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Synthesis of Adamantane and Bicyclo[3.3.1]nonane Derivatives with the Oxetane Moiety

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Abstract—A method of synthesis of 3-hydroxyoxetane esters with adamantane- and bicyclo[3.3.1]nonane-containing carboxylic acids is reported.

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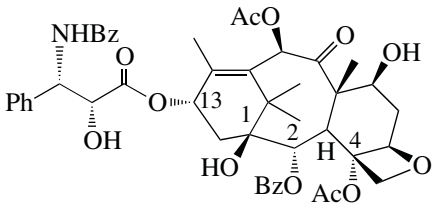
As part of our research on design of simplified analogues of the natural anticancer drug taxol (**1**), we synthesized a number of adamantane and bicyclo[3.3.1]nonane derivatives containing (2*R*,3*S*)-*N*-benzoyl-β-phenylisoserine, the substituent at the C-13 atom in taxol [1–5]. This moiety is very important for binding to tubulin, a target protein of the natural molecule in the body. Into some of the synthesized cage compounds, this amino acid fragment was introduced in combination with other groups, –OH, –OBz, and –OAc, which model the substituents at, respectively, the C-1, C-2, and C-4 atoms of taxol [6]. These groups also make a significant contribution to the interaction of taxol with the protein. Since the oxygen atom of the oxetane moiety of the natural molecule is also involved in binding to tubulin through the hydrogen bond with the Thr 276 residue, we were interested in introducing the oxetane ring as the second substituent into *N*-benzoylphenylisoseryloxyadamantane (or -bicyclo[3.3.1]nonane). The oxetane ring is linked with the cage through a small bridge (linker) (Fig. 1a).

The problem of synthesis of the structures shown in Fig. 1a can be solved in several steps. In this work, we suggest ways to obtain an OH–cage–linker–oxetane moiety, to which the amino acid substituent will be attached at the alcohol group. As the linker in this moiety, the ester group is used (Fig. 1b).

We have developed the scheme for the synthesis of 3-hydroxyoxetane, which is a combination of several available procedures [7–10] (Scheme 1). At the first stage, glycerol reacted with benzaldehyde under classical conditions of formation of acetals. Benzylation of the resulting compound **2** at the OH group yielded 2-phenyl-5-benzyloxy-1,2-dioxane **3**, which was treated with 80% aqueous acetic acid to give diol **4**.

The oxetane ring in compound **4** was closed by two methods [7, 9]. In one method, diol **4** was converted to its monotosylate, which was then introduced into the reaction with sodium hydride. It is worth noting that this method turned out to be unsuitable for preparative purposes due to the formation of ditosylate as a byproduct at the first stage, as well as due to the necessity of separation and purification of the intermediate monotosylate, which considerably decreases the yield of product **5** (14% from **4**).

As a second method of formation of the oxetane ring, we used a one-pot procedure, which was applied to diol **4** for the first time and allowed us to obtain 3-benzyloxyoxetane **5** in 44% yield (from **4**). It is worth noting that the product thus obtained was contaminated with impurities (about 10% according to ^{1}H NMR).



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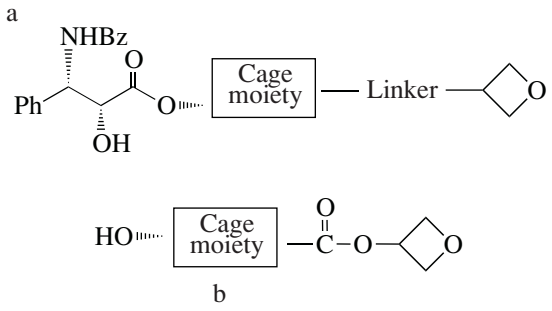
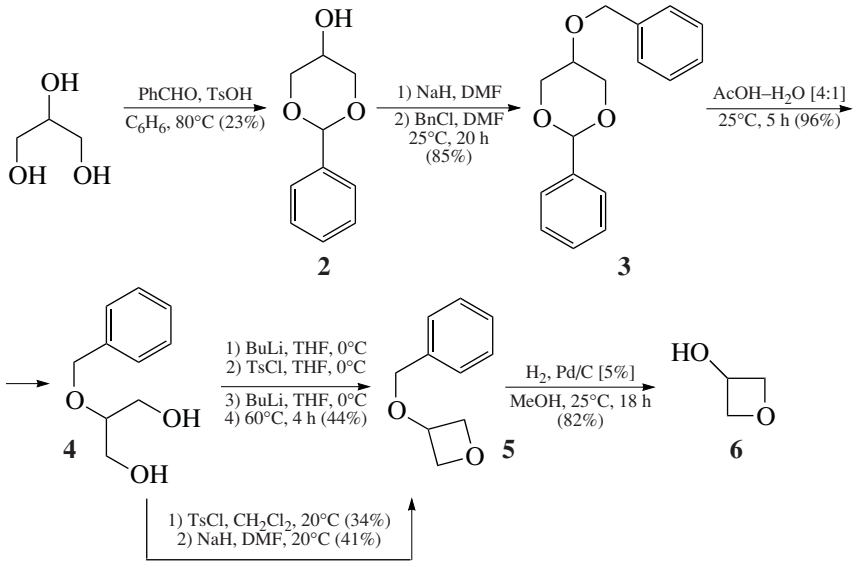


Fig. 1. Schematic representation of (**a**) a simplified analogue of taxol and (**b**) the oxetane alcohols synthesized in this work.



Scheme 1.

However, in the course of the subsequent hydrogenolysis of compound **5** in a hydrogen flow, these impurities converted to separable components. After chromatographic purification, 3-hydroxyoxetane **6** was obtained from **5** in 82% yield. The ^{1}H NMR spectrum of alcohol **6** shows a doublet at 2.88 ppm (1H, J = 6.06 Hz, OH) and a group of signals at 4.55–4.95 ppm corresponding to the protons of the oxetane system.

In the next step, we performed esterification of oxetane alcohol **6** with two bicyclo[3.3.1]nonanecarboxylic acids **7** and **8** (the subsequent regeneration of the alcohol group was assumed) (Scheme 2). The resulting esters **9** and **10** are new, and their structure was proved by ^{1}H and ^{13}C NMR and elemental analysis.

The ^{1}H NMR spectrum of compounds **9** and **10** shows the signals typical of the oxetane ring in the range 4.60–5.43 ppm, the multiplet of the proton in the 3-position being shifted downfield as compared with its position for 3-hydroxyoxetane and being separated from the signals of the methylene protons of the oxetane system. This fact unambiguously demonstrates that the oxetane ring binds to the ester group at the 3-position.

Then, we tried to "regenerate" the hydroxyl group in compounds **9** and **10**. However, the attempts to selectively reduce the keto group of ester **9** with sodium borohydride or with dehydrogenase from bakery yeast did not lead to the expected result (in the first case, only the products of hydrolysis of ester **9** were isolated).

We succeeded in obtaining ester **11** by means of hydrolytic removal of the trimethylsilyl protecting group from compound **10**, although there were some doubts about the possibility of this reaction because of the low stability of the oxetane ring to the action of acidic agents. However, the use of a minimal amount of acetic acid in a strongly diluted solution allowed us to avoid the destruction of the oxetane fragment.

The developed scheme was used for synthesizing the adamantane analogue of compound **11** (Scheme 3). The reaction of hydroxy acid **12** [11] with trimethylchlorosilane under classical conditions yielded compound **13**, which was esterified with 3-hydroxyoxetane (**6**) to form ester **14**, and the trimethylsilyl protection was removed (compound **15**). The structure of new esters **14** and **15** was proved by ^{1}H NMR, IR spectroscopy, and elemental analysis.

Thus, we synthesized for the first time the esters of 3-hydroxyoxetane with adamantane- and bicyclo[3.3.1]nonane-containing carboxylic acids. The synthesized esters are basic structures for further addition of an amino acid fragment aimed at obtaining compounds with potential antitumor activity.

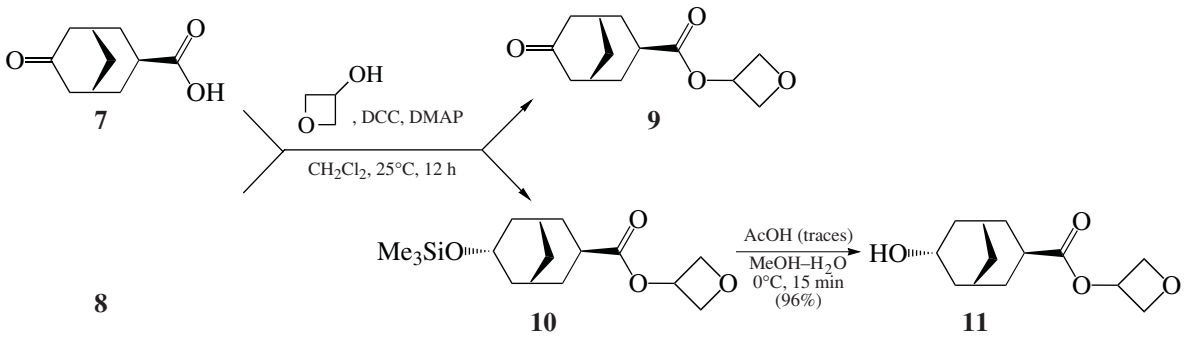
EXPERIMENTAL

2-Phenyl-5-hydroxy-1,3-dioxane 2 was synthesized as described in [10] using *p*-toluenesulfonic acid: mp 80–82°C (lit.: 83–84°C [10]).

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 3.08 (s, 1H, OH), 3.65 (m, 1H, CHOH), 4.12–4.24 (dd, 4H, 2 –OCH_2–), 5.58 (s, 1H, CHPh), 7.30–7.60 (m, 5H, arom.).

2-Phenyl-5-benzyloxy-1,3-dioxane 3 was synthesized by the common procedure of benzylation of alcohols using 9.0 g (0.23 mol) of NaH (60% in mineral oil) in DMF, 20.0 g (0.11 mol) of compound **2**, and 14.0 mL (0.12 mol) of benzyl chloride. The yield was 25.2 g (85%) of compound **3**, mp 86–88°C.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 3.38 (m, 1H, $CHOCH_2Ph$), 4.07 and 4.39 (each m, 4H, 2 –OCH_2–),



Scheme 2.

4.74 (s, 2H, OCH_2Ph), 5.59 (s, 1H, CHPh), 7.30–7.60 (m, 10H, arom.).

2-Benzyloxypropane-1,3-diol (4). A solution of 20.5 g (75.9 mmol) of compound **3** in 300 mL of 80% acetic acid was stirred at room temperature for 5 h. The reaction mixture was evaporated in vacuo, and the residue was treated with a saturated $NaHCO_3$ solution and extracted with three portions (70 mL each) of dichloromethane. The combined extract was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified on silica gel by flash chromatography. Mobile components (including benzaldehyde) were washed with an ethyl acetate–petroleum ether mixture (1 : 7), and the product was eluted with ethyl acetate. The eluate was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The product was a thick yellowish liquid. The yield was 13.2 g (96%).

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 1.90–2.60 (br s 2H, OH), 3.63 (m, 1H, $CHOCH_2Ph$), 3.70–3.85 (m, 4H, CH_2OH), 4.68 (s, 2H, $PhCH_2$), 7.38 (m, 5H, arom.).

3-Benzyloxyoxetane (5). Method 1. Benzyloxypropane-1,3-diol monotosylate (**4**) was obtained by a common procedure from 0.56 g (3.1 mmol) of diol **4**, 0.75 mL of pyridine in dichloromethane, and 0.64 g (3.4 mmol) of *p*-toluenesulfonyl chloride. The yield was 0.37 g (34%) of monotosylate and 0.58 g (39%) of ditosylate.

^{1}H NMR of monotosylate ($CDCl_3$/HMDS), δ, ppm: 0.88 (m, 1H, OH), 2.45 (s, 3H, CH_3), 3.58–3.60 (m, 1H, CHO), 3.68–3.74 (2H, CH_2OH), 4.11–4.18 (m, 2H, CH_2OTs), 4.02–4.28 (m, 4H, $2CH_2$ oxetane), 4.52 (s, 2H, $PhCH_2O$), 7.28–7.81 (m, 9H, arom.). ^{1}H NMR of ditosylate ($CDCl_3$/HMDS), δ, ppm: 2.49 (s, 6H, CH_3), 3.75 (m, 1H, CHO), 4.02–4.28 (m, 4H, $2CH_2$ oxetane), 4.51 (s, 2H, $PhCH_2O$), 7.18–7.82 (m, 13H, arom.).

A two-neck flask connected to an argon supply system was charged with 0.13 g (3.25 mmol) of NaH and 5 mL of DMF, and 0.37 (1.1 mmol) of the monotosylate obtained was then added in small portions with stirring. The resulting mixture was stirred for 12 h. The reaction mixture was diluted with a double volume of water and extracted with four 20-mL portions of dichloromethane. The extracts were dried over anhydrous Na_2SO_4, the combined extract was evaporated in vacuo, and the residue was separated chromatographically. An ethyl acetate–petroleum ether (1 : 7) system was used for elution. The yield was 70 mg (41%) of product **5** as a yellowish liquid. The overall yield from **4** was 14%.

Method 2. A 35-mL portion (56 mmol) of 1.6 M solution of *n*-butyllithium in hexane was added dropwise to a solution of 10.0 g (54.9 mmol) of diol **4** in 150 mL of THF at 0°C stirred in an argon flow. Half an hour later, a solution of 10.53 g (55.3 mmol) of *p*-toluenesulfonyl chloride in 50 mL of THF was added dropwise. An hour later, another 35 mL (56 mmol) of 1.6 M solution of *n*-butyllithium in hexane was added dropwise to a solution. The mixture was heated to boiling and refluxed (68–70°C) for 4 h. The solvent was evaporated, and the residue was diluted with 100 mL of water and extracted with ethyl acetate (5 × 50–60 mL). The extract was washed with 100 mL of a saturated sodium chloride solution, dried over anhydrous Na_2SO_4, and evaporated in vacuo, which left a yellowish brown liquid. This residue was distilled (2–4 mmHg), and the fractions with bp in the range 120–135°C were collected. The yield of product **5** was 3.9 g (44%). The purity of the product was about 90% according to ^{1}H NMR.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 4.48 (s, 1H, OCH_2Ph), 4.65–4.80 (m, 5H, oxetane), 7.37 (m, 5H, arom.).

3-Hydroxyoxetane (6) was obtained by hydrogenation of 3.5 g (21.3 mmol) of compound **5** with hydrogen in methanol in the presence 4.5 g (5%) Pd/C at room temperature for 18 h. The yield was 1.29 g (82%) of 3-hydroxyoxetane as a colorless transparent liquid, mp 55–60°C/1–2 mmHg.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 2.88 (d, 1H, J = 6.06 Hz, OH), 4.57 (m, 2H, CH_2 oxetane), 4.80–4.92 (m, 3H, CHOH + $2CH_2$ oxetane).

7-*exo*-[(Oxetan-3-yl)oxycarbonyl]bicyclo[3.3.1]nonan-3-one (9) was synthesized as described in [1] from 0.155 g (2.1 mmol) of 3-hydroxyoxetane (**6**) and 0.30 g (1.65 mmol) keto acid **7** in the presence of 0.42 g (2 mmol) of DCC and 0.012 g (0.1 mmol) of DMAP.

The yield was 0.33 g (83%) of compound **9** as a white solid with mp 106–108°C.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 1.54–2.58 (13H, skeleton), 4.59 and 4.86 (both m, 4H, $2CH_2$ oxetane), 5.39 (m, 1H, COOCH).

For $C_{13}H_{18}O_4$ anal. calcd. (%): C, 65.55; H, 7.56.

Found (%): C, 65.67; H, 7.59.

7-*endo*-Trimethylsilyloxybicyclo[3.3.1]nonane-3-*exo*-carboxylic acid (8) was obtained by a routine procedure by the reaction of 0.30 g (1.63 mmol) of the corresponding hydroxy acid with 0.211 g (1.94 mmol) of trimethylchlorosilane and 0.277 g (4.07 mmol) of imidazole in DMF. The yield was 0.22 g (53%) of **8** with mp 86–88°C.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 0.13 (s, 9H, Me_3Si), 1.2–2.2 (14H, skeleton), 3.55 (m, 1H, HC-3), 3.94 (m, 1H, SiOHC-7).

For $C_{13}H_{24}O_3Si$ anal. calcd. (%): C, 60.94; H, 9.38.

Found (%): C, 61.09; H, 9.39.

IR (Nujol), ν, cm^{-1}: 2700–2800 (OH), 1700 (C=O).

7-*endo*-Trimethylsilyloxy-3-*exo*-[(oxetan-3-yl)oxycarbonyl]bicyclo[3.3.1]nonane (10) was synthesized as described in [1] from 67 mg (0.91 mmol) of 3-hydroxyoxetane (**6**) and 180 mg (0.7 mmol) of acid **8** in the presence of 0.194 g (0.93 mmol) of DCC and 4 mg (0.03 mmol) of DMAP. The yield was 0.17 g (80%) of compound **10**.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 0.13 (s, 9H, Me_3Si), 1.25–2.13 (m, 12H, skeleton), 3.94 (m, 1H, CHOSi), 4.63 and 4.90 (both m, 4H, $2CH_2$ oxetane), 5.43 (m, 1H, CH oxetane). ^{13}C NMR ($CDCl_3$/HMDS), δ, ppm: 0.15 (Me_3Si), 26.31, 30.20, 34.05, 34.39, 37.16, 64.44 (CHOSi), 67.38 (CH oxetane), 77.81 (CH_2 oxetane), 175.24 (C=O).

For $C_{16}H_{28}O_4Si$ anal. calcd. (%): C, 61.54; H, 8.97.

Found (%): C, 61.42; H, 8.96.

7-*endo*-Hydroxy-3-*exo*-[(oxetan-3-yl)oxycarbonyl]bicyclo[3.3.1]nonane (11). To a stirred solution of 0.07 g (0.2 mmol) of compound **10** in a mixture of 5 mL of methanol and 0.8 mL of water cooled with ice, 0.03 mL of acetic acid was added. After 15 min, methanol was removed in vacuo, the residue was neutralized with sodium carbonate and extracted three times with 10 mL of dichloromethane, and the extract was washed with water. The organic solution was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo, which gave 55 mg of the product as a colorless crystalline mass. The yield was 96%.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 1.2–2.2 (12H, skeleton), 2.41 (br s, 1H, OH), 3.46 (m, 1H, HC-3), 4.01 (m, 1H, HC-7), 4.62 and 4.89 (both m, 4H, $2CH_2O$ oxetane), 5.41 (m, 2H, CH_2O oxetane). ^{13}C NMR ($CDCl_3$/HMDS), δ, ppm: 26.10, 30.16, 34.05, 34.40, 36.74, 64.01 (C-7), 67.56 (CHO oxetane), 77.73 (CH_2O oxetane), 176.54 (C=O).

For $C_{13}H_{20}O_4$ anal. calcd. (%): C, 64.98; H, 8.39.

Found (%): C, 65.41; H, 8.46.

3-(Trimethylsilyloxy)adamantane-1-carboxylic acid (13) was synthesized by a common procedure from 0.50 g (2.55 mmol) of hydroxy acid **12** in pyridine and 0.39 mL (3.05 mmol) of trimethylchlorosilane. The yield was 0.46 g (68%) of product **13** as white crystals, mp 76–78°C.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 0.11 (s, 9H, Me_3Si), 1.56 (2H), 1.73–1.78 (8H), 1.89 (2H), 2.22 (2H). ^{13}C NMR_3/HMDS), δ, ppm: 0.12 (Me_3Si), 26.33, 30.22, 33.97, 34.29, 37.14, 64.49 (CHOSi), 180.12 (C=O). IR (Nujol), ν, cm^{-1}: 2700–2900 (O–H), 1700 (C=O).

For $C_{14}H_{24}O_3Si$ anal. calcd. (%): C, 62.64; H, 9.01.

Found (%): C, 62.93; H, 8.84.

1-[(Oxetan-3-yl)oxycarbonyl]-3-trimethylsilyloxyadamantane (14) was obtained as described in [1] from 0.058 g (0.78 mmol) of 3-hydroxyoxetane **6** and 0.138 g (0.51 mmol) of acid **13** in the presence of 0.140 g (0.67 mmol) of DCC and 1.3 mg (0.01 mmol) of DMAP. The yield was 0.11 g (67%) of ester **14**.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 0.14 (s, 9H, Me_3Si), 1.59 (2H), 1.75–1.82 (8H), 1.90 (2H), 2.25 (2H), 4.61 and 4.90 (both m, 4H, $2CH_2$ oxetane), 5.41 (m, 1H, CHO oxetane). ^{13}C NMR ($CDCl_3$/HMDS), δ, ppm: 2.90 (Me_3Si), 30.28, 35.05, 37.57, 44.93, 46.70, 67.74 (CHO oxetane), 71.19 (C-3), 77.67 (CH_2O oxetane), 175.87 (C=O).

For $C_{17}H_{28}O_4Si$ anal. calcd. (%): C, 62.92; H, 8.70.

Found (%): C, 62,89; H, 8.72.

1-[(Oxetan-3-yl)oxycarbonyl]-3-hydroxyadamantane (15) was synthesized from 0.07 g (0.2 mmol) of compound **14** in a mixture of 5 mL of methanol and 0.8 mL of water and 0.03 mL of acetic acid at 0°C. The yield was 48 mg (97%) of compound **15** as a colorless oil.

^{1}H NMR ($CDCl_3$/HMDS), δ, ppm: 1.30 (br s, 1H, OH), 1.7–1.9 (12H, skeleton), 2.33 (2H), 4.64 and 4.94 (both m, 4H, $2CH_2$ oxetane), 5.45 (m, 1H, CHO oxetane).

For $C_{14}H_{20}O_4$ anal. calcd. (%): C, 66.65; H, 7.99.

Found (%): C, 66.73; H, 7.91.

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