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**FROM (-)-SCLAREOL TO NORLABDANE
HETEROCYCLIC HYBRID COMPOUNDS**

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FROM (-)-SCLAREOL TO NORLABDANE HETEROCYCLIC HYBRID COMPOUNDS

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Abstract. This review relates to the chemistry of the well-known biologically active natural labdane diterpenoid (-)-sclareol easily isolated from Clary sage (*Salvia sclarea* L.). This compound is used in industry, mainly for the synthesis of fragrances and natural analogues. The paper covers achievements reported in the respective publications from 2013 to 2021 on the synthesis, structure determination, and biological activity of molecular hybrid compounds bearing hydrazide and thiosemicarbazone fragments or diazine, 1,2,4-triazole, carbazole, 1,3-thiazole, 1,3,4-oxadiazole, and 1,3,4-thiadiazole units prepared basing on the studied compound.

Keywords: (-)-sclareol, norlabdane-heterocyclic compound, antimicrobial activity, biological activity.

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List of abbreviations and notations:

CDI	1,1'-Carbonyldiimidazole
CNBr	Cyanogen bromide
DCC	Dicyclocarbodiimide
DCM	Dichloromethane
DMAA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
Et ₃ N	Triethylamine
EtOH	Ethanol
MCF-7	Breast cancer cells
MeOH	Methanol
MIC	Minimum inhibitory concentration
MW	Microwave irradiation
NMR	Nuclear magnetic resonance
r.t.	Room temperature
R-NCS	Substituted isothiocyanates
SAR	Structure-activity relationship
THF	Tetrahydrofuran
TMTD	Tetramethylthiuram disulfide
XRD	X-ray diffraction

Introduction

Due to its abundance in nature and significant practical importance, the chemistry of (-)-sclareol (**1**) has experienced an impressive development in recent years. The commercial labdane diterpenoid (-)-sclareol (**1**) isolated from Clary sage (*Salvia sclarea* L.) has many areas of industrial usage including food, pharmaceutical, tobacco industry, and perfumery. Based on this compound or some of its dinorlabdane **2-4** and

trinorlabdane **5-7** intermediates (Figure 1), as well as tetranorlabdane **8-10** and pentanorlabdane **11-13** (Figure 2), a great number of synthetic terpenic compounds or natural analogues were obtained. An example of this is the natural ambergris substituent Ambrox®, an important synthetic derivative of (-)-sclareol (**1**) with a pronounced ambergris-type odor. Some other biologically active drimanic sesquiterpenoids synthesized from diol **1** can be mentioned here, such as polygodial, warburganal, pereniporines A and B, and others.

Unlike other classes of compounds, such as alkaloids, terpenes that contain heteroatoms, especially nitrogen, are less numerous and less studied [1]. Urones, J. *et al.* performed one of the first syntheses of C₉ nitrogenated drimanes during the preparation of pereniporin A and 9-*epi*-warburganal [2]. Barrero, A.F. *et al.* reported some nitrogen-containing intermediates obtained during the synthesis of natural 9,11-drimen-8 α -ol from (-)-sclareol (**1**) [3]. A new 11-guanidinodrimene derivative of drimenol with an increased antifungal activity was reported by Zarraga, M. *et al.* [4]. Kuchkova, K.I. *et al.* accomplished the synthesis of 11-aminodrim-7-ene, a nitrogenated analogue of drimenol, from (-)-sclareol (**1**) *via* the corresponding oxime and nitrile [5]. The same authors communicated about a series of oximes, amides, 1,2,6- and 1,3,6-oxazines, *N*-oxide prepared from 11-dihomodriman-8 α -ol-12-one **5**

and 11-dihomodriman-8(9)-en-12-one **6**, two important derivatives of (-)-sclareol (**1**) [6,7]. Later, Kuchkova, K. *et al.* [8,9] described the synthesis of some di- and trinorlabdane isomeric amines *via* corresponding oximes, starting from dinorlabdane **2-4** and trinorlabdane **5-7** ketones, derived from (-)-sclareol (**1**).

In the desire to obtain γ -bicyclohomofarnesal (Ambral), which is the key intermediate in the synthesis of Ambrox® and others terpenes, de la Torre, M.C. *et al.* prepared some nitrogen containing intermediates like Weinreb amides and its unsaturated derivatives from (+)-sclareolide (**8**), one of the most important derivatives of (-)-sclareol (**1**) [10]. A bit later, Boukouvalas, J. *et al.* substantially improved de la Torres's method [10] and performed for the first time the synthesis of the antitumor diterpenoid (+)-zerumin B starting from the same (+)-sclareolide (**8**) [11]. Boukouvalas, J. and Wang, J.-X. reported the Weinreb amide together with an intermediate nitrile after the synthesis and structure revision of a novel labdane diterpenoid ottensinin based on (+)-sclareolide (**8**) [12]. Unlike previous transformations performed in the outside chain, Lungu, L. presented the synthesis of the cycle B C₇ functionalized tetra- and pentanorlabdane oximes and amines based on ketoester **10** and drimenone **12**, well known derivatives of (-)-sclareol (**1**) [13].

In the last decade, the (-)-sclareol (**1**) carbon skeleton has been intensively used for the synthesis of some natural N-containing labdane-type analogues [14]. The biologically active tetracyclic diterpenes 4-methyldecarboxyhaumanamide, 4-methyl decarboxyspongolactames A and C isolated from marine organisms and synthesized by Basabe, P. *et al.* from (-)-sclareol (**1**) belong to this series of nitrogenated spongianes [15].

Some of the authors mentioned above state that the presence of a heteroatom, such as nitrogen, often increases the biological activity of the compounds derived from (-)-sclareol (**1**) or (+)-sclareolide (**8**). An even greater increase can

be expected in the case of terpene compounds that contain heteroatomic fragments or different heterocyclic rings in their molecules. The publications on the synthesis, chemistry, and biological activity of non-terpenic 1,2-diazines [16,17], 1,3-thiazole [18], 1,3,4-oxadiazole [19], 1,3,4-thiadiazole [19,20], 1,2,4-triazoles [19,21], and benzothiazole [22] are ascending nowadays.

It is well known that some ligands and their metal complexes bearing a thiosemicarbazone fragment show pronounced antibacterial, antifungal, antitumor, and antiviral activities [23,24]. Matesanz, A.I. *et al.* discussed a new family of Pt(II) and Pd(II) bis(thiosemicarbazone) compounds incorporating the 2,6-diacetylpyridine heterocyclic ring, which showed a high antiproliferative activity against cisplatin resistant A2780cisR cells and breast (MCF-7) cancer cells [25].

Starting from (-)- α -bisabolol, a series of thiosemicarbazones with high cytotoxicity and selectivity was prepared, and their structure-activity relationship was studied [26]. According to authors, some of thiosemicarbazones obtained from kaurenoic acid showed a significant antitrypanosomal activity [27]. A series of novel thiosemicarbazides, which exhibited considerable inhibitory effects on the growth of a wide range of cancer cell lines, was created by Vandresen, F. *et al.*, whose investigations were based on the natural monoterpene R-(+)-limonene [28].

The purpose of the present review is to discuss the current achievements in the field of the synthesis of hybrid norlabdane compounds containing heteroatomic fragments or heterocyclic rings, the chemistry of which is on the rise.

Background

Key norlabdane intermediates derived from (-)-sclareol

The (-)-sclareol (**1**) derivatives most frequently used for the synthesis of terpeno-heterocyclic hybrid compounds can be divided into several groups according to the number of atoms in their carbon skeletons (Figure 1).

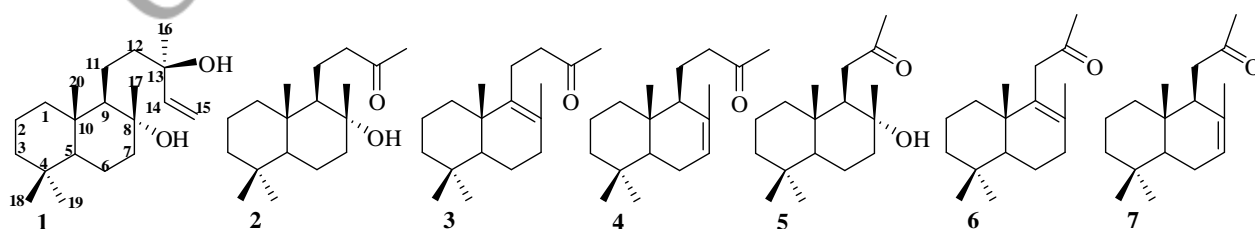


Figure 1. (-)-Sclareol (**1**) and its dinorlabdane **2-4** and trinorlabdane **5-7** derivatives [29,30].

One of the key dinorlabdane intermediate is methyl ketone **2** that can be easily prepared by the oxidative degradation of diol **1** according to [29]. Any further dehydration of compound **2** leads to isomeric ketones **3** and **4** [30] which are, as well, suitable starting materials for the synthesis of the target dinorlabdane heterocyclic hybrid compounds.

The methyl ketone **5** can be considered the head of the trinorlabdane compounds series, and it may be prepared from the commercial available (+)-sclareolide (**8**) according to the known procedure [31]. Its dehydration under the mentioned conditions [30] gives a mixture of chromatographically separable trinorlabdane ketones **6** and **7** in 4:1 ratio. The syntheses of molecular hybrids based on trinorlabdane compounds **5-7** are reported below. Both tetranorlabdane **9**, **10** and pentanorlabdane **11-13** precursors depicted in Figure 2 were prepared by the known [32-34] and new [35,36] procedures and used further for the synthesis of the title compounds of these series

Synthesis of norlabdane heterocyclic hybrid compounds

Among the first reported heterocyclic terpene compounds are those with diazine

units [37,38]. There, the authors used the $\Delta^{8,13}$ -bicyclohomofarnesenic acid **9**, a derivative of (-)-sclareol (**1**) as starting material and applied two synthetic pathways. The first method (Method I) included a coupling reaction of chloroanhydride **14** obtained *in situ* from acid **9** with amines, such as 4-aminopyrimidine **15a**, 3-aminopyrazine **15b**, and 2-aminopyrimidine **15c**, under presented conditions (Scheme 1). As a result, amides **16a** and **16b** were obtained in 60% and 15% yields, respectively, and amide **16c** (16%) was isolated from the reaction mixture together with the major *bis*-acylamide **17** (54%).

Kuchkova *et al.* reported attempts to increase the reaction yields and selectivity and to prove that a *bis*-acylation reaction of 2-aminopyrimidine **15c** occurs under any condition [37,38]. The direct one-step acylations of aminodiazines **15a-c** with acid **9** in the presence of dicyclocarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) (Method II) were performed for that purpose (Scheme 1). As a result, amides **16a, b** were obtained in 53% and 52% yields, respectively, and in both cases, bicyclohomofarnezenoyl-*N,N'*-dicyclohexylurea **19** was also formed (20% and 17%, respectively).

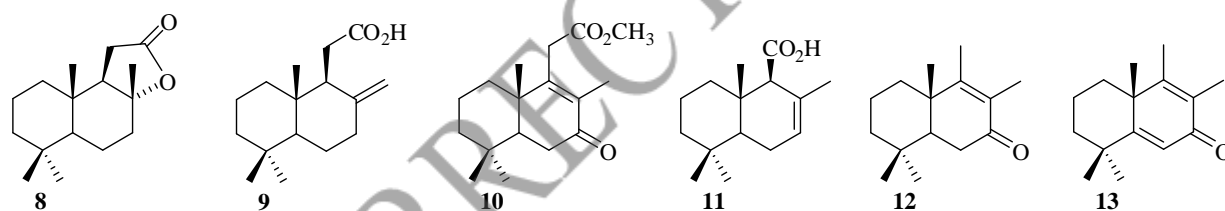
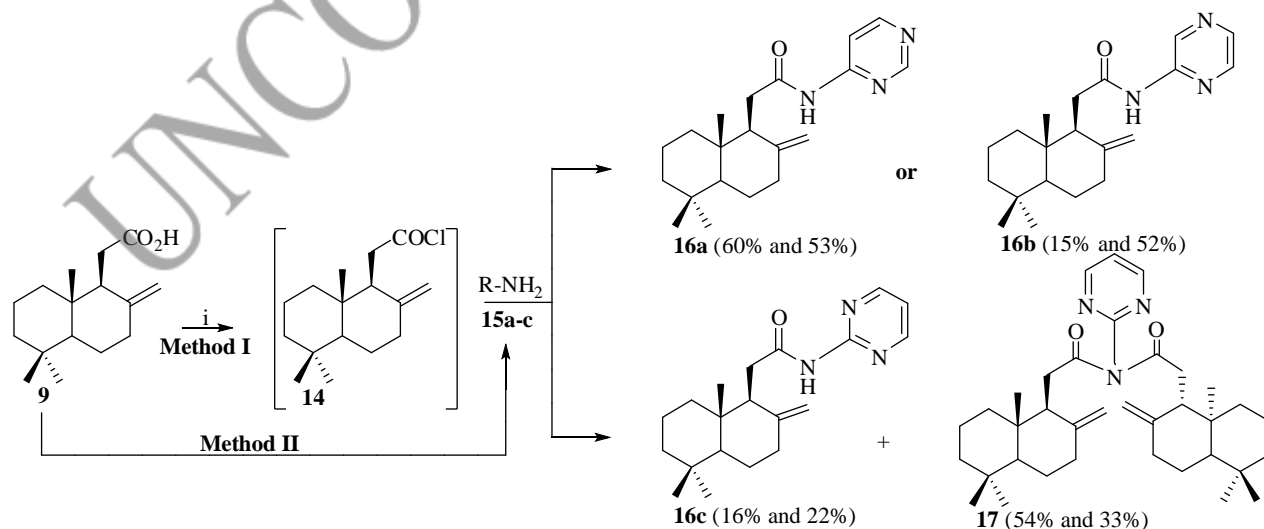


Figure 2. Tetranorlabdane **8-10** and pentanorlabdane **11-13** compounds [32-36].



Reagents and conditions: Method I: (i) $(\text{COCl})_2$, C_6H_6 , r.t. 1 h, Δ 1 h; (ii) R-NH_2 , DCM, Δ 2-15 h.

Method II: (i) R-NH_2 , DCC, DMAP, DCM, Δ , 5-28 h.

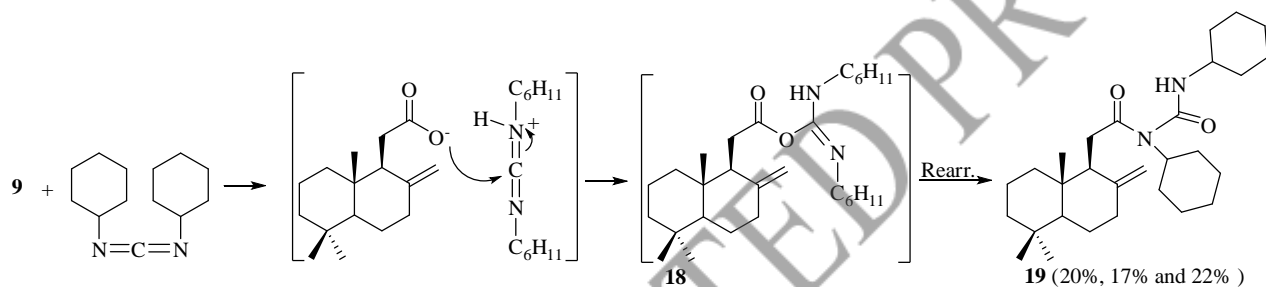
Scheme 1. Synthesis of diazines **16a-c** and **17** from $\Delta^{8,13}$ -bicyclohomofarnesenoic acid **9** [37,38].

From the reaction product of the interaction of acid **9** with 2-aminopyrimidine **15c**, together with amide **16c** (22%) and substituted urea **19** (22%), also *bis*-acylamide **17** was isolated in 33% yield. Based on the data obtained, those authors concluded that Method I was more efficient in terms of yields and selectivity.

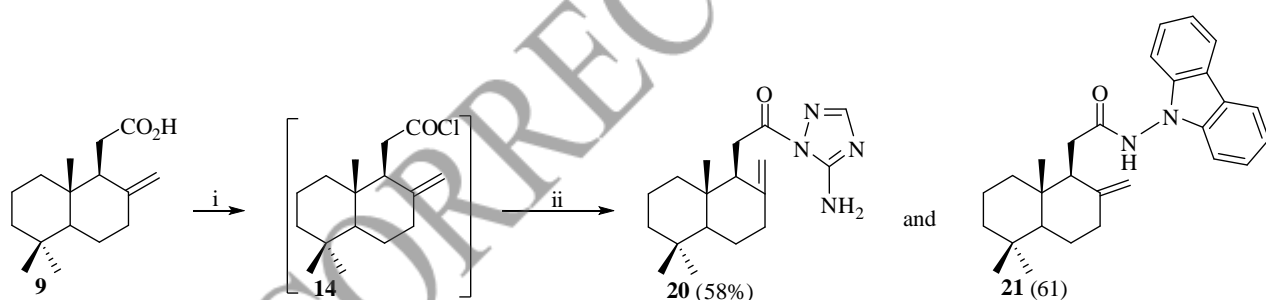
The proposed mechanism of compound **19** formation includes the protonation of a nitrogen atom from DCC, followed by a nucleophilic attack of a carboxyl ion, which leads to the intermediate **18** [38]. Its interaction with amines **15a-c** gives amides **16a-c** and *bis*-acylamide **17**, that fact being confirmed by the *N,N'*-dicyclohexylurea formation as by-product (Scheme 2). On the other hand, the rearrangement of intermediate **18** produces substituted urea **19**. The structures of the synthesized compounds were fully confirmed by the spectral methods and for *bis*-acylamide **17**, X-ray diffraction (XRD) was also performed.

In continuation, acid **9** was used for the synthesis of tetranorlabdane hybrids bearing 1,2,4-triazol and *N*-aminocarbazole units according to Scheme 3 and following the same Method I applied in the synthesis of diazines [37,38]. As described above, acid **9** was converted into chloroanhydride **14** that interacted with 3-amino-1,2,4-triazole (Amine 1) and *N*-aminocarbazole (amine 2) [39]. As a result of those transformations, hybrid compounds **20** and **21** containing substituted 1,2,4-triazole or *N*-aminocarbazole units, respectively, were obtained in 58% and 61% yields, and their structures were confirmed by both spectral methods and XRD.

Similar series of molecular hybrids containing diazine, 3-amino-1,2,4-triazole and *N*-aminocarbazole units were prepared by Aricu, A. *et al.* based on homodrimane acid **22** obtained earlier in five steps from (+)-sclareolide (**8**) [40] *via* its chloroanhydride **23** (Figure 3).



Scheme 2. Mechanism of formation of bicyclohomofarnezenoyl-*N,N'*-dicyclohexylurea **19** [37,38].



Reagents and conditions: (i) (COCl)₂, C₆H₆, r.t. 1 h, Δ 1 h; (ii) Amine I or II, DCM, r.t. 2 h and 10 h.

Scheme 3. Synthesis of tetranorlabdanes bearing 3-amino-1,2,4-triazole and *N*-aminocarbazole units [39].

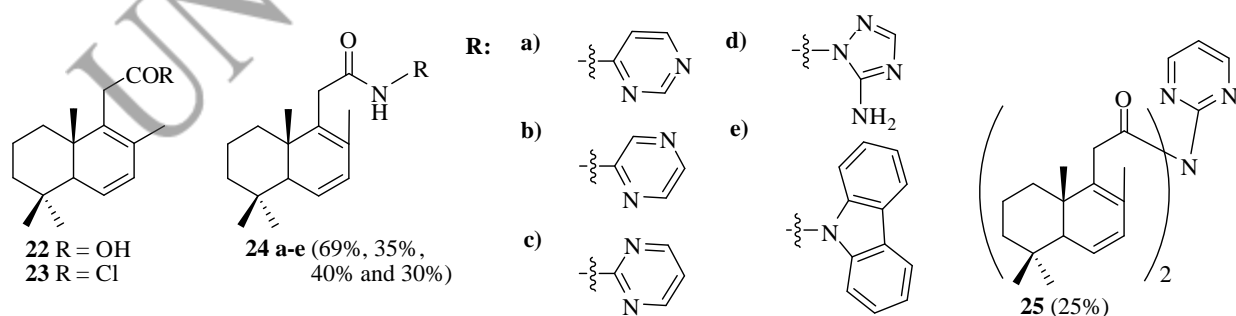


Figure 3. Hybrid homodrimane sesquiterpens **24a-e** and **25** derived from 11-homodrim-6,8-dien-12-oic acid **22** [40].

The same conditions as in Scheme 3 were applied in order to obtain, monoamides **24a-e** in 69%, 35%, 40%, 30%, and 40% yields, respectively. The *bis*-acylamide **25** was isolated from the reaction mixture in 25% yield together with diazine **24c**, thus confirming the hypothesis mentioned above.

Based on drimenic acid **11** and following the same chemical procedures, the syntheses of a series of pentanorlabdane heterocyclic compounds were described (Figure 4) [41]. The coupling reaction of chloroanhydride obtained *in situ* with 2-aminopyrimidine **15a**, 2-aminopyrazine **15b**, and 4-aminopyrimidine **15c** gave corresponding amides **26a-c** in 29%, 14%, and 11% yields, respectively, as well as amide **27c** (17%). Further interactions with *N*-aminocarbazol and 3-amino-1,2,4-triazole completed this series with amides **28e** and **29d**, obtained in 49% and 53% yields, respectively. Contrary to expectations, only the amides of the isodrimenic $\Delta^{8,9}$ **26a-c**, **28e**, and albicanic $\Delta^{8,12}$ **27c**, **29d** acids, as isomers of drimenic acid **11**, were obtained. This can be explained by the isomerization of the $C_{7,8}$ double bond in the tetrasubstituted and exocyclic ones upon interaction with oxalyl chloride. The structures of reported pentanorlabdane hybrid compounds containing diazine, 3-amino-1,2,4-triazole, and *N*-aminocarbazol units were fully

confirmed by the spectral data, and that of compound **28e** – by the crystallographic analysis.

Recently, a moderate number of publications devoted to the isolation or synthesis of tetranorlabdane compounds have appeared, and only in one of them, a tetranorlabdane pyridazinone hybrid **31** was reported [42]. The treatment of allyl bromide **30** derived from ketoester **10** with 6-(*p*-tolyl)-3(2*H*)-pyridazinone led to the desired hybrid compound **31** in 75% yield (Scheme 4). Contrary to that, the treatment of bromide **30** with 6-(*p*-tolyl)-4,5-dihydro-3(2*H*)-pyridazinone gave dimer **32** in 70% yield (Scheme 4), which can be explained by the different reactivity of (1,2)-diazines N-H bonds.

An attempt to substitute a bromine atom from a molecule of **30** by an acetoxy group gave the tetranorlabdane dimer **33** with an unprecedented carbon skeleton as the major product (86%) and acetate **36** (14%, Route I) as the minor one. The mechanism of dimer **33** formation was also reported, where dimer **32** was described as an intermediate (Scheme 5). It involved the formation of some intermediates like carbocation **34** (Route II), which, by a subsequent rearrangement of dienes and zwitterions **35a,b**, and **37**, and intermediate dimer **32**, gave dimer **33**. The structures of dimers **32** and **33** were proved by both spectroscopic and single-crystal XRD.

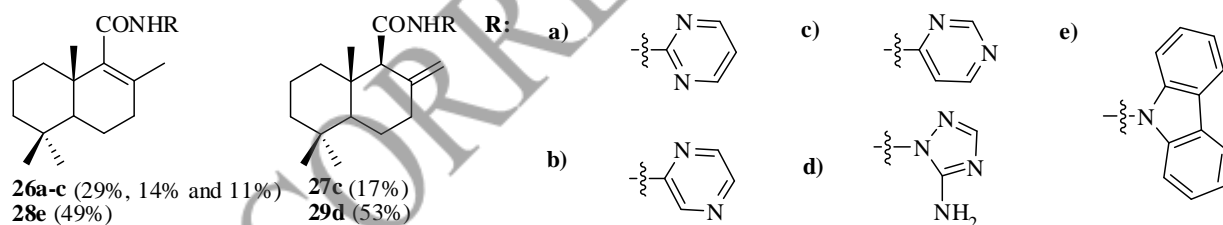
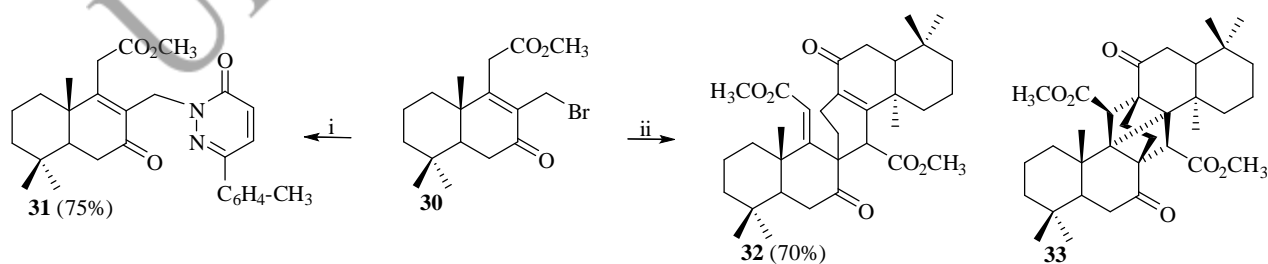


Figure 4. Syntheses of pentanorlabdane diazines **26a-c**, **27c**, carbazole **28e**, and 1,2,4-triazole **29d** [41].



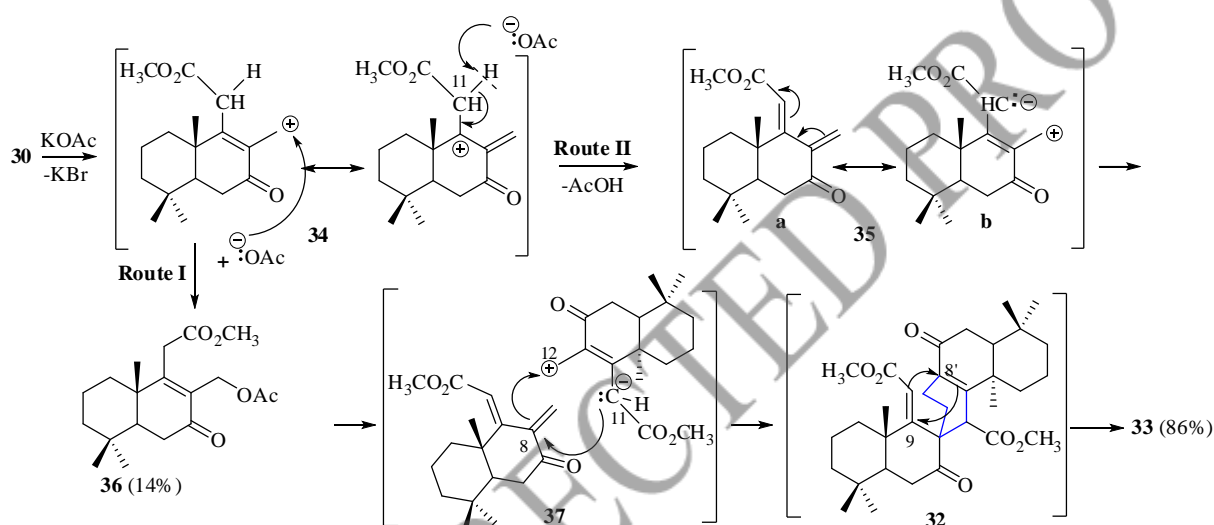
Reagents and conditions: (i) 6-(*p*-Tolyl)-3(2*H*)-pyridazinone, K_2CO_3 , DMAA, r.t., 48 h;

(ii) 6-(*p*-Tolyl)-4,5-dihydro-3(2*H*)-pyridazinone, K_2CO_3 , DMAA, r.t., 48 h.

Scheme 4. Synthesis of tetranorlabdane pyridazinone **31** and dimers **32**, **33** [42].

The monobrominated **38**, **39** and **41**, **42** and dibrominated derivatives **40** and **43** were prepared earlier from drimenone **12** and drimdienone **13** [34,43]. Those derivatives proved to be suitable intermediates for the synthesis of hybrid pentanorlabdane-pyridazinone compounds. By coupling the mentioned bromides with *p*-tolylpyridazinone (6-(*p*-tolyl)-3(2*H*)-pyridazinone), Aricu, A. *et al.* [35] performed the synthesis of individual monosubstituted **44**, **45** and disubstituted **46**, **47** hybrid compounds by classical (3-24 h) and microwave assisted (20 min-1.5 h) methods in good and comparable yields (34-84%), as depicted in Figure 5. The structure of hybrid compound **47** was confirmed additionally by single-crystal XRD.

D'Ambrosio M. *et al.* continued the investigations in order to obtain new tetranorlabdane compounds bearing the hydrazinecarbothioamide fragment or the 1,2,3-triazole unit [44]. Unlike previous syntheses, commercially available (+)-sclareolide (**8**) was chosen as starting material, which was transformed into corresponding hydrazide **48** via the known procedure [45]. The latter, after treatment with substituted isothiocyanates at room temperature (4.5-5 h), generated corresponding hydrazinecarbothioamides **49a-d** (Scheme 6, Method I). The same transformations were performed under MW-irradiation (5 min), resulting in higher yields (Scheme 6, Method II).



Scheme 5. Mechanism of formation of tetranorlabdane dimer **33** [42].

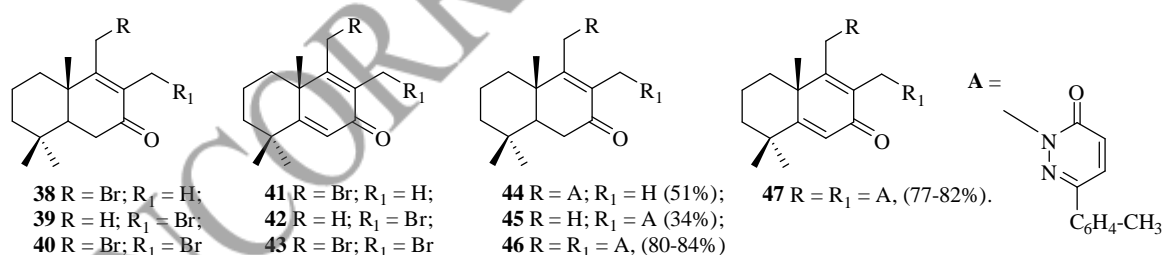
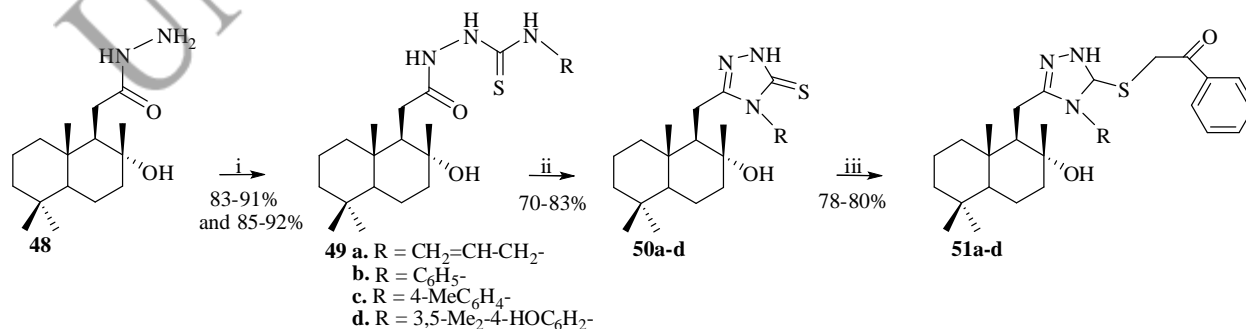


Figure 5. Synthesis of pentanorlabdane compounds with pyridazinone unit **44-47** [34,35,43].



Reagents and conditions: (i) Method I: RNCS, EtOH, r.t., 4.5-5 h; Method II: RNCS, EtOH, MW, 200 W, 5 min; (ii) NaOH, H₂O, 70°C, 2-3 h; (iii) Et₃N, Me₂CO, r.t., 2-3 h.

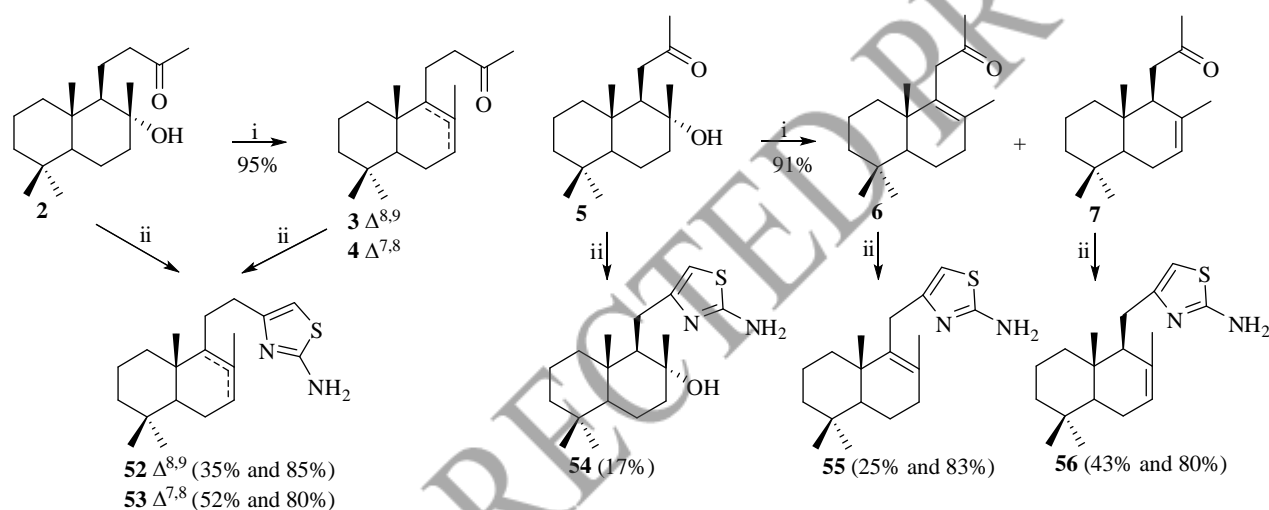
Scheme 6. Synthesis of tetranorlabdanes with hydrazinecarbothioamide fragment and substituted 1,2,4-triazole units [44].

The heterocyclization of compounds **49a-d** under alkaline aqueous solution conditions lead to *N*-substituted 1,2,4-triazoles **50a-d** which were easily alkylated with 2-bromoacetophenone giving *S*-substituted 1,2,4-triazoles **51a-d**. The structures of compounds **50c** and **51d** were confirmed by XRD.

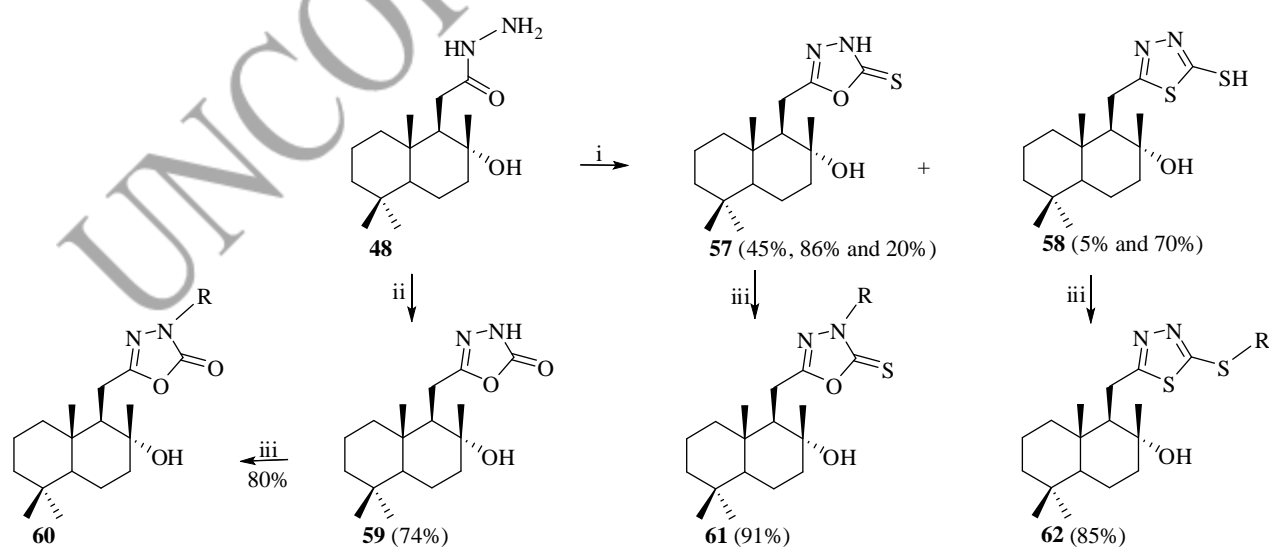
The synthesis of di- and trinorlabdane hybrids bearing a 2-amino-1,3-thiazole unit was reported by Blaja, S. [46]. The first series was obtained starting from hydroxyketone **2** which could be obtained directly by oxidation of (-)-sclareol (**1**) [29] and the second ketone **5** from (+)-sclareolide (**8**) [30]. The dehydration of ketones **2** and **5** after treatment with trimethylsilylmethanesulphonate led to chromatographically separable mixtures of ketones **3**, **4**, **6**, and **7** (Scheme 7). The standard conditions were used for individual

condensation-cyclization of ketones **3-7** [47] with thiourea and iodine in ethanol, thus giving dinorlabdane **52**, **53** and trinorlabdane **54-56** compounds bearing 2-amino-1,3-thiazoles units. Unfortunately, hydroxyketone **2**, under those conditions, suffered a dehydration favoured by iodine and formed only a mixture of compounds **3** and **4**.

Hydrazine **48** was used again for the synthesis of new tetranorlabdane compounds bearing 1,3,4-oxadiazole and 1,3,4-thiadiazole [48]. The reaction equilibrium of the compound **57** (45%→86%→20%) formation can be shifted to that of compound **58** (5%→70%) by the treatment of hydrazide **48** with an increasing amount of TMTD, 0.5→1.5 equivalents. The interaction of hydrazine **48** with CDI under the depicted condition (Scheme 8) [49] gave oxadiazole **59** in 74% yield.



Reagents and conditions: (i) $\text{MeSO}_3\text{SiMe}_3$, MeCN, r.t. 15 min; (ii) $\text{SC}(\text{NH}_2)_2$, I₂, EtOH, 12 h, Δ .
Scheme 7. Synthesis of di- and trinorlabdane compounds with 2-amino-1,3-thiazole unit [46].



Reagents and conditions: (i) TMTD, DMF, 90°C, 1.5 h;
(ii) CDI, Et₃O, THF, 0°C, 3 h; (iii) RBr, Et₃N, Me₂CO, r.t., 3 h.
Scheme 8. Synthesis of tetranorlabdane 1,3,4-oxadiazole and 1,3,4-thiadiazole [48].

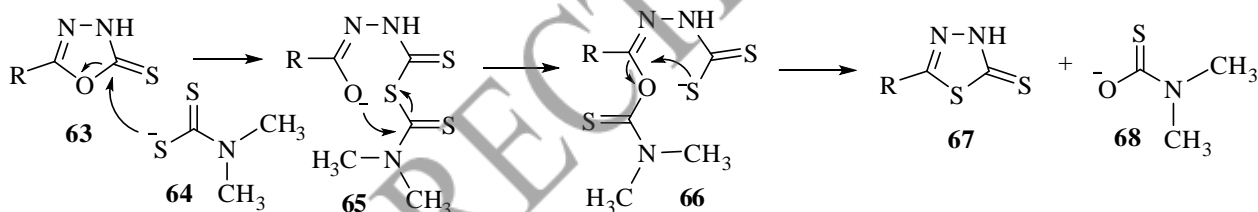
In continuation, hybrid compounds **57-59** were alkylated with bromoacetophenone ($R = -CH_2-C_6H_5$) under specified conditions yielding derivatives **60** (80%), **61** (91%), and **62** (85%). In addition to spectral data, the structures of oxadiazole **57** and thiadiazole **62** were confirmed by single-crystal XRD.

Boscheli, D.H. *et al.* mentioned that formation of thiadiazole **58** was surprising, still they presented the mechanism of oxadiazole cycle **63** conversion into thiadiazole cycle **67** (Scheme 9) [49]. As a result of acetohydrazide **48** interaction with TMTD, the *N,N*-dimethyldithiocarbamate ion **64** was formed. That ion attacks the oxadiazole cycle **63** causing its opening, and then two nucleophilic attacks follow in intermediates **65** and **66**, which leads to the formation of thiadiazole cycle **67** by elimination of the *N,N*-dimethylthiocarbamate ion **68**.

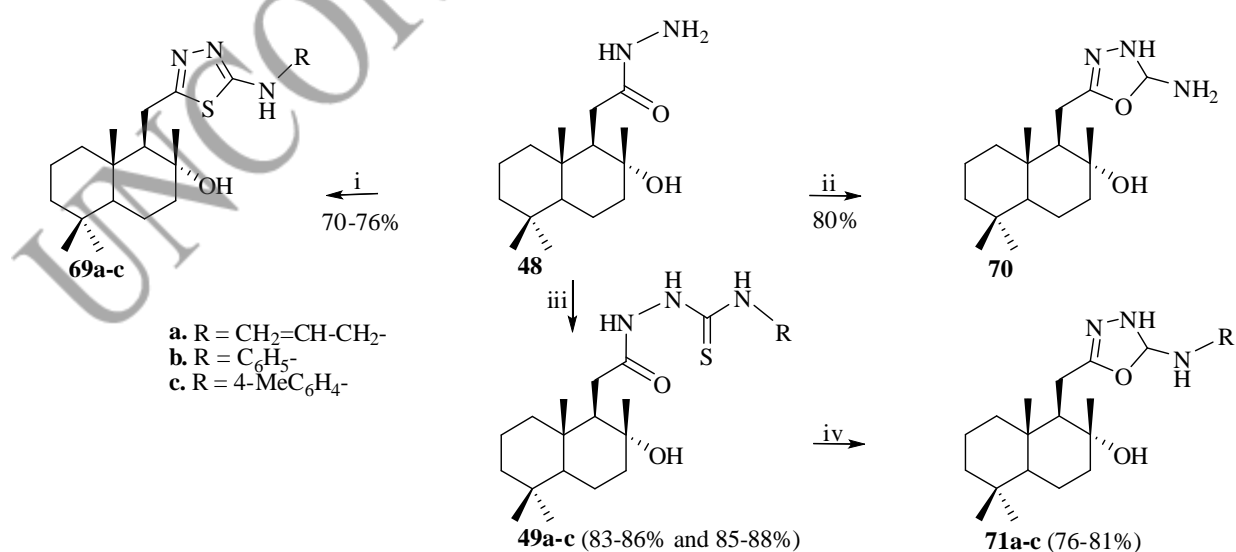
The syntheses of tetranorlabdane 2-aminosubstituted 1,3,4-thiadiazoles **69a-c** and 1,3,4-oxadiazoles **71a-c** were performed starting from hydrazine **48** [48]. Its interaction with CNBr in aqueous dioxane led to unsubstituted 2-amino-

1,3,4-oxadiazole **70** in 80% yield. The reaction of compound **48** with isothiocyanates in the presence of triethylamine (Et_3N) in water gave substituted 2-amino-1,3,4-thiadiazoles **69a-c** in 70-76% yields. The same transformation performed under slightly different conditions ($EtOH$, r.t. or MW) yielded intermediate hydrazinecarbothioamides **49a-c** (83-86% or 85-88%) which, after treatment with *N,N'*-dicyclohexylcarbodiimide, formed substituted 2-amino-1,3,4-oxadiazoles **71a-c** (Scheme 10).

Further, the synthesis of a series of new tetranorlabdane 2-functionalized 1,3,4-oxadiazoles **74-77** and 2-functionalized 1,3,4-thiadiazoles **78a,b** was performed based on the hydrazide of $\Delta^{8,9}$ -bicyclohomofarnesenic acid **72** (Scheme 11) [50]. The 2-amino substituted oxadiazoles **74a,b** were obtained from hydrazide **72** in two steps with 40-64% overall yields. One-step interactions of hydrazide **72** with CNBr led to 2-amino-1,3,4-oxadiazole **75** (91%), with CDI - to 2-keto-1,3,4-oxadiazole **76** (92%), with TMTD - to 2-thio-1,3,4-oxadiazole **77** (70%), and with RNCS - to 2-amino substituted thiadiazoles **78a,b** (75 and 72%).



Scheme 9. Mechanism of conversion of oxadiazole **63** cycle into thiadiazole **67** [48].

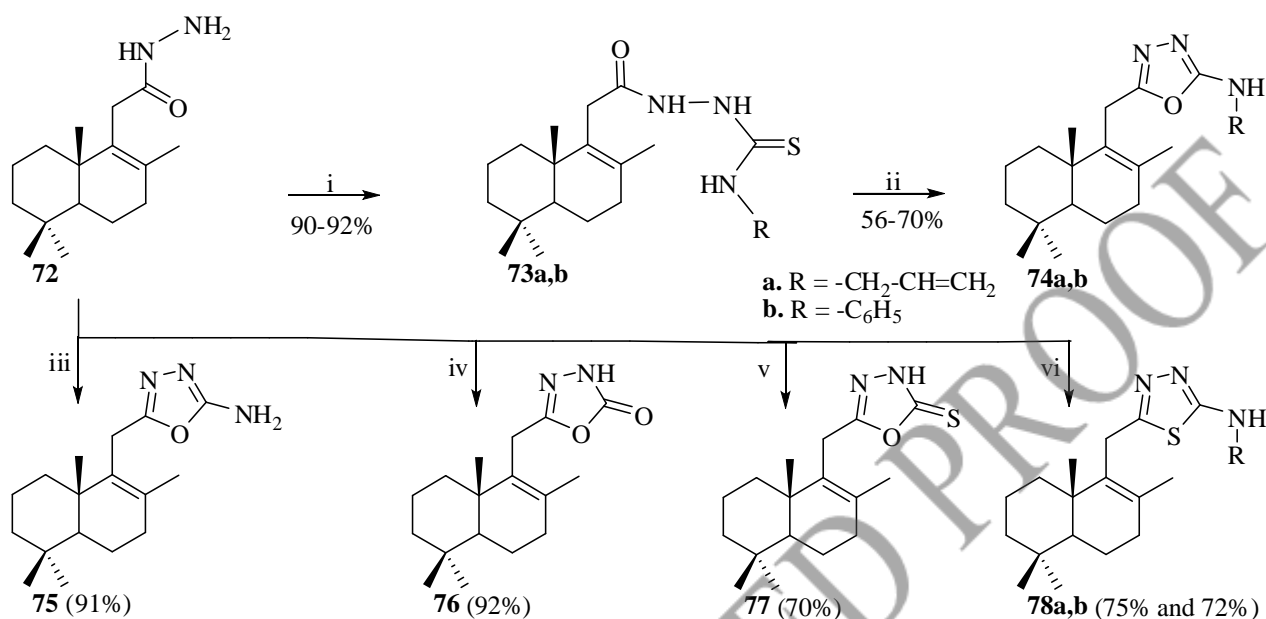


Reagents and conditions: (i) RNCS, Et_3N , Δ , 18 h; (ii) CNBr, $NaHCO_3$, dioxane (aq.), r.t., 1 h; (iii) RNCS, $EtOH$, r.t., 4-5 h or MW, 5 min; (iv) DCC, Me_2CO , $MeOH$, Δ , 5 h.

Scheme 10. Synthesis of tetranorlabdane compounds with unsubstituted and substituted 2-amino-1,3,4-oxadiazole and 2-amino-1,3,4-thiadiazole units [48].

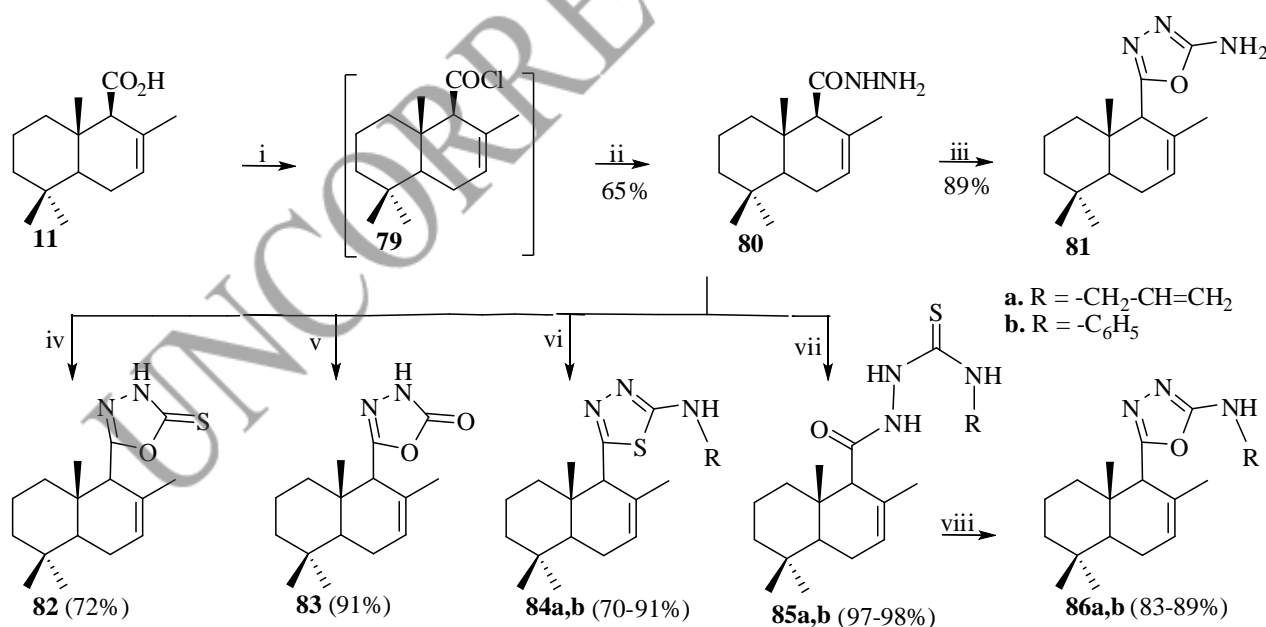
Aricu, A. *et al.* applied the same strategy for the synthesis of new pentanorlabdane 2-functionalized 1, 3,4-oxadiazoles **81-83**, **86a,b** and 1,3,4-thiadiazoles **84a,b** from

drimenic acid **11** via its chloranhydride **79** and hydrazide **80**, which led to the desired compounds in depicted yields (Scheme 12) [50].



Reagents and conditions: (i) RNCS, EtOH, 20°C, 4-5 h; (ii) DCC, Me₂CO, MeOH, Δ, 5 h; (iii) CNBr, NaHCO₃, dioxane (aq.), r.t., 5 h; (iv) CDI, Et₃N, THF, 0°C, 5 h; (v) TMTD, DMF, 90°C, 1.5 h; (vi) RNCS, Et₃N, H₂O, Δ, 20 h.

Scheme 11. Synthesis of tetranorlabdane compounds with 2-functionalized 1,3,4-oxadiazole and 1,3,4-thiadiazole units [50].



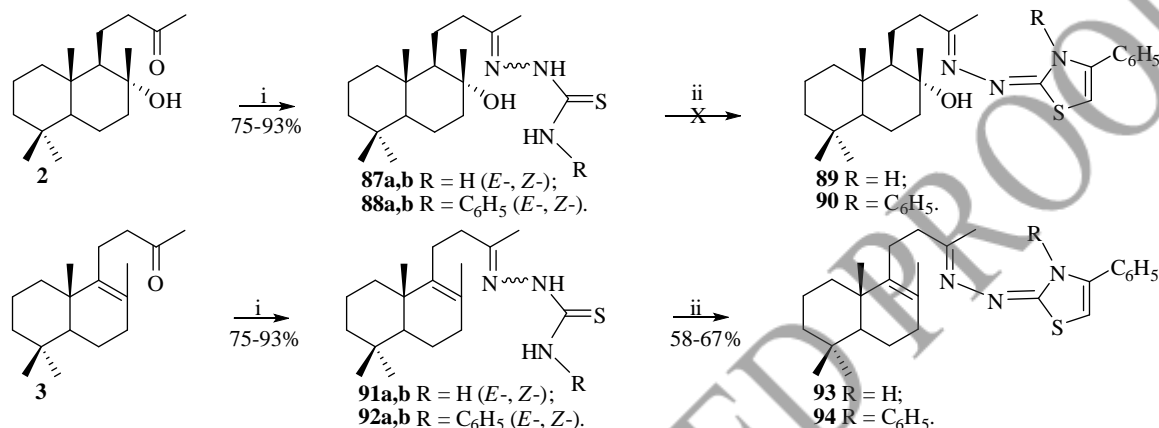
Reagents and conditions: (i) (COCl)₂, C₆H₆, 20°C, 1 h, Δ, 1 h; (ii) N₂H₄·H₂O, CDM, 20°C, 10 h; (iii) CNBr, NaHCO₃, dioxane (aq.), r.t., 5 h; (iv) TMTD, DMF, 90°C, 1.5 h; (v) CDI, Et₃N, THF, 0°C, 5 h; (vi) RNCS, Et₃N, H₂O, Δ, 20 h; (vii) RNCS, EtOH, 20°C, 4-5 h; (viii) DCC, Me₂CO, CH₃OH, Δ, 10 h.

Scheme 12. Synthesis of pentanorlabdane compounds with 2-functionalized 1,3,4-oxadiazole and 1,3,4-thiadiazole units [50].

Aricu, A. *et al.* developed the synthesis of a large series of norlabdane compounds bearing thiosemicarbazone fragment or 1,3-thiazole cycle [51]. For this, a general procedure that included the interaction of ketones **2**, **3**, **5-7**, **10**, and **12** with thiosemicarbazide or 4-phenylthiosemicarbazide was used [52]. Under those conditions, ketones **2** and **3** gave dinorlabdane thiosemicarbazones **87a,b**, **88a,b** and **91a,b**, and **92a,b**, each as mixture of *E/Z* stereoisomers (Scheme 13). The following interaction of thiosemicarbazones **91a,b** and

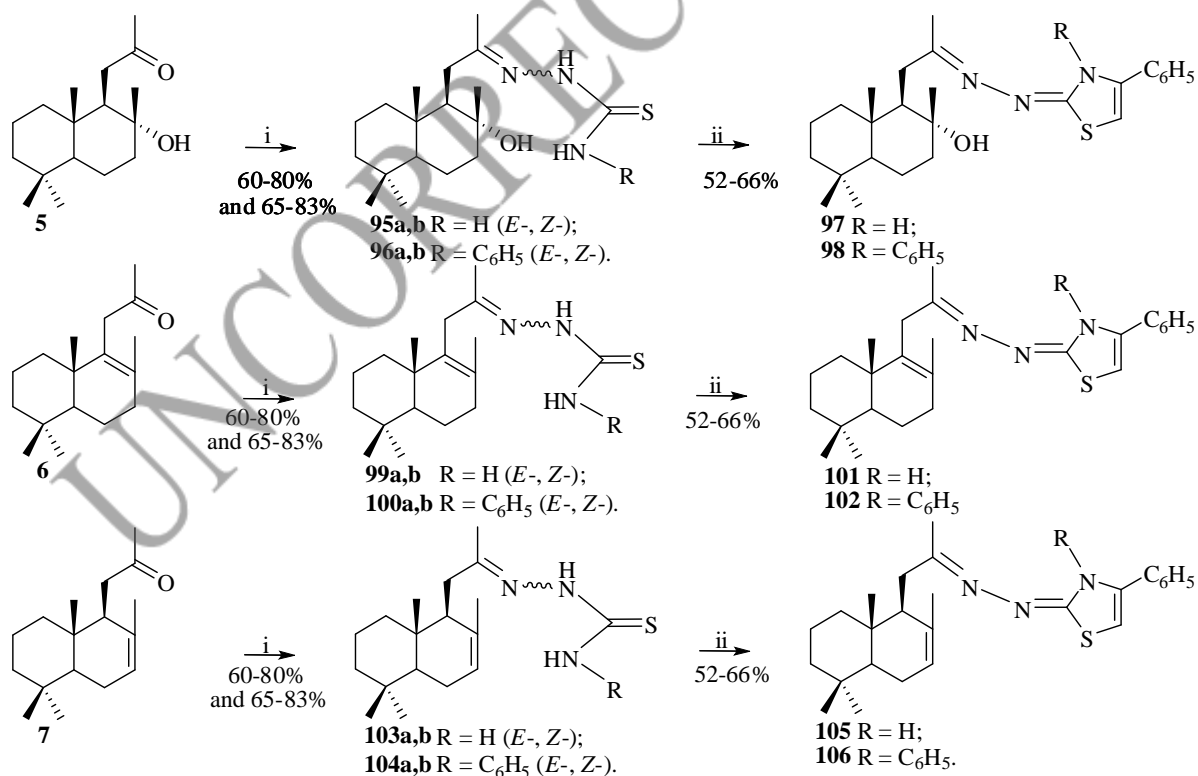
92a,b with 2-bromoacetophenone led to the target dinorlabdane compounds bearing 1,3-thiazole units **93** and **94** in 58-67% overall yields, but no reaction occurred in case of thiosemicarbazones **87a,b** and **88a,b**.

Using the same method, the mixtures of trinorlabdane (*E/Z*) thiosemicarbazones **95a,b-96a,b**, **99a,b-100a,b** and **103a,b-104a,b** were obtained from ketones **5-7** and converted without separation into desired trinorterpeno-1,3-thiazole hybrids **97**, **98**, **101**, **102**, **105**, and **106** in 31-55% overall yields (Scheme 14) [51].



Reagents and conditions: (i) $\text{NH}_2\text{NHCSNH}_2$ or $\text{NH}_2\text{NHCSNHC}_6\text{H}_5$, EtOH, 8-24 h, 60-80°C;
(ii) $\text{C}_6\text{H}_5\text{COCH}_2\text{Br}$, EtOH, 8-14 h, 20°C.

Scheme 13. Synthesis of dinorlabdane compounds containing thiosemicarbazone and 1,3-thiazole fragments [51].



Reagents and conditions: (i) $\text{NH}_2\text{NHCSNH}_2$ or $\text{NH}_2\text{NHCSNHC}_6\text{H}_5$, EtOH, 8-24 h, 60-80°C;
(ii) $\text{C}_6\text{H}_5\text{COCH}_2\text{Br}$, EtOH, 8-14 h, r.t..

Scheme 14. Synthesis of trinorlabdane compounds with thiosemicarbazone and 1,3-thiazole fragments [51].

Further, the known ketoester **10** and drimenone **12** [34] were used as starting materials for preparation of tetra- and pentanorlabdane thiosemicarbazones **107**, **108**, **111**, and **112** and corresponding 1,3-thiazoles **109**, **110**, **113**, and **114** (Scheme 15) by the method mentioned in [51]. In contrast to di- and trinorlabdane compounds presented in Schemes 13 and 14, the overall yields of the final tetra- and pentanorlabdane compounds were higher (57-74%).

Evaluation of antimicrobial activity of norlabdane heterocyclic hybrid compounds

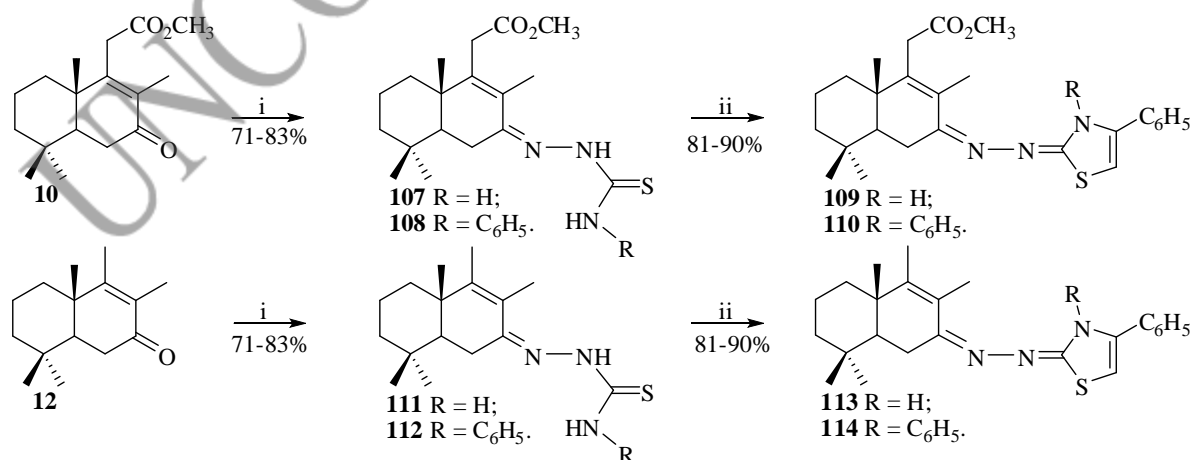
The majority of reported compounds were screened *in vitro* for their antimicrobial activity against pure cultures of fungi and bacteria.

Applying the agar diffusion assay [53] and using such reference drugs as ampicillin, chloramphenicol, and nystatin, Mangalagiu, I.I. *et al.* evaluated the *in vitro* antibacterial and antifungal activity of the newly synthesized compounds (Scheme 1 and 2) against strains of gram-positive (*Staphylococcus aureus* ATCC 25923, *Sarcina lutea* ATCC 9341, *Bacillus cereus* ATCC 14579, *B. subtilis* ATCC), gram-negative (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853) bacteria and three species of fungi (*Candida albicans* ATCC 10231, *C. glabrata* ATCC MYA 2950, *C. sake* ATCC) [38]. The most active of them proved to be the pyrimidine derivatives **16a,c**, both inhibiting the growth of five bacterial strains, except *P. aeruginosa*, with a 7-19 mm diameter of the inhibition zone. The pyrazine derivative **16b** showed an activity comparable to that of the no-diazine compound **19** against two strains of gram-positive bacteria (*S. aureus* and *B. cereus*), with an inhibition zone diameter of 10-19 mm, and to

bis-acylamide **17**, which inhibited only *S. aureus* species (10 mm). None of the mentioned compounds showed any antifungal activity. Kuchkova *et al.* also reported the structure-activity relationship (SAR) correlation concerning antimicrobial activity of the synthesized compounds [38].

Contrary to expectations, the tetranorlabdane pyridazinone hybrid compound **31**, in contrast to bromide **30** (MIC= 2.0 and 2.5 µg/mL) and dimer **32** (MIC= 3.5 and 4.0 µg/mL) (Scheme 4), did not show any antimicrobial activity against any of the tested species of fungi (*Aspergillus niger*, *Penicillium frequentans*, *Alternaria alternata*) or against both gram-negative (*Pseudomonas aeruginosa*) and gram-positive (*Bacillus polymyxa*) bacteria strains [42].

Some of the pentanorlandane pyridazinone hybrids described by Aricu, A. *et al.* showed good antimicrobial activity against five fungi species (*Aspergillus flavus*, *Fusarium solani*, *Penicillium chrysogenum*, *P. frequentans*, and *Alternaria alternata*) and against both gram-positive (*Bacillus polymyxa*) and gram-negative (*Pseudomonas aeruginosa*) bacteria [35]. The *in vitro* antimicrobial assessments performed according to procedures previously described [54,55] revealed good antifungal activity of monosubstituted hybrid **45** at MIC= $15 \cdot 10^{-1}$ µg/mL and high antifungal and antibacterial activities of disubstituted hybrid **47** at MIC= $5 \cdot 10^{-3}$ and $3.2 \cdot 10^{-2}$ µg/mL, respectively, compared to the reference compounds Caspofungin and Kanamycin (Figure 6). The antifungal and antibacterial activities of the disubstituted pentanorlabdane pyridazinone hybrid compound **47** [35] have been patented [56].



Reagents and conditions: (i) $\text{NH}_2\text{NHCSNH}_2$ or $\text{NH}_2\text{NHCSNHC}_6\text{H}_5$, EtOH, 8-24 h;
(ii) $\text{C}_6\text{H}_5\text{COCH}_2\text{Br}$, EtOH, 4-6 h, r.t.

Scheme 15. Synthesis of tetra- and pentanorlabdane compounds with thiosemicarbazone and 1,3-thiazole fragments [51].

Both tetranorlabdane hydrazine carbothioamide **49c** and *N*-substituted 1,2,4-triazole **50d** also manifested a comparatively high antimicrobial activity on the same microbe species (Scheme 5) as reported by D'Ambrosio, M. *et al.* [44]. Both compounds showed promising nonselective antifungal (MIC= 0.125 and $9.4 \cdot 10^{-2}$ $\mu\text{g/mL}$, respectively) and antibacterial (MIC= $6.4 \cdot 10^{-2}$ and $4.7 \cdot 10^{-2}$ $\mu\text{g/mL}$, respectively) activities, which are much higher than that of the reference compounds Caspofung and Kanamycin.

Compounds **49c** and **50d** were tested also for cytotoxicity on human ovarian carcinoma cells A2780 and A2780cis, as well as on noncancerous human embryonic kidney cells HEK293, and they showed the activity at IC₅₀ (9-11 mM, 14-15 mM and 18-17 mM, respectively). Those values are much smaller compared to those of Cisplatin (IC₅₀= 0.6, 11.0 and 4.3 mM).

The tetranorlabdane 1,3,4-oxadiazoles and 1,3,4-thiadiazoles (Schemes 7 and 9) reported by Aricu, A. *et al.* [48] were tested against fungal species *Aspergillus niger*, *Fusarium solani*, *Penicillium crysogenum*, *P. frequentans*, and *Alternaria alternata* and bacteria strains *Pseudomonas aeruginosa* and *Bacillus polymyxa*. Compounds **58** (Scheme 7) and **69a** (Scheme 9) showed high antifungal activity at MIC= $3.2 \cdot 10^{-2}$ and 0.25 $\mu\text{g/mL}$, respectively, and antibacterial activity at MIC= $9.4 \cdot 10^{-2}$ and 0.5 $\mu\text{g/mL}$, respectively. The activity of the reported compounds is much higher than that of the used standards Caspofungin and Kanamycin. The intellectual property rights on high antifungal and antibacterial activities of the tetranorlabdane 1,3,4-thiadiazole **58** were confirmed by the respective patent [57]. The same authors [50] reported some additional results of the biological activity assessment on the mentioned above microbial species of tetra- and pentanorlabdane oxadiazoles and thiadiazoles presented in Schemes 10 and 11. According to them, tetranorlabdane oxadiazole **76** possess higher antifungal and antibacterial activities (MIC= 0.125 and 2.5 $\mu\text{g/mL}$) than the standards, and pentanorlabdane hydrazinecarbothioamide showed moderate activities at MIC= 2.0 and 48 $\mu\text{g/mL}$.

In another paper, Aricu, A. *et al.* [51] reported the results of the biological investigation of the series of di-, tri-, tetra- and pentanorlabdane thiosemicarbazones and 1,3-thiazoles presented in Schemes 12-14. Compounds **88a,b** and **95a,b** were tested against the same species as mentioned in [48, 50] and showed both antifungal or

antibacterial activities, a bit higher than those of the standards at MIC= 0.25 and 0.19 $\mu\text{g/mL}$, and MIC= 4.0 and 3.0 $\mu\text{g/mL}$, respectively. The series of the patented bioactive norlabdane heterocyclic compounds can be completed by trinorlabdane thiosemicarbazones **95a,b** [51] drawn on Scheme 11, which have shown a promising antifungal activity. These mixtures of isomers were claimed as antifungal agents in [60].

As a result of the microbiological evaluation, it was established that substituted 1,2,4-triazole **20** and *N*-aminocarbazole **21** hybrids depicted in Scheme 3 possess obvious growth stimulating properties [39]. Both compounds were used as components of nutrient media for the cultivation of *Nostoc linckia* cyanobacterium. Those compounds substantially increase the antioxidant activity of the cyanobacterium biomass under the specified conditions, at the following concentrations for **20** (0.062–0.064 g/L) and **21** (0.060–0.062 g/L), respectively [58,59]. The antimicrobial assessments of the reported norlabdane heterocyclic hybrids frequently proved their antifungal and antibacterial activities. Those data were reported elsewhere and also claimed by the author and colleagues. All those mentioned compounds are of a real interest for medicine and agriculture as antifungal and antibacterial agents.

Conclusions

The available scientific data on a new direction of research in the chemistry of labdane diol (-)-sclareol, namely, the synthesis of norlabdane heterocyclic hybrids and some of its intermediates, published from 2013 to the present time, are reviewed.

The analysed publications pointed out a new class of biocompatible and biologically active terpeno-heterocyclic hybrids and led to the synthesis of numerous series of norlabdane compounds with hydrazide or thiosemicarbazonic moieties and diazine, triazole, carbazolic, thiazole, oxadiazole or thiadiazole heterocyclic structural units.

Many of the mentioned compounds showed excellent *in vitro* antimicrobial activity on several species of fungi and two bacterial strains, and two of them – a moderate cytotoxic activity. It should be noted here that the preparation methods and the properties of biologically active hybrids have been patented.

Based on the above, it can be concluded that (-)-sclareol and the heterocyclic hybrid compounds derived from it are a promising object of research.

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