Regio- and Enantioselective Synthesis of Planarly Chiral Cyclopentadienylmanganese Tricarbonyl Complexes via 2-Cymantrenyl-1,3-dioxolanes

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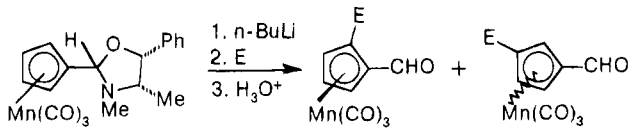
Received May 27, 1994[⊗]

With the aim of finding suitable models for the asymmetric synthesis of planarly chiral metallocenes developed by us recently, metalation of three chiral cyclic acetals, (4*R*,5*R*)-2-cymantrenyl-4,5-dimethyl-, (2*R*,4*R*)-2-cymantrenyl-4-phenyl-, and (2*S*,4*R*)-2-cymantrenyl-4-phenyl-1,3-dioxolanes (**4**–**6**), has been studied. While the reaction of **4** with n-BuLi appeared to be nonstereoselective, the corresponding reactions of **5** and **6** were diastereoselective and provided, upon the quenching of the lithiated intermediates with electophiles, enantiomeric chiral 1,2-disubstituted cymantrenes with ee values of 44 and 84%, respectively. Lithiation of 2-cymantrenyl-1,3-dioxolane is a convenient and regioselective method for the synthesis of 1,2-disubstituted derivatives of cymantrene.

We have recently described a novel approach to enantioselective synthesis of planarly chiral disubstituted cymantrenes, cyclopentadienylmanganese tricarbonyl, based on diastereoselective metalation of chiral derivatives of cymantrenecarboxaldehyde (**1**), followed by removal of an optically active auxiliary from the intermediate diastereomeric products.[1] In particular, lithiation of (2*S*,4*S*,5*R*)-3,4-dimethyl-5-phenyl-2-cymantrenyl-1,3-oxazolidine (**2**) prepared from **1** and (−)-ephedrine led to the formation of 1,2-disubstituted cymantrenes in 80% chemical yield and with an enantiomeric purity of 85–90%.[1,2] In this reaction, the formation of isomeric 1,3-disubstituted cymantrenes is also observed in 20% isolated yields with an extent of asymmetric induction (~30%) that is unprecedentedly high for a chiral inductor and a reaction site separated by such a long distance. This constituted the first example of a direct enantioselective synthesis of planarly chiral 1,3-disubstituted derivatives of metallocenes from an achiral precursor.



2 ee 85-90% ee ~30%

In our first report[1] we pointed out that the proposed stratagy of the enantioselective synthesis of planarly chiral cymantrenes can be also applied to other metallocene systems. Indeed, a little later but independently Green et al.[3] have successfully used a similar approach for the preparation of optically active 1,2-disubstituted benzenetricarbonylchromium complexes by lithiation of an intermediate chiral acetal of formylbenchrotrene. More recently, Kagan and co-workers[4] have described the same approach to the synthesis of enantiomers of planarly chiral ferrocenes without referring to refs 1, 2, and 3. With the aim of increasing the scope of this synthesis of cymantrenes with planar chirality, the regio- and stereoselectivity of the metalation of some cyclic acetals of aldehyde **1** has been investigated and the results are reported herein.

The cyclic acetals **3**, **4**, and **5**, **6** were easily prepared from **1** by condensation with ethylene glycol, (−)-(2*R*,3*R*)-2,3-butanediol, and (−)-(*R*)-1-phenyl-1,2-ethanediol, respectively, in boiling benzene using *p*-toluenesulfonic acid as a catalyst (Scheme 1). Reaction **1** with (*R*)-1-phenyl-1,2-ethanediol led to an equimolar mixture of *cis*- and *trans*-4-phenyl-2-cymantrenyl-1,3-dioxolanes, **5** and **6**, which were separated by column chromatography (SiO_2, 50/150 μm; eluent benzene/hexane). The structures of **5** and **6** and, consequently, the absolute configuration at C(2) in the dioxolane ring of these compounds were established by the analysis of NMR spectra of **5** and **6** based on the work of Eliel et al.[5] who had shown that in a series of similar 2,4-disubstituted 1,3-dioxolanes the signal of a proton at C(2) of the heterocycle is shifted downfield in *trans* isomers compared with that of *cis* isomers. In accordance with this assignment, dioxolane **6** (δ HC(2) 5.71 ppm) is the *cis*-(2*S*,4*R*) diastereomer and **5** (δ HC(2) 5.90 ppm) is the *trans*-(2*R*,4*R*) isomer.

The optically pure **5** and **6** exhibit one Cotton effect in CD spectra within 300–350 nm which corresponds to the absorption band of a cymantrene chromophore in UV–vis spectra of these compounds (see the Experimental Section). As in the case of 2-cymantrenyl-1,3-oxazolidines,[2] the sign of the Cotton effect in that region is defined by the absolute configuration of the C(2) chiral center directly bonded to the Cp ring. Since **6** has an (*R*) configuration at C(2), it must show a positive Cotton effect. In the case of (2*R*,4*R*)-**5** and also dioxolane **4**, which does not have chirality at C(2), the sign of the Cotton effect for the cymantrene chromophore is negative.

In order to establish the direction of attack of a metalation agent and the extent of deprotonation of dioxolanes **3**–**6**, the corresponding lithium derivatives of these compounds obtained by reaction with n-BuLi were treated with D_2O (Scheme 1), and the NMR spectra of the resulting deutero analogs of initial dioxolanes (**7**–

[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1994.

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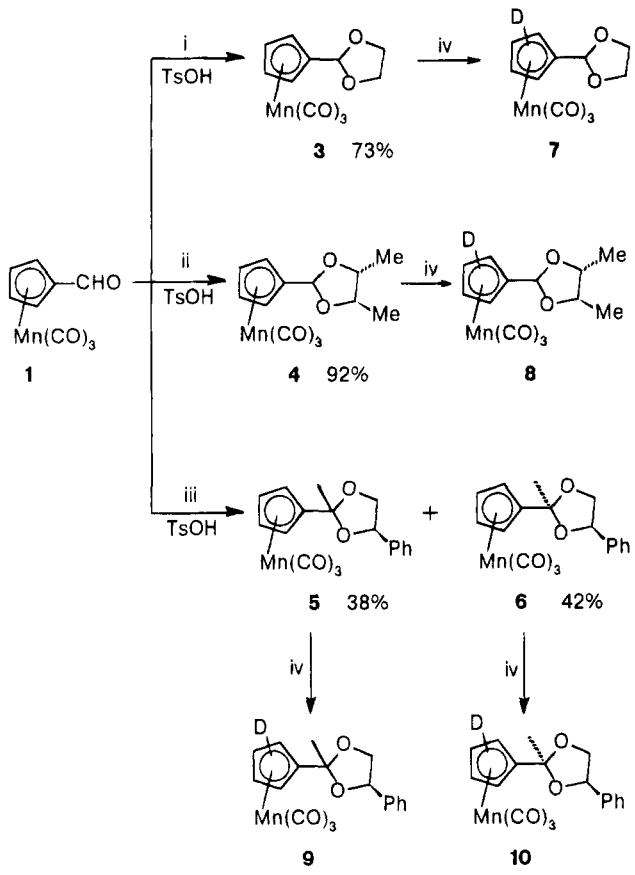
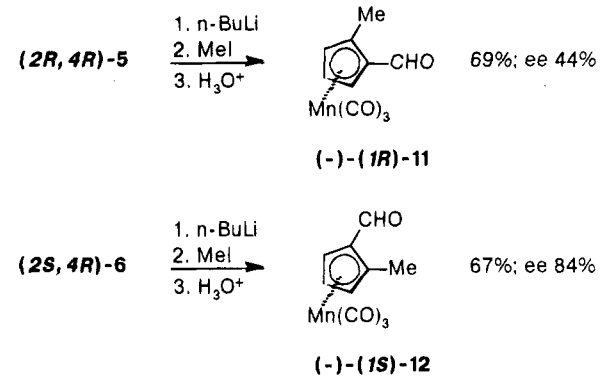
Scheme 1

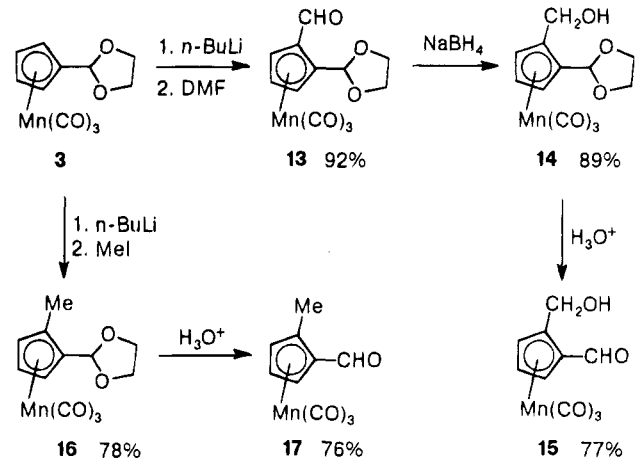


[a] Reagents: (i) ethylene glycol; (ii) (−)-2,3-butanediol; (iii) (−)-(*R*)-1-phenyl-1,2-ethanediol; (iv) n-BuLi, then D_2O.

Scheme 2



Scheme 3



10) were recorded. Analysis of the spectra has shown that in all cases the lithiation occurred at the CH position of the Cp ring only and with high regioselectivity in favor of the α position (α/β being 95/5 for **3** and 92/8 for both **5** and **6**). The lithiation of **4** was less regioselective: 75% α and 25% β.

The distribution of deuterium between diastereotopic α and α′ positions of the Cp ring of deuterated **4** indicates that diastereomeric deuterio products were obtained in equal amounts, indicating that the metalation of this dioxolane is nonstereoselective. In the cases of compounds **5** and **6**, the close values of chemical shifts of diastereotopic α and α′ protons does not allow assignment of deuterium distribution at these positions of the Cp ring for **9** and **10**. For this reason, the extent of diastereoselectivity of the lithiation of **5** and **6** was established by transforming the corresponding lithium species into methylcymantrenyldioxolanes and then, after acidic hydrolysis, into 2-methylcymantrenecarboxaldehydes (−)-**11** and (+)-**12**, respectively, the specific optical rotation and the absolute configuration of which are known[6] (Scheme 2). Thus (−)-**11** possessing (1*R*) absolute configuration of the chiral plane was obtained from **5** with an ee of 44%, whereas **6** gave (+)-(1*S*) enantiomer **12** with an ee of 84%. Hence, epimeric **5** and **6** along with **2** appeared to be suitable for the regio- and enantioselective synthesis of chiral 1,2-disubstituted cymantrenes with predictable absolute configuration.

Treatment of the lithium derivative of the achiral dioxolane **3** with dimethylformamide gave 2-(2-formylcymantrenyl)-1,3-dioxolane (**13**), which was reduced with $NaBH_4$ to provide 2-(2-(hydroxymethyl)cymantrenyl)-1,3-dioxolane (**14**) (Scheme 3), which led to the known 2-(hydroxymethyl)cymantrenecarboxaldehyde (**15**)[7] in 87% yield. The reaction of lithiated **3** with methyl iodide gave 2-(2-methylcymantrenyl)-1,3-dioxolane (**16**) (78% isolated yield). It was transformed to racemic 2-methylcymantrenecarboxaldehyde (**17**)[8] (76% yield). High yields of metalation products and simplicity of their preparation provide evidence that lithiation of **3** is a convenient way to synthesize different chiral 1,2-disubstituted derivatives of cymantrene in racemic form, including compounds with two reactive functional groups. The synthesis of **14** from **13** also shows that, in some cases, the 1,3-dioxolan-2-yl fragment remains unchanged in the course of a transformation of the second functional group introduced into the Cp ring.

In conclusion we would like to emphasize that our strategy is in principle applicable to any reaction in which a second substituent is introduced in a metallocene derivative in a regio- and stereoselective manner. For example, we have found that cyclopalladation of (4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-1,3-oxazolidine, a ferrocene analogue of **2**, proceeds stereoselectively and leads after some subsequent reactions to optically active ferrocenecarboxaldehydes.[9] The details of this study are being prepared for publication.

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Experimental Section

General. Benzene, ethylene glycol, methyl iodide, and DMF were purified and dried by standard methods. THF was distilled from sodium benzophenone ketyl under argon into a reaction vessel. (−)-(*R*)-1-Phenyl-1,2-ethanediol and (−)-(2*R*,3*R*)-2,3-butanediol were of commercial quality (Fluka AG) and were used without purification.

The reaction run was controled by IR and TLC on aluminum-backed plates coated with silica gel 60 F_{254} (Merck). Column chromatography was performed by using silica gel (50−150 μm). All reactions that involved butyllithium (a solution in hexane, 1.6 N, Fluka AG) were performed under a positive pressure of dry Ar. Drying of organic extracts was carried out with anhydrous Na_2SO_4−$MgSO_4$ followed by solvent removal in a rotatory evaporator.

^{1}H NMR spectra were recorded on a Bruker WP-200 SY or on a Bruker AM-400 spectrometer with TMS as internal standard. IR (CH_2Cl_2) and UV (isooctane) spectra were obtained on UR-20 and Specord UV−vis spectrophotometers, respectively. Mass spectral data (*m/z*) were obtained in the electron impact mode using a potental of 70 eV (Kratos MS 890). Circular dichroism (isooctane) spectra were recorded on a Jasco J-600 dichrograph and optical rotation on a Perkin-Elmer 241 polarimeter.

General Procedure for the Preparation of Compounds 3−6. A mixture of formylcymantrene (**1**)[7] (10 mmol, 2.32 g), 11 mmol of the appropriate diol, and 0.2 g of *p*-toluenesulfonic acid in benzene (40 mL) was heated to reflux for 1−2 h using a Dean−Stark trap. The solvent was evaporated, and the crude product was chromatographed with benzene for **3**, **4** or a 2:3 mixture of benzene−hexane for **5**, **6** as eluent.

2-Cymantrenyl-1,3-dioxolane (3) was obtained from **1** and ethylene glycol in 73% yield (2.1 g) as an orange oil which crystallized after a long time: mp 41−42 °C; ^{1}H NMR (200 MHz, C_6D_6) δ 5.23 (s, 1H, H-2), 4.56 (m, 2H, α-Cp), 3.88 (m, 2H, β-Cp), 3.56 (m, 2H, H-4A,5A), 3.32 (m, 2H, H-4B,5B); IR 1939, 2022 cm^{-1}; MS 276 (M^+, 28), 192 (M^+ − 3CO, 100). Anal. Calcd for $C_{11}H_9MnO_5$: C, 47.85; H, 3.29; Mn, 19.90. Found: C, 48.08; H, 3.35; Mn 19.61.

(4*R*,5*R*)-2-Cymantrenyl-4,5-dimethyl-1,3-dioxolane (4). (−)-(2*R*,3*R*)-2,3-Butanediol and **1** afforded 2.79 g (92%) of **4** as an orange oil: bp 108−112 °C/0.02 mm, n_D^{22} 1.541, $[\alpha]_D^{21}$ −25.5 (*c* 0.882, EtOH); ^{1}H NMR (200 MHz, toluene-d_8) δ 5.43 (s, 1H, H-2), 4.59 (m, 1H, α-Cp), 4.55 (m, 1H, α′-Cp), 3.96 (m, 2H, 2β-Cp), 3.50 (m, 1H, H-4), 3.33 (m, 1H, H-5), 1.50 (d, *J* = 6 Hz, 3H, Me-4), 0.96 (d, *J* = 6 Hz, 3H, Me-5); MS 304 (M^+, 21), 248 (M^+ − 2CO, 35), 220 (M^+ − 3CO, 100); UV λ_{max} 337 (log ε 3.02); CD λ_{ext} 341 (Δε −0.068), 272 (0.03). Anal. Calcd for $C_{13}H_{13}MnO_5$: C, 51.33; H, 4.31; Mn, 18.06. Found: C, 51.55; H, 4.48; Mn, 17.90.

(−)-(2*R*,4*R*)- and (−)-(2*S*,4*R*)-2-Cymantrenyl-4-phenyl-1,3-dioxolanes (5 and 6). The reaction of **1** with (−)-(*R*)-1-phenyl-1,2-ethanediol gave 3.2 g (91%) of a 1:1 mixture of diastereoisomers **5** and **6**: bp 152 °C/0.2 mm; n_D^{21} 1.6037; $[\alpha]_D^{21}$ −65.4 (*c* 2.8, acetone). Column chromatography of this mixture afforded diastereomeric pure **5** (1.32 g, 38%, eluted first) and **6** (1.45 g, 42%).

5: a viscous orange oil; $[\alpha]_D^{22}$ −61.8 (*c* 2.54, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.3 (m, 5H, Ph), 5.90 (s, 1H, H-2), 5.19 (dd, *J* = 8.1 and 6.0 Hz, 1H, H-4), 5.01 (m, 2H, 2α-Cp), 4.68 (m, 2H, 2β-Cp), 4.49 (dd, *J* = 8.1 and 6.1 Hz, 1H, H-5A), 3.80 (dd, *J* = *J* = 8.1 Hz, 1H, H-5B); IR 1956, 2038 cm^{-1}; MS 352 (M^+, 17), 268 (M^+ − 3CO, 100); UV λ_{max} 335 (log ε 3.01); CD λ_{ext} 340 (Δε −0.075), 278 (0.099). Anal. Calcd for $C_{17}H_{13}MnO_5$: C, 57.97; H, 3.72; Mn, 15.60. Found: C, 58.65; H, 4.04; Mn, 15.31.

6: a viscous orange oil; $[\alpha]_D^{23}$ −68.1 (*c* 2.66, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.3 (m, 5H, Ph), 5.71 (s, 1H, H-2), 5.12 (t, *J* = 6.9, 1H, H-4), 5.06 (m, 1H, α-Cp), 5.03 (m, 1H, α′-Cp), 4.70 (m, 1H, β-Cp), 4.67 (m, 1H, β′-Cp), 4.31 (dd, *J* = 7.8 and 6.9 Hz, 1H, H-5A), 3.85 (t, *J* = 7.6 Hz, 1H, H-5B); IR 1952, 2036 cm^{-1}; MS 352 (M^+, 22), 268 (M^+ − 3CO, 100); UV λ_{max} 342 (log ε 2.99); CD λ_{ext} 342 (Δε +0.04), 273 (0.22). Anal. Calcd for $C_{17}H_{13}MnO_5$: C, 57.97; H, 3.72; Mn, 15.60. Found: C, 58.28; H, 4.02; Mn, 15.27.

General Procedure for Lithiation of Dioxolanes 3−6. To a stirred 0.1 M solution of dioxolane in absolute THF at −70 °C was added 2 equiv of n-BuLi dropwise over 30 min. After addition, the reaction mixture was stirred at the same temperature for 1−2 h followed by quenching with the electrophile (4 equiv of D_2O, DMF, or MeI). The mixture was then allowed to warm to room temperature over 1 h, neutralized with 20% H_3PO_4 or 10% NH_4Cl, and extracted with ether. The extracts were washed with water, dried, and concentrated, and the residue was purified by column chromatography.

Deuterioproducts **7−10** were obtained in 93−96% yield.

(−)-(1*R*)-2-Methylcymantrenecarboxaldehyde (11). The reaction of lithiated **5** (140 mg, 0.4 mmol) with MeI was followed immediately by hydrolysis of the crude methylcymantrenyldioxolanes by 20% H_3PO_4 in dioxane (30 min, 50 °C). The resulting product was purified by chromatography. **11** was isolated as an oil in 69% (68 mg) yield: $[\alpha]_D^{22}$ −46.5 (*c* 0.082, benzene), 44% ee[6]; ^{1}H NMR (200 MHz, C_6D_6) δ 9.19 (s, 1H, CHO), 4.53 (m, 1H, Cp), 3.75 (m, 2H, Cp), 1.65 (s, 3H, Me); IR 1700, 1960, 2041 cm^{-1}; MS 246 (M^+, 21), 162 (M^+ − 3CO, 100).

(+)-(1*S*)-2-Methylcymantrenecarboxaldehyde (12). The same procedure was used for the preparation of **12** from 210 mg (0.6 mmol) of **6**. Column chromatography gave 91 mg (67%) of **12** as an oil: $[\alpha]_D^{22}$ +87.2 (*c* 0.166, benzene), 84% ee[6]; ^{1}H NMR (200 MHz, C_6D_6) δ 9.20 (s, 1H, CHO), 4.53 (m, 1H, Cp), 3.77 (m, 2H, Cp), 1.64 (s, 3H, Me); IR 1698, 1960, 2040 cm^{-1}; MS 246 (M^+, 19), 162 (M^+ − 3CO, 100).

(*RS*)-2-(2-Formylcymantrenyl)-1,3-dioxolane (13). The lithiation of **3** (1.5 g, 5.4 mmol) followed by quenching with DMF gave a mixture of α and β isomeric formyldioxolanes. Compound **13** was isolated by column chromatography as a yellow oil (1.51 g, 92%) and then it was used without additional purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.66 (s, 1H, CHO), 5.53 (s, 1H, H-2), 4.73 (m, 1H, Cp), 4.51 (m, 1H, Cp), 3.79 (m, 1H, Cp), 3.45 and 3.25 (2m, 4H, H-4,5); IR 1700, 1961, 2041 cm^{-1}; MS 304 (M^+, 23), 220 (M^+ − 3CO, 100).

(*RS*)-2-(2-(Hydroxymethyl)cymantrenyl)-1,3-dioxolane (14). To a stirred solution of **13** (1.22 g, 4 mmol) in ethanol (50 mL) was added $NaBH_4$ (230 mg, 6 mmol) portionwise at 15 °C. The reaction mixture was stirred for 30 min at rt, diluted with 100 mL of water, neutralized with 20% H_3PO_4, and extracted with ether. The extracts were washed with water, dried, and concentrated, and the residue was purified by column chromatography, giving **14** as a yellow oil (1.1 g, 89%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.64 (s, 1H, H-2), 4.95 (m, 1H, Cp), 4.76 (m, 1H, Cp), 4.57 (m, 1H, Cp), 4.5−3.6 (m, 6H, $3CH_2$), 2.95 (s, 1H, OH); IR 1960, 2043 cm^{-1}; MS 306 (M^+, 4), 304 (M^+ − 2H, 16), 222 (M^+ − 3CO, 20), 220 (M^+ − 2H − 3CO, 80). Anal. Calcd for $C_{12}H_{11}MnO_6$: C, 47.08; H, 3.62; Mn, 17.94. Found: C, 47.52; H, 3.91; Mn, 17.23.

(*RS*)-2-(Hydroxymethyl)cymantrenecarboxaldehyde (15).[7] The hydrolysis of **14** (0.92 g, 3 mmol) was carried out in 1,4-dioxane (10 mL) by a mixture of 20% H_3PO_4 and 10% HCl at rt over 1 h. After standard treatment of the reaction solution, **15** (0.61, 77%) was isolated by chromatography as a yellow solid: mp 59−60 °C (lit.[7] mp 60−62 °C).

(*RS*)-2-(2-Methylcymantrenyl)-1,3-dioxolane (16). Compound **16** was synthesized from 1.34 g (4.8 mmol) of **3** using methyl iodide as an electrophile as described above for the case of **13**. Compound **16** was obtained (1.1 g, 78%) as a yellow oil which was used without additional purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.64 (s, 1H, H-2), 4.95 (m, 1H, Cp), 4.66 (m, 1H, Cp), 4.57 (m, 1H, Cp), 4.15−3.85 (m ABCD, 4H, $2CH_2$), 2.95 (s, 3H, Me); IR 1958, 2039 cm^{-1}; MS 246 (M^+, 18), 162 (M^+ − 3CO, 100).

(*RS*)-2-Methylcymantrenecarboxaldehyde (17).[8] Acidic hydrolysis of **16** (500 mg, 1.7 mmol) was carried out as in the case of **14** and gave 320 mg (76%) **of 17**. Physical data were similar to those for compounds **11** and **12**.

Acknowledgment. This research was supported by the Russian Foundation for Fundamental Investigations (Grant 93-03-5827 of RFFI) and the Ministry of Science (project no. 4.3.405.0 of RGNTP).