SYNTHESIS OF *N*-ACETYL-3-PHENYLISOSERINATES OF SESQUITERPENOID ALCOHOLS OF *Lactarius* ORIGIN

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Dedicated to the memory of Dr Václav Černý.

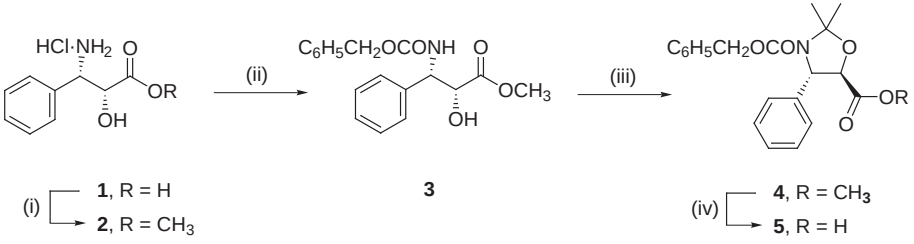
Important biological properties of Taxol® *i.e.* 13-*N*-benzoyl-(2R,3S)-3-phenylisoserinate of baccatin III and also *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserinates of several sesquiterpenoid alcohols of *Lactarius* origin prompted us to synthesize *N*-acetyl-3-phenylisoserinates of latter alcohols in order to check and compare their biological properties. Suitably protected phenylisoserine **5** when reacted with sesquiterpenoid alcohols in the presence of DCC gave appropriate esters **7**. These, after catalytic hydrogenation deprotection produced aminols **8**, which were acetylated and gave the required *N*-acetyl-3-phenylisoserinates **9a**–**9g**.

Keywords: *N*-Acetyl-3-phenylisoserine; Sesquiterpenoids; Alcohols; Amino acids; Taxol; Furandiol; Lactarorufin; *Lactarius* origin.

Study of structure and biological activity of paclitaxel (Taxol®) and its derivatives revealed the importance of the taxol side chain[1]. It was found that baccatin III, which is the diterpenoid part of the molecule of taxol does not have cytostatic activity[2]. Similarly our investigation of antifeedant properties of *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserinates of sesquiterpenoid alcohols showed a significant influence of introduction of *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine into their molecules[3]. Recently we reported antiviral and cytostatic activity of *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserinates sesquiterpenes of *Lactarius* origin[4]. Having considered all these findings we decided to synthesize *N*-acetyl derivatives of (2*R*,3*S*)-3-phenylisoserinates of various sesquiterpenoid alcohols to see the influence of the small amide group on biological properties of these compounds in comparison with those possess-

ing a bulkier group such as benzoyl or Boc. Results of biological investigations will be a subject of future publications.

The first synthesis that we have attempted was analogous to that described for the synthesis of *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserinates of sesquiterpenoid alcohols[3]. This unfortunately failed and we had to carry the synthesis according to the Scheme 1.



(i) MeOH, $SOCl_2$; (ii) $C_6H_5CH_2OCOCl$, $NaHCO_3$; (iii) 2-methoxypropene, pyridinium 4-toluenesulfonate; (iv) LiOH / H_2O

SCHEME 1

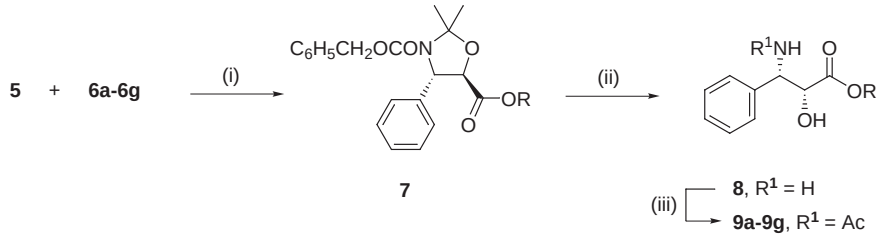
The (2*R*,3*S*)-3-phenylisoserine hydrochloride (**1**) was transformed into its methyl ester **2** in quantitative yield. Subsequently the amide derivative **3** was prepared by the reaction of the ester **2** with benzyl chloroformate in presence of sodium hydrogencarbonate. The hydroxy group of the amide **3** was protected with 2-methoxypropene with the formation of oxazolidine **4**. Alkaline hydrolysis of the ester group in **4** followed by acidification gave the acid **5** ready for esterification with various sesquiterpenoid alcohols in presence of DCC and DMAP. Esters **7** were deprotected by hydrogenolysis using 10% palladium catalyst and gave the phenylisoserine esters **8**. The deprotection step reaction conditions must be mild enough to prevent the decomposition of the sesquiterpenoid part of the molecule. Esters **8** are ready for acylation, when acetic anhydride was used the required *N*-Acetyl-3-phenylisoserinates **9a**–**9g** were prepared from following sesquiterpenoid alcohols: furandiol (**6a**), 8-epi,9-epi-furandiol (**6b**), lactarorufin A (**6c**), 8-epi,9-epi-lactarorufin A (**6d**), 3-*O*-ethyllactarorufin A (**6e**), 3-*O*-ethyl-8-epi-lactarorufin A (**6f**), 5-deoxylactarolide B (**6g**) (Scheme 2).

EXPERIMENTAL

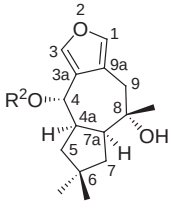
All melting points were measured on a Kofler hot plate and are uncorrected. ^1H and ^{13}C NMR spectra (ppm, δ-scale, coupling constants *J* in Hz) were run at 500 and 125 MHz, respectively (Bruker 500 MHz spectrometer) in $CDCl_3$ unless otherwise noted, using TMS as

internal standard. All signals of carbons were identified by DEPT, 2D ^{1}H and ^{13}C correlation, and ^{1}H and ^{13}C long range correlation. IR spectra (ν in cm^{-1}) were recorded on a Perkin–Elmer 1680 FT spectrometer. Mass spectra were obtained on an AMD 604 mass spectrometer. Column chromatography (CC) was carried out using silica gel, and TLC analyses were conducted on silica gel or RP-18 TLC plates.

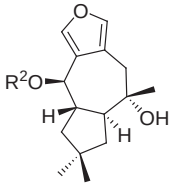
The phenylisoserinates were prepared from sesquiterpenoid alcohols isolated from mushrooms (*Lactarius rufus*, *Lactarius vellereus*, voucher numbers 33550 and 32260, respectively, specimen deposited at the Department of Systematics and Geography of Plants of the University of Warsaw) or synthesized by transformation of natural products. The references of



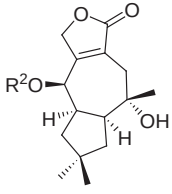
(i) DCC, DMAP/CH_2Cl_2; (ii) H_2, 10% Pd-C/MeOH; (iii) Ac_2O, $NaHCO_3/CH_2Cl_2$



6a, 9a



6b, 9b



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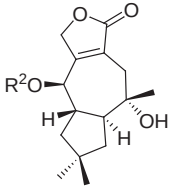
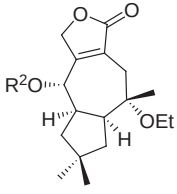
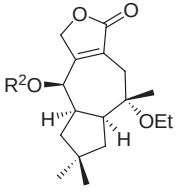


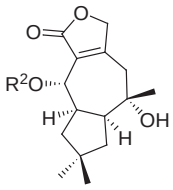
6d, 9d



6e, 9e

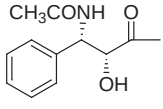


6f, 9f



6g, 9g

6: R^2 = H **9**: R^2 =



SCHEME 2

the procedures of isolation or preparation of all the sesquiterpenes **6a**–**6g** used for the preparation of esters **9a**–**9g** can be found in the recent review[5].

Methyl (2*R*,3*S*)-3-Phenylisoserinate Hydrochloride (**2**)

Phenylisoserine hydrochloride[6] (**1**; 16.0 g, 73.6 mmol) was dissolved in methanol (120 ml) and the sollution chilled to 0 °C. Subsequently thionyl chloride (11.0 ml, 130 mmol) was added dropwise. The reaction mixture was stirred during 3 h and the volatiles were removed by evaporation on rotary evaporator leaving a residue which contained the required ester **2** in quantitative yield. Oil, $[\alpha]_D^{20}$ –19.7 (*c* 1.0, H_2O). UV (EtOH): λ_{max} 205 nm, ε_{max} 9 020. IR (film), ν_{max}: 3 429, 2 955, 1 742, 1 615. ^{1}H NMR (400 MHz, D_2O): 3.68 s, 3 H (OCH_3); 4.70 ABq, 2 H, J_{AB} = 6.9 (H-2, H-3); 7.45–7.49 m, 2 H (arom. H); 7.50–7.54 m, 3 H (arom. H). ^{13}C NMR (100 MHz, D_2O): 53.21 (OCH_3); 57.12 (C-3); 72.06 (C-2); 127.52, 129.49, 130.06, 132.69 (arom. C); 172.40 (C-1). For $C_{10}H_{14}ClNO_3$ (231.7) calculated: 51.79% C, 6.04 % H, 6.04% N; found: 51.84% C, 5.98 % H, 6.21% N.

Methyl *N*-(Benzyloxycarbonyl)-(2*R*,3*S*)-3-phenylisoserinate (**3**)

Ester **2** (2.00 g, 0.96 mmol) dissolved in dichloromethane (40 ml) was treated with ground sodium hydrogencarbonate (20 g, 0.23 mol). Subsequently to the suspension benzyl chloroformate (1.50 ml, 1.07 mmol) was added dropwise with stirring. The reaction mixture was stirred for additional 2 h, the solids were filtered off, and the filtrate was concentrated *in vacuo*. Pure product (**3**; 2.57 g, 86%) was obtained by recrystallisation of the residue from dichloromethane–hexane, m.p. 120–121 °C, $[\alpha]_D^{20}$ –3.79 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$), ν_{max}: 3 435 (OH), 1 734 (C=O). ^{1}H NMR (200 MHz, $CDCl_3$): 3.35 d, 1 H, J_1 = 4.3 (OH); 3.80 s, 3 H (OCH_3); 4.48 dd, 1 H, *J* = 4.3, J_2 = 1.4 (H-2); 5.29 dd, 1 H, J_1 = 9.6, J_2 = 1.4 (H-3); 5.07 s, ($PhCH_2$); 5.09 s ($PhCH_2$); 5.90 d, 1 H, *J* = 9.6 (NH); 7.29–7.40 m, 10 H (arom. H). ^{13}C NMR (50 MHz, $CDCl_3$): 53.0 (OCH_3); 56.5 (C-3); 67.6 ($PhCH_2O$); 73.4 (C-2); 126.7, 127.8, 128.0, 128.1, 128.4, 128.6, 136.1, 138.8 (arom. C); 155.6 (CONH); 173.1 (C-1). LSIMS, *m/z*: 352 $(M + Na)^+$. HR-MS: for $C_{18}H_{19}NNaO_5$ calculated 352.11609, found 352.11781.

Methyl (4*S*,5*R*)-3-(Benzyloxycarbonyl)-2,2-dimethyl-4-phenyloxazolidine-5-carboxylate (**4**)

Amide (**3**) (2.12 g, 6.44 mmol) dissolved in toluene (50 ml) was treated with 2-methoxypropene (2.12 ml, 22.2 mmol) in presence of pyridinium 4-toluenesulfonate (126 mg, 0.50 mmol). The reaction mixture was stirred at ambient temperature for 20 min and subsequently at 90 °C during 1.5 h. The reaction mixture was cooled to room temperature and the next portion of 2-methoxypropene (1.06 ml, 11.1 mmol) was added. Heating was carried out as with the previous portion. Solvent was removed *in vacuo*, and the product **4** (1.61 g, 68%) was isolated by chromatography on silica gel using hexane–ethyl acetate 9 : 1. Oil, $[\alpha]_D^{20}$ –14.81 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$), ν_{max}: 1 703, 1 753 (C=O). ^{1}H NMR (200 MHz, $CDCl_3$): 1.71 s, 3 H (CH_3); 1.80 s, 3 H (CH_3); 3.80 s, 3 H (OCH_3); 4.55 d, 1 H, *J* = 4.7 (H-5); 4.94 ABq, 2 H, *J* = 10.9 ($PhCH_2O$); 5.26 d, 1 H, *J* = 4.7 (H-4); 6.82–7.35 m, 10 H (arom. H). ^{13}C NMR (50 MHz, $CDCl_3$): 25.8 (CH_3); 26.4 (CH_3); 52.6 (OCH_3); 63.3 (C-4); 66.7 ($PhCH_2$); 81.1 (C-5); 97.1 (C-2); 126.3, 127.6, 127.7, 128.2, 128.6, 135.8 (arom. C); 152.1 (NC=O); 170.6 (CO_2CH_3). HR-MS: for $C_{21}H_{23}NO_5$ calculated 369.15762, found 369.15780.

(4S,5R)-3-Benzyloxycarbonyl-2,2-dimethyl-4-phenyloxazolidine-5-carboxylic acid (**5**)

Oxazolidine **4** (1.88 g, 5.10 mmol) dissolved in methanol (30 ml) was treated with 0.5 M aqueous lithium hydroxide (10 ml). After 10 min, the reaction solution was neutralized with 0.1 M hydrochloric acid (50 ml). The precipitated acid **6** was filtered and dried (1.67 g, 92%), m.p. 58–60 °C, $[\alpha]_D^{20}$ –7.41 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$), ν_{max}: 1 708 (C=O). ^{1}H NMR (200 MHz, $CDCl_3$): 1.73 s, 3 H (CH_3); 1.79 s, 3 H (CH_3); 4.57 d, 1 H, *J* = 4.9 (H-5); 4.92 s, 1 H (PhC**H**$_2$O); 4.98 s, 1 H (PhC**H**$_2$O); 5.26 d, 1 H, *J* = 4.9 (H-4); 6.82–7.31 m, 10 H (arom. H). ^{13}C NMR (50 MHz, $CDCl_3$): 26.5 (CH_3); 26.6 (CH_3); 63.5 (C-4); 67.1 ($PhCH_2$); 80.8 (C-5); 97.4 (C-2); 126.3, 127.7, 127.8, 128.2, 128.7, 135.6, 140.2 (arom. C); 152.3 (NC=O); 174.0 (CO_2H). HR-MS: for $C_{19}H_{18}NO_5$ ($M^+ - CH_3$) calculated 340.11850, found 340.11803.

General Procedure for Preparation of *N*-Acetyl Derivatives **9a**–**9g**

Sesquiterpenoid alcohol **6a**–**6g** (2 mmol), the acid **5** (0.852 g, 2.40 mmol), DMAP (0.035 g, 0.28 mmol) and DCC (0.650 g, 3.60 mmol) were dissolved in dichloromethane (50 ml). The reaction mixture was stirred during 15 min, and the *N*,*N*′-dicyclohexyl urea formed during the reaction was filtered off. The filtrate was concentrated *in vacuo*, and the product **7** was isolated by filtration through silica gel in dichloromethane–diethyl ether 93 : 7. An ester **7** (0.65 mmol) was dissolved in methanol (10 ml), and the resulting solution was treated with palladium on charcoal (10%, 30 mg). The ester was deprotected with stoichiometric amount of hydrogen at atmospheric pressure and room temperature. The reaction was followed by TLC. The catalyst was filtered off and the filtrate evaporated on rotary evaporator leaving a residue which was dissolved in dichloromethane (25 ml). To the resulting solution, ground sodium hydrogencarbonate was added to form a thick suspension and subsequently to the reaction mixture acetic anhydride (0.105 ml, 0.85 mmol) while stirring. After 10 min the reaction mixture was treated with water (50 ml) and the product was extracted with dichloromethane (3 × 50 ml). The extract was dried over anhydrous $MgSO_4$, which was filtered off, and the filtrate evaporated *in vacuo* leaving a residue, from which the *N*-acetyl-3-phenylisoserinates **9a**–**9g** were isolated by column chromatography in solvents indicated separately for each compound.

(4S,4aR,7aS,8S)-6,6,8-Trimethyl-4,4a,5,6,7,7a,8,9-octahydrocyclopenta[4,5]cyclohepta[1,2-c]furan-4,8-diol 4-(N-acetyl-(2R,3S)-3-phenylisoserinate) (**9a**). Chromatography dichloromethane–2-propanol 49 : 1. Yield 31%, oil, $[\alpha]_D$ +12.8 (*c* 1.05, $CHCl_3$). IR ($CHCl_3$), ν_{max}: 3 432 (OH), 1 734 (C=O), 1 680 (C=O). ^{1}H NMR (CD_3OD): 1.03 s, 3 H (CH_3-6); 1.06 s, 3 H (CH_3-6); 1.27 s, 3 H (CH_3-8); 1.32 dd, 1 H, *J*(4a,5α) = 5.3, *J*(4a,5β) = 13.5 (H-5β); 1.46–1.54 m, 2 H (H-5α, H-7α); 1.63 dd, 1 H, *J*(7α,7β) = 12.6, *J*(7β,7a) = 7.0 (H-7β); 1.96 s, 3 H (C**H**$_3$CO); 2.40–2.55 m, 3 H (H-4a, H-7a, OH-8); 2.62 d, 1 H, *J*(9α,9β) = 15.4 (H-9α); 2.84 dd, 1 H, *J*(9α,9β) = 15.4, *J*(1,9β) = 1.4 (H-9β); 3.62 bs, 1 H (OH-2′); 4.52 d, 1 H, *J*(2′,3′) = 2.6 (H-2′); 5.54 dd, 1 H, *J*(3′,NH) = 9.1, *J*(3′,2′) = 2.6 (H-3′); 6.01 d, 1 H, *J*(4,4a) = 8.6 (H-4); 6.65 d, 1 H, *J*(NH,3′) = 9.1 (NH); 7.11 s, 1 H (H-3); 7.23 bs, 1 H (H-1); 7.27–7.39 m, 5 H (arom. H). ^{13}C NMR (CD_3OD): 23.2 (CH_3CO); 30.7 (CH_3-8); 30.8 (CH_3-6); 31.1 (CH_3-6); 32.5 (C-9); 35.6 (C-6); 43.5 (C-7); 43.6 (C-5); 44.2 (C-4a); 52.9 (C-7a); 54.6 (C-3′); 71.6 (C-4); 72.1 (C-8); 73.7 (C-2′); 118.6 (C-9a); 124.0 (C-3a); 126.9, 127.9, 128.6, 138.7 (arom. C); 140.3 (C-3); 141.8 (C-1); 169.6 (CH_3CO); 171.7 (C-1′). LSIMS, *m/z*: 478 $(M + Na)^+$. HR-MS: for $C_{26}H_{33}NNaO_6$ calculated 478.22056, found 478.22203.

(4R,4aS,7aS,8S)-6,6,8-Trimethyl-4,4a,5,6,7,7a,8,9-octahydrocyclopenta[4,5]cyclohepta[1,2-c]furan-4,8-diol 4-(N-acetyl-(2R,3S)-3-phenylisoserinate) (**9b**). Chromatography dichloromethane–

2-propanol 99 : 1. Yield 52%, m.p. 180–182 °C, $[\alpha]_D$ +44.9 (*c* 1.02, MeOH). IR ($CHCl_3$), ν_{max}: 1 732 (C=O), 1 679 (C=O). ^{1}H NMR (CD_3OD): 0.96 s, 3 H (CH_3-6); 1.02 s, 3 H (CH_3-6); 1.06 s, 3 H (CH_3-8); 1.31 dd, 1 H, *J*(5α,5β) = 12.7, *J*(4a,5β) = 10.7 (H-5β); 1.54 dd, 1 H, *J*(7α,7β) = 13.2, *J*(7α,7a) = 10.7 (H-7α); 1.74 dd, 1 H, *J*(5a,5β) = 12.7, *J*(4a,5α) = 7.0 (H-5α); 1.82 dd, 1 H, *J*(7α,7β) = 13.2, *J*(7β,7a) = 8.06 (H-7β); 1.98 s, 3 H (CH_3CO); 2.06 dq, 1 H, *J*(4,4a) = *J*(4a,5β) = *J*(4a,7a) = 10.7, *J*(4a,5α) = 7.0 (H-4a); 2.16 m, 1 H (H-7a); 2.55 d, 1 H, *J*(9α,9β) = 13.9 (H-9β); 2.69 d, 1 H, *J*(9α,9β) = 13.9 (H-9α); 4.51 d, 1 H, *J*(2′,3′) = 3.8 (H-2′); 5.45 d, 1 H, *J*(2′,3′) = ___ (H-3′); 5.74 dd, 1 H, *J*(4,3) = 1.5 *J*(4,4a) = 10.7 (H-4); 6.98 t, 1 H, *J*(1,3) = 1.6 (H-3); 7.24 t, 1 H, *J*(1,3) = 1.6 (H-1); 7.27–7.42 m, 5 H (arom. H). ^{13}C NMR (CD_3OD): 20.2 (CH_3-6); 22.7 (CH_3CO); 31.6 (CH_3-6); 31.8 (CH_3-8); 35.2 (C-6); 41.1 (C-9); 44.7 (C-7); 47.4 (C-5); 48.0 (C-4a); 56.3 (C-7a); 56.9 (C-3′); 73.8 (C-8); 75.1 (C-2′); 76.8 (C-4); 120.6 (C-9a); 126.2 (C-3a); 128.4, 128.6, 129.5 (arom. C); 139.8 (C-3); 140.7 (arom. C); 142.0 (C-1); 172.9 (C-1′ and CH_3CO). LSIMS, *m/z*: 478 $(M + Na)^+$. HR-MS: for $C_{26}H_{33}NNaO_6$ calculated 478.22056, found 506.22301.

(4R,4aR,7aS,8S)-4,8-Dihydroxy-6,6,8-trimethyl-1,3,4,4a,5,6,7,7a,8,9-octahydrocyclopenta[4,5]-cyclohepta[1,2-c]furan-1-one 4-(N-acetyl-(2R,3S)-3-phenylisoserinate) (**9c**). Chromatography dichloromethane–2-propanol 97 : 3. Yield 70%, m.p. 141–143 °C, $[\alpha]_D$ +12.6 (*c* 0.98, $CHCl_3$). IR ($CHCl_3$), ν_{max}: 1 743 (C=O), 1 677 (C=O). ^{1}H NMR ($CDCl_3$): 0.94 s, 3 H (CH_3-6); 1.03 s, 3 H (CH_3-6); 1.07 t, 1 H, *J*(7α,7a) = *J*(7β,7a) = 11.9 (H-7α); 1.21 t, 1 H, *J*(5α,5β) = *J*(5α,4a) = 13.5 (H-5); 1.27 s, 3 H (CH_3-8); 1.48 m, 1 H (H-5β); 1.56 m, 1 H (H-7β); 1.95 s, 3 H (CH_3CO); 2.05 bs, 1 H (OH-8); 2.48 d, 1 H, *J*(9α,4β) = 19.1 (H-9α); 2.55–2.67 m, 2 H (H-7a, H-9β); 2.91 m, 1 H (H-4a); 3.93 bs, 1 H (OH-2′); 4.50 bs, 1 H (H-2′); 4.75 bd, 1 H, *J*(3α,3β) = 18.0 (H-3α); 4.88 d, 1 H, *J*(3α,3β) = 18.0 (H-3β); 5.41 dd, 1 H, *J*(3′,NH) = 9.1, *J*(3′,2′) = 1.9 (H-3′); 6.64 bs, 1 H (NH); 6.90 bs, 1 H (H-4); 7.28–7.41 m, 5 H (arom. H). ^{13}C NMR: 23.0 (CH_3CO); 26.3 (CH_3-6); 29.0 (CH_3-6); 32.4 (CH_3-8); 34.9 (C-9); 37.8 (C-6); 42.4 (C-5); 43.9 (C-4a); 44.6 (C-7); 48.9 (C-7a); 54.9 (C-3′); 70.8 (C-3); 73.2 (C-2′); 73.7 (C-8); 74.8 (C-4); 122.2 (C-3a); 127.0, 128.1, 128.8, 138.5 (arom. C); 158.7 (C-9a); 170.3 (CH_3CO); 171.8 (C-1′); 174.9 (C-1). LSIMS, *m/z*: 472 $(M + H)^+$. HR-MS: for $C_{26}H_{34}NO_7$ calculated 472.23353, found 472.23449.

(4R,4aS,7aS,8S)-4,8-Dihydroxy-6,6,8-trimethyl-1,3,4,4a,5,6,7,7a,8,9-octahydrocyclopenta[4,5]-cyclohepta[1,2-c]furan-1-one 4-(N-acetyl-(2R,3S)-3-phenylisoserinate) (**9d**). Chromatography dichloromethane–2-propanol 48 : 2. Yield 40%, m.p. 112–114 °C, $[\alpha]_D$ +33.1 (*c* 1.04, $CHCl_3$). IR ($CHCl_3$), ν_{max}: 3 435 (OH), 1 754 (C=O), 1 676 (C=O). ^{1}H NMR: 1.01 s, 3 H (CH_3-6); 1.06 s, 3 H (CH_3-6); 1.10 s, 3 H (CH_3-8); 1.31 dd, 1 H, *J*(5α,5β) = 12.7, *J*(4a,5β) = 11.0 (H-5β); 1.54 dd, 1 H, *J*(7α,7β) = 13.2, *J*(7α,7a) = 10.3 (H-7α); 1.60 dd, 1 H, *J*(5α,5β) = 12.7, *J*(5α,4a) = 6.7 (H-5α); 1.86 dd, 1 H, *J*(7β,7α) = 13.2, *J*(7β,7a) = 8.2 (H-7β); 2.00 s, 3 H (CH_3CO); 2.12–2.28 m, 2 H (H-4a, H-7a); 2.33 dd, 1 H, *J*(9α,9β) = 15.0, *J*(9α,1) = 1.3 (H-9α); 2.79 d, 1 H, *J*(9α,9β) = 15.0 (H-9β); 4.54 d, 1 H, *J*(2′,3′) = 2.5 (H-2′); 4.66 dd, 1 H, *J*(3α,3β) = 18.2, *J*(3α,9β) = 1.9 (H-3α); 4.74 dd, 1 H, *J*(3α,3β) = 18.2, *J*(3β,4) = 1.1 (H-3β); 5.46 dd, 1 H, *J*(3′,NH) = 9.0, *J*(2′,3′) = 2.4 (H-3′); 5.82 bd, 1 H, *J*(4,4a) = 9.8 (H-4); 6.58 d, 1 H, *J*(NH,3′) = 9.0 (NH); 7.32–7.42 m, 5 H (arom. H). ^{13}C NMR ($CDCl_3$): 20.7 (CH_3-3); 23.1 (CH_3CO); 30.9 (CH_3-6); 31.1 (CH_3-6); 34.3 (C-6); 39.4 (C-9); 43.4 (C-5); 44.1 (C-4a); 46.3 (C-5); 54.5 (C-7a); 54.8 (C-3′); 69.2 (C-3); 72.1 (C-8); 73.4 (C-2′); 77.4 (C-4); 124.2 (C-3a); 127.0, 128.3, 128.8, 138.4 (arom. C); 159.8 (C-9a); 170.3 (CH_3CO); 172.1 (C-1′); 174.1 (C-1). LSIMS, *m/z*: 494 $(M + Na)^+$. HR-MS: for $C_{26}H_{33}NNaO_7$ calculated 494.21547, found 494.21496.

(4S,4aR,7aS,8S)-8-Ethoxy-4-hydroxy-6,6,8-trimethyl-1,3,4,4a,5,6,7,7a,8,9-octahydrocyclopenta-[4,5]cyclohepta[1,2-c]furan-1-one 4-(N-acetyl-(2R,3S)-3-phenylisoserinate) (**9e**). Chromatography

dichloromethane–2-propanol 49 : 1. Yield 43%, oil, $[\alpha]_D^{20}$ +2.4 (*c* 0.93, $CHCl_3$). IR ($CHCl_3$), ν_{max}: 3 433 (OH), 1 754 (C=O), 1 683 (C=O). ^{1}H NMR: 1.03 s, 3 H (CH_3-6); 1.04 t, 3 H, *J* = 7.0 ($OCH_2C\mathbf{H}_3$); 1.07 s, 3 H (CH_3-6); 1.19 dd, 1 H, *J*(4a,5β) = 4.3, *J*(5α,5β) = 13.7 (H-5β); 1.20 s, 3 H (CH_3-8); 1.49 dd, 1 H, *J*(4a,5α) = 7.0, *J*(5α,5β) = 13.7 (H-5α); 1.54 dd, 1 H, *J*(7α,7β) = 13.0, *J*(7α,7a) = 12.9 (H-7α); 1.63 dd, 1 H, *J*(7β,7a) = 6.7, *J*(7α,7β) = 13.0 (H-7β); 1.99 s, 3 H (CH_3CO); 2.51 m, 2 H (H-7a, H-9α); 2.67 m, 1 H (H-4a); 2.70 d, 1 H, *J*(9α,9β) = 16.2 (H-9β); 3.24 m, 1 H and 3.41 m, 1 H ($OC\mathbf{H}_2CH_3$); 3.83 bs, 1 H (OH-2′); 4.39 m, 1 H (H-3α); 4.54 d, 1 H, *J*(2′,3′) = 3.0 (H-2′); 4.65 m, 1 H (H-3β); 5.47 dd, 1 H, *J*(3′,NH) = 8.8, *J*(2′,3′) = 3.0 (H-3′); 5.94 d, 1 H, *J*(4,4a) = 10.5 (H-4); 6.59 d, 1 H, *J*(3′,NH) = 8.8 (NH); 7.28–7.38 m, 5 H (arom. H). ^{13}C NMR: 15.8 (OCH_2CH_3); 23.1 (CH_3CO); 25.2 (CH_3-8); 29.7 (C-9); 30.6 (CH_3-6); 31.1 (CH_3-6); 35.1 (C-6); 41.7 (C-4a); 42.1 (C-7); 43.5 (C-5); 51.0 (C-7a); 54.8 (C-3′); 56.1 (OCH_2CH_3); 69.2 (C-3); 72.9 (C-4); 73.6 (C-2′); 74.8 (C-8); 124.7 (C-3a); 126.8, 128.0, 128.6, 138.3 (arom. C); 158.2 (C-9a); 169.6 (CH_3CO); 172.0 (C-1′); 174.0 (C-1). LSIMS, *m/z*: 522 $(M + Na)^+$. HR-MS: for $C_{28}H_{37}NNaO_7$ calculated 522.24677, found 22.24622.

(4R,4aR,7aS,8S)-8-Ethoxy-4-hydroxy-6,6,8-trimethyl-1,3,4,4a,5,6,7,7a,8,9-octahydrocyclopenta-[4,5]cyclohepta[1,2-c]furan-1-one 4-(N-acetyl-(2R,3S)-3-phenylisoserinate) (**9f**). Chromatography dichloromethane–2-propanol 49 : 1. Yield 26%, oil, $[\alpha]_D^{20}$ +44.9 (*c* 0.92, $CHCl_3$). IR ($CHCl_3$), ν_{max}: 3 435 (OH), 1 753 (C=O), 1 677 (C=O). ^{1}H NMR: 1.00 s, 3 H (CH_3-6); 1.05 s, 6 H (CH_3-6, CH_3-8); 1.13 t, 3 H, *J* = 6.9 ($OCH_2C\mathbf{H}_3$); 1.29 dd, 1 H, *J*(4a,5α) = 10.5, *J*(5α,5β) = 12.6 (H-5α); 1.53 dd, 1 H, *J*(7α,7β) = 12.6, *J*(7α,7a) = 10.3 (H-7α); 1.58 dd, 1 H, *J*(4a,5β) = 6.7, *J*(5α,5β) = 12.6 (H-5β); 1.79 dd, 1 H, *J*(7a,7β) = 8.2, *J*(7α,7β) = 12.6 (H-7β); 1.99 s, 3 H (CH_3CO); 2.25 m, 1 H (H-4a); 2.32 m, 1 H (H-7a); 2.39 dd, 1 H, *J*(9α,9β) = 14.9, *J*(9α,3α) = 2.0 (H-9α); 2.80 d, 1 H, *J*(9α,9β) = 14.8 (H-9β); 3.33 m, 2 H ($OC\mathbf{H}_2CH_3$); 4.54 d, 1 H, *J*(2′,3′) = 2.5 (H-2′); 4.69 ABq, J_{AB} = 18.0 (H-3); 5.46 dd, 1 H, *J*(3′,NH) = 9.0, *J*(2′,3′) = 2.5 (H-3′); 5.79 dd, 1 H, *J*(4,4a) = 10.5, *J*(3,4) = 1.3 (H-4); 6.59 d, 1 H, *J*(3′,NH) = 9.0 (NH); 7.28–7.38 m, 5 H (arom. H). ^{13}C NMR: 16.0 (OCH_2CH_3); 18.0 (CH_3-6); 23.1 (CH_3CO); 30.9 (CH_3-6); 31.1 (CH_3-8); 33.8 (C-9); 34.3 (C-6); 43.3 (C-7); 44.2 (C-4a); 46.1 (C-5); 52.5 (C-7a); 54.8 (C-3′); 56.3 (OCH_2CH_3); 69.3 (C-3); 73.4 (C-2′); 75.9 (C-8); 77.3 (C-4); 124.4 (C-3a); 127.0, 128.3, 128.8, 138.5 (arom. C); 159.4 (C-9a); 170.2 (CH_3CO); 172.1 (C-1′); 174.2 (C-1). LSIMS, *m/z*: 522 $(M + Na)^+$. HR-MS: for $C_{28}H_{37}NNaO_7$ calculated 522.24677, found 522.24736.

(4S,4aR,7aS,8S)-4,8-Dihydroxy-6,6,8-trimethyl-1,3,4,4a,5,6,7,7a,8,9-octahydrocyclopenta[4,5]-cyclohepta[1,2-c]furan-3-one 4-(N-acetyl-(2R,3S)-3-phenylisoserinate) (**9g**). Chromatography dichloromethane–2-propanol 49 : 1. Yield 38%, m.p. 98–101 °C, $[\alpha]_D^{20}$ +9.6 (*c* 0.94, $CHCl_3$). IR ($CHCl_3$), ν_{max}: 3 444 (OH), 1 750 (C=O), 1 654 (C=O). ^{1}H NMR: 0.98 s, 3 H (CH_3-6); 1.04 s, 3 H (CH_3-6); 1.06 m, 1 H (H-7α); 1.14 t, 1 H, *J*(4a,5α) = *J*(5α,5β) = 11.2 (H-5α); 1.29 s, 3 H (CH_3-8); 1.64–172 m, 2 H (H-7β, H-5β); 2.03 s, 3 H (CH_3CO); 2.58 d, 1 H, *J*(9α,9β) = 19.4 (H-9α); 2.64–2.73 m, 2 H (H-7a, H-9a); 2.78 d, 1 H, *J*(9α,9β) = 19.4 (H-9β); 4.60 d, 1 H, *J*(2′,3′) = 1.9 (H-2′); 4.69 bs, 2 H (H-1); 5.61 dd, 1 H, *J*(3′,NH) = 10.0, *J*(2′,3′) = 1.9 (H-3′); 5.82 d, 1 H, *J*(4,4a) = 2.1 (H-4); 6.69 d, 1 H, *J*(NH,3′) = 10.0 (NH); 7.23–7.38 m, 5 H (arom. H). ^{13}C NMR: 23.4 (CH_3CO); 26.0 (CH_3-6); 29.0 (CH_3-6); 32.1 (CH_3-8); 36.4 (C-6); 37.1 (C-9); 42.3 (C-4a); 45.8 (C-5); 46.2 (C-7); 49.0 (C-7a); 53.8 (C-3′); 69.9 (C-4); 72.3 (C-1); 72.6 (C-2′); 73.0 (C-8); 122.6 (C-9a); 126.9, 127.7, 128.5, 138.2 (arom. C); 164.2 (C-3a); 170.1 (CH_3CO); 172.3 (C-1′); 174.0 (C-3). LSIMS, *m/z*: 494 $(M + Na)^+$. HR-MS: for $C_{26}H_{33}NNaO_7$ calculated 494.21547, found 494.21582.

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