, I_2 , EtOH , 12 h, Δ , **11** (17%), **12** (25%), **13** (43%); *e.* $\text{SC}(\text{NH}_2)_2$, I_2 , EtOH , 12 h, Δ , **12** (82%), **13** (80%).

Scheme 2. Synthesis of tri-norlabdane compounds with 2-amino-1,3-thiazole fragment.

Tri-norlabdane compounds with 2-amino-1,3-thiazole fragment **11-13** were obtained by treating ketones **8-10** with thiourea and iodine in ethanol, according to [22]. In the case of hydroxyketone **8**, a mixture of thiazoles **11-13**, at a ratio of 1:1.5:2.5 was obtained, with 85% overall yield.

The formation of this mixture may be explained analogically as in the case of hydroxyketone **2**, with the difference that hydroxyketone **8** undergoes partial dehydration, which leads to 2-amino-4-(14,15,16-trinorlabd-8(9)-en-13-on)-1,3-thiazole **12** and 2-amino-4-(14,15,16-trinorlabd-7(8)-en-13-on)-1,3-thiazole **13**, obtained in 25% and 43% yields, respectively. This fact is confirmed by the formation of minor hydroxylated 2-amino-4-(8 α -hydroxy-14,15,16-trinorlabd-13-on)-1,3-thiazole **11**, isolated from the reaction mixture in a 17% yield.

The condensation-cyclization reaction of unsaturated ketones **9** and **10**, under the same conditions, led to tetra-substituted **12** and tri-substituted **13** thiazoles, with 82% and 80% overall yields, respectively.

The structures of all synthesized compounds were confirmed by IR, ^1H and ^{13}C NMR data. The spectroscopic data of the new compounds are given in the experimental section and are fully consistent with the suggested structures. The IR spectra of compounds **5**, **6** and **11-13** had strong absorption maxima characteristic for the $\text{N}=\text{C}$ group around

1620-1610 cm^{-1} and comparative absorptions at 3308-3116 cm^{-1} , which were assigned to the amino group bounded to the thiazole fragment. The ^1H NMR spectra of the compounds **5**, **6** and **11-13** fully confirm their structures by the presence of singlet signals belonging to C-17, C-18, C-19 and C-20 methyl groups of the terpenic fragment in the 1.81-0.76 ppm region, a broad singlet of protons related to the amine group of the thiazole fragment at 5.41-5.05 ppm, and a singlet of the proton from the thiazole fragment at 6.15-5.92 ppm (Figure 1). The ^{13}C NMR spectra of the obtained compounds **5**, **6**, and **11-13** clearly confirmed their structures by the presence of the chemical shift for C-2' from the thiazole ring that was assigned to 167 ppm, while the signals of C-4' and C-5' from the thiazole ring appeared around 152-155 ppm and 102 ppm, respectively (Figure 2).

A proposed mechanism for the synthesis of di- and tri-norlabdane compounds with 2-amino-1,3-thiazole fragment is given in Scheme 3, which involves the initial formation of the iodine derivative **14**. Then, the nucleophilic substitution of the iodine atom in **14** by the thiocarbonyl sulphur atom of thiourea **15** takes place and affords intermediate **16**. Intramolecular addition of the nitrogen to the carbonyl group in **16** gives intermediate **17**, which then undergoes dehydration with the formation of the 2-amino-1,3-thiazole compound.

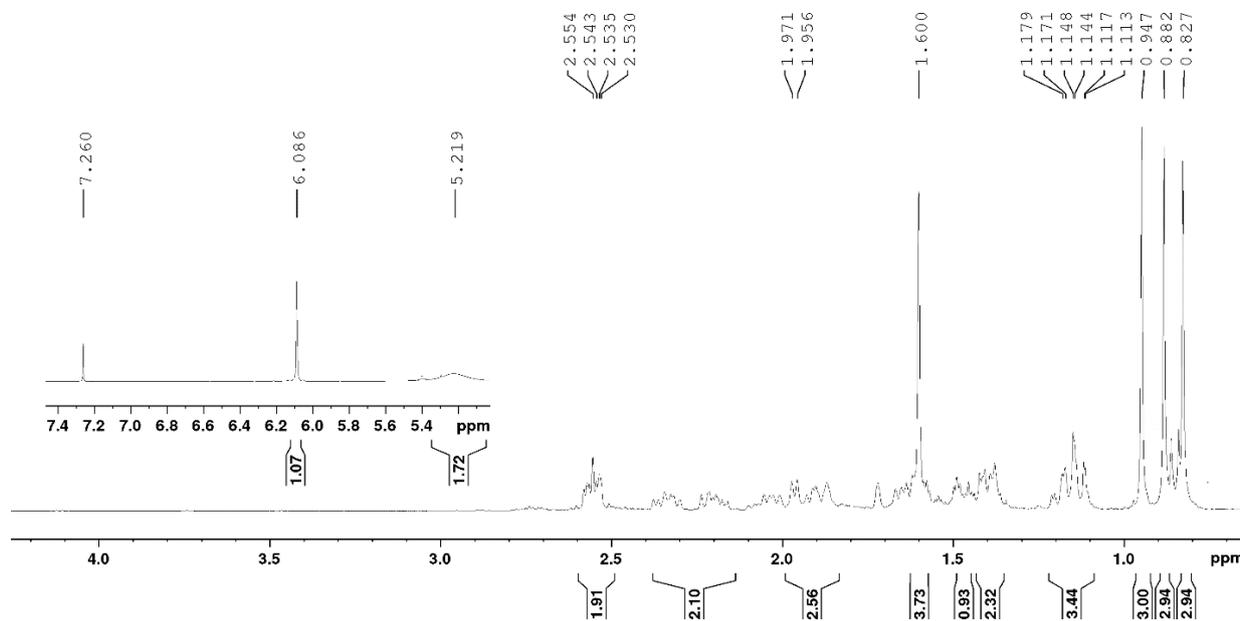
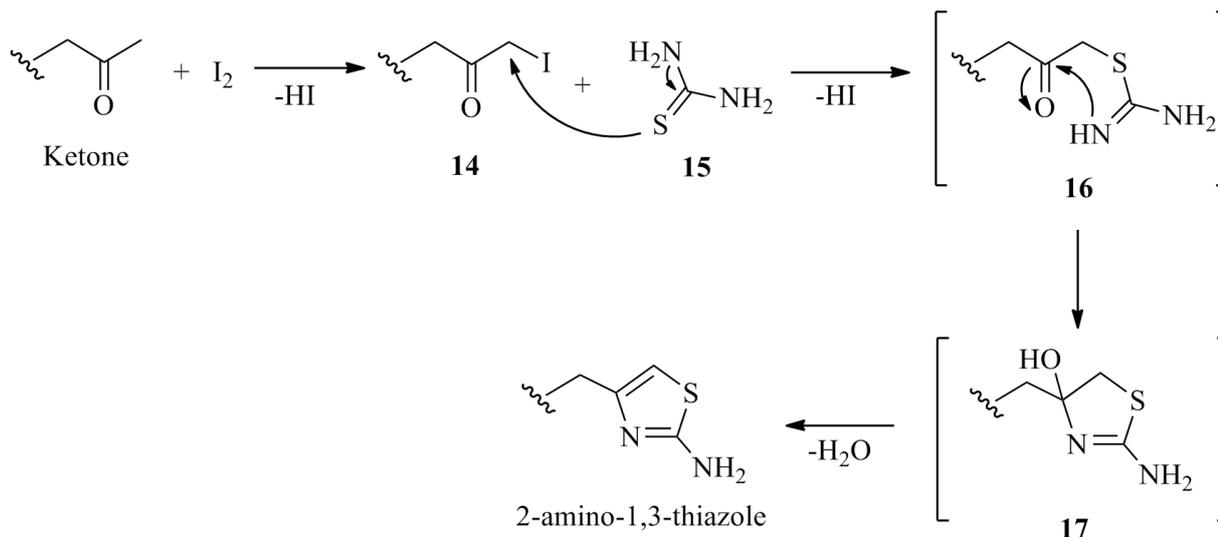


Figure 1. ¹H NMR spectrum of 2-amino-4-(15,16-di-norlabd-8(9)-en-13-on)-1,3-thiazole.

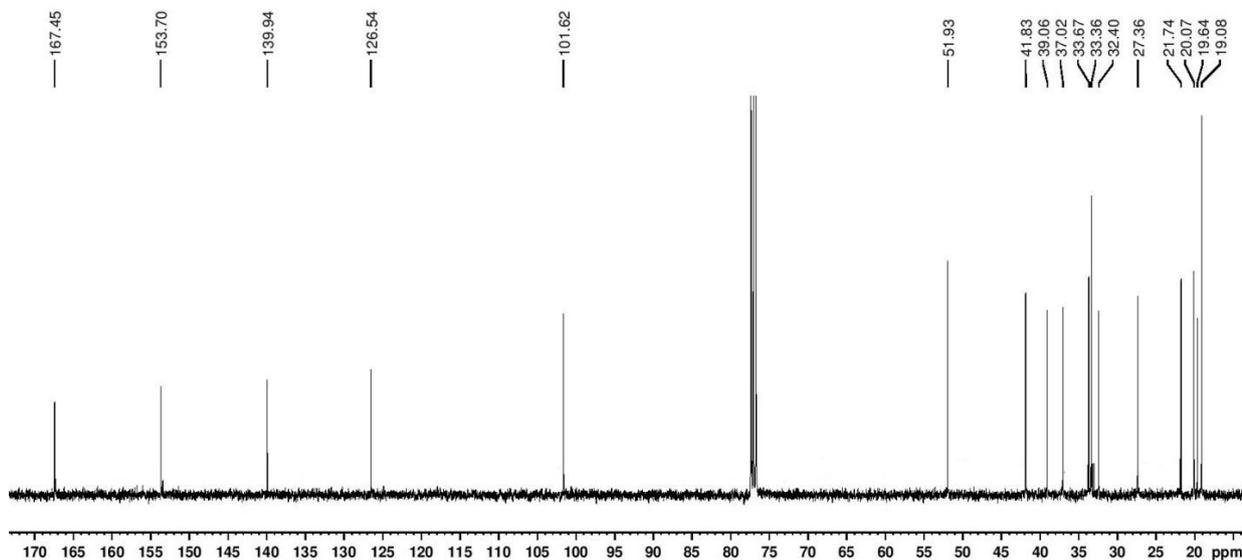


Figure 2. ¹³C NMR spectrum of 2-amino-4-(15,16-di-norlabd-8(9)-en-13-on)-1,3-thiazole.

Conclusions

The present paper describes a short and efficient synthesis of novel hybrid terpeno-heterocyclic compounds. Starting from natural labdane diterpenoid (-)-sclareol **1**, *via* its intermediate 8 α -hydroxy-15,16-dinorlabd-13-one **2**, di-norlabdanes **5** and **6** containing 2-amino-1,3-thiazole unit were synthesized in ~30.0-70% overall yields. The synthetic route *via* sclareolide **7** led to tri-norlabdanes **11-13** bearing the 2-amino-1,3-thiazole unit that were obtained in 6.5-31.5% overall yields. In contrast to pure isomers **3,4** and **9,10**, the use of hydroxyketones **2** and **8**, offered some disadvantages because of the formation of the mixture of 2-amino-1,3-thiazole compounds. The formation of these mixtures can be explained by the suggested reaction mechanism which proves that the presence of molecular iodine encourages dehydration of hydroxy group in the mentioned compounds. The spectral analysis (IR, ¹H and ¹³C NMR) of newly synthesized compounds fully confirmed their structure and the presence of the 2-amino-1,3-thiazole unit.

Acknowledgments

The author is grateful to Professor, Doctor habilitatus Aculina Aricu for her guidance and overall support.

References

- Blunt, J.W.; Copp, B.R.; Keyzers, R.A.; Munro, M.H.G.; Prinsep, M.R. Marine natural products. *Natural Product Reports*, 2015, 32(2), pp. 116-211. DOI: <https://doi.org/10.1039/C4NP00144C>
- Brahmkshatriya, P.P.; Brahmkshatriya, P.S. Terpenes: chemistry, biological role, and therapeutic applications. *Natural Products*, 2013, pp. 2665-2691. DOI: https://doi.org/10.1007/978-3-642-22144-6_120
- Mayer, A.M.S.; Rodríguez, A.D.; Tagliatalata-Scafati, O.; Fusetani, N. Marine pharmacology in 2009–2011: marine compounds with antibacterial, antidiabetic, antifungal, anti-inflammatory, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous systems, and other miscellaneous mechanisms of action. *Marine Drugs*, 2013, 11(7), pp. 2510-2573. DOI: <https://doi.org/10.3390/md11072510>
- Williams, P.; Sorribas, A.; Howes, M.-J.R. Natural products as a source of Alzheimer's drug leads. *Natural Product Reports*, 2011, 28(1), pp. 48-77. DOI: <https://doi.org/10.1039/c0np00027b>
- Frija, L.M.T.; Frade, R.F.M.; Afonso, C.A.M. Isolation, chemical, and biotransformation routes of labdane-type diterpenes. *Chemical Reviews*, 2011, 111(8), pp. 4418-4452. DOI: <https://doi.org/10.1021/cr100258k>
- Hanson, J.R. Diterpenoids of terrestrial origin. *Natural Product Reports*, 2012, 29(8), pp. 890-899. DOI: <https://doi.org/10.1039/C2NP20051A>
- Hanson, J.R. Diterpenoids. *Natural Product Reports*, 2004, 21(2), pp. 312-320. DOI: <https://doi.org/10.1039/B300377A>
- Marcos, I.S.; Castañeda, L.; Basabe, P.; Díez, D.; Urones, J.G. Labdane diterpenes with highly functionalized B rings. *Mini-Reviews in Organic Chemistry*, 2012, 9(1), pp. 54-86. DOI: [10.2174/157019312799080044](https://doi.org/10.2174/157019312799080044)
- Chinou, I. Labdanes of natural origin-biological activities (1981-2004). *Current Medicinal Chemistry*, 2005, 12(11), pp. 1295-1317. DOI: [10.2174/0929867054020990](https://doi.org/10.2174/0929867054020990)
- Songsri, S.; Nuntawong, N. Cytotoxic labdane diterpenes from *Hedychium ellipticum* Buch.-Ham. ex Sm. *Molecules*, 2016, 21(6), pp. 749-755. DOI: <https://doi.org/10.3390/molecules21060749>
- Singh, M.; Pal, M.; Sharma R.P. Biological activity of the labdane diterpenes. *Planta Medica*, 1999, 65(1), pp. 2-8. DOI: [10.1055/s-1999-13952](https://doi.org/10.1055/s-1999-13952)
- Catalán, L.E.; Maturana, E.B.; Marín, K.C.; Olivares, M.O.; Altamirano, H.C.; Fritis, M.C.; García, J.V. Synthesis and antitumor activity of diterpenylhydroquinone derivatives of natural ent-labdanes. *Molecules*, 2010, 15(9), pp. 6502-6511. DOI: <https://doi.org/10.3390/molecules15096502>
- Kuchkova, K.; Aricu, A.; Barba, A.; Vlad, P.; Shova, S.; Secara, E.; Ungur, N.; Zbancioc, Gh.; Mangalagiu, I.I. An efficient and straightforward method to new organic compounds: homodrimane sesquiterpenoids with diazine units. *Synlett*, 2013, 24(6), pp. 697-700. DOI: [10.1055/s-0032-1318253](https://doi.org/10.1055/s-0032-1318253)
- Aricu, A.; Ciocarlan, A.; Lungu, L.; Barba, A.; Shova, S.; Zbancioc, Gh.; Mangalagiu, I.I.; D'Ambrosio, M.; Vornicu, N. Synthesis, antibacterial, and antifungal activities of new drimane sesquiterpenoids with azaheterocyclic units. *Medicinal Chemistry Research*, 2016, 25(10), pp. 2316-2323. DOI: <https://doi.org/10.1007/s00044-016-1665-0>
- Fu, X.; Palomar, A.J.; Hong, E.P.; Schmitz, F.J.; Valeriote, F.A. Cytotoxic lissoclimide-type diterpenes from the molluscs *Pleurobranchus albiguttatus* and *Pleurobranchus forskalii*. *Journal of Natural Products*, 2004, 67(8), pp. 1415-1418. DOI: <https://doi.org/10.1021/np0499620>
- Siddiqui, N.; Arshad, M.F.; Ahsan, W.; Alam, M.S. Thiazoles: A valuable insight into the recent advances and biological activities. *International Journal of Pharmaceutical Sciences and Drug Research*, 2009, 1(3), pp. 136-143. <http://ijpsdr.org/index.php/ijpsdr/article/view/46>
- Kashyap, S.J.; Garg, V.K.; Sharma, P.K.; Kumar, N.; Dudhe R.; Gupta, J.K. Thiazoles: having diverse biological activities. *Medicinal Chemistry Research*, 2012, 21(8), pp. 2123-2132. DOI: <https://doi.org/10.1007/s00044-011-9685-2>

18. Davyt, D.; Serra, G. Thiazole and oxazole alkaloids: isolation and synthesis. *Marine Drugs*, 2010, 8(11), pp. 2755-2780.
DOI: <https://doi.org/10.3390/md8112755>
19. Gupta, V.; Kant, V. A review on biological activity of imidazole and thiazole moieties and their derivatives. *Science International*, 2013, 1(7), pp. 253-260.
DOI: [10.17311/sciintl.2013.253.260](https://doi.org/10.17311/sciintl.2013.253.260)
20. Hua, S.-K.; Wang, J.; Chen, X.-B.; Xu, Z.-Y.; Zeng, B.-B. Scalable synthesis of methyl *ent*-isocopalate and its derivatives. *Tetrahedron*, 2011, 67(6), pp. 1142-1144.
DOI: [10.1016/j.tet.2010.12.008](https://doi.org/10.1016/j.tet.2010.12.008)
21. Cucicova, C.; Aricu, A.; Secara, E.; Vlad, P.; Ungur, N. Process for producing 14,15-bisnorlabdane-8(9)-en-13-one. MD Patent, 2013, No. 4248. (in Romanian.)
22. Tsai, C.-Y.; Kapoor, M.; Huang, Y.-P.; Lin, H.-H.; Liang, Y.-C.; Lin, Y.-L.; Huang, S.-C.; Liao, W.-N.; Chen, J.-K.; Huang, J.-S.; Hsu, M.-H. Synthesis and evaluation of aminothiazole-paeonol derivatives as potential anticancer agents. *Molecules*, 2016, 21(2), pp. 145-153.
DOI: <https://doi.org/10.3390/molecules21020145>
23. Porcescu, P.; Postovoi, A.; Grama, I.; Leonov, A.; Iorga, T.; Ungur, N.; Colța, M.; Vlad, P.; Kulcički, V.; Barba, A. Smoking aromatizing tobacco product, process for obtaining thereof, aromatic composition (variants), process for obtaining compositions for tobacco products (variants). MD Patent, 2003, No. 2253. (in Romanian)
24. Kuchkova, K.I.; Chumakov, Yu.M.; Simonov, Yu.A.; Bocelli, G.; Panasenکو, A.A.; Vlad, P.F. A short efficient synthesis of 11-monoacetate of drimane-8 α ,11-diol from norambreinolide. *Synthesis*, 1997, 9, pp.1045-1048.
DOI: [10.1055/s-1997-1302](https://doi.org/10.1055/s-1997-1302)