Electronic supplementary materials

Mendeleev Commun., 2008, **18**, 183–185

Design, synthesis and bioactivity of simplified taxol analogues on the basis of bicyclo[3.3.1]nonane derivatives

Olga N. Zefirova,* Evgeniya V. Nurieva, Heiko Lemcke, Andrei A. Ivanov, Nikolai V. Zyk, Dieter G. Weiss, Sergei A. Kuznetsov and Nikolai S. Zefirov

General information

All reaction temperatures correspond to internal temperatures unless otherwise noted. Solvents for extraction and chromatography were technical grade and distilled from indicated drying agents: petroleum ether (P_2O_5); ethyl acetate (K_2CO_3); methylene chloride and chloroform (P_2O_5); diethyl ether (sodium, benzophenone). Flash and column chromatography were performed on silica gel Acros (40-60 μm). Reaction control was carried out by thin-layer chromatography on "Silufol" plates. If otherwise was not stated ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz correspondingly. Spectra are referenced to residual chloroform (d 7.26 ppm ^{1}H; d 77.0ppm ^{13}C). Chemical shifts are given in ppm (d); multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet). Electron impact mass spectra were obtained with typical voltage of 70 eV. Elemental analysis of synthesised compounds was performed on CNH analyser "Carlo-Erba" ER-20. Infrared spectra (IR) were registered on UR-20 apparatus (thin layer in liquid paraffin) and reported in cm^{-1}. Melting points were measured in block with sealed capillaries and are uncorrected.

5-Bicyclo[3.3.1]non-3-ol (7) was synthesized as described earlier.[1] M.p. 165-167^{o}C. ^{1}H NMR (δ): 1.12–1.65 (m, 7H), 1.78–1.92 (m, 2H), 2.01-2.26 (m, 6H), 3.96 (m, 0.9H, *endo* C<u>H</u>OH, *J* 16.63, 6.4, 2.5 Hz); and 4.41 (m,0.1H, *exo* C<u>H</u>OH, *J* 16.9, 5,18 Hz).

*General protocol for preparation of (2***R,3S***)-phenylisoserine esters*

Step 1. Preparation of protected phenylisoserine esters. To a solution of dimethyloxazolidine-type protected N-Boc-amino acid (1 mmol) and bridgehead alcohol (1.1-1.2 mmol) in dry CH_2Cl_2 (Ar-atmosphere) N,N'-dicyclohexylcarbodi–imide (DCC) (1.3-1.4 mmol) and 4-(dimethylamino)pyridine (DMAP) (0.02 mmol) were added and the reaction mixture was stirred at room temperature. In 12 h a drop of acetic acid was added and in 15 min the solvent was evaporated in vacuum. The residue was dissolved in ethyl acetate and kept at 4^{o}C for 8-12 h. The sediment was filtered and filtrate was washed with 0.1N HCl, water, dried over $MgSO_4$ and evaporated. The product was purified by column chromatography.

Step 2. Cleavage of protection groups. Dimethyloxazolidine-type protected phenylisoserine ester (1 mmol) was dissolved in of 85% formic acid (40-50 ml) and stirred 2 h at room temperature, followed by evaporation of the solvent. The residue was mixed with ethyl acetate (40-50 ml) and saturated aqueous solution of $NaHCO_3$ (40-50 ml), then at vigorous stirring benzoyl chloride (1.1-1.2 mmol) was added dropwise to this mixture. In 15 min the organic layer was separated, washed with solution of $NaHCO_3$, water, dried over $MgSO_4$ and evaporated to dryness. Column chromatography of the residue gave pure (*2R,3S*)-N-benzoylphenylisoserine ester.

5-(Bicyclo[3.3.1]non-3-*endo*-yl) 3-*tert*-butyl (*4S,5R*)-2,2-dimethyl-4-phenyl-1,3-oxazolidine-3,5-dicarboxylate (8) was isolated by column chromatography (1:5, EtOAc/petroleum ether) in 75% yield. ^{1}H NMR (δ): 1.09 (s, 9H, *t*-Bu), 1,19–1,43 (m, 6H), 1,57–1.92 (m, 4H), 1.66 (s, 3H, Me), 1.72 (s, 3H, Me), 2.06-2.08 (m, 4H), 4.37 (d, 1H, OC<u>H</u>CHN, *J* 5.3 Hz), 4.96 (d, 1H, OCHC<u>H</u>N, *J* 5.3 Hz), 5.16 (m, CHO_{endo}, 1H, 16.7, 2.5 Hz), 7.19 (m, 1H, C^{4}H in Ph), 7.21–7.30 (m, 4H, Ph).

Bicyclo[3.3.1]non-3-yl (*2R,3S*)-N-benzoylphenylisoserinate (2) was isolated as white crystals by column chromatography (1:5, then 1:2.5 EtOAc/petroleum ether) in 92% yield as single stereoisomer. Anal. Calcd. for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 74.01; H, 7.10; N, 3.28. ^{1}H NMR (δ): 1.07–1,15 (m, 4H), 1,44–1,63 (m, 7H), 1,63–2.08 (m, 4H), 4.54 (dd, 1H, C<u>H</u>OH, *J* 2,3 Hz), 5.16 (m, 1H, CHO_{endo}), 5.77 (d, 1H, NCH, *J* 11,4 Hz), 7.11 (d, 1H, NH, *J* 9.38 Hz), 7.23–7.52 (m, 8H), 7.74 (m, 2H).

3-*tert*-Butyl 5-(6-oxobicyclo[3.3.1]non-3-*endo*-yl) (*4S,5R*)-2,2-dimethyl-4-phenyl-1,3-oxazolidine-3,5-dicarboxylate (12) was chromatographically isolated as colorless oil (1:10, EtOAc/petroleum ether) in 77% yield. Anal. Calcd. for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found, %: C, 68.36; H, 7.70; N, 2.99. ^{1}H NMR (δ): 1.12 (m, 2H), 1.14–1.20 (m, 2H), 1.24 (s, 9H, *t*-Bu), 1.73 (s, 3H, Me), 1.75 (s, 3H, Me), 1.85–2.4 (m, 7H), 2.67 (m, 1H, *J* 17.58, 3.22 Hz), 4.33 (d, 1H, C^{5}H$_{oxazol}$, *J* 4.4 Hz), 4.82 (m, 1H, HC^3-bicyclic), 5.18 (m, 1H, C^{4}H$_{oxazol}$), 7,24-7.42 (m, 5H, Ph). ^{13}C NMR (δ): 23.82, 25.19,26.08, 27.80 (C<u>Me</u>$_3$), 30.56, 34.23, 35.38, 35.47, 35.90, 35.99, 40.83, 63.76, 69.99, 79.98 (<u>C</u>Me$_3$), 80.80 (<u>C</u>HCO$_2$), 96.13 (N<u>C</u>Me$_2$O), 126.11, 127.48, 128.27, 139.05 (Ph), 151.36 (CO_2), 169.49 (CO_2), 216.33 (C=O bicyclic)

5-[6-(Benzoyloxy)bicyclo[3.3.1]non-3-*endo*-yl] 3-*tert*-butyl (*4S,5R*)-2,2-dimethyl-4-phenyl-1,3-oxazolidine-3,5-dicarboxylate (13) was prepared as described in[2] from compound **12** and

$NaBH_4$ in 72% yield. ^{1}H NMR (δ): 1.10 (m, 2H), 1.14–1.22 (m, 2H), 1.25 (s, 9H, *t*-Bu), 1.70 (s, 3H, Me), 1.73 (s, 3H, Me), 1.78–2.2 (m, 8H), 4.32 (d, 1H, C^5H_{oxazol}, *J* 4.2 Hz), 4.34 (m, 0.88H, *endo* CHOBz, *J* 9.1 Hz), 4.51 (m, 0.12H, *exo* CHOBz, *J* 6.4 Hz), 4.80 (m, 1H, HC^3 bicyclic), 5.18 (m, 1H, C^4H_{oxazol}); 7,24-7.42 (m, 9H, Ph); 7.76 (m, 1H, C^4H in Bz).

7-*endo*-{[(*2R,3S*)-N-Benzoylphenylisoserinyl]oxy}bicyclo[3.3.1]non-2-yl benzoate (3) was isolated as white crystals by column chromatography (1:7, then 1:2 EtOAc/petroleum ether) in 68% yield. M.p. 53-58 °C. $[\alpha]_D^{24}$: -10.4 (c = 0.02, CH_2Cl_2). Anal. Calcd. for $C_{32}H_{33}NO_6$: C, 73.07; H, 6.12; N, 2.80. Found: C, 72.85; H, 6,30; N, 2.65. ^{1}H NMR (δ): 1.14 (m, 4H), 1.19–1.25 (m, 8H), 3.96 (s, 1H, OH), 4.34 (m, 0.88 H, *endo* CHOBz, *J* 9.5 Hz) and 4.51 (m, 0.11H, *exo* CHOB z, *J* 6.2 Hz), 4.76 (dd, 1H, C<u>H</u>OH, *J* 3.5 Hz), 4.80 (m, 1H, HC^7), 5.34 (dd, 1H, *J* 8.9 Hz, CHN), 7,21 (d, 1H, *J* 8.9 Hz), 7.22-7.89 (m, 15H, Ph). ^{13}C NMR (major isomer) (δ): 23.81, 25.40, 26.12, 27.92, 30.69, 32.48, 33.58, 55.39 (CHN), 66.39 (C^7), 72.59 (CHOH), 73.50 (CHOBz), 126.78, 127.05, 128.30, 128.43, 128.66, 129.52, 129.62, 131.60, 133.12, 133.87, 138.66, 139.53, 160.50 (O_2CBz), 166.55 (C^2-bicyclic), 172.28 (NHCOBz).

7-*exo*-Acetoxymethyl-3-*endo*-(tetrahydro-2*H*-pyran-2-yloxy)bicyclo[3.3.1]-nonane (18) was prepared from alcohol **17**[3] (0.1 g, 0.39 mmol) by reaction with acetyl chloride (0.031 g, 0.39 mmol) in pyridine (1 ml) and CH_2Cl_2 (2 ml) at room temperature. In 5 h the mixture was evaporated under reduced pressure, diluted with water and extracted with $CHCl_3$ (2*15 ml). Organic extracts were dried over $MgSO_4$, filtered and evaporated to give acetate **18** (yield 0.106 g, 92%) which was used in the next step without further purification. ^{1}H NMR (δ): 1.10–1.26 (m, 3H), 1.28–1.31 (m, 1H), 1.42–1.45 (m, 1H), 1.48–1.82 (m, 9H), 2.05 (s, 3H), 2.10–2.23 (m, 4H), 2.51–2.57 (m, 1H, C^7H, *J* 23.1, 5.7 Hz), 3.49 (m, 1H, C^3H, *J* 11.2 Hz), 3.86–3.93 (m, 4H, CH_2OAc + CH_2O, *J* 6,3 Hz), 4,68 (m, 1H, CHO). ^{13}C NMR (δ): 19.85, 20.97, 25.55, 26.10, 26.20, 27.32, 29.98, 31.27, 32.79, 34.62, 36.03, 62.61, 69.24, 70.27, 96.97 (CHO), 171.31 (C=O).

7-*exo*-Acetoxymethylbicyclo[3.3.1]non-3-*endo*-ol (19) was synthesised from compound **18** (0.1 g, 0.34 mmol), which was treated with acetic acid (0.1 ml) in water (3 ml) and THF (10 ml) at 40 °C. After 3.5 h the reaction mixture was evaporated under reduced pressure, then diluted with 10 ml of water and extracted with $CHCl_3$ (3*15 ml). Organic extracts were dried over $MgSO_4$, filtered and evaporated. Flash chromatography (1:5 EtOAc/petroleum ether) afforded alcohol **19** as colourless oil (yield 0.070 g, 98 %). Anal. Calcd. for $C_{12}H_{20}NO_3$: C, 67.89; H, 9.50. Found: C, 67.72; H, 9.41. ^{1}H NMR (δ): 1.10–1.15 (m, 4H), 1.21–1.30 (m, 4H), 1.60–1.63 (m, 3H), 2.07 (s,

3H, Me), 2.14 – 2.23 (m, 2H), 2.40 – 2.49 (m, 1H, C^7H, *J* 22.1 Hz), 3.91 – 3.92 (d, 2H, $C\underline{H}_2OAc$, *J* 6.1 Hz), 3.97 –4.01 (m, 1H, C^3H, *J* 15.0, 6.3 Hz).

5-{7-*exo*-[(Acetyloxy)methyl]bicyclo[3.3.1]non-3-*endo*-yl} 3-*tert*-butyl (*4S,5R*)-2,2-dimethyl-4-phenyl-1,3-oxazolidine-3,5-dicarboxylate (20) was isolated by column chromatography as viscous oil (1:10, EtOAc/petroleum ether) with 82% yield. ^1H NMR (δ): 1.13 (s, 9H, *t*-Bu), 1.18–1.52 (m, 8H, bicycle), 1.60–1.63 (m, 2H), 1.17 (s, 3H, Me), 1.79 (s, 3H, Me), 2.03 (s, 3H, $CH_2O_2CC\underline{H}_3$), 2.14–2.22 (m, 2H), 2.30–2.34 (m, 1H, C^7H), 3.82 (d, 2H, $C\underline{H}_2OAc$, *J* 6.1 Hz), 4.43 (d, 1H, $OC\underline{H}CHN$, *J* 5.7 Hz), 5.00 (m, 1H, $OCHC\underline{H}N$), 5.12 (m, 1H, C^3H, *J* 13.9, 7.0 Hz), 7.27–7.36 (m, 5H, Ar). ^{13}C NMR (δ): 20.95, 24.67, 25.85, 27.16, 28.01, 29.96, 30.60, 30.65, 32.73, 32.80, 35.25, 35.58, 64.04 (CHN), 69.95, 70.05, 81.17 ($NCH\underline{C}HO$), 81.60 ($\underline{C}Me_3$), 96.49 ($\underline{C}Me_2$), 126.45,127.60, 128.45, 135.96, 151.61 (C=O), 171.23 (C=O), 175.00 (C=O).

7-*exo*-(Acetoxymethyl)bicyclo[3.3.1]non-3-*endo*-yl (*2R,3S*)-N-benzoylphenyl-isoserinate (4) was isolated by column chromatography as white solid (1:3, then 1:1 EtOAc/petroleum ether) in 80 % yield. M.p. 123 °C. $[\alpha]_D^{26}$: 4.5 (c = 0.01, CH_2Cl_2). Anal. Calcd. for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94, N, 2.92. Found: C, 69.91; H, 6,98, N, 2.75. ^1H NMR (δ): 1.12–1.62 (m, 8H), 1.68 (m, 1H), 2.04 (s, 3H, Me), 2.14–2.22 (m, 4H), 2.48 (m, 1H, C^7H, *J* 9.1 Hz), 3.90–3.95 (m, 2H, $C\underline{H}_2OAc$, *J* 14.8, 10.6, 4.3 Hz), 4.62 (dd, 1H, $C\underline{H}OH$, *J* 2.2 Hz), 5.15 (m, 1H, C^3H, *J* 13.8 Hz), 5.77 (dd, 1H, $C\underline{H}N$, *J* 9.1, 2.15 Hz), 7,14 (d, 1H, NH, *J* 9.2 Hz), 7.30–7.52 (m, 8H, Ar), 7.81 (m, 2H, *o*-H in Bz). ^{13}C NMR (δ): 20.97, 25.88, 27.38, 29.98, 32.63, 32.82, 35.38, 35.51, 54.80 (CHN), 70.33, 70.80, 73.64 (CHOH), 126.90, 127.85, 128.44, 128.65, 130.14, 131.74, 133.55, 138.80, 166.85 (C=O), 171.55 (C=O), 172.40 (C=O).

3-*tert*-Butyl 5-{7-*exo*-[(oxetan-3-yloxy)carbonyl]bicyclo[3.3.1]non-3-*endo*-yl} (4*S*,5*R*)-2,2-dimethyl-4-phenyl-1,3-oxazolidine-3,5-dicarboxylate was prepared from bridgehead alcohol **21** and dimethyloxazolidine-type protected phenylisoserine according to general procedure. Chromatographic purification (1:9 EtOAc/petroleum ether) afforded the title compound in 71% yield. Anal. Calcd. for $C_{30}H_{41}NO_8$: C, 66,28; H, 7,60; N 2,58; Found, %: C, 66,35; H, 7,57; N 2,62. ^1H NMR (δ): 1.13 (s, 9H, *t*-Bu), 1.30–1.85 (m, 8H, bicyclic), 1.71 (s, 3H, Me), 1.78 (s, 3H, Me), 2.18 (m, 4H), 3.16 (m, 1H, $C^7H_{bicyclic}$, *J* 17.6 Hz), 4.45 (d, 1H, C^5H_{oxazol}, 5.5 Hz), 4.57 (dd, 2H, $CH_{2oxetane}$, *J* 6.8, 6.0 Hz), 4,87 (dd, 2H, $CH_2O_{oxetane}$, *J* 5.9 Hz), 5.02 (m, 1H, C^4H_{oxazol}), 5.15 (m, 1H, $C^3H_{bicyclic}$, *J* 11.5, 6.2 Hz), 5.37 (m, 1H, $CHO_{oxetane}$), J 11.5, 6.1 Hz, 7.25–7.40 (5H, m., Ar). ^{13}C NMR (δ): 25.59, 25.71, 28.02, 30.10, 33.14, 33.68, 34.08, 63.95 ($PhC\underline{H}$), 67.60 ($CHO_{oxetane}$), 68.81 ($C^3{}_{bicyclic}$), 77.67 ($CH_2O_{oxetane}$), 79.51 ($\underline{C}(CH_3)_3$), 81.22 (C^5), 96.56 (C^2),

126.32, 127.60, 128.46, 141.15 (Ar), 151.58 (*t*-BuO<u>C</u>O), 169.84(C=O), 175.98 (C=O). The attempt to cleave protecting groups in this ester using general procedure (see Step 2) failed to give the desired product because of the oxetane ring opening. Therefore (*p*-methoxy–phenyl)oxazolidine-type protected phenylisoserine was chosen for preparation of ester **5**.

3-*tert*-Butyl 5-{7-*exo*-[(oxetan-3-yloxy)carbonyl]bicyclo[3.3.1]non-3-*endo*-yl} (4*S*,5*R*)-2-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-3,5-dicarboxylate (22) was isolated by column chromatography (1:5 EtOAc/petroleum ether, then 1:2) as colorless oil in 70% yield. ^{1}H NMR (δ): 1.08 (s, 9H, *t*-Bu), 1.53-1.90 (m, 8H, bicyclic), 2.19-2.25 (m, 4H, bicycl.), 3.05 (m, 1H, J 17.8, 5.3 Hz, C^{7}H), 3.82 (s, 3H, OMe), 4.55 (d, 1H, C^{5}H$_{oxazol}$, J 4.2 Hz), 4.59 (dd, CH$_{2oxetane}$2H, J 7.3, 5.6 Hz,), 4.88 (dd, 2H, CH$_2$O$_{oxetane,}$ J 7.0 Hz), 4.98 (m, 1H, C^{3}H$_{bicyclic}$), 5.34–5,42 (br m, 3H, CH$_{oxetane}$+ C^{4}H$_{oxazol}$), 6,89 (d, 2H, Ar, J 8.84 Hz), 7.28–7.39 (m, 7H, Ph). ^{13}H NMR (δ):.25.64, 25.59, 28.12, 30.07, 33.18, 33.80, 33.88, 55.15 (OMe), 63.67 (CHN), 67.46, 68.82, 77.50 (CH$_{2oxetane}$), 81.16 (<u>C</u>Me$_3$), 91.11 (NCHO), 113.43, 126.90, 127.84, 128.38, 130.77, 139.47, 153.67, 159.81, 169.47, 175.84. MS (MALDI) m/z found for (M+K)$^+$ 660.

Oxetan-3-yl 7-*endo*-[(2*R*,3*S*)-3-N-(*tert*-butoxycarbonyl)phenylisoseryloxy]bicyclo[3.3.1]no–nane-3-*exo*-carboxylate (5). Protected ester **22** (1 mmol) and *p*-toluenesulfonic acid monohydrate (1.1 mmol) were dissolved in methanol (30 ml) and stirred 2 h at room temperature. Reaction mixture was neutralized (by $NaHCO_3$) and evaporated. The residue was mixed with ethyl acetate (40-50 ml), washed with water, dried over $MgSO_4$ and evaporated to dryness. Column chromatography of the residue (1:5 EtOAc/petroleum ether, then 1:1) gave pure product in 82% yield. Anal. Calcd. for $C_{27}H_{37}NO_8$: C, 64.40; H, 7.41; N, 2.78. Found, %:C, 64.36; H, 7.63; N, 2.71. ^{1}H NMR (δ): 1.43 (s, 9H, *t*-Bu), 1.55–1.92 (m, 8H, bicycle), 2.18–2.29 (m, 4H, bicyclic), 3.18 (s, 1H, OH), 3.32 (m, 1H, C^{7}H, *J* 12.3, 8.0 Hz), 4.48 (d, 1H, *J* 5,2 Hz), 4.61 (dd, 2H, CH$_{2oxetane}$, *J* 7.2, 5.6 Hz), 4.87 (m, 2H, CH$_{2oxetane}$, *J* 8.9, 7.2 Hz), 5.20 (m, 1H), 5.29 (m, 1H, *J* 9.0 Hz), 5.42–5.47 (br m, 2H, CH$_{oxetane}$+NH), 7.30-7.41 (5H, Ar). ^{13}C NMR (δ): 25.68, 28.26, 30.09, 33.19, 33.76, 34.17, 55.80 (CHN), 67.74, 69.88, 73.90 (CHOH), 77.58 (CH$_{2oxetane}$), 126.68, 127.68, 128.56, 139.45, 154.95, 169.57, 175.98. MS (MALDI) m/z found for (M+K)$^+$ 542.

---

[1] T. Momose and O. Muraoka, *Chem. Pharm. Bull.*, **1978**, *26*, 228.
[2] O. N. Zefirova, E. V. Selunina, V. N. Nuriev, N. V. Zyk and N. S. Zefirov, *Zh. Org. Khim*. **2003**, *39*, 880 (*Russ. J. Org. Chem*., **2003**, *39*, 831).
[3] O. N. Zefirova, E. V. Nurieva, V. N. Nuriev, K. A. Potekhin, A. V. Maleev, N. V. Zyk and N. S. Zefirov, *Mendeleev Commun*., **2007**, *17*, 332.