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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Synthetic Approaches to Physiologically Active Polycyclic Compounds: VI.* Synthesis of 1-[(2*R*,3*S*)-*N*-Benzoylphenylisoseryloxy]-4,4-dimethyladamantane

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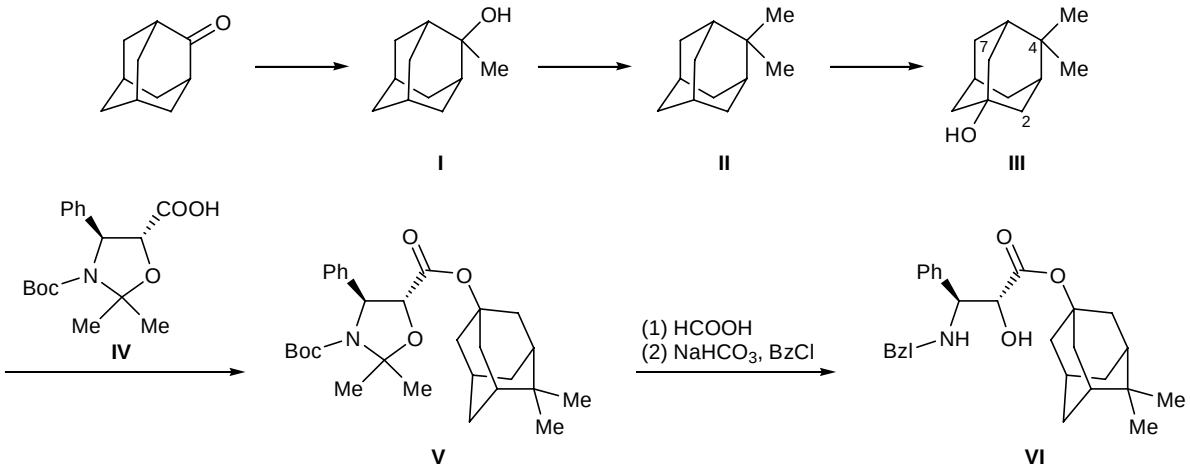
Abstract—A convenient procedure was proposed for the synthesis of 4,4-dimethyladamantan-1-ol from 2-adamantanone. Esterification of the product with protected amino acid gave 1-[(2*R*,3*S*)-*N*-benzoylphenylisoseryloxy]-4,4-dimethyladamantane.

In the framework of our studies on the synthesis of potential antitumor agents, we are developing methods for preparation of derivatives of the adamantane and bicyclo[3.3.1]nonane series, which contain functional groups capable of binding to cell targets (e.g., *N*-benzoylphenylisoseryloxy group) in definite positions of the carbon skeleton [1–5]. The goal of the present work was to synthesize 1-[(2*R*,3*S*)-*N*-benzoylphenylisoseryloxy]-4,4-dimethyladamantane (**V**).

We planned to obtain the target compound via esterification of the corresponding cage-like alcohol with amino acid according to the procedure developed by us previously [6]. However, the only reported method for the preparation of 4,4-dimethyladamantan-1-ol (**III**) [7] includes a number of steps and is laborious; moreover, it implies the use of organoboron reagents. Therefore, we have developed a fairly simple and convenient procedure for the synthesis of alcohol **III**. As starting compound we used 2-adamantanone which was converted into 2-methyladamantan-2-ol (**I**) following the standard procedure (treatment with methylmagnesium iodide in dry diethyl ether. To obtain 2,2-dimethyladamantane (**II**), compound **I** was subjected to methylation with $(TiMe_2)Cl_2$ which was generated *in situ* from $TiCl_4$ and $ZnMe_2$ [8]. Insofar as the reaction with a commercial solution of $ZnMe_2$ in toluene was characterized by a very poor yield, we have developed a laboratory method for the synthesis

Scheme 1.



* For communications I–V, see [1–5].

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of $ZnMe_2$ in methylene chloride on the basis of the procedures described in [9, 10]. In this case, the yield of the methylation process was 64%. It should be noted that in the reaction of 2-adamantanone with 4 equiv of $(TiMe_2)Cl_2$ the product yield did not exceed 40%.

Alcohol **III** was synthesized by oxidation of 2,2-dimethyladamantane (**II**). The best result (yield 49%) was obtained with the use of *m*-chloroperoxybenzoic acid as oxidant [11]. The ^{1}H NMR spectrum of the oxidation product contained signals from the methyl protons at δ 0.87 and 0.88 ppm, while no signal from proton on C^1 was present; this means that the product is a tertiary alcohol. The structure of the product as 4,4-dimethyladamantan-1-ol rather than isomeric 2,2-dimethyladamantan-1-ol follows from the presence of a single downfield signal at δ 2.13 ppm in the ^{1}H NMR spectrum, which corresponds to 7-H. The symmetry of 2,2-dimethyladamantan-1-ol implies that signals from two protons, 5-H and 7-H, should appear in a weak field. In the ^{13}C NMR spectrum of **III** we observed signals from the methyl carbon atoms at δ_C 26.70 and 28.70 ppm and a signal at δ_C 67.25 ppm belonging to C^1.

(2*R*,3*S*)-*N*-Benzoylphenylisoserine ester **VI** was synthesized in three steps with intermediate isolation of protected amino acid ester **V** according to the procedure described in [6] (Scheme 1). The structure of previously unknown compounds **V** and **VI** was proved by the ^{1}H and ^{13}C NMR and IR spectra and elemental analyses.

Thus we have developed a convenient procedure for the synthesis of 4,4-dimethyladamantan-1-ol whose esterification gives 1-[(2*R*,3*S*)-*N*-benzoylphenylisoseryloxy]-4,4-dimethyladamantane.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz for ^{1}H) using hexamethyldisiloxane as internal reference. The IR spectra were measured on a UR-20 instrument from samples dispersed in mineral oil. The mass spectra were run on a JMS-D300 GC–MS system. The progress of reactions was monitored by TLC on Silufol UV-254 plates. Silica gel (40–60 μm, Acros) was used for column chromatography.

2-Methyladamantan-2-ol (I). A solution of 1.34 ml (0.22 mol) of methyl iodide in 20 ml of diethyl ether was added dropwise over a period of 20 min to a suspension of 0.52 g (0.22 mol) of magnesium powder in 50 ml of dry diethyl ether under argon at room temperature. When the mixture became homogeneous (magnesium dissolved completely), a solution of 3 g (0.02 mol) of 2-adamantanone in 50 ml of diethyl ether was added dropwise, and the mixture was heated for 2 h under reflux. The mixture was then treated with 50 ml of water, and the organic phase was separated, washed with water (2×30 ml), dried over Na_2SO_4, and evaporated on a rotary evaporator. The product was recrystallized from 2-propanol. Yield 3.29 g (99%), colorless crystals, mp 181–184°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.3 d (3H), 1.50–1.84 m (12H), 1.56 s (1H, OH), 2.14–2.17 d (2H).

Dimethylzinc in methylene chloride. To a solution of 2.35 g (0.011 mol) of citric acid monohydrate in 30 ml of water we added at room temperature 2.69 g (0.011 mol) of $Cu_2(OH)_2CO_3 \cdot H_2O$. The mixture was stirred until gas no longer evolved and was evaporated to dryness on a rotary evaporator. Zinc dust, 26 g (0.4 mol), was added to the residue (copper citrate hydrate), and the mixture was heated under stirring in a stream of dry argon until water vapor no longer evolved. Methyl iodide, 5 ml (0.1 mol), was added dropwise to the resulting Zn/Cu couple under stirring in a counterstream of argon. The mixture was heated for 2 h under reflux, cooled, and distilled in a stream of argon to collect a fraction with bp 78°C in a receiver containing 8 ml (10 g) of methylene chloride. We thus obtained 6.11 g (65%) of $ZnMe_2$ as a solution in CH_2Cl_2 (4 mmol of $ZnMe_2$ per gram of the solution).

2,2-Dimethyladamantane (II). A solution of 0.66 ml (6 mmol) of $TiCl_4$ in 30 ml of dry methylene chloride was cooled to –30 to –40°C, and a solution of 1.5 g (6 mmol) of $ZnMe_2$ in methylene chloride was added through a Teflon tube under stirring in an argon atmosphere. After 20 min, a solution of 1 g (6 mmol) of 2-methyladamantan-2-ol (**I**) in 10 ml of dry methylene chloride was added dropwise at –30°C. The mixture was kept for 30 min at that temperature, allowed to warm up to room temperature, and stirred for 1 h. Water, 10 ml, was then added dropwise on cooling with ice, and the organic layer was separated, washed with 2 N hydrochloric acid (3×15 ml), a saturated solution of $NaHCO_3$ (25 ml), and water (15 ml), dried over Na_2SO_4, and evaporated on a rotary evaporator. The product was purified by vacuum sublimation (1 mm) on heating on a water bath. Yield 0.63 g (64%), colorless crystals, mp 139–140°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.05 s (6H), 1.33 s (2H), 1.53 d (4H), 1.65 s (2H), 1.78 t (2H), 2.07 d (4H).

4,4-Dimethyladamantan-1-ol (III). A solution of 1.5 g (4.3 mmol) of 50% *m*-chloroperoxybenzoic acid in 30 ml of 1,2-dichloroethane was added to 400 mg (2.4 mmol) of 2,2-dimethyladamantane (**II**), and the mixture was heated for 24 h at 65°C. It was then cooled to room temperature and diluted with 25 ml of 1,2-dichloroethane, and 8 ml of a 1 N solution of sodium hydroxide was added. The organic phase was washed with 10 ml of a 1 N solution of sodium hydroxide and water (2×10 ml), dried over Na_2SO_4, and evaporated on a rotary evaporator. The residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether (bp 40–60°C) (first 1:9 and then 1:5) as eluent to isolate 190 mg of initial compound **II** and 210 mg (49%) of product **III** as colorless crystals with mp 98–100°C. IR spectrum, ν, cm^{-1}: 3350 (OH), 1465, 1380, 1369. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.87 s and 0.88 s (3H each, CH_3), 1.12 s (1H, OH), 1.28–1.66 m (8H), 2.02 m (2H), 2.11 m (2H), 2.13 m (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.70 and 28.70 (CH_3), 32.36, 33.45, 35.33, 39.59, 41.74, 46.21, 67.25 (C^1). Mass spectrum, *m*/*z* (I_{rel}, %): 180 $[M]^+$ (37), 166 (25), 123 (85), 109 (100), 95 (55), 81 (32), 55 (35), 43 (35).

***tert*-Butyl (4*S*,5*R*)-2,2-dimethyl-5-(4,4-dimethyl-1-adamantylcarbonyloxy)-4-phenyloxazolidine-3-carboxylate (V)** was synthesized according to the procedure described in [6] from 0.15 g (0.8 mmol) of 4,4-dimethyladamantan-1-ol (**III**) and 0.27 g (0.84 mmol) of *tert*-butyl (4*S*,5*R*)-5-carboxy-2,2-dimethyl-4-phenyloxazolidine-3-carboxylate (**IV**) in dry methylene chloride. The product was isolated by column chromatography on silica gel using ethyl acetate–petroleum ether (bp 40–70°C) (1:10) as eluent. Yield 0.2 g (53%), colorless liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.03 s and 1.09 s (3H each, CH_3), 1.12 s (9H, *t*-Bu), 1.28–2.08 m (12H, CH, CH_2, and CH_3 in adamantane), 2.50 m (1H, CH, adamantane), 4.50 d (1H, OC**H**CHN), 4.96 s (1H, OCHC**H**N), 7.17–7.36 m (5H, Ph).

4,4-Dimethyl-1-adamantyl (2*R*,3*S*)-3-benzoylamino-2-hydroxy-3-phenylpropionate (VI) was synthesized according to the procedure described in [6] from 0.15 g (0.31 mmol) of ester **V** in 10 ml of 85% formic acid. Intermediate product was treated with 0.05 g (0.35 mmol) of benzoyl chloride. The product was isolated by column chromatography on silica gel using ethyl acetate–petroleum ether (bp 40–70°C) (first 1:5 and then 1:1) as eluent. Yield 0.13 g (93%), colorless crystals, mp 115–117°C, $[\alpha]_D^{23}$ = –16.1° (*c* = 0.01, CH_2Cl_2). IR spectrum, ν, cm^{-1}: 3280–3320 (OH, NH), 1720 (C=O, ester), 1645 (C=O, amide), 1610, 1580, 1560. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.03 s and 1.09 s (3H each, CH_3), 1.12–2.08 m (13H, CH and CH_2 in adamantane, OH), 2.50 (1H, CH, adamantane), 4.54 d (1H, C**H**OH), 5.78 d.d (1H, CHN), 7.16 d (1H, NH), 7.29–7.81 m (10H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.60 and 27.95 (CH_3), 30.17, 31.85, 34.54, 36.60, 36.72, 40.14, 42.90, 54.74 (CHN), 73.52 (CHOH), 84.23 (C^1), 126.96–138.96 (C_{arom}), 166.90 (CONH), 171.82 (COO). Found, %: C 75.33; H 7.86; N 3.50. $C_{28}H_{33}NO_4$. Calculated, %: C 75.14; H 7.43; N 3.13.

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