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SYNTHESIS OF NEW HOMODRIMANE SESQUITERPENOIDS CONTAINING DIAZINE, 1,2,4-TRIAZOLE AND CARBAZOLE RINGS

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Abstract. The present paper reports on six step synthesis of 11-homodrim-6,8-dien-12-oic acid *N*-substituted amides containing diazine, 1,2,4-triazole and carbazole rings based on commercially available sclareolide. The mentioned compounds were prepared for the first time by interaction of the generated *in situ* acyl chloride with some heterocyclic amines: 2- and 4-aminopyrimidine, 2-aminopyrazine, 5-amino-1,2,4-triazole and *N*-aminocarbazole. Their structures were fully elucidated by elemental and spectral analyses (IR, ^{1}H and ^{13}C NMR).

Keywords: sesquiterpenoid, *N*-substituted amide, heterocyclic amine, diazine, 1,2,4-triazole, carbazole, synthesis.

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Introduction

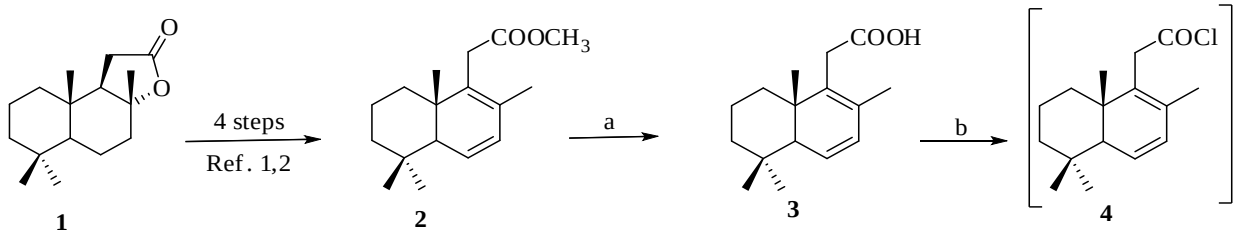
Sesquiterpenoids are natural compounds with a wide range of biological activities [1,2]. Azaheterocyclic derivatives have a wide range of biological activities, such as antimicrobial, antifungal, antituberculosis, antiviral, anti-HIV, anticancer, *etc*. [3,4]. In search for new biologically active substances and to reveal the structure-activity relationship, we have previously synthesized a series of heterocycle-containing drimane and homodrimane derivatives [5,6], including amides of $\Delta^{8,13}$-bicyclohomofarnesenoic acid containing pyrimidine and pyrazine rings, which had a significant antimicrobial activity [7]. Later synthesized amides of $\Delta^{8,13}$-bicyclohomofarnesenoic acid, including 1,2,4-triazole and carbazole units, showed an antioxidant activity [8-10].

As a continuation of our research into the synthesis of novel compounds containing both terpenic and heterocyclic fragments and in order to obtain a cumulative biological potential of the homodrimane structure and related heterocycles, herein we report the synthesis of some new homodrimane sesquiterpenoids with azaheterocyclic fragments.

Results and discussion

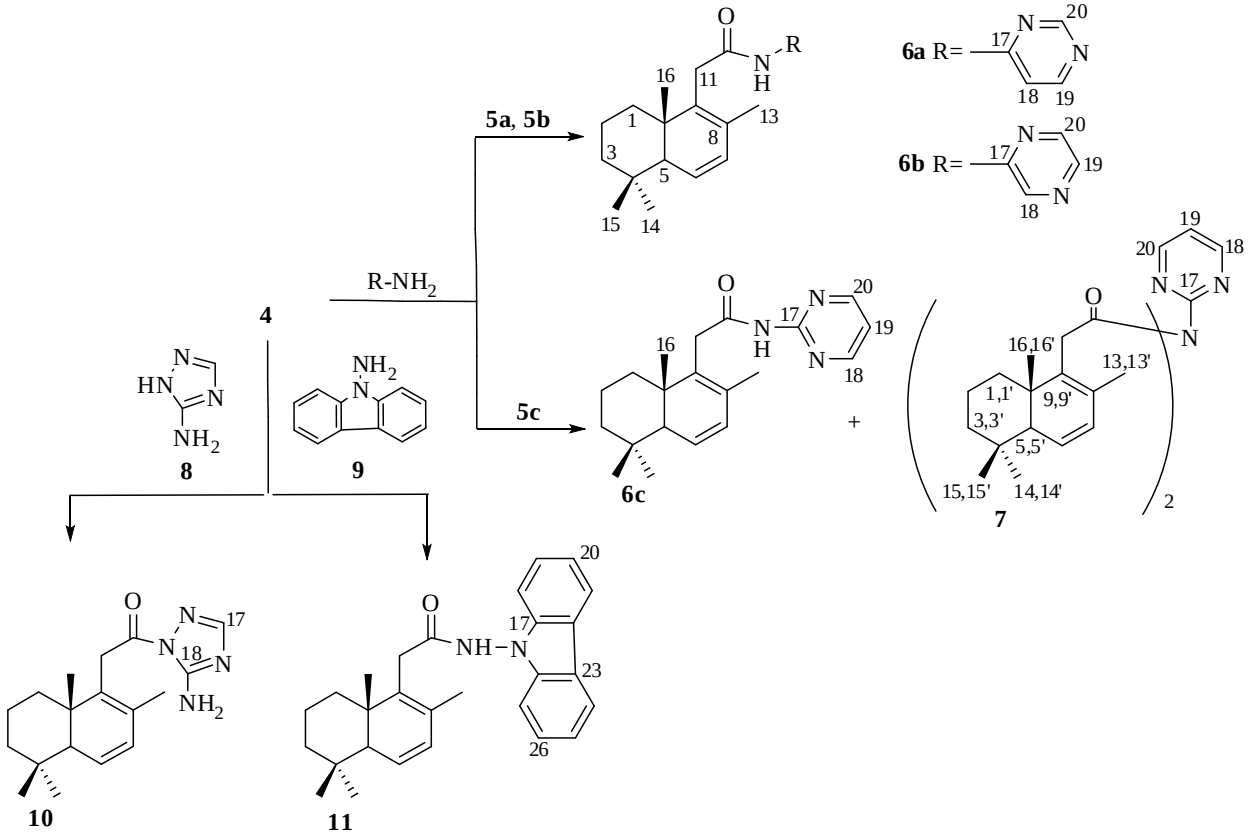
As the starting material for the synthesis of homodrimane compounds with diazine, triazole and carbazole units was used methyl 11-homodrim-6,8-dien-12-oate **2** obtained before from commercially available sclareolide **1** in 4 steps, with an overall yield of 85% [11] (Scheme 1). The saponification of ester **2** led to acid **3** in 96% yield and its structure was confirmed by IR, ^{1}H, and ^{13}C NMR data.

The 11-homodrim-6,8-dien-12-oic acid chloride **4** (generated *in situ* from acid **3**) was treated with 4-aminopyrimidine **5a**, 2-aminopyrazine **5b**, 2-aminopyrimidine **5c**, 5-amino-1,2,4-triazole **8** and *N*-aminocarbazole **9** [7,8].



Scheme 1. Synthesis of 11-homodrim-6,8-dien-12-oic acid chloride 4.
Reagents and conditions: *a.* KOH, EtOH, 3 h, 96%; *b.* $(COCl)_2$, C_6H_6, 20°C, 1 h, then Δ, 1 h.

The reactions are highly selective only for monoacyl amides **6a**, **6b**, **10** and **11** in 69%, 35%, 30% and 40% yields, respectively (see Scheme 2 and Table 1). In the case of 5-amino-1,2,4-triazole **8**, an analysis of the spectral data of the reaction product showed that this amine reacted with acid chloride **4** in a tautomeric form and the resulting amide **10** contained an NH_2 group. In the case of 2-aminopyrimidine **5c**, monoacyl amide **6c** and *bis*-acylamide **7** were also obtained in 40% and 25% yields, respectively (see Scheme 2 and Table 1).



Scheme 2. Synthesis of new homodrimane sesquiterpenoids containing diazine, 1,2,4-triazole and carbazole rings. Reagents and conditions: CH_2Cl_2, 20°C, 5-10 h, 25-69%.

Table 1

Results of 11-homodrim-6,8-dien-12-oic acid chloride amination.

No.	*Amine*	*N-substituted amide*	*Yield, %*
1	4-aminopyrimidine (**5a**)	**6a**	69
2	2-aminopyrazine (**5b**)	**6b**	35
3	2-aminopyrimidine (**5c**)	Mixture of **6c** and **7**	40 and 25
4	5-amino-1,2,4-triazole (**8**)	**10**	30
5	*N*-aminocarbazole (**9**)	**11**	40

With the exception of amide **10**, all the other *N*-substituted amides resulted from condensation of primary amine groups with acyl chloride **4**. Virtually, all the secondary amides may react again with acyl chloride but, according to the experimental data, only monoacyl amide **6c** underwent *bis*-acylation to give **7**. Probably, this occurred, as a result of delocalization of nonbonding electrons of nitrogen to the adjacent carbonyl group (resonance of the amide bond) that reduced the reactivity of amides versus amines. In addition to this, the resonance structures for amides **6a-c** also show delocalization over the aromatic cycle so the aryl substituents determine their reactivity. Probably, the reaction time is important in order for the *bis*-acylation to occur.

Conclusions

Starting from commercially available sclareolide **1**, a series of novel compounds **6a-c**, **7**, **10** and **11**, containing both homodrimane and heterocyclic (diazine, 1,2,4-triazole and carbazole) fragments, were synthesized and their structures were confirmed using IR, NMR spectroscopy (^{1}H and, ^{13}C NMR, two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) and HR-EI-MS.

In the case of 5-amino-1,2,4-triazole **8**, analysis of the spectral data of the reaction product showed that the amine reacted with acyl chloride **4** in its tautomeric form and the resulting amide **10** contained an amino group. In the case of 2-aminopyrimidine **5c**, besides monoacyl amide **6c**, *bis*-acylamide **7** was also obtained, because of an unusual one pot *bis*-acylation.

Experimental

Generalities

Melting points (m.p.) were taken on a Boetius hot stage apparatus.

Optical rotations were determined on a Jasco DIP 370 polarimeter with a 1 dm microcell, in $CHCl_3$ and MeOH.

The IR spectra were registered on a Spectrum-100FT-IR spectrometer (Perkin-Elmer) by the ATR technique. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker Avance DRX 400 spectrometer. Chemical shifts are given in ppm in the δ scale and referred to $CHCl_3$ (δ_H at 7.26 ppm) and to $CDCl_3$ (δ_C 77.00 ppm), respectively, and to DMSO-d_6 (δ_H at 2.50 ppm) and to DMSO-d_6 (δ_C 39.52 ppm), respectively. The 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 product compositions were determined and mass spectra were recorded on an Agilent 7890A chromatograph with an MSD 5975C VL quadrupole MS detector and an HP-5ms capillary column (30 m x 0.25 μm). The vaporizer temperature was 250°C; the ionization potential – 70 eV. Analysis conditions: T_1= 180°C, 10°C/min to 300°C, T_2= 300°C (15 min), or T_1= 60°C (5 min), 15°C/min to 200°C, T_2= 200°C, 15°C/min to 300°C, T_3= 300°C (10 min). The He flow rate was 1 mL/min.

For the analytical TLC, Merck silica gel plates 60G in 0.25 mm layers were used. The TLC plates were sprayed with concentrated H_2SO_4 and heated at 80°C. The column chromatography was carried out on the Across 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.

Synthesis of 11-homodrim-6,8-dien-12-oic acid (3)

Solid KOH (410 mg, 11.5 mmol) was added to a solution of ester **2** (300 mg, 1.15 mmol) in EtOH (10 mL). The resulted reaction mixture was heated at 50°C for 3 h and 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 over anhydrous sodium sulfate, concentrated, and the title compound **3** (270 mg, 96% yield) was obtained, as a white solid (EtOH), m.p. 71-72°C, $[\alpha]_D^{20}$= -59.0° (*c* 1.2, $CHCl_3$). IR (ATR) ν 2926, 1701, 1458, 1370, 1202, 941 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 5.87 (1H, dd, *J* 9.6, 3.0 Hz, H-7), 5.79 (1H, dd, *J* 9.6, 2.6 Hz, H-6), 3.19 (1H, d, *J* 16.50 Hz, H-11), 3.06 (1H, d, *J* 16.50 Hz, H-11), 2.06 (1H, t, *J* 2.80 Hz, H-5), 1.74 (3H, s, H-13), 0.98 (3H, s, H-14), 0.95 (3H, s, H-15), 0.82 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 178.50 (C-12), 135.68 (C-9), 129.16 (C-7), 128.85 (C-8), 128.25 (C-6), 52.42 (C-5), 40.78 (C-3), 38.74 (C-10), 35.11 (C-1), 32.94 (C-4), 32.46 (C-11), 32.34 (C-15), 22.74 (C-14), 18.89 (C-2), 18.28 (C-13), 14.98 (C-16). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 248 (M^+, 20), 233 (100), 205 (16), 187 (4), 173 (6), 163 (11), 150 (12), 135 (28), 132 (7), 123 (71), 119 (27), 109 (33), 105 (20), 91 (28), 79 (18), 77 (18), 67 (10), 65 (7), 55 (21), 51 (3), 41 (21), 39 (8).

Typical procedure for the synthesis of 11-homodrim-6,8-dien-12-oic acid amides (6a-c), 7, 10 and 11 with diazine, triazole and carbazole skeletons

A solution of $(COCl)_2$ (0.4 mL, 0.58 g, 4.58 mmol) in anhydrous benzene (1 mL) was added to a solution of acid **3** (100 mg, 0.40 mmol) in anhydrous benzene (2 mL). The reaction mixture was stirred at r.t. for 1 h and then refluxed for additional 1 h. Benzene and excess of $(COCl)_2$ were evaporated under reduced pressure. Next, 4-aminopyrimidine **5a**, or 2-aminopyrazine **5b** or 2-aminopyrimidine **5c** (43 mg, 0.45 mmol), or 5-amino-1,2,4-triazole **8** (50 mg, 0.60 mmol) or *N*-aminocarbazole **9** (102 mg, 0.65 mmol), were added to the residue of the solution of acyl chloride **4** in CH_2Cl_2 (4 mL), and the resulting mixture was stirred at r.t. for 5 to 10 h. Further the precipitate was filtered off, washed with CH_2Cl_2, and the filtrate was concentrated to dryness. Crude reaction products were purified by flash column chromatography on SiO_2 (eluent: CH_2Cl_2/MeOH 2-4%) to give products **6a-c**, **7**, **10** and **11**.

N-(pyrimidin-4-yl)-2-((8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)acetamide ***6a*** (69%), white solid (MeOH), m.p. 78-79°C, $[\alpha]_D^{20}$= -50.2° (*c* 4.6, $CHCl_3$). IR (ATR) ν 3242, 2930, 1705, 1571, 1505, 1157, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.86 (1H, s, H-20), 8.63 (1H, s, H-18), 8.41 (1H, s, NH), 8.23 (1H, s, H-19), 5.96, 5.94 (1H, dd, *J* 9.66, 2.52 Hz, H-7), 5.92, 5.89 (1H, dd, *J* 9.76, 2.08 Hz, H-6), 3.35 (1H, d, *J* 17.12 Hz, H-11), 3.12 (1H, d, *J* 17.12 Hz, H-11), 2.08 (1H, t, *J* 2.24 Hz, H-5), 1.81 (3H, s, H-13), 0.96 (3H, s, H-14), 0.95 (3H, s, H-15), 0.84 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 171.04 (C-12), 158.01 (C-18), 157.96 (C-20), 156.95 (C-17), 136.31 (C-9), 130.68 (C-8), 129.50 (C-7), 128.85 (C-6), 110.16 (C-19), 53.12 (C-5), 40.62 (C-3), 39.13 (C-10), 36.76 (C-11), 35.10 (C-1), 33.00 (C-4), 32.34 (C-15), 22.76 (C-14), 18.73 (C-2), 18.43 (C-13), 15.10 (C-16). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 326 (M^+, 10), 310 (89), 230 (64), 215 (8), 202 (2), 197 (1), 187 (21), 173 (20), 159 (22), 148 (35), 145 (21), 133 (12), 131 (20), 119 (28), 115 (13), 105 (16), 96 (100), 95 (13), 91 (23), 79 (19), 77 (9), 55 (9), 52 (6), 41 (14).

N-(pyrazin-2-yl)-2-((8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)acetamide ***6b*** (35%), white solid (MeOH), m.p. 174-175°C, $[\alpha]_D^{20}$= -84.4° (*c* 0.8, MeOH). IR (ATR) ν 3115, 2927, 1690, 1593, 1514, 1408, 1348, 1150, 974 cm^{-1}; ^1H NMR (DMSO, 400 MHz, ppm): δ 11.9 (1H, s, NH), 8.15 (1H, s, H-18), 7.92-7.89 (1H, m, H-20), 7.73 (1H, d, *J* 3.05 Hz, H-19), 5.88 (1H, dd, *J* 9.1, 2.7 Hz, H-7), 5.78 (1H, dd, *J* 9.4, 2.9 Hz, H-6), 3.00 (2H, dd, *J* 16.5, 3.0 Hz, H-11), 1.65 (3H, s, H-13), 0.92 (3H, s, H-14), 0.90 (3H, s, H-15), 0.77 (3H, s, H-16); ^{13}C NMR (DMSO, 100 MHz, ppm): δ 173.48 (C-12), 154.01 (C-17), 137.75 (C-9), 137.59 (C-20), 135.24 (C-18), 130.86 (C-19), 129.80 (C-7), 127.51 (C-8), 127.63 (C-6), 52.62 (C-5), 41.02 (C-3), 38.72 (C-10), 34.98 (C-1), 32.34 (C-11), 33.04 (C-4), 32.65 (C-14), 23.00 (C-15), 18.90 (C-2), 18.32 (C-13), 15.29 (C-16). Mass spectrum (EI, 70 eV), m/z (I_{rel}, %): 326 (M^+, 9), 310 (65), 281 (3), 262 (23), 247 (3), 230 (5), 219 (3), 203 (6), 187 (55), 173 (76), 159 (14), 143 (25), 133 (43), 131 (21), 119 (100), 105 (20), 91 (22), 77 (12), 65 (4), 55 (13), 41 (15).

N-(pyrimidin-2-yl)-2-((8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)acetamide ***6c*** (40%), white solid (MeOH), m.p. 84-85°C, $[\alpha]_D^{20}$ = -20.5° (*c* 1.9, $CHCl_3$). IR (ATR) ν 3220, 2926, 1689, 1577, 1512, 1434, 1369, 1265, 1189, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.67 (1H, s, NH), 8.61 (2H, s, H-18, H-20), 7.01 (1H, s, H-19), 5.93, 5.92 (1H, dd, *J* 9.58, 2.8 Hz, H-7), 5.88, 5.85 (1H, dd, *J* 9.66, 2.56 Hz, H-6), 3.40 (1H, d, *J* 17.16 Hz, H-11), 3.24 (1H, d, *J* 17.36 Hz, H-11), 2.08 (1H, t, *J* 2.64 Hz, H-5), 1.80 (3H, s, H-13), 0.95 (3H, s, H-14), 0.94 (3H, s, H-15), 0.84 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 169.66 (C-12), 158.40 (C-18, C-20), 157.34 (C-17), 137.10 (C-9), 130.05 (C-8), 129.02 (C-7), 128.98 (C-6), 116.65 (C-19), 53.00 (C-5), 40.69 (C-3), 39.07 (C-10), 36.93 (C-11), 34.94 (C-1), 32.98 (C-4), 32.36 (C-15), 22.75 (C-14), 18.74 (C-2), 18.37 (C-13), 15.06 (C-16). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 326 (M^+, 0.9), 311 (22), 310 (94), 280 (0.5), 230 (6), 215 (4), 207 (4), 190 (0.6), 187 (7), 173 (7), 165 (2), 145 (10), 131 (11), 119 (14), 115 (8), 108 (3), 96 (100), 91 (14), 79 (11), 69 (4), 63 (0.7), 41 (7).

N-(pyrimidin-2-yl)-2-((8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)-N-(2-((8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)acetyl)acetamide ***7*** (25%), white solid (MeOH), m.p. 145-146°C, $[\alpha]_D^{20}$= -102.5° (*c* 0.9, $CHCl_3$). IR (ATR) ν 2930, 1708, 1647, 1572, 1455, 1403, 1326, 1151, 1133 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.88 (4H, s, H-18, H-18′, H-20, H-20′), 7.36 (2H, s, H-19, H-19′), 5.86, 5.83 (2H, dd, *J* 9.56, 3.0 Hz, H-7, H-7′), 5.77, 5.75 (2H, dd, *J* 9.54, 2.68 Hz, H-6, H-6′), 3.37 (2H, d, *J* 18.04 Hz, H-11, H-11′), 3.26 (2H, d, *J* 18.04 Hz, H-11, H-11′), 2.16 (2H, t, *J* 2.76 Hz, H-5, H-5′), 1.67 (6H, s, H-13, H-13′), 0.94 (6H, s, H-14, H-14′), 0.91 (6H, s, H-15, H-15′), 0.77 (6H, s, H-16, H-16′); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 173.95 (C-12, C-12′), 159.81 (C-17), 159.49 (C-18, C-20), 136.25 (C-9, C-9′), 128.76 (C-8, C-8′), 129.08 (C-7, C-7′), 128.00 (C-6, C-6′), 120.45 (C-19), 52.20 (C-5, C-5′), 40.76 (C-3, C-3′), 38.40 (C-10, C-10′), 36.51 (C-11, C-11′), 34.78 (C-1, C-1′), 32.91 (C-4, C-4′), 32.27 (C-15, C-15′), 22.73 (C-14, C-14′), 18.94 (C-2, C-2′), 18.24 (C-13, C-13′), 15.02 (C-16, C-16′). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 325 (M^+, -231 ($C_{16}H_{23}O$), 4), 311 (22), 310 (99), 281(2), 230 (7), 215 (4), 206 (5), 187 (7), 173 (8), 159 (9), 148 (9), 145 (11), 133 (7), 131 (10), 129 (7), 122 (6), 119 (15), 115 (8), 105 (8), 96 (100), 91 (13), 79 (12), 68 (3), 65 (2), 55 (5), 41 (8).

1-(5-amino-1H-1,2,4-triazol-1-yl)-2-((8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)ethanone ***10*** (30%), oil, $[\alpha]_D^{20}$= -43.0° (*c* 2.5, $CHCl_3$). IR (ATR) ν 3447, 3218, 2928, 1723, 1631, 1517, 1372, 1200, 997, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.47 (1H, s, H-17), 6.91 (2H, s, NH_2),

5.91 (1H, dd, *J* 9.56, 3.0 Hz, H-7), 5.83 (1H, dd, *J* 9.56, 2.64 Hz, H-6), 3.87 (1H, d, *J* 18.5 Hz, H-11), 3.71 (1H, d, *J* 18.6 Hz, H-11), 2.13 (1H, t, *J* 2.80 Hz, H-5), 1.69 (3H, s, H-13), 0.95 (3H, s, H-14), 0.92 (3H, s, H-15), 0.84 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 173.30 (C-12), 156.94 (C-18), 150.12 (C-17), 134.79 (C-9), 129.54 (C-8), 129.00 (C-7), 128.49 (C-6), 52.45 (C-5), 40.75 (C-3), 38.53 (C-10), 33.31 (C-1), 32.94 (C-4), 33.31 (C-11), 32.31 (C-15), 22.71 (C-14), 18.84 (C-2), 18.28 (C-13), 14.93 (C-16). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 314 (M^+, 10), 299 (9), 230 (4), 215 (4), 203 (5), 202 (26), 187 (33), 173 (12), 171 (3), 159 (20), 156 (2), 147 (6), 145 (25), 141 (6), 134 (19), 133 (100), 131 (28), 129 (10), 121 (4), 119 (28), 117 (13), 105 (15), 91 (20), 85 (42), 77 (9), 69 (5), 54 (9), 41 (11).

N-(9H-carbazol-9-yl)-2-((8aS)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-1-yl)acetamide ***11*** (40%), white solid (MeOH), m.p. 185-186°C, $[\alpha]_D^{20}$= -99.2° (*c* 0.5, $CHCl_3$). IR (ATR) ν 3289, 2927, 1733, 1594, 1486, 1443, 1321, 1258, 1163, 1046, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 8.47 (s, NH), 8.05 (2H, d, *J* 8.0 Hz, H-21,24), 7.45 (2H, t, *J* 6.8 Hz, H-19,26), 7.25-7.43 (4H, m, H-18, 20, 25,27), 5.96 (1H, dd, *J* 9.5, 2.6 Hz, H-7), 5.92 (1H, dd, *J* 9.3, 2.2 Hz, H-6), 3.49 (1H, d, *J* 17.5 Hz, H-11), 3.38 (1H, d, *J* 17.0 Hz, H-11), 2.16 (1H, t, *J* 2.1 Hz, H-5), 2.02 (3H, s, H-13), 1.02 (3H, s, H-14), 0.97 (3H, s, H-15), 0.95 (3H, s, H-16); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 169.41 (C-12), 140.12 (C-17,28), 136.84 (C-9), 130.32 (C-8), 129.31 (C-7), 128.86 (C-6), 126.30 (C-19,26), 121.89 (C-22,23), 120.64 (C-21,24), 120.51 (C-20,25), 108.31 (C-18,27), 53.51 (C-5), 41.05 (C-3), 39.27 (C-10), 35.38 (C-1), 33.97 (C-11), 33.12 (C-4), 32.35 (C-15), 22.64 (C-14), 18.85 (C-2), 18.71 (C-13), 15.24 (C-16). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 412 (M^+, 13), 397 (62), 355 (2), 327 (2), 281 (9), 252 (3), 230 (2), 207 (28), 187 (12), 182 (44), 179 (13), 166 (100), 152 (15), 145 (10), 133 (14), 131 (10), 128 (6), 119 (30), 115 (9), 113 (2), 105 (12), 95 (3), 91 (13), 79 (4), 73 (3), 63 (2), 55 (9), 41 (8).

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