Synthesis of New Conjugates of Modified Podophyllotoxin and Stavudine

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To find podophyllotoxin compounds with superior bioactivitiy and less toxicity, a series of novel conjugates of ring-*A*-modified 4-epipodophyllotoxin and stavudine with amino acids as spacers were synthesized, *i.e.*, the *N*-[(2′,3′-didehydro-3′-deoxythymidin-5′-*O*-yl)carbonyl]-substituted L-amino acid *rel*-(3a*R*,4*S*,9*R*,9a*R*)-1,3,3a,4,9,9a-hexahydro-6,7-dimethoxy-1-oxo-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-4-yl esters **8a**–**8f**.

Introduction. – Podophyllotoxin (**1**; *Fig. 1*) is an antimitotic natural product. Its inhibitory activity on cell growth led to the development of the clinically valuable anticancer agents etoposide, teniposide, and the H_2O-soluble prodrug, etoposide phosphate. The cytotoxic mechanism of these drugs is the inhibition of topoisomerase II, unlike the lead compound which inhibits mitosis [1][2]. Through extensive structure–activity relationship studies, several potential drug candidates were synthesized such as GL-331 [3], TOP 53 [4], NK 611 [5], and F11782 [6]. Recently, more complex and diverse analogues have been synthesized either to get more potent compounds or to overcome drug resistance [2][7]. In addition, **1** was used as antiviral agent in the treatment of herpes simplex type I and II, of *condyloma acuminatum* caused by human papilloma virus, and of other venereal and perianal warts [8]. *Lee* and co-workers recently reported modified podophyllotoxin derivatives which show anti-HIV-1 results [9]. Up to now, continued research on the *Podophyllum* lignans is currently focused on structure optimization to generate derivatives with superior pharmacological profiles and broader therapeutic scope, and the development of alternative and renewable sources of **1** [2].

Nucleoside analogues, such as stavudine (=2′,3′-didehydro-3′-deoxythymidine (**2**; *Fig. 1*), are used in clinical treatment as antiviral (*e.g.*, anti-HIV-1) and antitumor agents [10]. Simultaneously, to achieve efficient inhibition of HIV-1 replication in patients and to delay or prevent appearance of drug-resistant viruses, current searches for new anti-HIV agents are focused on discovering compounds with novel structures and different mechanisms of action [11].

To explore the range of biological activities of the podophyllotoxin compound class and find efficient anti-HIV-1 agents with low toxicity, we have synthesized some

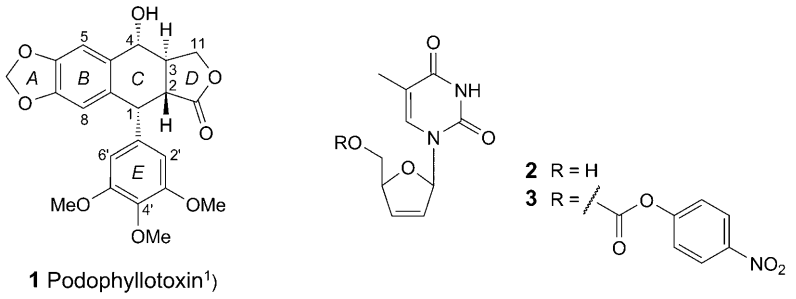


Fig. 1. *Podophyllotoxin* (**1**) *and Stavudine* (**2**)

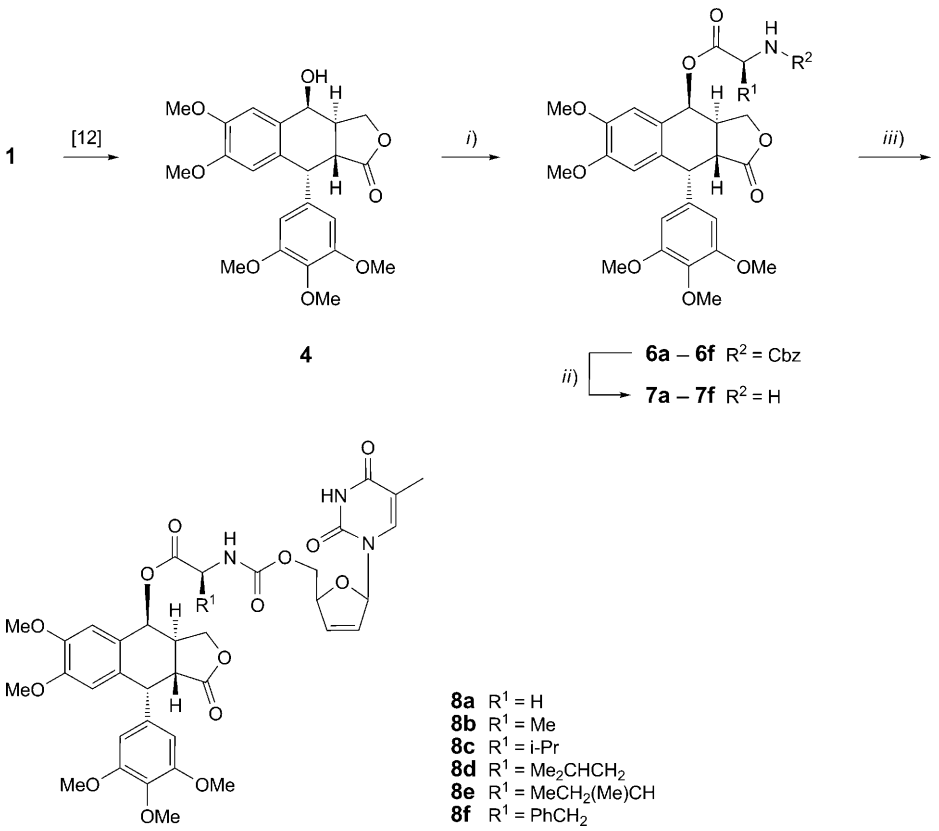
derivatives of podophyllotoxin as anti-HIV-1 agents which were conjugates of different structural podophyllotoxin analogues and **2** [12]. Considering that amino acids are actively transplanted into mammalian tissue, show good H_2O solubility, and are often used as carrier vehicles for some drugs, we synthesized now in this work a series of new conjugates of ring-*A*-modified 4-epipodophyllotoxin and stavudine containing amino acids as spacers.

Results and Discussion. – The synthetic route to the target compounds involved the intermediate 6,7-de-*O*-methylene-6,7-di-*O*-methyl-4-epipodophyllotoxin[1]) (**4**) which was prepared from **1** [13], and **3** (*Fig. 1*) which was synthesized by treatment of **2** with 4-nitrophenyl chloroformate (=4-nitrophenyl carbonochloridate) [14] according to a previously published method [12]. Compound **4** was condensed with the appropriate (benzyloxy)carbonyl(Cbz)-protected amino acids **5a**–**5f** in the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC) and *N*,*N*-dimethylpyridin-4-amine (DMAP) to provide **6a**–**6f** in high yield [15]. Subsequent deprotection of **6a**–**6f** by catalytic hydrogenation yielded **7a**–**7f**, and formation of the carbamate linker was performed by reacting **3** with the appropriate amines **7a**–**7f** in the presence of Et_3N, affording compounds **8a**–**8f**. The structures of the final products **8a**–**8f** were established by IR, ^{1}H- and ^{13}C-NMR spectroscopy, and high-resolution mass spectrometry (HR-MS).

Biological activities of the podophyllotoxin compounds are heavily affected by their configurations at C(4) and C(2)[1]), *i.e.*, the compounds which are β-substituted at C(4) with a *trans*-lactone ring generally show potent biological activities [9][12]. The configuration at C(4) and C(2) of **4** and **8a**–**8f** was confirmed by the coupling constants J(3,4) and J(1,2) in the ^{1}H-NMR spectra or by the 1D-NOEs. In 4-β-substituted compounds, J(3,4) is *ca.* 4.0 Hz due to a *cis* relationship between H–C(3) and H–C(4), *e.g.*, $J(3,4) = 4.2$ and 3.9 Hz for **4** and **8b**, respectively. The 4-α-substituted compounds, however, have $J(3,4) \geq 10.0$ Hz, because H–C(3) is *trans*-positioned to H–C(4). Compounds with a *trans*-lactone moiety have $J(1,2) < 5.0$ Hz owing to a *cis* relationship between H–C(1) and H–C(2), *e.g.*, $J(1,2) = 4.8$ and 3.9 Hz for **4** and **8b**, respectively [16]. We also found that δ(H) of H–C(4) changed from 4.89 to *ca.* 6.00 on

[1]) Arbitrary atom numbering; for systematic names, see *Exper. Part.*

Scheme



i) CbzNHCH(R^1)COOH (**5a**–**5f**), DCC, DMAP, CH_2Cl_2, 1–2 h. *ii*) Pd/C, MeOH. *iii*) **3**, Et_3N, dry DMF, 50°, 5 h.

ester-bond formation. The relative configurations at C(4) and C(2) were also easily demonstrated by the observation of 1D-NOEs (*Fig. 2*). When H–C(4) was irradiated in the ^{1}H-NMR spectrum of **4**, H–C(3), H–C(5), and H–C(2′,6′) were enhanced by 4.06, 1.74, and 1.95%, respectively; however, only H–C(2) was enhanced by 2.62% when H–C(1) of **4** was irradiated. This confirmed that H–C(4) is *cis* to H–C(3) and H–C(2) is *trans* to H–C(3) in **4**. For compounds **8a**–**8f**, similar phenomena were observed as shown in *Fig. 2:* H–C(4) was enhanced by 5.61% when H–C(3) of **8b** was irradiated, and H–C(2) was enhanced by 2.62% when H–C(1) was irradiated. So the configurations at C(4) and C(2) were retained during the formation of the target esters from **4**. The new compounds **8a**–**8f** showed a 100 times lower toxicity than the patented compound podophyllotoxin.

In conclusion, six new conjugates of ring-*A*-modified derivatives of 4-epipodophyllotoxin and stavudine with L-amino acids as spacers were synthesized in high yield. It is necessary to encourage and warrant the synthesis of compounds with further

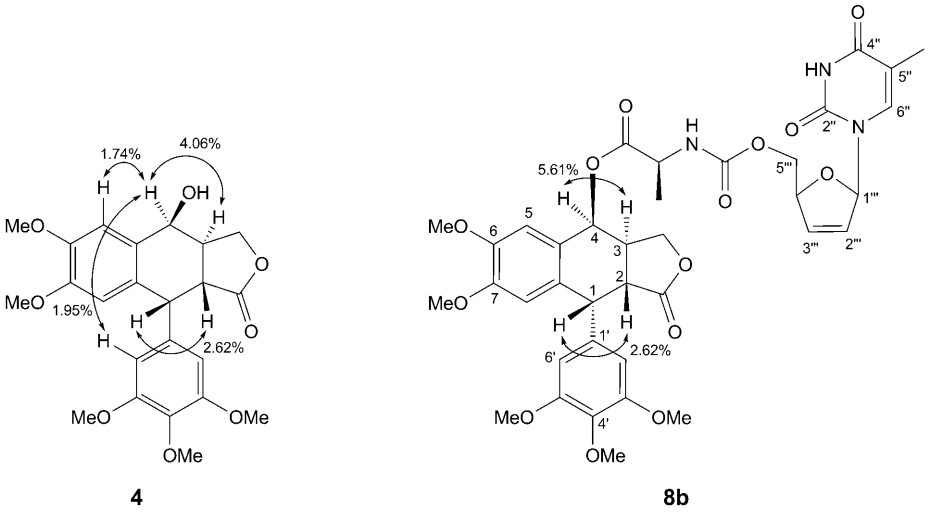


Fig. 2. *1D-NOE of compounds* **4** *and* **8b**

structural modification of podophyllotoxin to both decrease the toxicity and increase the antiviral inhibitory activity.

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Experimental Part

General. Dry solvents were distilled prior to use: CH_2Cl_2, Et_3N, and pyridine were distilled from CaH_2. Podophyllotoxin (**1**) was isolated from a Chinese medicinal herb, *Podophyllum emodi* WALL var. *Chinensis* Sprague; other starting materials and reagents were commercially available and used without further purification, unless otherwise stated. Column chromatography (CC): silica gel (SiO_2; 230–400 mesh; *Qingdao Ocean Chemical Ltd.*, China). TLC: *Merk-60-F*$_{254}$ SiO_2 plates. M.p.: *Kofler* apparatus; uncorrected. Optical rotations: *Perkin-Elmer-341* polarimeter; at 23°. IR Spectra: *Nicolet-5DX-FT-IR* spectrometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian-Mercury-300BB* spectrometer; $CDCl_3$ solns.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Bruker-Daltonics-APEX-II49e* and *-VGZAB-HS* (70 eV) spectrometer; in *m*/*z*.

Compounds **7a**–**7f**: *General Procedure.* A mixture of one of the *N*-Cbz protected L-amino acids **5a**–**5f** (2.0 mmol), **4** (430 mg, 1.0 mmol), and DMAP (100 mg) was stirred in dried DMF (20 ml) for 5 min at r.t. under Ar. DCC (1 mmol) was added, and the mixture was stirred for 1–2 h (TLC monitoring). The mixture was filtered, and the filtrate was evaporated. The residue was separated by CC (CH_2Cl_2/acetone) yielding **6a**–**6f**. Subsequent deprotection of **6a**–**6f** by catalytic hydrogenation in MeOH yielded **7a**–**7f**.

Compounds **8a**–**8f**: *General Procedure.* To a stirred soln. of **3** (0.2 mmol, 78 mg) in DMF (10 ml) were added one of the amines **7a**–**7f** (0.22 mmol, 1.1 equiv.) and dried Et_3N (0.1 ml), under Ar at 50°, and then the mixture was stirred for 5 h under the same conditions. The mixture was concentrated and the residue purified by CC (CH_2Cl_2/acetone 20:1): **8a**–**8f**.

N-*[(2′,3′-Didehydro-3′-deoxythymidin-5′*-O-*yl)carbonyl]glycine* rel-*(3a*R,*4*S,*9*R,*9a*R*)-1,3,3a,4,9,9a-Hexahydro-6,7-dimethoxy-1-oxo-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-4-yl Ester* (**8a**). Yield 98%. M.p. 122–124°. $[\alpha]_D^{23} = -52$ ($c = 0.3$, $CHCl_3$). IR: 3353, 3073, 2939, 2834, 1762, 1710, 1691, 1590,

1511, 1463, 1331, 1244, 1180, 1125, 1082, 1047, 998. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 9.38 (br., 1 NH); 7.19 (br. *s*, H–C(6″)); 6.89 (br. *s*, H–C(5), H–C(1‴)); 6.44 (*s*, H–C(8)); 6.41 (*s*, H–C(2′), H–C(6′)); 6.28 (*d*, *J* = 5.7, H–C(3‴)); 6.05 (*d*, *J* = 3.6, H–C(4)); 5.87 (*t*, *J* = 6.6, 1 NH); 5.82 (*d*, *J* = 6.0, H–C(2‴)); 4.96 (br., H–C(4‴)); 4.39 (*t*, *J* = 9.3, H_a–C(11)); 4.36 (*d*, *J* = 4.2, H–C(1)); 4.29 (br., 2 H–C(5‴), H_b–C(11)); 3.94 (*dd*, *J* = 12.6, 5.7, $CH_2(\alpha)$); 3.87 (*s*, 1 MeO); 3.80 (*s*, 1 MeO); 3.77 (*s*, 2 MeO); 3.67(*s*, 1 MeO); 3.32 (*dd*, *J* = 10.2, 4.5, H–C(2)); 3.10–3.20 (*m*, H–C(3)); 1.83 (*s*, 1 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.4; 169.5; 163.9; 156.0; 153.3; 150.8; 149.4; 147.7; 138.2; 136.6; 135.7; 133.4; 130.2; 126.6; 124.9; 111.8; 110.8; 110.5; 105.2; 89.7; 84.5; 72.5; 68.4; 65.5; 60.7; 56.0; 55.8; 44.4; 44.1; 42.8; 38.1; 30.8; 12.4. ESI-MS: 760 ($[M+Na]^+$), 738, 689, 471, 413. HR-MS: 738.2502 ($[M+H]^+$, $C_{36}H_{40}N_3O_{14}^+$; calc. 738.2505).

N-*[(2′,3′-Didehydro-3′-deoxythymidin-5′-*O*-yl)carbonyl]-*L*-alanine* rel-*(3a*R*,4*S*,9*R*,9a*R*)-1,3,3a,4,9,9a-Hexahydro-6,7-dimethoxy-1-oxo-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-4-yl Ester* (**8b**). Yield 96%. M.p. 110–112°. $[\alpha]_D^{23} = -53$ (*c* = 0.3, $CHCl_3$). IR: 3327, 3071, 2940, 2836, 1770, 1710, 1692, 1590, 1511, 1461, 1421, 1331, 1245, 1176, 1124, 1065, 1038, 997. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 9.12 (br., 1 NH); 7.13 (*s*, H–C(6″)); 6.93 (br. *s*, H–C(1‴)); 6.87 (*s*, H–C(5)); 6.48 (*s*, H–C(8)); 6.40 (*s*, H–C(2′), H–C(6′)); 6.27 (*d*, *J* = 5.7, H–C(3‴)); 6.02 (*d*, *J* = 3.9, H–C(4)); 5.83 (*d*, *J* = 5.4, H–C(2‴)); 5.57 (*d*, *J* = 7.2, 1 NH); 4.95 (br., H–C(4‴)); 4.41 (*t*, *J* = 9.3, H_a–C(11)); 4.37 (*d*, *J* = 3.9, H–C(1)); 4.29 (br., H–C(α), H_b–C(11)); 4.24 (*d*, *J* = 3.9, 2 H–C(5‴)); 3.86 (*s*, 1 MeO); 3.82 (*s*, 1 MeO); 3.78 (*s*, 2 MeO); 3.69 (*s*, 1 MeO); 3.32 (*dd*, *J* = 10.5, 3.9, H–C(2)); 3.15–3.25 (*m*, H–C(3)); 1.87(*s*, 1 Me); 1.40 (*d*, *J* = 6.9, 1 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.3; 172.0; 163.7; 155.2; 153.4; 150.7; 149.3; 147.8; 138.3; 136.7; 135.5; 133.4; 129.9; 126.8; 125.0; 111.8; 110.9; 110.2; 105.1; 89.7; 84.4; 72.3; 68.4; 65.5; 60.8; 56.1; 55.9; 55.8; 53.4; 49.8; 44.6; 44.1; 37.8; 30.9; 17.7; 12.5. ESI-MS: 774 ($[M+Na]^+$), 752 ($[M+1]^+$), 563, 471, 413, 329. HR-MS: 752.2663 ($[M+H]^+$, $C_{37}H_{42}N_3O_{14}^+$; calc. 752.2661).

N-*[(2′,3′-Didehydro-3′-deoxythymidin-5′-*O*-yl)carbonyl]-*L*-valine* rel-*(3a*R*,4*S*,9*R*,9a*R*)-1,3,3a,4,9,9a-Hexahydro-6,7-dimethoxy-1-oxo-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-4-yl Ester* (**8c**). Yield 86%. M.p. 184–185°. $[\alpha]_D^{23} = -34$ (*c* = 0.3, $CHCl_3$). IR: 3318, 3060, 2964, 2939, 1753, 1711, 1693, 1588, 1509, 1463, 1423, 1320, 1242, 1182, 1124, 1082, 1036, 1004, 987. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 9.21–9.17 (br., 1 NH); 8.02 (*s*, 1 NH); 7.18 (*s*, H–C(6″)); 6.98 (br., H–C(1‴)); 6.93 (*s*, H–C(5)); 6.51 (*s*, H–C(8)); 6.43 (*s*, H–C(2′), H–C(6′)); 6.30 (*d*, *J* = 6.0, H–C(3‴)); 6.08 (*d*, *J* = 3.3, H–C(4)); 5.90 (*d*, *J* = 5.4, H–C(2‴)); 5.39 (*d*, *J* = 8.4, 1 NH); 5.00 (br. *s*, H–C(4‴)); 4.46 (*t*, *J* = 9.9, 7.2, H_a–C(11)); 4.39 (*d*, *J* = 3.3, H–C(1)); 4.29 (br., H_b–C(11), H–C(α)); 4.24 (*d*, *J* = 3.9, 2 H–C(5‴)); 3.89 (*s*, 1 MeO); 3.85 (*s*, 1 MeO); 3.82 (*s*, 2 MeO); 3.72 (*s*, 1 MeO); 3.33 (*dd*, *J* = 9.9, 3.6, H–C(2)); 3.10–3.18 (*m*, H–C(3)); 2.10–2.18 (*m*, 1 CH); 1.93 (*s*, 1 Me); 0.92 (*d*, *J* = 6.3, 1 Me); 0.77 (*d*, *J* = 7.2, 1 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.2; 171.3; 163.7; 162.5; 155.7; 153.4; 150.7; 149.4; 147.7; 138.6; 136.7; 135.2; 133.1; 129.9; 127.0; 124.9; 111.8; 111.1; 110.4; 105.1; 89.8; 84.5; 72.2; 68.4; 65.8; 60.8; 59.1; 56.1; 55.9; 55.8; 44.5; 43.9; 37.6; 30.7; 18.8; 17.3; 12.6. ESI-MS: 802 ($[M+Na]^+$), 780 ($[M+H]^+$), 687, 563, 471, 413. HR-MS: 802.2785 ($[M+Na]^+$, $C_{39}H_{45}N_3NaO_{14}^+$; calc. 802.2794).

N-*[(2′,3′-Didehydro-3′-deoxythymidin-5′-*O*-yl)carbonyl]-*L*-leucine* rel-*(3a*R*,4*S*,9*R*,9a*R*)-1,3,3a,4,9,9a-Hexahydro-6,7-dimethoxy-1-oxo-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-4-yl Ester* (**8d**). Yield 86%. M.p. 114–116°. $[\alpha]_D^{23} = -46$ (*c* = 0.3, $CHCl_3$). IR: 3325, 3067, 2957, 2836, 1767, 1710, 1693, 1590, 1511, 1564, 1331, 1244, 1173, 1125, 1083, 1045, 1000. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 8.85 (br., 1 NH); 7.15 (*s*, H–C(6″)); 6.97 (br., H–C(1‴)); 6.89 (*s*, H–C(5)); 6.53 (*s*, H–C(8)); 6.42 (*s*, H–C(2′), H–C(6′)); 6.29 (*d*, *J* = 6.3, H–C(3‴)); 6.04 (*d*, *J* = 3.9, H–C(4)); 5.87 (*d*, *J* = 5.7, H–C(2‴)); 5.29 (*d*, *J* = 8.4, 1 NH); 4.98 (br., H–C(4‴)); 4.44 (*t*, *J* = 9.9, H_a–C(11)); 4.41 (*d*, *J* = 3.6, H–C(1)); 4.31–4.29 (*m*, H–C(α), H_b–C(11)); 4.26 (*d*, *J* = 3.9, 2 H–C(5‴)); 3.89 (*s*, 1 MeO); 3.85 (*s*, 1 MeO); 3.81 (*s*, 2 MeO); 3.73 (*s*, 1 MeO); 3.35 (*dd*, *J* = 10.5, 3.9, H–C(2)); 3.22–3.28 (*m*, H–C(3)); 1.91 (*s*, 1 Me); 1.63–1.61 (*m*, 1 CH, 1 CH_2); 0.91 (*d*, *J* = 2.7, 2 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.3; 172.1; 163.5; 155.5; 154.3; 150.6; 149.3; 147.8; 138.2; 136.7; 135.4; 133.3; 129.8; 126.9; 125.0; 111.8; 111.0; 110.1; 105.1; 89.8; 84.5; 72.1; 65.7; 60.8; 56.1; 55.9; 52.8; 44.6; 44.2; 40.8; 37.7; 24.7; 22.7; 21.7; 12.6. ESI-MS: 816 ($[M+Na]^+$), 794 ($[M+H]^+$), 563, 471, 413. HR-MS: 816.2959 ($[M+Na]^+$, $C_{40}H_{47}N_3NaO_{14}^+$; calc. 816.2959).

N-*[(2′,3′-Didehydro-3′-deoxythymidin-5′-*O*-yl)carbonyl]-*L*-isoleucine* rel-*(3a*R*,4*S*,9*R*,9a*R*)-1,3,3a,4,9,9a-Hexahydro-6,7-dimethoxy-1-oxo-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-4-yl Ester*

(**8e**). Yield 72%. M.p. 182–184°. $[\alpha]_D^{23} = -47$ ($c = 0.3$, $CHCl_3$). IR: 3326, 2966, 2937, 2881, 1754, 1721, 1694, 1664, 1589, 1510, 1463, 1423, 1322, 1270, 1241, 1179, 1124, 1078, 1047, 1005, 987. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 9.11 (br., 1 NH); 7.17 (*s*, H–C(6″)); 6.97 (br., H–C(1‴)); 6.94 (*s*, H–C(5)); 6.49 (*s*, H–C(8)); 6.44 (*s*, H–C(2′), H–C(6′)); 6.30 (*d*, $J = 6.0$, H–C(3‴)); 6.06 (*d*, $J = 4.2$, H–C(4)); 5.90 (*d*, $J = 5.4$, H–C(2‴)); 5.34 (*d*, $J = 9.0$, 1 NH); 5.00 (br., H–C(4‴)); 4.44 (*t*, $J = 7.2$, H_a–C(11)); 4.37 (*d*, $J = 4.2$, H–C(1)); 4.33–4.29 (*m*, H–C(α), H_b–C(11), 2 H–C(5‴)); 3.89 (*s*, 1 MeO); 3.85 (*s*, 1 MeO); 3.82 (*s*, 2 MeO); 3.71 (*s*, 1 MeO); 3.32 (*dd*, $J = 10.2, 4.5$, H–C(2)); 3.20–3.28 (*m*, H–C(3)); 1.92 (*s*, 1 Me); 1.82–1.88 (*m*, 1 CH); 1.02–1.18 (*m*, 1 CH_2); 0.87 (*d*, $J = 6.9$, 1 Me); 0.81 (*t*, $J = 7.2$, 1 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.1; 171.4; 163.6; 155.7; 153.4; 150.7; 149.4; 147.7; 138.6; 136.7; 135.3; 133.1; 130.0; 127.0; 124.9; 111.7; 111.1; 110.6; 105.2; 89.8; 84.5; 72.5; 65.8; 60.8; 58.5; 56.1; 55.9; 55.8; 44.4; 44.0; 37.6; 37.4; 24.7; 15.4; 12.6; 11.5. ESI-MS: 816 ($[M + Na]^+$), 794 ($[M + H]^+$), 563, 471, 413. HR-MS: 816.2950 ($[M + Na]^+$, $C_{40}H_{47}N_3NaO_{14}^+$; calc. 816.2955).

N-*[(2′,3′-Didehydro-3′-deoxythymidin-5′*-O-*yl)carbonyl]*-L-*phenylalanine* rel-*(3a*R,*4*S,*9*R,*9a*R*)-1,3,3a,4,9,9a-Hexahydro-6,7-dimethoxy-1-oxo-9-(3,4,5-trimethoxyphenyl)naphtho[2,3-*c*]furan-4-yl Ester* (**8f**). Yield 87%. M.p. 118–120°. $[\alpha]_D^{23} = -58$ ($c = 0.3$, $CHCl_3$). IR: 3412, 3228, 3014, 2940, 2838, 1751, 1710, 1692, 1590, 1511, 1463, 1426, 1356, 1320, 1245, 1185, 1125, 1082, 1052, 1002, 982. ^{1}H-NMR (300 MHz, $CDCl_3$)[1]): 9.33 (br., 1 NH); 7.12–7.10 (*m*, 1 H of Ph); 7.04 (*s*, H–C(6″)); 7.01 (*t*, $J = 6.9$, 2 H of Ph); 6.94 (br. *s*, H–C(1‴)); 6.90 (*s*, H–C(5)); 6.63 (*d*, $J = 7.2$, 2 H of Ph); 6.44 (*s*, H–C(2′), H–C(6′), H–C(8)); 6.29 (*d*, $J = 6.0$, H–C(3‴)); 6.05 (*d*, $J = 3.0$, H–C(4)); 5.85 (*d*, $J = 6.3$, H–C(2‴)); 5.27 (*d*, $J = 7.8$, 1 NH); 4.98 (br., H–C(4‴)); 4.58 (*q*, $J = 6.9$, H–C(α)); 4.38–4.46 (*m*, H_a–C(11)); 4.35 (*d*, $J = 4.2$, H–C(1)); 4.28 (*d*, $J = 5.1$, 2 H–C(5‴)); 4.20 (*dd*, $J = 12.3$, 3.0, H_b–C(11)); 3.85 (*s*, 1 MeO); 3.84 (*s*, 1 MeO); 3.81 (*s*, 2 MeO); 3.69 (*s*, 1 MeO); 3.25 (*dd*, $J = 10.2$, 4.8, H–C(2)); 3.11–3.15 (*m*, H–C(3)); 2.98–3.08 (*m*, PhCH_2); 1.62 (*s*, 1 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.2; 170.7; 163.8; 155.0; 153.4; 150.7; 149.7; 147.6; 139.2; 136.7; 135.3; 134.8; 133.2; 130.7; 129.0; 128.3; 127.1; 126.9; 124.8; 111.7; 111.5; 111.0; 105.4; 89.6; 84.5; 77.2; 73.2; 68.6; 65.4; 60.8; 56.1; 56.0; 55.9; 54.6; 44.3; 43.5; 37.8; 37.2; 22.5; 12.2. ESI-MS: 850 ($[M + Na]^+$), 828 ($[M + H]^+$), 563, 471, 413. HR-MS: 850.2800 ($[M + Na]^+$, $C_{43}H_{45}N_3NaO_{14}^+$; calc. 850.2794).

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