

## Synthetic transformations of natural diterpenes. Synthesis of alkaloid-like compounds from lambertianic acid

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**Dedicated to Professor Boris Alexandrovich Trofimov on his 65<sup>th</sup> birthday**

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### Abstract

By oxidation of methyl lambertianate with potassium permanganate, the esters of 17-nor-8-keto- and 17-hydroxy-8,12-epoxy-labdadienic acids have been obtained. Reductive amination of the above carbonyl compounds and subsequent intramolecular aminomethylation of 17-nor-8(*R*)-methylamino- and 17-methylamino-labdadienoates by formaldehyde leads to the formation of novel polycyclic compounds, which are derivatives of furoazocines and furoazonines.

**Keywords:** Lambertianic acid, oxidation, reductive amination, aminomethylation

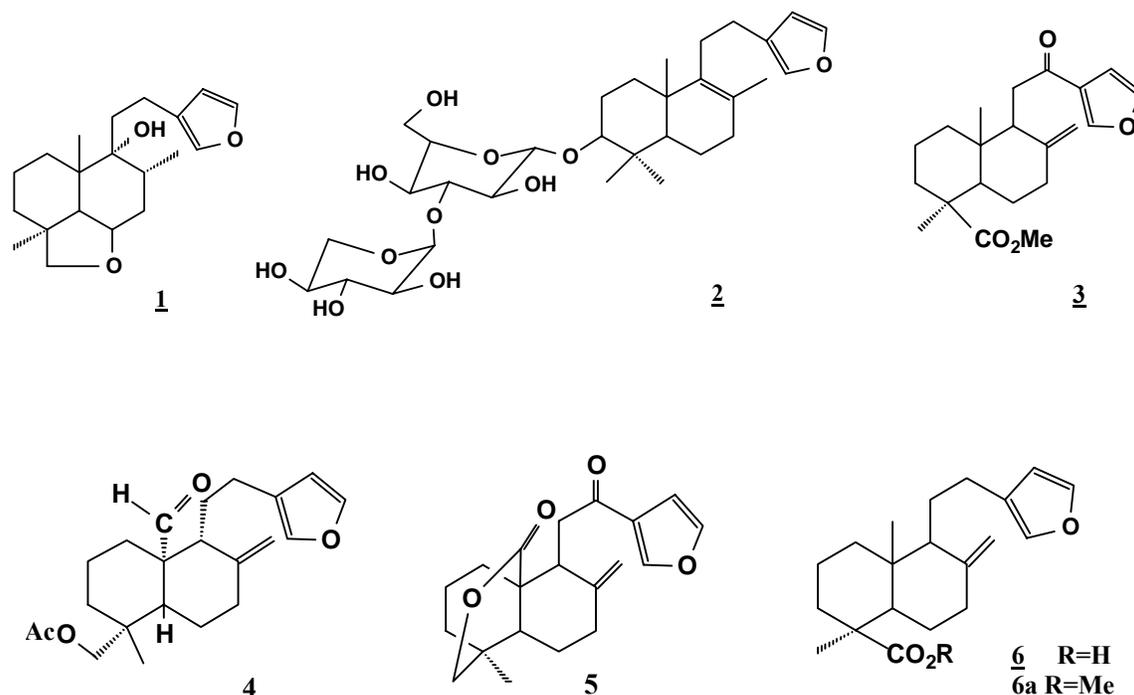
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### Introduction

Terpenoids and alkaloids containing the furan ring as a structural fragment often show valuable biological activity. The wide representation of the furanoid *labdane* diterpenes in plant materials must be noted. In this series, the origin of marubien bitter principle, marrubiin **1**, isolated from *Marrubium vulgare*, and the sweet glucoside **2**, isolated from *Salvia digitaloides*<sup>1</sup> have been considered. The ketofuran **3** is distinguished by the simplicity of its structure, is produced by the water plant *Potamogeton plotinatus* L., and has been shown to have cytotoxic action.<sup>2</sup> The Labdanoids **4** and **5**, isolated from the plant *Potamogeton malaianus*, have antiviral, antibacterial, and antitumor activities.<sup>3</sup>

In a series of articles, it has been shown that the transformation of the furan cycle was accompanied by the appearance of new activity or intensification of the original activity of the native terpenoid. Probably because of this connection, the number of examples of direct modification of furanoterpenoids has multiplied.

Our attention has been focused on lambertianic acid **6** (Figure 1), the accessible diterpene acid of the Siberian cedar, *Pinus sibirica* J. Mayr. The compound possesses neurotropic activity<sup>4</sup> and was earlier used as a precursor to biologically active compounds.<sup>5-8</sup> In the present paper we describe the transformation of lambertianic acid into polycyclic compounds of novel structural types, containing furo[3,4-*b*]azacyclo-octane and furo[3,4-*b*]azacyclononane fragments.



**Figure 1**

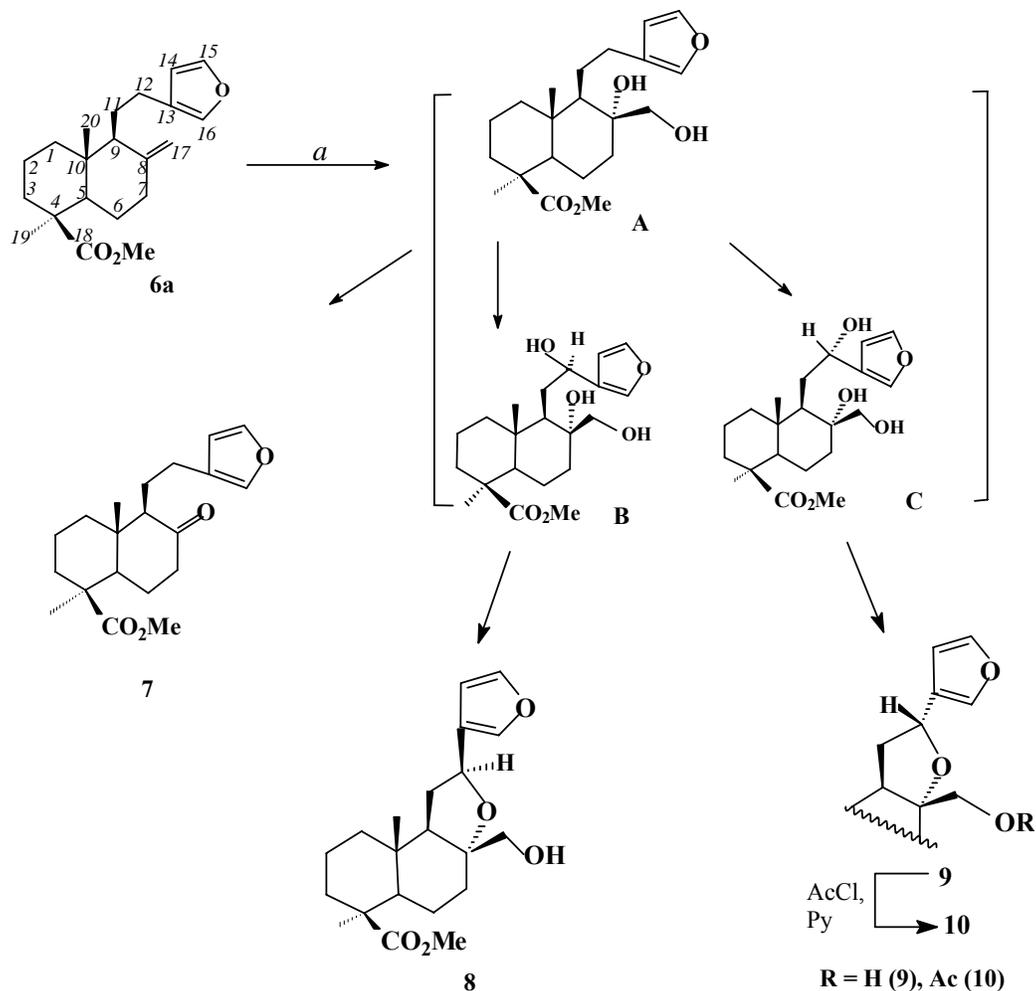
## Results and Discussion

We found that the potassium permanganate oxidation of methyl lambertianate **6a** in a two-phase system<sup>9</sup> proceeds with the formation of the ketone **7** (21%), the (8*R*,12*S*)-oxidolabdaneoids **8** (39%) and its (8*R*,12*R*)-diastereomer **9** (11%), which could be separated by column chromatography (Figure 2). The reaction proceeds in a neutral medium, which is provided by the addition of magnesium sulfate\*.

The structure of the compound **7** has been confirmed by spectroscopic data. The structure and stereochemistry of the major product, the oxide **8**, has been unambiguously established by X-ray crystallographic analysis (Figure 3). The structure and stereochemistry of the minor stereoisomeric 8,12-epoxide **9** has been corroborated from NOE difference spectra (NOESY).

\* Note that Compounds **7-16** are named in the text according to the labdane numbering depicted in Figure 2 (compound **6a**).

The assignment of the  $\beta$ -disposition of the C-17 hydroxymethyl substituent in **9** and its acetate **10** was based on the following NOE result. Irradiation of the 20-Me at  $\delta$  0.64 gave an enhancement of the diastereotopic protons at  $\delta$  3.96 and 4.36. Additional enhancements were also observed to the axial protons at H-2 and H-6, the pseudoaxial proton at H-11, and the 19-Me. Irradiation of the H-17 diastereotopic proton at  $\delta$  3.96 showed an enhancement of the second H-17, to the axial protons at H-2,6,7 and the 20-Me.

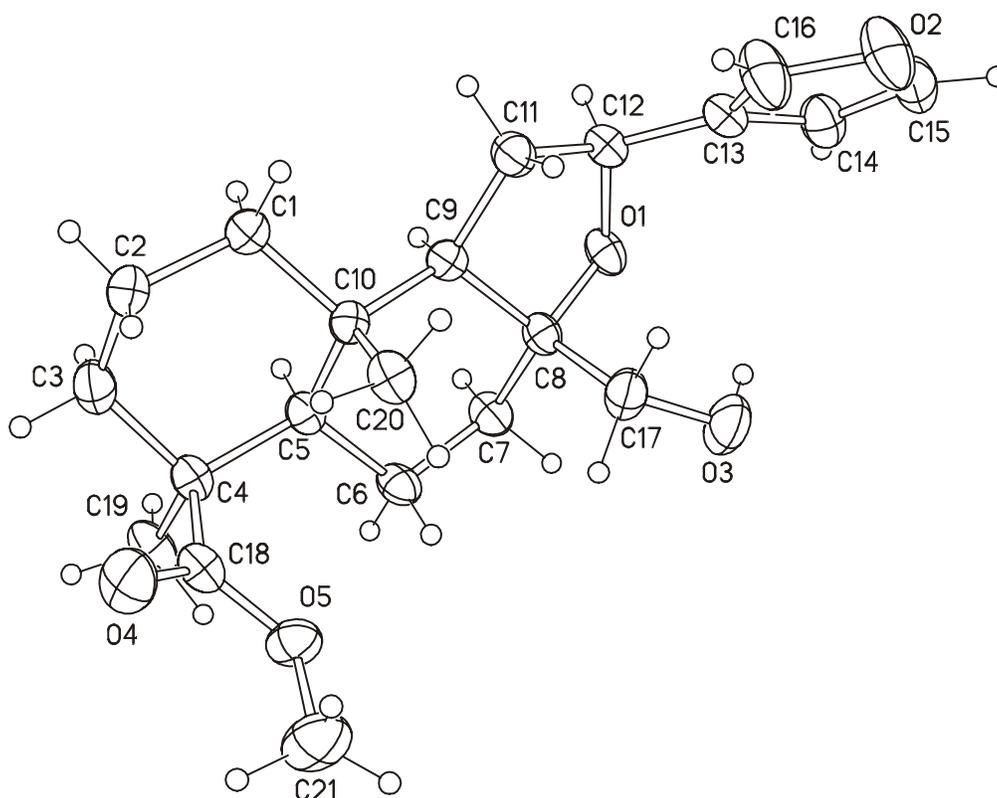


**Figure 2**

Irradiation of the H-17 diastereotopic proton  $\delta$  4.36 showed no enhancement of the H-6 axial proton but showed a strong enhancement to the H-11 pseudoaxial proton along with weaker enhancement to the 20-Me. The above results are consistent with the stereochemical assignment shown in **9,10**, thus establishing indirectly that the stereogenic center at C-12 must be 12-*S*.

As can be seen from the implemented scheme (Figure 2), the first process of the furanoterpenoid **6a** oxidation by  $\text{KMnO}_4$  was the expected double-bond hydroxylation, which proceeds mainly from the less hindered  $\alpha$ -side and leads to the glycol **A** as an intermediate. The

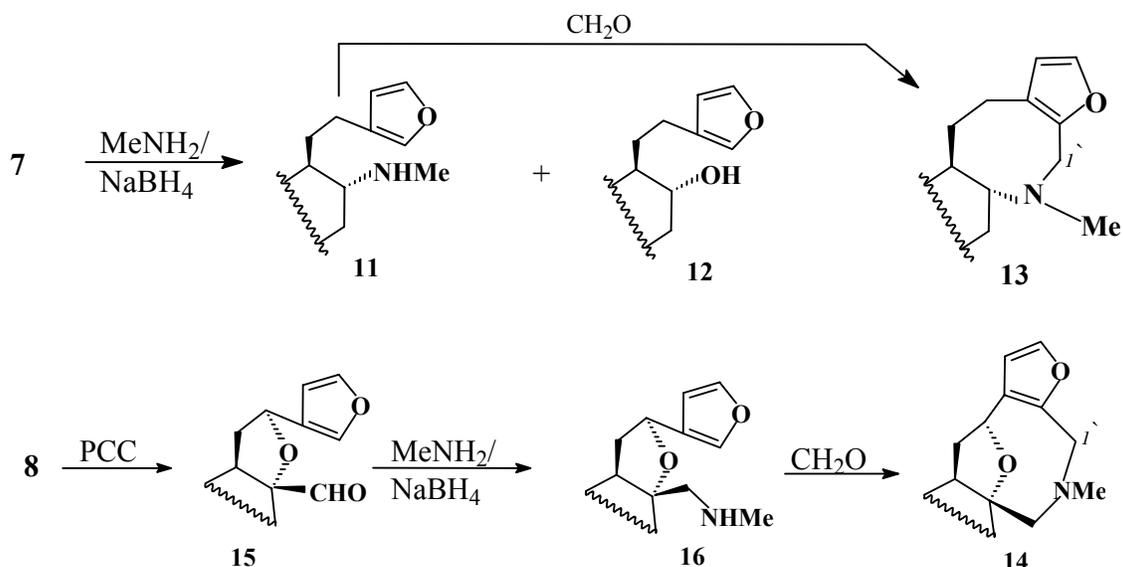
transformation of this compound could proceed by two routes. Its splitting leads to the ketone **7**, whereas the oxidation of C-12 methylene groups gives the triols **B** and **C**, whose cyclization in the course of the reaction leads to the (12*S*,8*R*)- and (12*R*,8*R*)- tricyclic compounds **8** and **9**. The crystal structure of **8** is given in Figure 3.



**Figure 3.** Crystal structure of **8**.

To obtain alkaloids of novel structural type, reductive amination of the above carbonyl compounds and subsequent intramolecular aminomethylation of the 17-nor-8(*R*)-methylamino- and 17-methylamino-labdadienoates with formaldehyde have been used. Reductive amination of the ketone **7** by  $\text{CH}_3\text{NH}_2$  and  $\text{NaBH}_4$  proceeds with high stereoselectivity and leads to the 17-nor-8 $\alpha$ -methylamino-labdanoid **11** and the hydroxy ester **12** in yields of 52 and 33%, respectively. The amino ester **11** that was formed reacted smoothly with formaldehyde by intramolecular Mannich reaction, with the formation of an aza-cyclo-octane **13** (Figure 4).

The transformation of oxide **8** into the alkaloid-like compound **14** included the stage of oxidation in the aldehyde **15**, reductive amination in an amine **16**, and Mannich cyclization by action of formaldehyde under acidic conditions.



**Figure 4**

The stereostructure of the aza-cyclo-octane **13** has been established by X-ray crystallographic analysis (Figure 5), while the structure of epoxy-hexahydrofuroazocine **14** was determined from a series of COSY- and COLOC 2D- NMR studies. The stereochemistry depicted in **14** has been proved by NOE observations. Characteristically, both the diastereotopic protons H-17 gave strong enhancements of the 20-Me ( $\delta$  0.57). The low field H-17 ( $\delta$  2.49) showed an enhancement of the H-6 axial proton ( $\delta$  1.85) with a weaker enhancement to the H-1' ( $\delta$  4.50). Irradiation of the H-17 diastereotopic proton at  $\delta$  2.18 showed a strong enhancement of H-12 ( $\delta$  5.04) and to both the pseudo-axial H-11 ( $\delta$  1.69) and H-9 ( $\delta$  1.50), but gave no enhancement of the H-1' protons. It is of interest that the furan ring protons (H-14 and H-15) gave enhancements on the H-12 or the 20-Me protons, respectively.

## Conclusions

We have achieved effective synthetic routes to novel alkaloid-like polycyclic compounds by synthetic transformations of the accessible natural furanoid labdane diterpene, lambertianic acid.

## Experimental Section

**General Procedures.** IR spectra were obtained in KBr pellets with a VEKTOR-22 spectrometer. Melting points were determined with a Kofler melting-point microscope. Mass spectra at 70 eV using electron impact mode were performed on a Finnigan MAT 8200 spectrometer (evaporation temperature 190–230°C). NMR spectra were recorded on Bruker AC-200 (200.13 MHz for  $^1\text{H}$ ,

50.32 MHz for  $^{13}\text{C}$ ) and Bruker DRX-500 (500.13 MHz for  $^1\text{H}$ , 125.76 MHz for  $^{13}\text{C}$ ). Chemical shifts ( $\delta$  in ppm) are given from internal  $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$  or  $\text{CDCl}_3+\text{CCl}_4$ ; coupling constants,  $J$ , are in Hz.  $^{13}\text{C}$  NMR spectra are summarized in Table 1. Optical rotations were measured on a Palomat A polarimeter in chloroform solution.

**X-ray Analysis.** Reflection data for **8** and **13** were collected on a Bruker P4 diffractometer with graphite-monochromated Mo  $K\alpha$  radiation ( $2\theta/\theta$ -scanning  $2\theta < 50^\circ$ ) at  $296^\circ\text{K}$ .

Column chromatography was performed on aluminum oxide. Reaction progress was monitored by TLC on Silufol UV 254 plates.

**Oxidation of methyl lambertianate (6a) by  $\text{KMnO}_4$ .** To a stirred solution of methyl lambertianate **6a** (3.3 g, 10 mmol) and tetrabutylammonium bromide (0.1 g) in benzene (20 ml) was added a solution of  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  (5 g) in 50 ml water. The reaction mixture was heated to  $45\text{--}50^\circ\text{C}$ , and a solution of potassium permanganate (3.0 g, 19 mmol) in water (60 ml) was added during 2 h, with vigorous stirring. After additional stirring for 1 h (TLC monitoring) the non-organic salt precipitate was filtered off and washed with *t*-BuOMe. The organic layer was separated, washed with water and concentrated in vacuum. The resulting oil was purified by column chromatography on aluminum oxide [eluent, petroleum: *t*-BuOMe (1:1–1:3)], and the products isolated by crystallization from a mixture of petroleum–acetone: 0.7 g (21%) of ketone **7**, 1.4 g (39%) (*8R,12R*)-oxido-labdanoid **8**, and 0.4 g (11%) of (*8R,12S*)-oxido-labdanoid **9** are obtained.

**Methyl 17-nor-8-oxo-15,16-epoxy-13(16),14-labdadien-18-oate (7).** mp  $61\text{--}62^\circ\text{C}$ ;  $[\alpha]_{580}^{20} + 55$  (*c* 5.1). IR (KBr,  $\text{cm}^{-1}$ ): 755, 873, 971, 984, 1026, 1066, 1090, 1117, 1502, 1716, 1721.  $^1\text{H-NMR}$  ( $\text{CCl}_4+\text{CDCl}_3$ ),  $\delta$  0.49 (s, 3H, 20-Me), 0.87 (ddd, 1H, H-3,  $J$  14.0, 12.5, 3.5), 1.03 (ddd, 1H, 1-H,  $J$  14.0, 12.8, 4.8), 1.21 (s, 3H, 19-Me), 1.23 (m, 1H, H-5), 1.56 (m, 3H, H-1,7,12), 1.70 (m, 1H, H-11), 1.75 (ddd, 1H, H-2,  $J$  13.4, 6.7, 3.8), 1.82 (ddd, 1H, H-6,  $J$  14.0, 12.6, 4.6), 1.92 (m, 2H, H-3,12), 2.15 (m, 3H, H-2,6,11), 2.36 (ddd, 1H, H-7,  $J$  13.6, 12.0, 3.6), 3.58 (s, 3H, OMe), 3.61 (dd, 1H, H-9,  $J$  11.2, 8.6), 6.15 (d, 1H, H-14,  $J$  2.6), 7.08 (d, 1H, H-16,  $J$  1.9), 7.24 (dd, 1H, H-15,  $J$  1.9, 2.6). MS (EI)  $m/z$  (%): 332 ( $\text{M}^+$ , 13), 238 (37), 223 (100), 163 (41), 121 (28), 95 (23). Exact mass, Calcd. for  $\text{C}_{20}\text{H}_{28}\text{O}_4$ : 332.19875. Found: 332.19955.

**(1S,3R,3aR,5aS,6S,9aS)-3a-Hydroxymethyl-6,9a-dimethyl-1-(3-furyl)-6-methoxycarbonyl-1,2,3,3a,4,5,5a,6,7,8,9,9a-dodecahydronaphtho[2,1-b]furan (8).** mp  $121\text{--}123^\circ\text{C}$ ;  $[\alpha]_{580}^{20} + 35$  (*c* 6.6).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ),  $\delta$  0.57 (s, 3H, 20-Me), 1.00 (ddd, 1H, H-3,  $J$  14.0, 12.2, 3.3), 1.05 (ddd, 1H, H-1,  $J$  14.1, 10.9, 3.8), 1.07 (m, 1H, H-7), 1.13 (s, 3H, 19-Me), 1.16 (m, 1H, H-5), 1.43 (m, 1H, H-2), 1.49 (m, 1H, H-1), 1.73 (ddd, 1H, H-6,  $J$  14.0, 7.2, 3.8), 1.78 (m, 1H, H-9), 1.86 (m, 2H, H-2,11), 1.92 (ddd, 1H, H-6,  $J$  14.0, 12.6, 3.0), 2.07 (ddd, 1H, H-11,  $J$  12.8, 8.0, 1.8), 2.15 (m, 1H, H-3), 2.18 (s, 1H, OH), 2.30 (ddd, 1H, H-7,  $J$  14.8, 6.8, 1.9), 3.30, 3.52 (d of d, 2H, H-17,  $J$  13.1), 3.57 (s, 3H, OMe), 4.95 (d, 1H, H-12,  $J$  8.0, 6.2), 6.35 (d, 1H, H-14,  $J$  1.9), 7.329 (d, 1H, H-16,  $J$  1.7), 7.331 (dd, 1H, H-15,  $J$  1.7, 1.9). MS (EI)  $m/z$  (%) 332 (21) ( $\text{M}-16$ ), 331 (100), 271 (22), 253 (20), 121 (28), 107 (25).

**(1R,3R,3aR,5aS,6S,9aS)-3a-Hydroxymethyl-6,9a-dimethyl-1-(3-furyl)-6-methoxycarbonyl-1,2,3,3a,4,5,5a,6,7,8,9,9a-dodecahydronaphtho[2,1-b]furan (9)** isolated as an oil,  $[\alpha]_{580}^{20} + 12$  (*c* 4.5).  $^1\text{H NMR}$  data ( $\text{CDCl}_3$ ),  $\delta$  0.58 (s, 3H, 20-Me), 0.87 (ddd, 1H, H-3, *J* 14.0, 12.1, 3.0), 1.01 (m, 1H, H-1), 1.10 (m, 1H, H-5), 1.16 (s, 3H, 19-Me), 1.28 (m, 1H, H-7, *J* 13.8), 1.41 (m, 2H, H-1,2), 1.70 (ddd, 1H, H-6, *J* 14.0, 12.5, 2.8), 1.83 (m, 1H, H-2), 1.90 (m, 3H, H-6,9,11), 2.13 (m, 2H, H-3,11), 2.40 (ddd, 1H, H-7, *J* 13.9, 6.8, 2.2), 3.40, 3.45 (d of d, *J* 8.9, 2H, H-17), 3.60 (s, 3H, OMe), 5.01 (dd, 1H, H-12, *J* 10.1, 7.6), 6.22 (dd, 1H, H-14, *J* 1.6, 0.9), 7.27 (d, 1H, H-16, *J* 1.0), 7.31 (dd, 1H, H-15, *J* 1.6, 1.0).

**(1R,3R,3aR,5aS,6S,9aS)-3a-Acetoxyethyl-6,9a-dimethyl-1-(3-furyl)-6-methoxycarbonyl-1,2,3,3a,4,5,5a,6,7,8,9,9a-dodecahydronaphtho[2,1-b]furan (10)**. Acetyl chloride (0.3 ml) was added with stirring to compound **9** (0.36 g, 1 mmol) in a mixture of benzene (5 ml) and pyridine (0.3 ml). After 1 h at room temperature the mixture was washed with water, dried and evaporated under reduced pressure, and the oily residue purified by chromatography. The acetate **10** (0.31 g, 82%) was isolated as an oil.  $[\alpha]_{580}^{20} + 25$  (*c* 2.1).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ),  $\delta$  0.64 (s, 3H, 20-Me), 0.99 (ddd, 1H, H-3, *J* 13.8, 12.6, 3.0), 1.05 (ddd, 1H, H-1, *J* 13.2, 10.5, 2.8), 1.16 (s, 3H, 19-Me), 1.19 (dd, 1H, H-5, *J* 12.7, 3.4), 1.27 (ddd, 1H, H-7, *J* 13.8, 12.2, 11.8), 1.41 (ddd, 1H, H-1, *J* 13.2, 5.8, 2.9), 1.44 (ddd, 1H, H-2, *J* 14.2, 10.2, 4.8), 1.62 (dd, 1H, H-9, *J* 7.0, 2.5), 1.67 (dd, 1H, H-11, *J* 7.0, 7.8), 1.82 (ddd, 1H, H-2, *J* 14.2, 6.9, 2.2), 1.86 (ddd, 1H, H-6, *J* 14.2, 3.6, 2.8), 1.97 (ddd, 1H, H-6, *J* 14.2, 11.8, 6.8), 2.05 (s, 3H, Ac), 2.14 (dd, 1H, H-11, *J* 7.8, 1.6), 2.17 (ddd, 1H, H-3, *J* 13.8, 5.8, 2.5), 2.26 (dt, 1H, H-7, *J* 12.4, 3.4), 3.61 (s, 3H, O Me), 3.96 (d, 1H, H-17, *J* 11.4), 4.36 (dd, 1H, H-17, *J* 11.4, 1.7), 5.06 (dd, 1H, H-12, *J* 10.3, 8.3), 6.22 (dd, 1H, H-14, *J* 1.8, 0.85), 7.26 (dt, 1H, H-16, *J* 1.7, 0.85), 7.29 (dd, 1H, H-15, *J* 1.8, 1.7). MS (EI) *m/z* (%): 332 (22), 331 (100), 271 (24), 253 (20), 121 (22), 107 (25), 81 (22).

**Methyl (8R)-methylamino-17-nor-15,16-epoxy-13(16),14-labdadien-18-oate (11)**. A solution of methylamine (1 g) in methanol (10 ml) containing was added to a solution of compound **7** (0.33 g, 1 mmol) in methanol (5ml). The reaction mixture was stirred at ambient temperature during 18 h, and then cooled to 0° C. Sodium borohydride (0.12 g, 2.7 mmol) was added portionwise under N<sub>2</sub>. The reaction mixture was allowed to warm to room temperature, quenched with water, and the product extracted with t-BuOMe. Two compounds were separated by column chromatography (solvent petroleum/t-BuOMe (1:1–1:3): **11** (0.18 g, 52%) and **12** (0.11 g, 33%). Compound **11**, mp 65–67° C (from petroleum),  $[\alpha]_{580}^{20} + 21$  (*c* 2.8).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ),  $\delta$  0.69 (s, 3H, 20-Me), 0.88 (ddd, 1H, H-1, *J* 13.8,12.6, 3.0), 0.95 (ddd, 1H, H-3, 13.6,10.5, 2.7), 1.08 (m, 2H, H-5,11), 1.13 (s, 3H, 19-CH<sub>3</sub>), 1.36 (ddd, 1H, H-7, *J*13.7, 6.8, 3.2), 1.55–1.80 (m, 6H, H-1,2,2,6,9,12), 2.14 (ddd, 1H, H-11, *J* 14.2, 12.2, 5.6), 2.24 (m, 2H, H-3,6), 2.31 (m, 1H, H-12), 2.33 (s, 3H, NMe), 2.42 (m, 1H, H-7), 2.58 (dd, 1H, H-8, *J* 4.2, 3.8), 3.60 (s, 3H, OMe), 5.12 (s, 1H, NH), 6.17 (d, 1H, H-14, *J* 2.6), 7.12 (d, 1H, H-16, *J* 1.5), 7.26 (dd, 1H, H-15, *J* 2.6, 1.5). MS (EI) *m/z* (%): 347 (15, M<sup>+</sup>), 264 (47), 81 (16), 70 (100).

**Methyl (8R)-hydroxy-17-nor-15,16-epoxy-13(16),14-labdadien-18-oate (12)**. Oil,  $[\alpha]_{580}^{20} + 47$  (*c* 3.3).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ),  $\delta$  0.74 (s, 3H, 20- Me), 0.89 (ddd, 1H, H-3, *J* 13.6, 12.4, 3.0), 0.95 (m, 1H, H-1), 1.13 (s, 3H, 19-Me), 1.15 (m, 2H, H-5,11), 1.39 (ddd, 1H, H-7, *J* 12.9, 6.7, 3.0),

1.55–1.84 (m, 6H, H-1,2,2,9,6,12), 1.98 (ddd, 1H, H-11, J 14.0, 12.1, 5.1), 2.25 (m, 1H, H-3), 2.35 (m, 2H, H-6,12), 2.47 (ddd, 1H, H-7, J 14.0, 12.2, 2.6), 3.60 (s, 3H, OMe), 3.92 (dd, 1H, H-8, J 4.8, 3.0), 6.16 (d, 1H, H-14, J 1.5), 7.12 (d, 1H, H-16, J 1.6), 7.25 (dd, 1H, H-15, J 1.5, 1.6). MS (EI)  $m/z$  (%): 334 (44,  $M^+$ ), 319 (34), 316 (26), 223 (52), 163 (47), 121 (81), 109 (51), 95 (51), 81 (100).

**(1R,11S,14S,19S)-15-Methoxycarbonyl-10,15,19-trimethyl-7-oxa-10-aza-tricyclo-[14.4.0.0<sup>4,8</sup>.0<sup>1,11</sup>]-nonadeca-4(8),5-diene (13).** Paraformaldehyde (0.11 g, 3.3 mmol) and trifluoroacetic acid (0.14 g, 1.2 mmol) were added to a solution of amine **11** (0.35 g, 1 mmol) in benzene (10 ml). The mixture was heated at reflux for 15 min, cooled to room temperature, diluted with benzene (10 ml) and washed with ammonium hydroxide (3% solution, 5 ml). After evaporation of the solvent the solid residue was purified by column chromatography (petroleum/t-BuOMe 1:1). Crystallization from a mixture of petroleum–acetone gave the azacyclo-octane derivatives **13** (0.25 g 71%). Mp 133–135° C,  $[\alpha]_{580}^{20} + 32$  (c 3.1). <sup>1</sup>H NMR data (CDCl<sub>3</sub>),  $\delta$  0.97 (ddd, 1H, H-1, J 14.3, 4.4, 0.9), 1.00 (ddd, 1H, H-1, J 13.4, 13.0, 4.3), 0.99 (s, 3H, 20-Me), 1.16 (s, 3H, 19-Me), 1.18 (ddd, 1H, H-7, J 12.7, 2.6), 1.20 (m, 1H, H-5), 1.44 (m, 2H, H-2,9), 1.61 (ddd, 1H, H-6, J 14.0, 10.1, 5.4), 1.70 (ddd, 1H, H-1, J 13.4, 6.7, 3.5), 1.84 (ddd, 1H, H-2, J 14.0, 12.2, 4.6), 1.87 (ddd, 1H, H-12, J 18.0, 12.0, 6.2), 1.95 (m, 1H, H-11, J 12.8), 2.04 (ddd, 1H, H-7, J 14.0, 6.7, 3.0), 2.06 (ddd, 1H, H-6, 14.0, 12.0, 3.6), 2.09 (s, 3H, NMe), 2.17 (dddd, 1H, H-3, J 13.2, 3.8, 2.9, 1.6), 2.21 (dd, 1H, H-8, J 3.1), 2.40 (dd, 1H, H-12, J 12.7, 3.9, 1.4), 2.76 (dddd, 1H, H-11, J 17.2, 12.8, 2.3, 1.0), 3.44 (ddd, 1H, H-1', J 12.2, 6.5, 1.7), 3.65 (s, 3H, OMe), 4.33 (d, 1H, H-1', J 12.2), 6.16 (d, 1H, H-14, J 2.8), 7.21 (d, 1H, H-15, J 2.8). MS (EI)  $m/z$  (%): 359 ( $M^+$ , 100), 300 (26), 236 (20), 162 (21), 107 (29), 94 (36), 70 (24). Exact mass Calcd. for C<sub>22</sub>H<sub>33</sub>NO<sub>3</sub>: 359.24603. Found: 359.24715.

**(1S,3R,3aR,5aS,6S,9aS)-3a-Formyl-6,9a-dimethyl-1-(3-furyl)-6-methoxycarbonyl-1,2,3,3a,4,5,5a,6,7,8,9,9a-dodecahydronaphtho[2,1-b]furan (15).** To a solution of 17-hydroxy-labdanoid **8** (0.35 g, 1 mmol) in anhydrous methylene chloride (20 ml), pyridinium chlorochromate (0.35 g, 1.6 mmol) was added portionwise. The mixture was stirred for 2 h, and then passed through a short column of aluminum oxide (3 g, 230–400 mesh) eluting with t-BuOMe (30 ml), the combined solvent was evaporated, and the residue crystallized from petroleum–acetone. Aldehyde **15** (0.27 g, 76%) was isolated; mp 102–105° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>),  $\delta$  0.60 (s, 3H, 20-Me), 0.88 (ddd, 1H, H-3, J 14.3, 10.2, 3.3), 0.95 (ddd, 1H, H-1, J 14.2, 10.8, 3.6), 1.06 (dd, 1H, H-5, J 11.2, 3.3), 1.16 (s, 3H, 19-Me), 1.21 (m, 2H, H-2,7), 1.50 (m, 2H, H-1,9), 1.80–2.08 (m, 4H, H-2,6,6,11), 2.12 (m, 1H, H-3), 2.20 (ddd, 1H, H-7, J 14.3, 6.5, 2.0), 2.43 (ddd, 1H, H-11, J 12.6, 8.0, 1.8), 3.57 (s, 3H, OMe), 5.11 (dd, 1H, H-12, J 8.0, 6.6), 6.33 (dd, 1H, H-14, J 1.8, 0.8), 7.30 (m, 2H, H-15,16), 9.56 (s, 1H, CHO).

**(1S,3R,3aR,5aS,9aS)-3a-Methylamino-6,9a-dimethyl-1-(3-furyl)-6S-methoxycarbonyl-1,2,3,3a,4,5,5a,6,7,8,9,9a-dodecahydronaphtho[2,1-b]furan (16).** Methanol (15 ml) containing methylamine (1 g) was added to a solution of **15** (0.43 g, 1 mmol) in methanol (5 ml). The obtained solution was allowed to stand at ambient temperature 20 hours, then cooled to 0° C under N<sub>2</sub>. Sodium borohydride (0.12 g, 2.7 mmol) was added portionwise over 15 min. The

reaction mixture was allowed to warm to room temperature, quenched with water, and the product extracted with *t*-BuOMe. The combined organic solution was washed with water and concentrated. By chromatography of the residue in petroleum /*t*-BuOMe (1:2–1:5) and crystallization the amine **16** was isolated (yield 77%). Mp 115–118 °C (petroleum–acetone).  $[\alpha]_{580}^{20}$  29 (*c* 5.2).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ),  $\delta$  0.65 (s, 3H, 20-Me), 0.99 (m, 2H, H-1,3), 1.08 (dd, 1H, H-5, *J* 10.9, 3.2), 1.15 (s, 3H, 19-Me), 1.20 (m, 1H, H-2,7), 1.50 (m, 2H, H-1,11), 1.60 (ddd, 1H, H-9, *J* 10.1, 7.6, 1.2), 1.63 (ddd, 1H, H-6, *J* 12.6, 12.0, 4.0), 1.86 (m, 2H, H-2,6), 2.08 (ddd, 1H, H-3, *J* 14.2, 6.6, 3.2), 2.16 (s, 3H, NMe), 2.18 (m, 2H, H-17), 2.44 (dt, 1H, H-7, *J* 12.6, 12.0, 3.1), 2.56 (dt, 1H, H-11, *J* 12.1, 1.8), 3.61 (s, 3H, OMe), 4.86 (dd, 1H, H-12, *J* 7.8, 6.8), 5.62 (s, 1H, NH), 6.25 (d, 1H, H-14, *J* 1.6), 7.26 (d, 1H, H-16, *J* 1.3), 7.32 (dd, 1H, H-15, *J* 1.6, 1.3). MS (EI) *m/z* (%): 375 ( $\text{M}^+$ , 1.6), 332 (29), 331 (100), 271 (34), 253 (32), 107 (24), 94 (19). Exact mass. Calcd. for  $\text{C}_{22}\text{H}_{33}\text{NO}_4$ : 375.24094. Found: 375.24122.

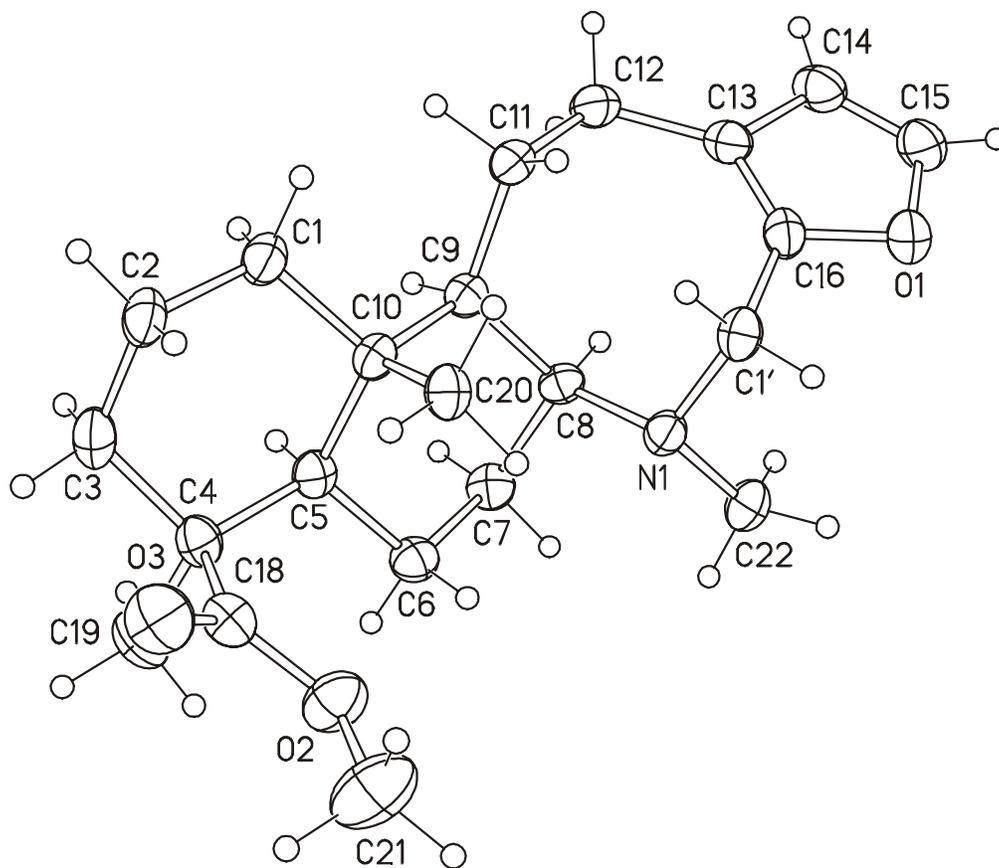
**(1S,10S,13S,18S,19S)-14-Methoxycarbonyl-8,14,18-trimethyl-5,21-dioxa-8-aza-pentacyclo-[15.3.1.0.0.0<sup>2,6</sup>.0<sup>10,19</sup>.0<sup>10,21</sup>]-heneicosa-2(6),3-diene (14)**. Paraformaldehyde (0.1 g, 3.3 mmol) and trifluoroacetic acid (0.14 g, 1.2 mmol) were added to a solution of amine **16** (0.37 g, 1 mmol) in benzene (10 ml). The mixture was heated at reflux 15 min, cooled, diluted with benzene (10 ml), washed with ammonium hydroxide (3% aq. solution) and concentrated in vacuo to give an oil. After column chromatography (petroleum–*t*-BuOMe, 1:1), evaporation of the solvent and crystallization the cyclic amine **14** (0.29 g, 77%) was isolated. Mp 186–187°C (petroleum–acetone).  $[\alpha]_{580}^{20} + 37^\circ$  (*c* 2.2).  $^1\text{H NMR}$  data ( $\text{CDCl}_3$ ),  $\delta$  0.57 (s, 3H, 20-Me), 0.99 (ddd, 1H, H-3, *J* 13.3, 12.7, 3.5), 1.02 (ddd, 1H, H-1, *J* 13.4, 10.8, 3.6), 1.12 (dd, 1H, H-5, *J* 13.2, 3.2), 1.16 (s, 3H, 19-Me), 1.21 (ddd, 1H, H-7, *J* 13.3, 4.3, 1.8), 1.40 (m, 1H, H-2), 1.46 (m, 1H, H-1, 14.1), 1.50 (dd, 1H, H-9, *J* 13.2, 7.4), 1.69 (ddd, 1H, H-11, *J* 13.2, 11.4, 6.3), 1.81 (m, 1H, H-2), 1.85 (m, 1H, H-6, *J* 15.1, 7.4, 6.5), 1.95 (dddd, 1H, H-6, *J* 14.1, 6.0, 3.8, 1.9), 2.13 (m, 1H, H-3), 2.16 (m, 1H, H-11), 2.18 (d, 1H, H-17, *J* 13.5), 2.34 (s, 3H, NMe), 2.36 (dt, 1H, H-7, *J* 14.0, 6.2, 1.8), 2.49 (d, 1H, H-17, *J* 13.5), 3.42 (d, 1H, H-1', *J* 14.8, 0.6), 3.60 (s, 3H, OCH<sub>3</sub>), 4.50 (d, 1H, H-1', *J* 14.8), 5.04 (dd, 1H, H-12, *J* 8.2, 6.3), 6.05 (dd, 1H, H-14, *J* 1.9, 0.6), 7.18 (d, 1H, H-15, *J* 1.9). MS (EI) *m/z* (%): 387 ( $\text{M}^+$ , 14), 345 (23), 344 (100), 284 (44), 195 (23), 163 (40), 162 (29), 121 (30), 107 (30). Exact mass Calcd. for  $\text{C}_{23}\text{H}_{33}\text{NO}_4$ : 387.24094. Found: 387.24004.

**Crystal data for 8.**  $\text{C}_{21}\text{H}_{30}\text{O}_5$ , *M* = 348.28, white plates, orthorhombic: *a* = 7.6106(9), *b* = 10.982(1), *c* = 23.079(2) Å, *V* = 1928.9(3) Å<sup>3</sup>, space group *P* 2<sub>1</sub> 2<sub>1</sub> 2<sub>1</sub>, *Z* = 4, *d*<sub>cal</sub> = 1.248 g/cm<sup>3</sup>,  $\mu$  = 0.088 mm<sup>-1</sup>. 1961 independent reflection were collected. The structure was solved by direct methods and refined by full-matrix least-squares on *F*<sup>2</sup> with SHELXS-97. *wR*<sub>2</sub> = 0.1013, *S* = 1.059, 356 parameters were corrected (*R* = 0.0407 for 1542 *F* > 4σ).

**Crystal data for 13.**  $\text{C}_{22}\text{H}_{33}\text{NO}_3$ , *M* = 359.25, white block, monoclinic: *a* = 8.147(1), *b* = 11.044(2), *c* = 11.334(2) Å,  $\beta$  = 100.55(1)°, *V* = 1002.5(3) Å<sup>3</sup>, space group *P* 2<sub>1</sub>, *Z* = 2, *d*<sub>cal</sub> = 1.191 g/cm<sup>3</sup>,  $\mu$  = 0.078 mm<sup>-1</sup>. 1828 independent reflections were collected. The structure was solved by direct methods and refined by full-matrix least-squares on *F*<sup>2</sup> with SHELXS-97. *wR*<sub>2</sub> = 0.1044, *S* = 1.028, 368 parameters were corrected (*R* = 0.0388 for 1434 *F* > 4σ).

**Table 1.**  $^{13}\text{C}$ - NMR data of compounds **7**, **8**, **9**, **11**, **13**, **14**, **15**, **16** [ppm] in  $\text{CDCl}_3$ 

Atom number	<b>7</b>	<b>8</b>	<b>9</b>	<b>11</b>	<b>13</b>	<b>14</b>	<b>15</b>	<b>16</b>
C-1	39.5	39.9	39.9	39.7	39.9	40.3	39.6	40.2
C-2	19.7	18.67	18.7	18.5	19.2	18.9	18.8	18.6
C-3	38.1	38.1	38.2	38.3	38.1	38.4	38.2	38.2
C-4	43.8	43.3	43.2	43.8	43.8	43.5	43.3	43.1
C-5	55.1	56.7	57.0	56.3	55.8	57.5	56.3	57.1
C-6	22.3	21.7	21.6	19.1	18.8	21.9	21.6	21.9
C-7	42.8	34.5	34.3	30.3	32.9	35.8	31.7	35.7
C-8	208.9	82.7	83.2	57.5	57.8	82.1	84.0	82.1
C-9	61.7	60.5	58.5	52.9	59.1	62.8	61.6	61.2
C-10	44.2	36.6	36.4	38.4	39.2	36.6	37.1	36.5
C-11	25.5	30.0	30.9	25.0	24.0	32.1	32.4	29.7
C-12	23.8	72.7	70.9	23.4	24.0	73.4	74.8	71.7
C-13	124.6	127.6	128.8	124.9	121.3	127.1	127.6	128.5
C-14	110.8	108.6	108.2	110.8	111.7	107.9	108.7	108.6
C-15	138.7	138.9	138.9	138.6	140.2	141.0	138.8	138.0
C-16	140.2	143.6	142.5	142.5	146.9	145.4	141.6	141.5
C-17	-	62.4	60.5	-	51.6	55.7	195.7	54.1
C-18	175.9	177.1	176.2	176.7	178.1	176.7	176.2	175.9
C-19	29.3	28.3	26.8	28.8	28.9	38.8	28.4	28.3
C-20	13.1	12.9	12.6	14.4	13.1	12.9	13.9	12.9
OCH <sub>3</sub>	51.0	50.9	50.7	50.9	51.2	51.1	50.8	50.5
NCH <sub>3</sub>	-	-	-	35.9	43.7	47.9	-	36.4
C-1'	-	-	-	-	51.7	53.4	-	-



**Figure 5.** Crystal structure of **13**.

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