SYNTHESIS OF NEW NITROGEN-CONTAINING DRIMANE AND HOMODRIMANE SESQUITERPENOIDS FROM SCLAREOLIDE

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Abstract. The synthesis of new nitrogen-containing drimane and homodrimane sesquiterpenoids in cycle B is reported. A comparative study of the microwave (MW) assisted synthesis of drimenone versus classical conditions has been done. The drimanic and homodrimanic oximes were prepared on the base of ketones derived from commercially available sclareolide. The drimanic amine was obtained by reduction of corresponding oxime with $LiAlH_4$. The structure of novel compounds was confirmed using IR, ^1H and ^{13}C NMR analyses.

Keywords: synthesis, sesquiterpenoids, oxime, reduction, 7-amino-drim-8(9)-ene.

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Introduction

Drimane and homodrimane sesquiterpenoids are classes of natural products with a broad spectrum of biological activities, including antifungal, antibacterial, antiviral, cytotoxic, antifeedant, and others [1]. The presence of nitrogen in a molecule is usually accompanied either by the appearance of new activities or by intensification of the original activity characteristic for the native terpenoids.

So far, some drimanic and homodrimanic amines have been synthesized. Urones et al. [2] prepared dihydroxyamine **1** and its derivatives, Barrero et al. [3] – hydroxylamine **2** and products of amino and/or hydroxy group derivatization (Figure 1). Later, 11-aminodrim-7-ene **3** was synthesized from drimenol **4** [4-6]. Recently, 12-amino-11-dihomodrim-8-ol **5** and products **6** and **7** of its dehydration have been synthesized from sclareolide **8** [7] and 13-amino-14,15-dinorlabd-8(9)-ene **9** from sclareol **10** [8] (Figure 1).

In scientific literature there are few examples about syntheses of cycle B functionalized drimanic and homodrimanic amines [2]. Thus, the aim of this research is the synthesis of drimanic and homodrimanic compounds with nitrogen containing functional groups in cycle B.

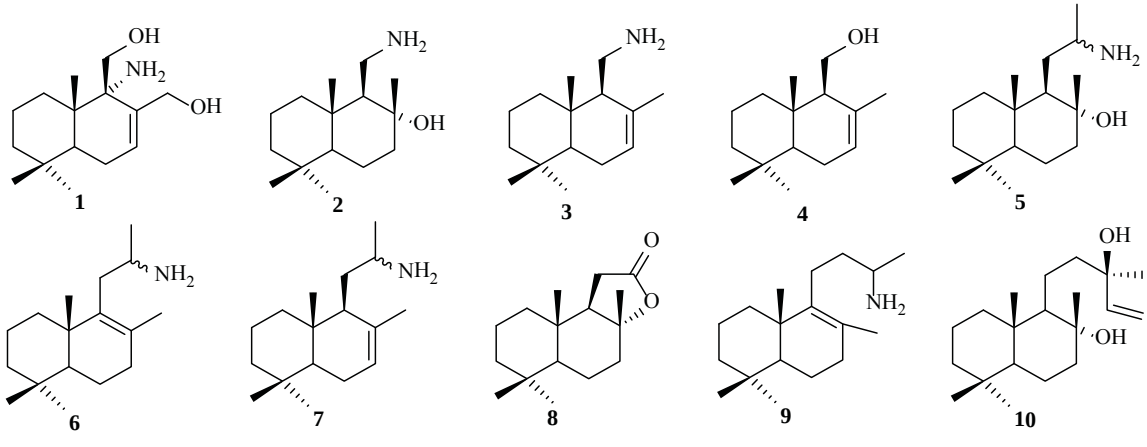


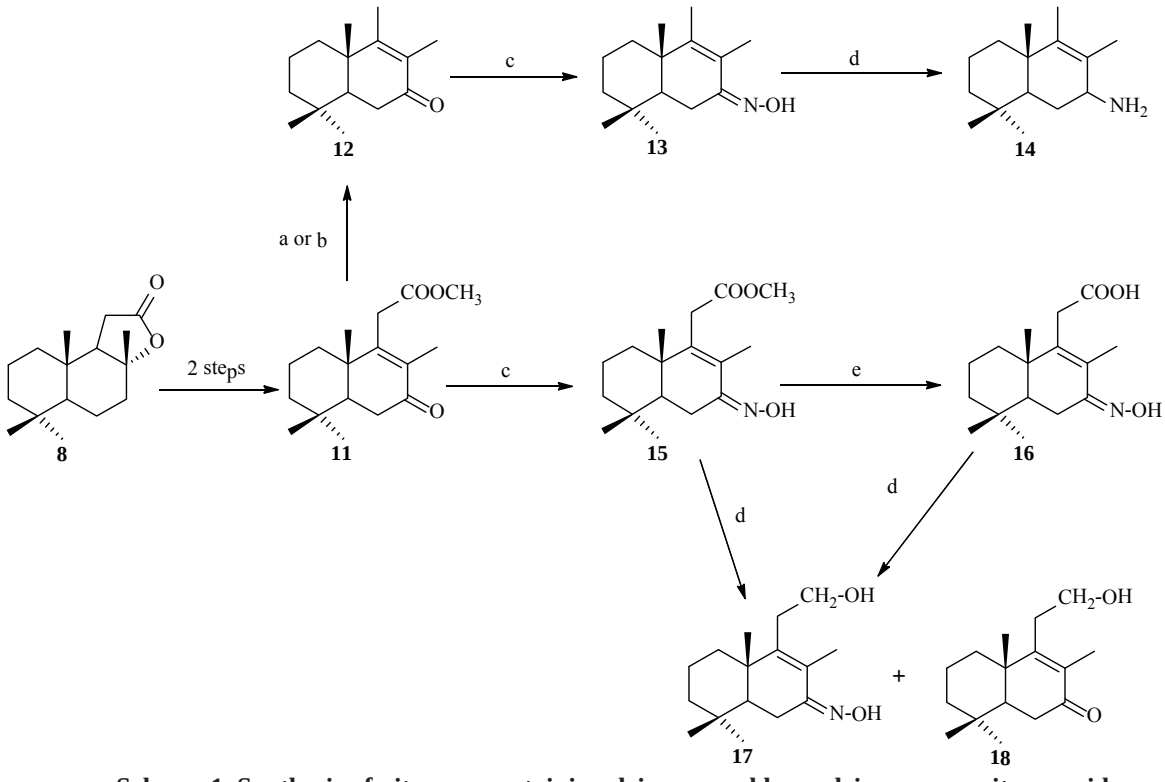
Figure 1. Norlabdanic amines and their precursors.

Results and discussion

Herein we report the preparation of new nitrogen-containing drimane and homodrimane sesquiterpenoids in cycle B (Scheme 1).

As starting material for the synthesis of the reported compounds methyl 7-oxo-13,14,15,16-tetranorlabd-8-en-12-oate **11** was used, obtained in two steps in 76% overall yield from the commercially available sclareolide **8** [9] (Scheme 1). Drim-8-en-7-one **12** can be obtained from ketoester **11** by known method as depicted in Scheme 1(a) as in [10]. We prepared compound **12** from the same ester **11** using MW irradiation (Scheme 1(b)) in the same 98% yield but two times faster.

Drimene oxime **13** was prepared by the reaction of drim-8-en-7-one **12** with hydroxylamine hydrochloride in a mixture of ethanol:pyridine (1:1) in 98% yield as in [11].



Scheme 1. Synthesis of nitrogen-containing drimane and homodrimane sesquiterpenoids.

Reagents and conditions: a) KOH, EtOH, reflux, 3h, 98%; b) KOH, EtOH, MW, 1.5h, 98%.; c) $NH_2OH{\cdot}HCl$, EtOH, Py, 24h, 96-98%; d) $LiAlH_4$, THF, 5h-24h, 51-60%; e) KOH, MeOH, 95%.

The desired product, 7-amino-drim-8(9)-ene **14**, was obtained in 51% yield by refluxing oxime **13** with $LiAlH_4$ in anhydrous THF as in [8]. The structure of compound **14** was confirmed by IR, ^1H, and ^{13}C NMR data.

In another case, ketoester **11** was treated with hydroxylamine hydrochloride in a mixture of ethanol:pyridine (1:1), giving ester oxime **15** described in [11], which was subsequently saponificated with KOH in methanol into the oxime **16** in 95% yield.

Oximes **15** and **16** were reduced with $LiAlH_4$ in anhydrous THF as in [8], giving two compounds: hydroxy oxime **17**, in 55% and 60% yield and hydroxy ketone **18**, in 10% and 12% yield. The structure of compound **17** was confirmed by IR, ^1H, and ^{13}C NMR data.

Several attempts to reduce oximic functions from molecules of compounds **15** and **16** were unsuccessful, probably because of steric impediments which appear in the molecules of the mentioned homodrimanic oximes **15** and **16**, but not in the molecules of drimanes.

Conclusion

Novel nitrogen-containing drimane and homodrimane sesquiterpenoids in cycle B were synthesized. They are of scientific interest as compounds with potential biological activity.

Experimental

General experimental procedure

Melting points (m.p.) were taken on a Boetius hot stage apparatus. Optical rotations were determined on a Jasco DIP 370 polarimeter with a 1dm microcell, in $CHCl_3$. IR spectra were obtained on Spectrum-100FT-IR spectrometer (Perkin-Elmer) with ATR technique.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Avance DRX 400 spectrometer. Chemical shifts are given in ppm in δ scale and referred to $CHCl_3$ (δ_H at 7.26 ppm) and to $CDCl_3$ (δ_C 77.00 ppm), respectively. Coupling constants (*J*) are reported in Hertz (Hz). The 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 Bruker Corporation. Carbon substitution degrees were established by the DEPT pulse sequence.

The microwave assisted (MW) transformations were carried out using a monomode reactor (800W, STAR SYSTEM-2, under a constant irradiation power, but at varying temperature. The best results were obtained when 30% of the full power of the magnetron was used.

For analytical TLC, Merck silica gel plates 60G in 0.25 mm layers were used. The TLC plates were sprayed with conc. H_2SO_4 and heated at 80°C. Column chromatography was carried out on Across silica gel (60–200 mesh) using petroleum ether (PE) (b.p. 40–60°C) and the gradient mixture of PE and EtOAc or the gradient mixture of methanol and $CHCl_3$.

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 a reduced pressure.

General procedure of drimenone 12 preparation under microwave irradiation

Caution! It is hazardous to rapidly heat reactions under microwave irradiation. Therefore, caution should be exercised when conducting reactions of this type.

A solution of ketoester **11** (1g, 3.6 mmol) and potassium hydroxide (4.17g, 74.3 mmol) in ethanol (36 mL) was prepared as described in [10] and placed in the reaction vessel (quartz). The tube was then placed in the microwave cell and irradiated at 240 W for 1.5 h. Once the heating cycle was complete, the tube was cooled to ambient temperature and removed from the reactor. The 2/3 of the solvent volume were removed under a reduced pressure, then the residue was diluted with water (15 mL), extracted with Et_2O (3 x 10 mL), and the organic layer was washed with water (2 x 20 mL) and dried. After the solvent removal, drim-8(9)-en-7-one **12** (0.776 mg, 98 %) was obtained, as white crystals m.p. 51-52°C. The spectral data of compound **12** are in accordance with those mentioned in [10].

General procedure of drimanic and homodrimanic oximes preparation

A solution of **11** (0.57 g, 2.5 mmol), or **12** (0.7 g, 2.5 mmol) in EtOH (5 mL) and Py (5 mL) was treated with $NH_2OH{\cdot}HCl$ (0.2 g). The resulted mixture was stirred for 24 h at room temperature, then diluted with water (20 mL) and extracted with Et_2O (3 x 10 mL). The organic layer was washed with 10% HCl (10 mL), $NaHCO_3$ solution (10 mL) and water (15 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent removal under a reduced pressure as in [11] led to oximes **13** (0.59 g, 98%) or **15** (0.72 g, 98%), as white solids.

7-Hydroxyimino-drim-8(9)-ene (**13**), 98% yield, as a white solid (EtOH), m.p. 183-184 °C, $[\alpha]_D^{20}$ = -35.5° (*c* 13.5, $CHCl_3$). IR (ATR)ν : 3257, 2930, 1626, 1614, 1439, 950, 928, 772 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, ppm): *δ* 9.85 (1H, s, N-OH); 1.37 (1H, d, *J* 14.0 Hz, H-5); 1.86 (3H, s, H-12); 1.81 (3H, s, H-13), 0.98 (9H, s, H-13, H-14, H-15). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): *δ* 158.44 (C-7), 151.13 (C-9), 122.36 (C-8), 48.26 (C-5), 41.73 (C-3), 39.02 (C-10), 36.60 (C-1), 33.31 (C-4), 32.76 (C-14), 21.25 (C-13), 20.90 (C-6), 18.84 (C-2), 17.78 (C-15), 13.78 (C-11), 13.25 (C-12).

Methyl-7-hydroxyimino-homodrim-8(9)-en-12-oate (**15)**, 98% yield, as a white solid (EtOH), m.p. 130-131˚C, $[\alpha]_D^{20}$ = +27.9° (*c* 8.5, $CHCl_3$). IR (ATR)ν : 3257, 2928, 1739, 1725, 1629, 1435, 1322, 1247, 1161, 955, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): *δ* 9.39 (1H, s, N-OH); 3.29 (1H, d, *J* 16.8 Hz, H-11); 3.19 (1H, d, *J* 16.8 Hz, H-11); 1.44 (1H, d, *J* 14.4 Hz, H-5); 3.69 (3H, s, CO_2Me); 1.82 (3H, s, H-13), 0.95 (9H, s, H-14, H-15, H-16). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): *δ* 171.93 (C-12), 158.17 (C-7),146.57 (C-9), 127.10 (C-8), 51.99 (C-17), 48.12 (C-5), 41.54 (C-3), 39.21 (C-10), 35.18 (C-1), 33.60 (C-11), 33.31 (C-4), 32.66 (C-15), 21.27 (C-14), 20.83 (C-6), 18.71 (C-2), 18.38 (C-16), 13.59 (C-13).

Synthesis of 7-amino-drim-8(9)-ene (14). A solution of oxime **13** (0.5 g, 2.1 mmol) in anhydrous THF (40 mL) was treated with $LiAlH_4$ (0.84 g). The resulted mixture was refluxed and stirred for 10 h, then it was diluted with water (20 mL), and treated dropwise with HCl (10%, 20 mL) until the acidic level of pH is reached. The aqueous layer was extracted with Et_2O (2x 20 mL), neutralized with the aqueous saturated Na_2CO_3 solution (20 mL) and extracted with EtOAc (3 x 15 mL). The organic layer was washed with water (20 mL) and dried. After the solvent removal, the crude product (0.35 g) was purified by column chromatography on silica gel (10 g, eluent: methanol/$CHCl_3$ 1:9) to give 7-amino-drim-8(9)-ene (8) (0.24 g, 51%), as an oil, $[\alpha]_D^{20}$ = +17.6° (*c* 2.7, $CHCl_3$).

IR (ATR)ν : 3279, 2924, 1569, 1459, 1442, 1383, 1367 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz, ppm): *δ* 3.16 (1H, s, H-7); 2.07 (2H, s, NH_2); 1.59 (3H, s, H-12); 1.49 (3H, s, H-11), 0.96 (3H, s, H-15), 0.86 (3H, s, H-13), 0.82 (3H, s, H-14). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): *δ* 139.17 (C-9), 127.97 (C-8), 54.40 (C-7), 50.38 (C-5), 41.53 (C-3), 38.96 (C-10), 36.89 (C-1), 33.05 (C-14), 32.95 (C-4), 30.37 (C-6), 21.50 (C-13), 19.58 (C-15), 18.93 (C-2), 16.11 (C-12), 13.14 (C-11).

Saponification of methyl 7-hydroxyimino-homodrim-8(9)-en-12-oate (**15)**. To a solution of ester oxime **15** (0.3 g, 1.02 mmol) in EtOH (10 mL) solid KOH (1.2 g) was added. The resulted reaction mixture was refluxed for 3 hrs, then 2/3 of alcohol were distilled. The remained mixture was diluted with water (10 mL) and extracted with Et_2O (3x10 mL). The organic layer was washed with water (20 mL), dried on anhydrous sodium sulfate, concentrated, and the title compound **16** (0.27g, 95% yield) was obtained, as a white solid (EtOH), m.p. 197-199°C, $[\alpha]_D^{20}$ = +7.4° (*c* 2.3, $CHCl_3$).

IR (ATR)ν : 3239, 2931, 1689, 1620, 1422, 1334, 1241, 1216, 973, 723 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz, ppm): *δ* 12.15 (1H, s, OH); 10.78 (1H, s, N-OH); 3.17 (1H, d, *J* 16.8 Hz, H-11); 3.10 (1H, d, *J* 16.8 Hz, H-11); 1.30 (1H, d, *J* 3.6 Hz, H-5); 1.72 (3H, s, H-13), 0.88 (9H, s, H-14, H-15, H-16). ^{13}C NMR

($CDCl_3$, 100 MHz, ppm): δ 172.50 (C-12), 155.54 (C-7),145.03 (C-9), 126.38 (C-8), 48.04 (C-5), 41.18 (C-3), 38.55 (C-10), 35.15 (C-1), 33.48 (C-11), 32.86 (C-4), 32.56 (C-15), 21.03 (C-14), 20.30 (C-6), 18.22 (C-2), 18.07 (C-16), 13.07 (C-13).

Reduction of methyl 7-hydroxyimino-homodrim-8(9)-en-12-oate (**15) and 7-hydroxyimino-homodrim-8(9)-en-12-oic acid (15).** A solution of oximes **15** (0.109 g, 0.37 mmol) or **16** (0.103 g, 0.36 mmol) in anhydrous THF (10 mL) was treated with $LiAlH_4$ (0.14 g). The resulted mixture was refluxed and stirred for 10 h, then it was diluted with water (10 mL), and treated dropwise with HCl (10%, 5 mL) until the acidic level of pH is reached. The aqueous layer was extracted with Et_2O (2 x 5 mL), neutralized with saturated aqueous Na_2CO_3 solution (10 mL), and extracted with EtOAc (3 x 5 mL). The organic layer was washed with water (10 mL) and dried. After the solvent removal, the crude product (305 mg and 325 mg) was purified by column chromatography on silica gel (0.070 g and 0.076 g, eluent: methanol/$CHCl_3$ 2:9) to give 7-hydroxyimino-homodrim-8(9)-en-12-ol **17** (0.054 g, 55% and 0.058 g, 60%), and 12-hydroxi-homodrim-8(9)-en-7-one **18** (0.009 g, 10% and 0.011 g, 12%), respectively.

7-hydroxyimino-homodrim-8(9)-en-12-ol **17,** as a white solid, m.p. 111-113°C, $[\alpha]_D^{20}$ = -15.07° (*c* 0.5, $CHCl_3$).

IR (ATR)ν : 3280, 2927, 1611, 1452, 1442, 1388, 1375, 1028, 955, 757 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 10.72 (1H, s, N-OH); 4.66 (1H, t, *J* 5.26 Hz OH); 1.77 (3H, s, H-13); 0.88 (6H, s, H-14, H-16), 0.87 (3H, s, H-15). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 156.08 (C-7), 148.95 (C-9), 125.34 (C-8), 60.96 (C-12), 48.50 (C-5), 41.73 (C-3), 39.00 (C-10), 36.32 (C-1), 33.45 (C-4), 33.11 (C-15), 32.81 (C-11), 21.64 (C-14), 20.83 (C-6), 18.98 (C-16), 18.85 (C-2), 13.39 (C-13).

12-hydroxy-homodrim-8(9)-en-7-one **18**, as a white solid, m.p. 97-98°C, $[\alpha]_D^{20}$ = +58.0° (*c* 0.4, $CHCl_3$).

IR (ATR)ν : 3456, 2979, 1664, 1455, 1392, 1380, 1145, 1074 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 1.78 (3H, s, H-13); 1.07 (3H, s, H-16); 0.90 (3H, s, H-14). 0.86 (3H, s, H-15), ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 200.05 (C-7), 163.59 (C-9), 131.56 (C-8), 61.28 (C-12), 50.11 (C-5), 40.61 (C-10), 41.24 (C-3), 36.14 (C-1), 35.23 (C-6), 33.11 (C-4), 32.98 (C-11), 32.45 (C-15), 21.27 (C-14), 18.87 (C-2), 18.10 (C-16), 17.75 (C-13).

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