ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 8, pp. 1134–1138. © Pleiades Publishing, Ltd., 2008.
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Synthetic Approaches to Physiologically Active Polycyclic Compounds: VII.* Synthesis of 2-(7-Hydroxybicyclo-[3.3.1]non-3-ylmethyl)propane-1,3-diol

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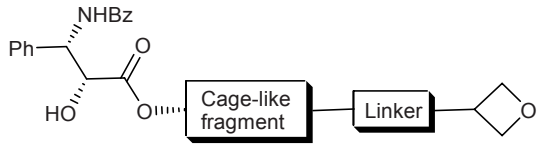
Received January 5, 2008

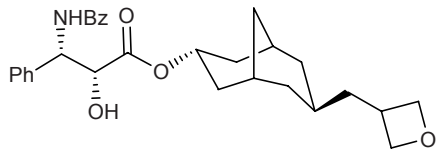
Abstract—2-(*endo*-7-Hydroxybicyclo[3.3.1]non-*exo*-3-ylmethyl)propane-1,3-diol was synthesized in seven steps starting from *endo*-7-hydroxybicyclo[3.3.1]nonane-*exo*-3-carboxylic acid. The title compound attracts interest as intermediate product for the synthesis of potential tubulin ligands.

DOI: 10.1134/S1070428008080058

In the framework of our studies on the synthesis of simple analogs of the known antitumor agent taxol [1–6] we are developing methods for the preparation of substituted adamantanes and bicyclo[3.3.1]nonanes containing an amino acid fragment [(2*R*,3*S*)-*N*-benzoylphenylisoserine] and an oxetane ring connected to the cage-like fragment through a short linker [7].

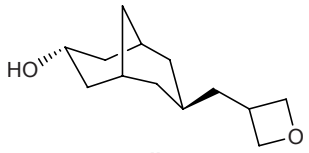


Simulation of docking of such structures into the taxol binding site on β-tubulin** showed that the length of the linker should be equal to the length of one methylene group to ensure the same orientation of the amino acid residue as in the taxol molecule (structure **I**).



I

Provided that the substituent on C^7 has *exo* orientation, the oxygen atom in the oxetane ring of molecule **I** can be involved in hydrogen bonding with the amino group in the main Thr276 chain of tubulin, in a way similar to the natural molecule (Fig. 1).



II

We planned to synthesize compound **I** via esterification of the corresponding cage-like alcohol **II** with amino acid [8]. In the initial stage of the development

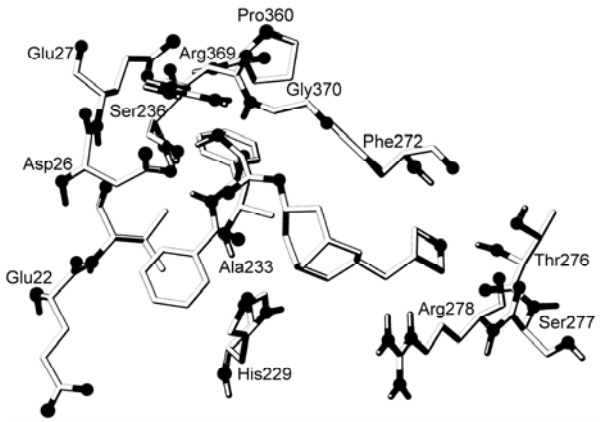
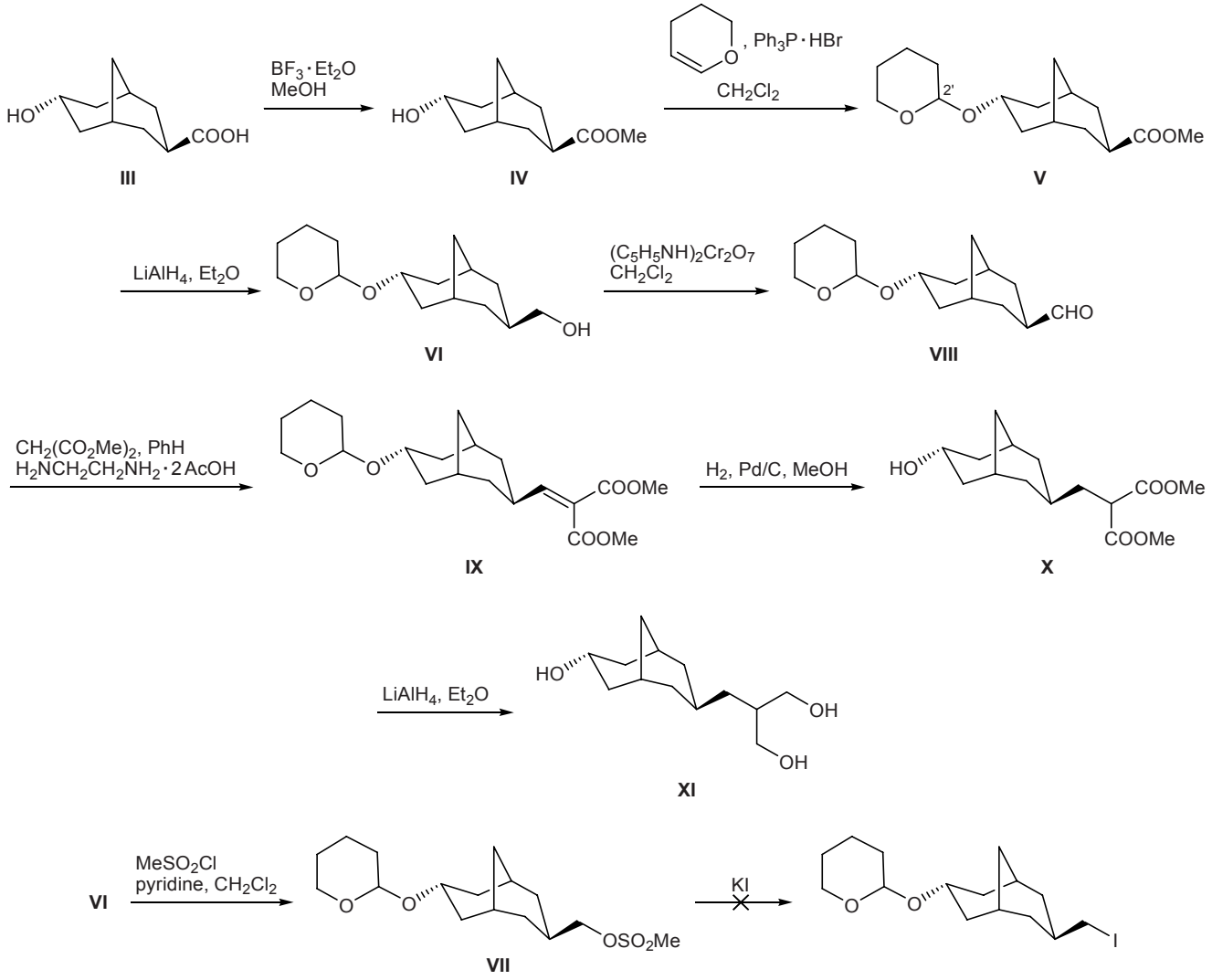


Fig. 1. Docking of compound **I** into the taxol binding site on β-tubulin.

* For communications I–VI, see [1–6].

** The model was kindly provided by Prof. J. Snyder (USA). Molecular modeling studies were performed in collaboration with the Prof. K.A. Jacobson Laboratory (National Institute of Diabetes & Digestive & Kidney Diseases, NIH, USA).

Scheme 1.



of synthetic procedure we tried to obtain an intermediate compound capable of forming oxetane fragment, namely 2-(*endo*-7-hydroxybicyclo[3.3.1]non-*exo*-3-ylmethyl)propane-1,3-diol (**XI**). It should be noted that ring closure of 1,3-diols is one of the main methods for building up oxetane ring (oxetan-3-ol and the corresponding taxol fragment are obtained just in this way) [7, 9, 10].

As starting compound for the synthesis of diol **XI** we used *endo*-7-hydroxybicyclo[3.3.1]nonane-*exo*-3-carboxylic acid (**III**) which was prepared by alkaline hydrolysis of 2-oxahomoadamantan-3-one. Acid **III** is a template with the required configuration of substituents (*endo*, *exo*) [11, 12]; following standard procedures including protection of the hydroxy group and reduction of the carboxy group, we obtained alcohol **VI** (Scheme 1). We tried to effect further modification of alcohol **VI** in two ways. However, our attempt to convert it into the corresponding iodide (with a view to react the latter with dimethyl malonate sodium salt) was unsuccessful: only the initial compound was isolated in the reaction of methanesulfonate **VII** with potassium iodide in acetone [9]. On the other hand, we succeeded in oxidizing compound **VI** to aldehyde **VIII** for subsequent condensation with dimethyl malonate. The oxidation of **VI** with pyridinium dichromate gave aldehyde **VIII** in 69% yield. Swern oxidation of compound **VI** was characterized by very poor yield, so that aldehyde **VIII** could not be isolated as individual substance.

The condensation of aldehyde **VIII** with dimethyl malonate afforded compound **IX** which was reduced with hydrogen in methanol over palladium catalyst. The reduction was accompanied by removal of the tet-

rahydropyranyl protection with formation of hydroxy ester **X**. The subsequent reduction of **X** with lithium tetrahydridoaluminate gave the target triol **XI**. The structure of the isolated compounds (compounds **V**–**XI** were previously unknown) was proved by elemental analysis and ^{1}H and ^{13}C NMR spectroscopy. Studies on the synthesis of compounds **II** and **I** from triol **XI** are now in progress.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer at 400 and 100 MHz, respectively, using hexamethyldisiloxane (for **IV**) or tetramethylsilane as internal reference. The progress of reactions was monitored by TLC on Silufol UV-254 plates. Column chromatography was performed on silica gel (Acros, 40–60 μm).

Methyl *endo*-7-hydroxybicyclo[3.3.1]nonane-*exo*-3-carboxylate (IV) was synthesized according to standard procedure from 2 g (11 mmol) of acid **III** and 2 ml of boron trifluoride–diethyl ether complex in 20 ml of methanol. The product was purified by chromatography using ethyl acetate–petroleum ether (bp 40–60°C) (3:1) as eluent. Yield 1.9 g (90%), colorless crystals (in the cold), mp 50–51°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.21–1.44 m (3H), 1.66–1.79 m (3H), 2.02–1.90 m (3H), 2.26–2.43 m (4H), 3.20 m (1H, 3-H), 3.52 s (3H, CH_3O), 3.84 m (7-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.01 (CH_2), 29.70, 30.01, 34.61 (CH_2), 36.18, 51.42 (OCH_3), 63.77 (CHOH), 177.68 (C=O).

Methyl *endo*-7-(tetrahydro-2*H*-pyran-2-yloxy)bicyclo[3.3.1]nonane-*exo*-3-carboxylate (V) was synthesized according to standard procedure from 0.66 g (3.3 mmol) of hydroxy ester **IV** and 0.48 ml (5.5 mmol) of 3,4-dihydro-2*H*-pyrane in 20 ml of methylene chloride in the presence of 0.07 g of triphenylphosphine hydrobromide. Yield 0.92 g (98%). Yellowish oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.28–1.31 m (1H), 1.42–1.45 m (1H), 1.56–1.62 m (8H), 1.71–1.84 m (4H), 2.06–2.19 m (4H), 3.42–3.52 m (2H, 7-H, 3-H), 3.67 s (3H, CH_3), 3.88–3.95 m (2H, CH_2O), 4.70–4.72 m (1H, OCHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (a mixture of two stereoisomers at $C^{2'}$): 19.73, 26.16, 26.24, 30.55, 31.27, 33.18, 34.08, 34.53, 34.57, 35.02 (C^3), 51.43 (CH_3), 62.52 (CH_2O), 68.71 (C^7), 96.97 (OCHO), 177.85 (C=O). Found, %: C 68.11; H 9.18. $C_{16}H_{26}O_4$. Calculated, %: C 68.06; H 9.28.

endo*-7-(Tetrahydro-2*H*-pyran-2-yloxy)bicyclo[3.3.1]non-*exo*-3-ylmethanol (VI).** Compound **V**, 0.50 g (1.8 mmol), was added to a suspension of 0.12 g (3 mmol) of $LiAlH_4$ in 20 ml of diethyl ether, the mixture was heated for 3 h under reflux, and 0.2 ml of water was added dropwise. The product was purified by flash chromatography using ethyl acetate–petroleum ether (bp 40–60°C) (1:3) as eluent. Yield 0.44 g (97%), colorless crystals, mp 86–87°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10–1.38 m (5H), 1.55–1.86 m (10H), 2.16–2.35 m (5H), 3.46–3.52 m (3H, CH_2OH, 3-H), 3.89–3.94 m (2H, CH_2O), 4.69 m (1H, OCHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (a mixture of two stereoisomers at $C^{2'}$): 19.82, 26.19, 26.28, 29.88, 30.41, 31.29, 32.83, 34.62, 36.02, 36.12, 62.41 (CH_2O), 69.27 (CH_2OH), 69.32 (C^7), 96.14, 96.84 (OCHO). Found, %: C 70.50; H 10.26. $C_{15}H_{26}O_3$. Calculated, %: C 70.83; H 10.30.

***endo*-7-(Tetrahydro-2*H*-pyran-2-yloxy)bicyclo[3.3.1]non-*exo*-3-ylmethyl methanesulfonate (VII)** was synthesized according to standard procedure from 0.46 g (1.8 mmol) of alcohol **VI** in 20 ml of methylene chloride and 0.15 ml (2 mmol) of methanesulfonyl chloride in the presence of 0.2 ml of pyridine. The product was purified by flash chromatography using ethyl acetate–petroleum ether (bp 40–60°C) (1:3) as eluent. Yield 0.51 g (85%), oily liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.19–1.85 m (14H), 2.09–2.29 m (4H), 2.76–2.83 m (1H, 3-H, J = 12.72, 6.06 Hz), 3.01 s (3H, CH_3), 3.49–3.53 m (1H, 7-H), 3.87–3.94 m (2H, C**H**$_2$OCH), 4.05 d (2H, C**H**$_2$OMs, J = 6.06 Hz), 4.68 m (1H, OCHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (a mixture of two stereoisomers at $C^{2'}$): 19.90, 26.05, 26.15, 27.95, 30.51, 31.28, 33.13, 34.94, 35.08, 35.17, 37.21 (CH_3); 62.70 (CH_2O), 68.87 (C^7), 75.89 (**C**H_2OMs), 97.10 (OCHO). Found, %: C 57.78; H 8.45. $C_{16}H_{28}O_5S$. Calculated, %: C 57.80; H 8.49.

***endo*-7-(Tetrahydro-2*H*-pyran-2-yloxy)bicyclo[3.3.1]nonane-*exo*-3-carbaldehyde (VIII).** Pyridinium dichromate, 1.1 g (3 mmol), was added to a solution of 0.5 g (2 mmol) of alcohol **VI** in 30 ml of methylene chloride. The mixture was stirred for 2 h at room temperature and filtered, the precipitate was washed with methylene chloride, and the filtrate was evaporated. The residue was purified by chromatog-

***** The syntheses of compounds **IV**–**VI** were performed with participation of student M.V. Kiryukhin (Faculty of Chemistry, Moscow State University).

raphy using ethyl acetate–petroleum ether (bp 40–60°C) (1:7) as eluent. Yield 0.34 g (69%), oily liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24–1.43 m (1H), 1.46–1.50 m (9H), 1.67–1.88 m (4H), 2.02–2.20 m (4H), 3.39–3.52 m (2H, 3-H, 7-H), 3.86–3.94 m (2H, C**H**$_2$OCH), 4.68 m (1H, OCHO), 9.63 m (1H, CHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (a mixture of two stereoisomers at $C^{2'}$): 19.86, 25.50, 25.85, 25.97, 31.07, 31.27, 31.30, 33.45, 35.25, 41.83 (C^3); 62.65 (CH_2O), 68.55 (C^7), 97.10 (OCHO), 205.86 (CHO).

Dimethyl 2-{*endo*-7-(tetrahydro-2*H*-pyran-2-yloxy)bicyclo[3.3.1]non-*exo*-3-ylmethylidene}malonate (IX). A mixture of 0.30 g (1.2 mmol) of aldehyde **VIII**, 0.16 mg (1.2 mmol) of dimethyl malonate, and 0.01 g of ethylenediammonium diacetate in 50 ml of benzene was heated for 8 h in a flask equipped with a Dean–Stark trap. The product was isolated by chromatography using ethyl acetate–petroleum ether (bp 40–60°C) (1:7) as eluent. Yield 0.23 g (52%), colorless crystals, mp 82–84°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.09–1.12 m (1H), 1.19–1.37 m (4H), 1.48–1.68 m (8H), 1.76–1.81 m (1H), 2.09–2.19 m (4H), 3.14–3.23 m (1H, 3-H), 3.42–3.46 m (1H, 7-H), 3.73 s (3H, CH_3), 3.81 s (3H, CH_3), 3.83–3.87 m (2H, CH_2O), 4.60 m (1H, OCHO), 6.82 d (1H, CH=C, J = 9.85 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (a mixture of two stereoisomers at $C^{2'}$): 20.07, 25.48, 25.74, 25.85, 29.30, 29.57, 31.20, 32.53, 34.35, 37.84, 52.19 (CH_3), 52.25 (CH_3), 62.89 (CH_2O), 68.72 (C^7), 97.15 (OCHO), 126.26 (CH=**C**), 155.35 (**C**H=C), 164.64 (C=O), 165.91 (C=O). Found, %: C 65.55; H 8.31. $C_{20}H_{30}O_6$. Calculated, %: C 65.55; H 8.25.

Dimethyl 2-(*endo*-7-hydroxybicyclo[3.3.1]non-*exo*-3-ylmethyl)malonate (X). A mixture of 0.12 g (0.3 mmol) of compound **IX** and 0.10 g of Pd/C in methanol was stirred for 12 h at room temperature in a stream of hydrogen (1 atm). The mixture was filtered, the filtrate was evaporated, and the residue was purified by flash chromatography using ethyl acetate–petroleum ether (bp 40–60°C) (1:5) as eluent. Yield 0.09 g (99%), oily liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.98–1.15 m (5H), 1.55–1.58 m (3H), 1.77–1.81 m (2H), 1.92–2.02 m (2H), 2.07–2.17 m (4H), 3.44–3.48 t [1H, C**H**$(CO_2CH_3)_2$, J = 7.71 Hz], 3.72 s (6H, OCH_3), 3.89–3.92 m (1H, 7-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.42, 26.55, 29.40, 36.34, 36.40, 39.40, 49.29, 52.51 (CH_3), 64.77 (C^7), 170.20 (C=O). Found, %: C 63.40; H 8.48. $C_{15}H_{24}O_5$. Calculated, %: C 63.36; H 8.51.

2-(*endo*-7-hydroxybicyclo[3.3.1]non-*exo*-3-ylmethyl)propane-1,3-diol (XI). Compound **X**, 0.08 g (0.3 mmol), was added to a suspension of 0.04 g (1 mmol) of $LiAlH_4$ in 20 ml of diethyl ether, the mixture was heated for 3 h under reflux, and 0.1 ml of water was added. The organic phase was separated by decanting, and the residue was washed with boiling THF (3×10 ml). The combined organic extracts were dried over sodium sulfate and evaporated, and the residue was purified by chromatography using ethyl acetate–petroleum ether (bp 40–60°C) (1:1) as eluent. Yield 0.057 g (95%), oily liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.98–1.13 m (5H), 1.20–1.29 m (2H), 1.58–1.62 m (3H, J = 12.5 Hz), 1.83–1.88 m (1H, J = 10.5, 7.0, 3.4 Hz), 2.07–2.22 m (5H), 3.20–3.45 br.m (3H, OH), 3.59–3.64 d.d (2H, C**H**$_2$OH, J = 10.8, 7.2 Hz), 3.74–3.78 d.d (2H, C**H**$_2$OH, J = 10.8, 7.2 Hz), 3.91–3.99 m (1H, 7-H, J = 15.9, 8.22 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 24.33, 26.76, 29.60, 35.55, 36.37, 38.92, 40.31, 64.94 (C^7), 65.63 (CH_2OH). Found, %: C 68.42; H 10.64. $C_{13}H_{24}O_3$. Calculated, %: C 68.38; H 10.59.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 07-03-12110-ofi), by the Chemistry and Materials Science Department of the Russian Academy of Science, and by the Program for Support of Leading Scientific Schools (project no NSh-2552.2006.3).

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