Amphiphilic α-cyclodextrin derivatives containing residues of pharmacologically important acids

M. K. Grachev,[a] A. V. Edunov,[a] G. I. Kurochkina,[a] N. O. Soboleva,[b] L. K. Vasyanina,[a] and E. E. Nifant´ev[a]*

[a]*Department of Chemistry, Moscow Pedagogical State University, 3 Nesvizhsky per., 119021 Moscow, Russian Federation. Fax: +7 (499) 246 5453. E-mail: andro-h@yandex.ru*
[b]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation*

New representatives of amphiphilic α-cyclodextrin derivatives containing residues of pharmacologically important acids both at the primary and secondary hydroxyl groups were synthesized using acyl chlorides of palmitic acid and a series of aromatic monocarboxylic acids. The acyl chloride groups were assigned to the positions C(2), C(3), or C(6) of the carbohydrate fragments of α-cyclodextrin by ^{13}C NMR spectroscopy.

Key words: α-cyclodextrin, acylation, amphiphilic derivatives, conjugates.

One of the most important properties of cyclodextrins (CD), namely, to form inclusion compounds with appropriate hydrophobic guests, found wide use in pharmacology and, therefore, they are used as containers for diverse drugs due to the formation of host—guest complexes (see, *e.g.*, reviews[1—4]). This encapsulation favors enhanced solubility in water and, in some cases, more efficient and site drug delivery and also protects drugs from biodegradation. However, this method of drug delivery has restrictions and drawbacks and, hence, special attention has been given during the recent decade to amphiphilic CD derivatives with the purpose for the search for new pharmacological possibilities of CD as excipients* of drugs. The amphiphilic CD derivatives give rise to numerous liposomes, vesicles, nanospheres, and nanocapsules, which are of interest for targeted drug delivery and were discussed in a series of recent articles and reviews.[5] These molecular structures combine the ability of CD to inclusion with transport properties of organized, "self-assembling" structures, such as vesicles and micelles, especially when amphiphilic CD are introduced into pre-organized lipid matrices (liposomes or their analogs). For example, to synthesize fragments close in structure and nature to the lipid matrix in the cell membrane, the first representatives of the new class of amphiphilic CD were obtained: cholesterol covalently attached to β-CD [6,7] and phospholipidocyclodextrins.[6—8]

In addition, the unique amphiphilic CD derivatives were synthesized that served as transport carriers (mediators) of a series of monosaccharides through a bulk liquid membrane[9] and are in the composition of films favoring the decrease in toxicity and the ability of biological molecules to undergo denaturation.[10] In the chemical respect, the amphiphilic CD usually contain hydrophobic fragments, most frequently alkyl and acyl fragments covalently bound to the primary hydroxyl groups at the narrow side of the CD framework, which leaves free a wide part for guest inclusion. Amphiphilic CD containing hydrophobic fragments on the secondary hydroxyl groups are mentioned considerably more rarely because of their decreased ability to inclusion.[11]

Along with this, there are attempts to synthesize other systems based on CD, which would be capable of more efficient drug delivering to a certain organ, tissue, or cell. The matter is that the inclusion complexes of CD with a drug are equilibrated with the "guest" and a "host," whose degree of association depends, in a complicated manner, on the stability constant of the complex, nature of the solvent, temperature, and several other factors.[1,3,12] It is desirable that the complex would decompose to free CD and the drug at the adsorption site, and then the drug in the free form would enter system circulation. However, when the inclusion complex is weak, drug delivery is impeded, because the complex dissociates before it reaches the corresponding organ or tissue for which it is designed.[1] For example, the CD complexes are inconvenient for intestinal-specific drug delivery: when orally administrated, the complex often decomposes in the stomach and does not get into the bowels.[2] Therefore, noticeable attention is recently given to the covalent addition (conjugation) of a drug to CD, which allows one, in some cases, to obtain drugs of more prolonged and targeting site delivery.[2,13]

* Excipient is a pharmacologically inert substance combined with a drug to improve its administration, effect, *etc*.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 178—184, January, 2012.

This targeting site delivery is possible due to the fact that CD are only insignificantly hydrolyzed and absorbed upon passing through the stomach and small intestine and are fermented to small saccharides by microflora to evolve the drug already in the large intestine.[2] The most part of bacterial strains isolated from the human large intestine are able to decompose CD, and they grow on CD using them as a nutrient source. Thus, conjugated CD (prodrugs) can be used for site specific drug delivery and, for amphiphilic CD, lead to the enhanced ability to pass through biological barriers, for instance, the hematoencephalic barrier.[7]

Results and Discussion

We have recently[14,15] synthesized a series of conjugates of the drugs with β-CD, whose preliminary tests showed that their further pharmacological studies are promising.[15,16] In the present work, we took into account our data on the possibility of the regioselective acylation[17,18] of free CD and aimed at synthesizing new amphiphilic derivatives of α-CD (**1**) containing the residues of pharmacologically important acids at the side of both the primary and secondary hydroxyl groups of the CD framework. At the first stage, the interaction of CD **1** with 2.5 mol. equivalents of palmitic acid chloride (**2**) in a DMF solution in the presence of pyridine as an acceptor of hydrogen chloride gave amphiphilic derivative α-CD **3** containing two acyl residues at the "narrow" side of the CD framework (Scheme 1).

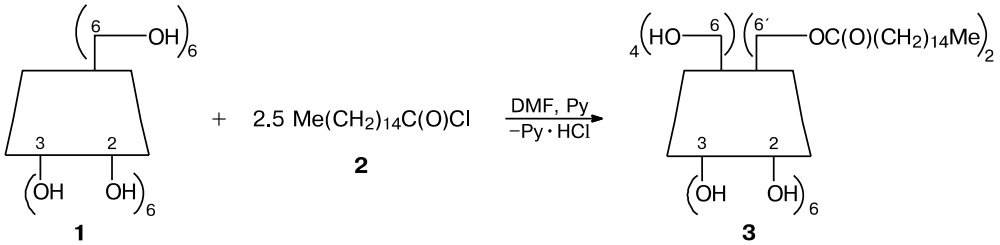
The choice of α-CD **1** as a supporting matrix for a drug is caused by its considerably higher solubility in water (145 g L^{-1}) compared to more popular and cheaper β-CD (18.5 g L^{-1}), which can improve the pharmacological properties during the subsequent biomedical studies. The average degree of substitution was determined by comparing the integral intensities of signals from the methyl protons in the ^{1}H NMR spectrum (δ 0.75—0.88) and the cyclodextrin protons (C(2)H—C(6)H) (δ 3.15—4.50). As earlier,[17,18] under these conditions acylation occurred only at the primary hydroxyl groups, which was confirmed by the ^{13}C NMR spectroscopy data. The spectrum of compound **3** contains the signals from the unsubstituted C(6) carbon atoms at δ 60.0 and the characteristic[17—20] downfield signal from the C(6′) nuclei* containing the acyl groups at δ 63.8. The signals from the C(5′) atoms of the same carbohydrate fragment containing the acyl residue at the C(6′) atom, which exhibit the upfield shift to δ 69.6 compared to the corresponding signals of the C(5) atoms of the carbohydrate fragment with the free (unsubstituted) C(6) atom at δ 71.8—73.7, appeared additionally. At the same time, no shifts of positions of the signals from the C(2) and C(3) nuclei were observed, indicating that these positions were not involved in acylation. Note that the introduction of 8 mol. equivalents of palmitoyl chloride into the reaction resulted in the unusual product, which after isolation in the solid state, as in the case of the palmitoylation of β-CD,[17] lost solubility in all accessible solvent, even in DMF from which it was isolated by evaporation and further drying *in vacuo* at 20 °C. It is most likely that, when there are many palmitoyl substituents in CD, the molecules are noncovalently bonded due to numerous acts of supramolecular interactions between adjacent molecules (due to the inclusion of long aliphatic radicals into the CD cavity, the so-called supramolecular polymer[21]), and this system is so stable that is not solvated by solvents.

At the second stage of the work, the reaction of acid chlorides of pharmacologically important acids RCl (Scheme 2), which are febrifugal and antiphlogistic, namely, benzoic **4** (R = R^1, model compound) acetylsalicylic **5** (R = R^2, medication aspirin), and 1-(4-isobutylphenyl)-propionic **6** (R = R^3, medication Ibuprofen) acids, with CD derivative **3** yielded amphiphilic derivatives α-CD **7**—**9** containing the residues of the mentioned pharmacologically important acids at the side of the primary hydroxyl groups.

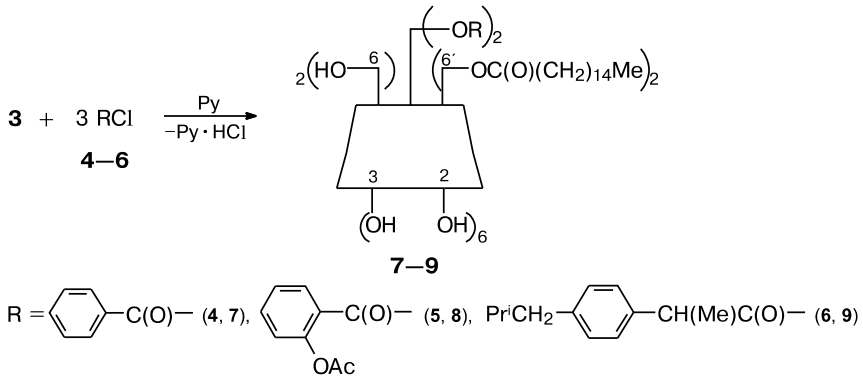
Acylation was carried out in a pyridine solution at 0 °C using 3 mol. equivalents of acid chlorides **4**—**6**, and the products were isolated as described in Experimental. In this case, the average degree of substitution was also 2, which was estimated by the ratio of integral intensities of the ^{1}H NMR characteristic signals from the protons of the residues of benzoic (compound **7**), acetylsalicylic (compound **8**), and 1-(4-isobutylphenyl)propionic (compound **9**) acids and the signals from the protons of the cyclodextrin

* Hereinafter strokes mark the CD carbon atoms at which the hydroxyl groups are substituted.

Scheme 1



Scheme 2



framework (δ_H 3.15—4.55). The more prolonged storage of the reaction mixture did not increase the degree of acylation but induced only the accumulation of by-products in the reaction mixture. As for compound **3**, it turned out to be possible to determine regioselectivity of acylation (at the primary hydroxyl groups at the C(6) atoms or at the secondary hydroxyl groups at the C(2) and C(3) atoms) using ^{13}C NMR spectroscopy. The spectra of all compounds **7—9** exhibits an increase in the ratio of integral intensities of the signals from the C(6′) atoms* bearing the acyl substituent in a lower field (δ 63.8—64.2) compared to the corresponding signals from the free C(6) atoms (δ 60.0—60.2). An increase in the intensity of the signals from the C(5′) atoms in the same carbohydrate fragment, which contains the acyl fragment at C(6′), in a higher field (δ 69.6—69.7) compared to the corresponding signals from the C(5) atoms at δ 71.8 in the carbohydrate fragment with the free C(6) atom was similarly detected. In addition, we have previously[18,19] found for the regio- and peracetylation of α- and β-CD that the signals from the carbonyl carbon atoms of the acetyl residues can also be characteristic for the determination of the substituent position: in the ^{13}C NMR spectra the signals of the carbonyl carbon atoms at C(2), C(3), and C(6) are manifested by three separate signals. In our case, the signals from the carbonyl carbon atoms in substituents R in compounds **7—9** appeared as only one signal (in addition to the signals of the carbonyl carbon atoms of the palmitoyl residues), which indicates that in all experiments described substitution occurs only at the C(6) carbon atoms. In the spectrum of compound **8**, the carbonyl carbon atom of the acetyl group is manifested by an isolated signal (see Experimental).

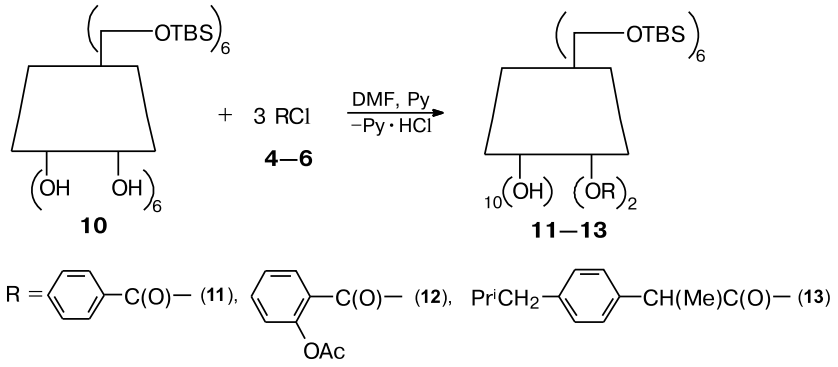
In the development of this direction, it seemed of practical interest to synthesize the amphiphilic derivatives related to compounds **7—9** described above but containing the residues of pharmacologically important acids ROH at the broad side of the CD framework (at the secondary hydroxyl groups). Accessible 6-hexa-*O*-[(*tert*-butyl)(dimethyl)]silyl-α-cyclodextrin (**10****) containing the protective silyl groups at the primary hydroxyl groups at the C(6) atom was used as the initial substrate (Scheme 3). Taking into account specific features of synthesis of compounds **7—9**, we carried out acylation in a pyridine solution using 3 mol. equivalents of acid chlorides **4—6** (see Experimental).

The average degree of substitution was determined by the ratio of integral intensities of the ^{1}H NMR characteristic signals from the protons of the residues of the corresponding acids R and the signals from the methyl protons of the *tert*-butyl groups at the silicon atom at δ 0.60—1.00. In all cases, silyl derivatives **11—13** containing two acyl substituents R at the broad part of the CD framework, *i.e.*, at the secondary hydroxyl groups at the C(2) and C(3) atoms, were isolated. Using ^{13}C NMR spectroscopy it turned out possible to determine the position of the substituents at the C(2) and/or C(3) atoms. For example, the ^{13}C NMR spectrum of derivative **11** exhibits the signals from the unsubstituted C(2) and C(3) carbon atoms at δ 70.9—72.3 and the characteristic downfield signal from the C(2′) nuclei containing the RO residue at δ 73.9. The appearance of signals from the C(1′) atoms at δ 98.9 was detected in a stronger field. The C(1′) atoms are in the same carbohydrate fragment that contains the RO residue, and their signals are compared to the signals from the C(1) atoms at δ 101.6 existing in the carbohydrate fragment with the free C(2) atom. At the same time, the signal with the chemical shift δ 81.1 corresponding to the C(4) atom remained unchanged. This confirms that the acylation involved, in this case, only the hydroxyl groups at the C(2) atom. A similar pattern was observed in the spectra of compounds **12** and **13**. Derivatives **11—13** were desilylat-

* In order to integrate the indicated signals, the ^{13}C NMR spectra of compounds **7—9** were recorded with a long delay between the pulses (8 s).

** Silyl derivative **10** was obtained by an ealier described procedure[22] with slight modifications (see Experimental).

Scheme 3



ed by the treatment with a ammonium fluoride solution in methanol (Scheme 4) as described in the literature.[23] The desilylation occurred in high yields and with retention of the existing acyl groups, which is confirmed by the ^{1}H NMR spectra of products **14—16** (see Experimental).

At the final stage of the work, the interaction of 3 mol. equivalents of acid chloride **2** and 1 mol. equivalent of desilylated derivatives **14—16** in pyridine gave amphiphilic derivatives **17—19** containing the hydrophobic palmitic acid residues at the primary hydroxyl groups and the covalently bonded residues of acids ROH at the secondary hydroxyl groups (see Scheme 4).

The structures and compositions of products **17—19** were confirmed by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. Regioselectivity of acylation with acid chloride **2** (at the primary hydroxyl groups) was established by ^{13}C NMR spectroscopy as described above for compounds **3**, **7—9**, and **11—13*** (see Experimental).

* Except for compound **10**, all synthesized products are not individual chemical compounds but consist of a mixture of different amounts of positional isomers, which were not separated.

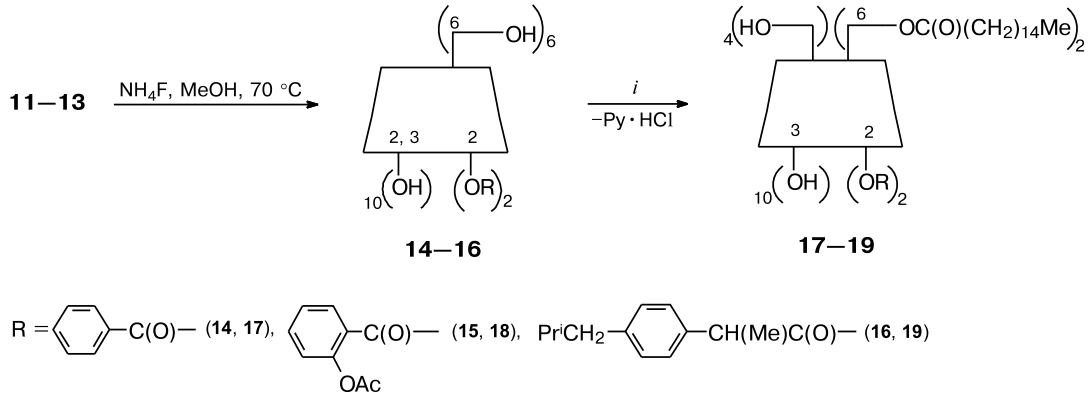
Thus, we synthesized the new amphiphilic α-CD derivatives containing the residues of pharmacologically important monocarboxylic acids, which are interesting for medical biological studies in various directions.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Jeol ECX-400 instrument at the frequencies 400.13 and 100.53 MHz, respectively. The ^{1}H and ^{13}C chemical shifts are presented relative to Me_4Si. Elemental analyses were carried out on a FlashEA 1112HT instrument. Aluminum plates with the supported silica gel layer were used for TLC (Silufol UV-254) (eluents $CHCl_3$—MeOH (1 : 1) (*A*), (7 : 1) (*B*), benzene—EtOH (7 : 1) (*C*), MeCN—H_2O (5 : 1) (*D*), and MeCN—H_2O—25% aqueous ammonia (6 : 3 : 1) (*E*)). α-Cyclodextrin (Merck, Germany) dried *in vacuo* (1 Torr) for 10 h at 90 °C over P_2O_5 was used.

6-Di-*O*-palmitoyl-α-cyclodextrin (3). A solution of acid chloride **2** (3.53 g, 12.8 mmol) in DMF (15 mL) was added with stirring for 30 min at 0 °C to a solution of α-CD (5.00 g, 5.14 mmol) and pyridine (1.12 g, 14.1 mmol) in DMF (50 mL). The mixture was stirred and kept for 24 h at 20 °C. The solution was concentrated to a volume of 10 mL *in vacuo*, and the precip-

Scheme 4



i. 3 equiv. $Me(CH_2)_{14}C(O)Cl$ (**2**), Py.

itate that formed was filtered off, washed with water (3×25 mL), dried, triturated with hexane (20 mL), washed with hexane (3×10 mL), and dried *in vacuo* (1 Torr) at 80 °C for 4 h. The yield was 5.59 g (75%), m.p. 253—254 °C (decomp.), R_f 0.62 (*A*). ^{1}H NMR (DMSO-d_6), δ: 0.75—0.88 (m, 6 H, Me); 1.07—1.33 (m, 48 H, (C$\underline{H}_2$)$_{12}$Me); 1.37—1.56 (m, 4 H, C$\underline{H}_2$(CH$_2$)$_{12}$Me); 2.11—2.36 (m, 4 H, C$\underline{H}_2$CH$_2$(CH$_2$)$_{12}$Me); 3.15—4.50 (m, 36 H, C(2)H—C(5)H, C(6)H$_2$); 4.70—4.90 (m, 6 H, C(1)H); 5.30—5.88 (m, 16 H, C(2), C(3), C(6)OH). ^{13}C NMR (DMSO-d_6), δ: 14.5 (Me); 22.8, 24.8, 29.7, 32.1, 33.7 ((C$\underline{H}_2$)$_{14}$Me); 60.0 (C(6)); 63.8 (C(6′)); 69.6 (C(5′)); 71.8—73.7 (C(2), C(3), C(5)); 82.4 (C(4)); 102.4 (C(1)); 173.2 (CH$_2$C(O)). Found (%): C, 56.41; H, 8.45. $C_{68}H_{120}O_{32}$. Calculated (%): C, 56.34; H, 8.34.

6-Di-*O*-palmitoyl-6-di-*O*-benzoyl-α-cyclodextrin (7). A solution of acid chloride **4** (0.29 g, 2.07 mmol) in pyridine (5 mL) was added with stirring at 0 °C for 20 min to a solution of derivative α-CD **3** (1.00 g, 0.699 mmol) in pyridine (10 mL). The mixture was stirred and kept for 24 h at 20 °C. The solution was concentrated to a volume of 4 mL *in vacuo* and poured into 75 mL of diethyl ether. The precipitate that formed was filtered off, washed with ether (3×10 mL), dried, triturated with 10 mL of water, washed with water (3×10 mL), and dried *in vacuo* (1 Torr) at 80 °C for 4 h. The yield was 0.91 g (80%), m.p. 297—298 °C (decomp.), R_f 0.72 (*A*). ^{1}H NMR (DMSO-d_6), δ: 0.75—0.88 (m, 6 H, Me); 1.07—1.33 (m, 48 H, (C$\underline{H}_2$)$_{12}$Me); 1.37—1.56 (m, 4 H, C$\underline{H}_2$(CH$_2$)$_{12}$Me); 2.11—2.36 (m, 4 H, C$\underline{H}_2$CH$_2$(CH$_2$)$_{12}$Me); 3.15—4.50 (m, 36 H, C(2)H—C(5)H, C(6)H$_2$); 4.70—4.90 (m, 6 H, C(1)H); 5.20—5.50 (m, 14 H, C(2), C(3), C(6)OH); 7.27—8.10 (m, 10 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 14.5 (Me); 22.8, 24.8, 29.8, 32.1, 33.7 ((C$\underline{H}_2$)$_{14}$Me); 60.0 (C(6)); 63.8 (C(6′)); 69.6 (C(5′)); 71.6—73.8 (C(2), C(3), C(5)); 82.5 (C(4)); 102.5 (C(1)); 129.2—133.8 (Ar); 166.5 (Ar$\underline{C}$(O)); 173.2 (CH$_2\underline{C}$(O)). Found (%): C, 59.53; H, 7.61. $C_{82}H_{128}O_{34}$. Calculated (%): C, 59.41; H, 7.78.

6-Di-*O*-palmitoyl-6-di-*O*-(2-acetoxybenzoyl)-α-cyclodextrin (8) was synthesized similarly to compound **7** from derivative α-CD **3** (1.00 g, 0.699 mmol) in pyridine (10 mL) and acid chloride **5** (0.41 g, 2.07 mmol) in benzene (5 mL). The yield was 1.00 g (82%), m.p. 300—301 °C (decomp.), R_f 0.75 (*A*). ^{1}H NMR (DMSO-d_6), δ: 0.75—0.88 (m, 6 H, CH$_2$C$\underline{H}_3$); 1.07—1.33 (m, 48 H, (C$\underline{H}_2$)$_{12}$Me); 1.37—1.56 (m, 4 H, C$\underline{H}_2$(CH$_2$)$_{12}$Me); 2.11—2.32 (m, 10 H, C$\underline{H}_2$CH$_2$(CH$_2$)$_{12}$Me, C(O)Me); 3.22—4.55 (m, 36 H, C(2)H—C(5)H, C(6)H$_2$); 4.75—4.91 (m, 6 H, C(1)H); 5.15—5.52 (m, 14 H, C(2)OH, C(3)OH, C(6)OH); 7.05—7.95 (m, 8 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 14.5 (Me); 21.0 (C(O)C$\underline{H}_3$); 22.8, 24.6, 29.8, 32.1, 33.6 ((C$\underline{H}_2$)$_{14}$Me); 60.0 (C(6)); 64.2 (C(6′)); 69.8 (C(5′)); 72.0—73.8 (C(2), C(3), C(5)); 82.5 (C(4)); 102.6 (C(1)); 122.16—135.14 (Ar); 150.6 (C(Ar)OC(O)); 164.3 (Ar$\underline{C}$(O)); 169.5 (O$\underline{C}$(O)Me); 173.3 (CH$_2\underline{C}$(O)). Found (%): C, 58.33; H 7.45. $C_{86}H_{132}O_{38}$. Calculated (%): C, 58.23; H, 7.50.

6-Di-*O*-palmitoyl-6-di-*O*-[1-(4-isobutylphenyl)propionyl]-α-cyclodextrin (9) was synthesized similarly to compound **7** from derivative α-CD **3** (1.00 g, 0.699 mmol) in pyridine (10 mL) and acid chloride **6** (0.47 g, 2.07 mmol) in pyridine (5 mL). The yield was 0.98 г (78%), m.p. 305—306 °C (decomp.), R_f 0.77 (*A*). ^{1}H NMR (DMSO-d_6), δ: 0.75—0.88 (m, 18 H, CH$_2$C$\underline{H}_3$, Me$_2$); 1.07—1.42 (m, 54 H, (C$\underline{H}_2$)$_{12}$Me, CHC$\underline{H}_3$); 1.37—1.56 (m, 4 H, C$\underline{H}_2$(CH$_2$)$_{12}$Me); 1.73—1.89 (m, 2 H, C$\underline{H}$Me$_2$); 2.11—2.36 (m, 4 H, C$\underline{H}_2$CH$_2$(CH$_2$)$_{12}$Me); 2.38—2.42 (m, 4 H, CHC$\underline{H}_2$); 3.15—4.50 (m, 38 H, CH, C(2)H—C(5)H, C(6)H$_2$); 4.70—4.90 (m, 6 H, C(1)H); 5.15—5.40 (m, 14 H, C(2)OH, C(3)OH, C(6)OH); 6.98—7.22 (m, 8 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 14.5 (Me); 18.2 (CH$\underline{C}$H$_3$); 22.3 (Me$_2$); 22.9, 24.8, 29.8, 32.1, 33.6 ((C$\underline{H}_2$)$_{14}$Me, C$\underline{H}$Me$_2$); 60.2 (C(6)); 64.0 (C(6′)); 69.7 (C(5′)); 71.9—73.9 (C(2), C(3), C(5)); 82.4 (C(4)); 102.5 (C(1)); 126.4—140.2 (Ar); 173.2 (CH$_2\underline{C}$(O)); 174.3 (Ar$\underline{C}$(O)). Found (%): C, 61.90; H, 8.21. $C_{94}H_{152}O_{34}$. Calculated (%): C, 61.82; H, 8.39.

6-Hexa-*O*-[(*tert*-butyl)(dimethyl)silyl]-α-cyclodextrin (10). A solution of *tert*-butyl(dimethyl)silyl chloride (2.33 g, 15.4 mmol) in pyridine (10 mL) was added with stirring at 0 °C for 30 min to a solution of α-CD (2.00 g, 2.06 mmol) in pyridine (30 mL). The mixture was stirred, stored for 24 h at 20 °C, and filtered. The solution was poured into 200 mL of ice-cold water, and the precipitate that formed was triturated with water (40 mL), filtered off, washed with water (3×10 mL), and dissolved in benzene (50 mL). Water residues were removed by azeotropic distillation on an apparatus device with a Dean—Stark trap. The solution was evaporated to dryness, and the residue was dried *in vacuo* (1 Torr) at 80 °C for 8 h. The yield was 2.56 г (75%), m.p. 322—325 °C (decomp.) (*cf.* Ref. 24: 323—326 °C (decomp.)), R_f 0.60 (*B*). ^{1}H NMR (CDCl$_3$), δ: 0.03 (s, 36 H, SiMe$_2$); 0.89 (s, 54 H, Bu^t); 3.58 (dd, 6 H, C(4)H, $^3J_{H(3),H(4)}$ = 8.7, $^3J_{H(4),H(5)}$ = 10.0); 3.65 (dd, 6 H, C(2)H, $^3J_{H(2),H(3)}$ = 9.7, $^3J_{H(1),H(2)}$ = 3.2); 3.76 (dd, 6 H, C(6)H, $^2J_{H(6),H(6′)}$ = 11.3, $^3J_{H(5),H(6)}$ = 3.4); 3.82 (dd, 6 H, C(5)H, $^3J_{H(4),H(5)}$ = 10.0, $^3J_{H(5),H(6)}$ = 3.4); 3.90 (dd, 6 H, C(6′)H, $^3J_{H(5),H(6)}$ = 3.4, $^2J_{H(6),H(6′)}$ = 11.3); 4.01 (dd, 6 H, C(3)H, $^3J_{H(3),H(4)}$ = 8.7, $^3J_{H(2),H(3)}$ = 9.7); 4.86 (d, 6 H, C(1)H, $^3J_{H(1),H(2)}$ = 3.2); 5.25, 6.52 (both s, 6 H each, C(2), C(3)OH). ^{13}C NMR (CDCl$_3$), δ: −5.1, −5.0 (SiMe$_2$); 18.5 (C$\underline{M}$e$_3$); 26.1 (C(C$\underline{H}_3$)$_3$); 62.1 (C(6)); 72.34 (C(2)); 73.3 (C(5)); 74.6 (C(3)); 81.4 (C(4)); 101.6 (C(1)). Found (%): C, 52.30; H, 8.80. $C_{72}H_{144}O_{30}Si_6$. Calculated (%): C, 52.14; H, 8.75.

6-Hexa-*O*-[(*tert*-butyl)(dimethyl)silyl]-2-di-*O*-benzoyl-α-cyclodextrin (11). A solution of acid chloride **4** (0.35 g, 1.81 mmol) in pyridine (4 mL) was added with stirring at 0 °C for 20 min to a solution of derivative **10** (1.00 g, 0.603 mmol) in pyridine (10 mL). The mixture was stirred and kept for 24 h at 20 °C. The solution was filtered, concentrated to a volume of 2 mL, and poured to water (50 mL). The residue was filtered off, triturated with 10 mL of a 0.5 *M* solution of NaHCO$_3$ in water, washed with water (3×5 mL), and dried *in vacuo* (1 Torr) at 80 °C for 4 h. The yield was 0.94 г (84%), m.p. 195—196 °C, R_f 0.79 (*B*). ^{1}H NMR (CDCl$_3$), δ: 0.06 (s, 36 H, SiMe$_2$); 0.89 (s, 54 H, Bu^t); 3.41—4.30 (m, 36 H, C(2)H—C(5)H, C(6)H$_2$); 4.75—5.00 (br.s, 10 H, (C(2)OH, C(3)OH); 5.10—4.29 (m, 6 H, C(1)H); 7.30—8.12 (m, 10 H, Ar). ^{13}C NMR (CDCl$_3$), δ: −5.1, −5.0 (SiMe$_2$); 18.4 (C$\underline{M}$e$_3$); 26.0 (C(C$\underline{H}_3$)$_3$); 62.2 (C(6)); 70.9—72.3 (C(2), C(3), C(5)); 73.9 (C(2′)); 81.2 (C(4)); 98.9 (C(1′)); 101.6 (C(1)); 128.0—134.1 (Ar); 166.0 (C(O)). Found (%): C, 55.42; H, 8.16. $C_{86}H_{152}O_{32}Si_6$. Calculated (%): C, 55.34; H, 8.21.

6-Hexa-*O*-[(*tert*-butyl)(dimethyl)silyl]-2-di-*O*-(2-acetoxybenzoyl)-α-cyclodextrin (12) was synthesized similarly to compound **11** from derivative **10** (1.00 g, 0.603 mmol) in pyridine (10 mL) and acid chloride **5** (0.36 g, 1.81 mmol) in benzene (4 mL). The yield was 0.98 g (84%), m.p. 174—175 °C, R_f 0.54 (*B*). ^{1}H NMR (CDCl$_3$), δ: 0.06 (s, 36 H, SiMe$_2$); 0.89 (s, 54 H, Bu^t); 2.25 (s, 6 H, MeC(O)C(2)); 3.27—4.50 (m, 36 H, C(2)H—C(5)H, C(6)H$_2$); 4.61—5.05 (br.s, 10 H, C(2), C(3)OH); 5.10—5.37 (m, 6 H, C(1)H); 6.98—8.12 (m, 8 H, Ar). ^{13}C NMR (CDCl$_3$),

δ: −5.1, −5.0 ($SiMe_2$); 18.4 ($\underline{C}Me_3$); 21.0 (C(2)(O)$\underline{C}H_3$); 26.0 (C($\underline{C}H_3)_3$); 62.1 (C(6)); 71.6—72.4 (C(2), C(3), C(5)); 75.3 (C(2′)); 82.0 (C(4)); 98.9 (C(1′)); 101.6 (C(1)); 122.6—135.6 (Ar); 150.2 (C(Ar)OC(O)); 164.2 (ArC(O)); 170.0 (OC(O)Me). Found (%): C, 56.41; H, 8.14. $C_{90}H_{156}O_{32}Si_6$. Calculated (%): C, 56.34; H, 8.20.

6-Hexa-*O*-[(*tert*-butyl)(dimethyl)silyl]-2-di-*O*-[1-(4-isobutylphenyl)propionyl]-α-cyclodextrin (13). A solution of acid chloride **6** (0.41 g, 1.81 mmol) in pyridine (4 mL) was added with stirring at 0 °C for 20 min to a solution of derivative **10** (1.00 g, 0.603 mmol) in pyridine (10 mL). The mixture was stirred and kept for 24 h at 20 °C. The solution was filtered off, concentrated to a volume of 2 mL, and poured into water (50 mL). The precipitate was filtered off, triturated with 10 mL of a 0.5 *M* solution of $NaHCO_3$ in a water—acetone (1 : 1) mixture, washed with water (3×5 mL), and dried *in vacuo* (1 Torr) at 90 °C for 4 h. The yield was 0.57 g (93%), m.p. 141—142 °C, R_f 0.82 (*B*). ^{1}H NMR ($CDCl_3$), δ: 0.06 (s, 36 H, $SiMe_2$); 0.70—1.00 (m, 66 H, Me_2, Bu^t); 1.30—1.42 (m, 6 H, Me); 1.75—1.92 (m, 2 H, C$\underline{H}Me_2$); 2.42 (d, 4 H, CH_2, J = 4.7 Hz); 3.03—4.25 (m, 38 H, CH, C(2)H—C(5)H, C(6)H_2); 4.87 (d, 6 H, C(1)H, J = 3.3 Hz); 4.90—5.10 (br.s, 10 H, C(2), C(3)); 6.95—7.34 (m, 8 H, Ar). ^{13}C NMR ($CDCl_3$), δ: −5.1, −5.0 ($SiMe_2$); 18.3 (Me); 18.43 ($\underline{C}Me_3$); 22.4 (Me_2); 26.0 (C($\underline{C}H_3)_3$); 30.3 ($\underline{C}HMe_2$); 40.7 ($\underline{C}$HMe); 45.2 (CH_2); 62.0 (C(6)); 70.0—72.5 (C(2), C(3), C(5)); 74.1 (C(2′)); 82.0 (C(4)); 99.0 (C(1′)); 101.7 (C(1)); 126.2—141.9 (Ar); 173.5 (C(O)). Found (%): C, 57.93; H, 8.61. $C_{98}H_{176}O_{32}Si_6$. Calculated (%): C, 57.84; H, 8.72.

2-Di-*O*-benzoyl-α-cyclodextrin (14). A solution of derivative **11** (0.50 g, 0.268 mmol) and ammonium fluoride (0.15 g, 4.02 mmol) in methanol (15 mL) was refluxed for 24 h with a reflux condenser at 70 °C, evaporated to dryness, triturated with 5 mL of water, washed with water (3×5 mL), and dried *in vacuo* (1 Torr) at 90 °C for 4 h. The yield was 0.29 g (92%), m.p. 227—228 °C (decomp.), R_f 0.51 (*D*). ^{1}H NMR (DMSO-d_6), δ: 3.45—4.30 (m, 36 H, C(2)H—C(5)H, C(6)H_2); 4.40—4.90 (br.s, 16 H, C(2)OH, C(3)OH, C(6)OH); 5.08 (m, 6 H, C(1)H); 7.35—8.12 (m, 10 H, Ar). Found (%): C, 50.93; H, 5.71. $C_{50}H_{68}O_{32}$. Calculated (%): C, 50.85; H, 5.80.

2-Di-*O*-(2-acetoxybenzoyl)-α-cyclodextrin (15) was synthesized similarly to compound **14** from compound **12** (0.50 g, 0.261 mmol) and ammonium fluoride (0.14 g, 3.91 mmol) in methanol (15 mL). The yield was 0.31 g (91%), m.p. 215—216 °C (decomp.), R_f 0.57 (*E*). ^{1}H NMR (DMSO-d_6), δ: 2.20 (s, 6 H, H_3CC(O)); 3.46—4.32 (m, 36 H, C(2)H—C(5)H, C(6)H_2); 4.40—4.85 (br.s, 16 H, C(2)OH, C(3)OH, C(6)OH); 5.09 (m, 6 H, C(1)H); 7.35—8.12 (m, 8 H, Ar). Found (%): C, 50.09; H, 5.50. $C_{54}H_{72}O_{36}$. Calculated (%): C, 50.00; H, 5.59.

2-Di-*O*-[1-(4-isobutylphenyl)propionyl]-α-cyclodextrin (16) was synthesized similarly to compound **14** from compound **13** (0.50 g, 0.246 mmol) and ammonium fluoride (0.14 g, 3.69 mmol) in methanol (15 mL). The yield was 0.31 g (93%), m.p. 213—214 °C (decomp.), R_f 0.68 (*C*). ^{1}H NMR (DMSO-d_6), δ: 0.85 (d, 12 H, Me_2, J = 7.9 Hz); 1.23—1.45 (m, 6 H, Me); 1.65—1.88 (m, 2 H, C$\underline{H}Me_2$); 2.35 (d, 4 H, CH_2, J = 4.7 Hz); 3.10—4.12 (m, 38 H, CH, C(2)H—C(5)H, C(6)H_2); 4.20—4.60 (m, 6 H, C(6)OH); 4.70—5.15 (m, 6 H, C(1)H); 5.15—5.85 (br.s, 10 H, C(2)OH, C(3)OH); 6.95—7.30 (m, 8 H, Ar). Found (%): C, 55.27; H, 6.77. $C_{62}H_{92}O_{32}$. Calculated (%): C, 55.19; H, 6.87.

6-Di-*O*-palmitoyl-2-di-*O*-benzoyl-α-cyclodextrin (17). A solution of acid chloride **2** (0.17 g, 0.635 mmol) in benzene (1 mL) was added with stirring at 0 °C for 10 min to a solution of derivative **14** (0.25 g, 0.212 mmol) in pyridine (3 mL). The mixture was stirred and kept for 24 h at 20 °C, and diethyl ether (20 mL) was added. The precipitate that formed was separated by decantation, washed with ether (3×5 mL), dried, triturated with 5 mL of water (3×5 mL), and dried *in vacuo* (1 Torr) at 80 °C for 4 h. The yield was 0.22 g (65%), m.p. 187—188 °C, R_f 0.77 (*A*). ^{1}H NMR (DMSO-d_6), δ: 0.75—0.88 (m, 6 H, C$\underline{H}_3$); 1.07—1.33 (m, 48 H, ($C\underline{H}_2)_{12}$Me); 1.37—1.56 (m, 4 H, C$\underline{H}_2$($CH_2)_{12}$Me); 2.11—2.36 (m, 4 H, C$\underline{H}_2CH_2$($CH_2)_{12}$Me); 3.15—4.50 (m, 36 H, C(2)H—C(5)H, C(6)H_2); 4.70—4.90 (m, 6 H, C(1)H); 5.20—5.50 (m, 14 H, C(2)OH, C(3)OH, C(6)OH); 7.35—08.11 (m, 10 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 14.5 (Me); 22.9, 24.8, 29.7, 32.2, 33.6 (($\underline{C}H_2)_{14}$Me); 60.2 (C(6)); 64.0 (C(6′)); 69.6 (C(5′)); 71.8—74.5 (C(2), C(3), C(5)); 82.5 (C(4)); 99.5 (C(1′)); 102.5 (C(1)); 129.0—133.9 (Ar); 166.7 (Ar$\underline{C}$(O)); 173.2 ($CH_2\underline{C}$(O)). Found (%): C, 59.53; H, 7.61. $C_{82}H_{128}O_{34}$. Calculated (%): C, 59.41; H, 7.78.

6-Di-*O*-palmitoyl-2-di-*O*-(2-acetoxybenzoyl)-α-cyclodextrin (18) was synthesized similarly to compound **17** from compound **15** (0.25 g, 0.193 mmol) and acid chloride **2** (0.16 g, 0.578 mmol) in benzene (1 mL). The yield was 0.22 g (62%), m.p. 174—175 °C, R_f 0.79 (*A*). ^{1}H NMR (DMSO-d_6), δ: 0.75—0.88 (m, 6 H, $CH_2C\underline{H}_3$); 1.07—1.33 (m, 48 H, ($C\underline{H}_2)_{12}$Me); 1.37—1.56 (m, 4 H, C$\underline{H}_2$($CH_2)_{12}$Me); 2.11—2.32 (m, 10 H, C$\underline{H}_2CH_2$($CH_2)_{12}$Me, C(O)Me); 3.22—4.55 (m, 36 H, C(2)H—C(5)H, C(6)H_2); 4.75—4.91 (m, 6 H, C(1)H); 5.15—5.52 (m, 14 H, C(2)OH, C(3)OH, C(6)OH); 7.09—7.97 (m, 8 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 14.5 (Me); 21.1 (C(O)$\underline{C}H_3$); 22.9, 24.9, 29.7, 32.1, 33.6 (($\underline{C}H_2)_{14}$Me), 60.4 (C(6)); 64.0 (C(6′)); 69.5 (C(5′)); 72.0—74.6 (C(2), C(3), C(5)); 82.7 (C(4)); 99.2 (C(1′)); 102.9 (C(1)); 122.9—135.2 (Ar); 151.0 ($\underline{C}$(Ar)OC(O)); 164.6 (Ar$\underline{C}$(O)); 170.0 ($\underline{C}$(O)Me); 173.3 ($CH_2\underline{C}$(O)). Found (%): C, 58.32; H, 7.41. $C_{86}H_{132}O_{38}$. Calculated (%): C, 58.23; H, 7.50.

6-Di-*O*-palmitoyl-2-di-*O*-[1-(4-isobutylphenyl)propionyl]-α-cyclodextrin (19) was synthesized similarly to compound **17** from compound **16** (0.25 g, 0.186 mmol) and acid chloride **2** (0.15 g, 0.556 mmol) in benzene (1 mL). The yield was 0.20 g (59%), m.p. 213—214 °C, R_f 0.82 (*A*). ^{1}H NMR (DMSO-d_6), δ: 0.75—0.88 (m, 18 H, $CH_2C\underline{H}_3$, Me_2); 1.13—1.35 (m, 54 H, ($C\underline{H}_2)_{12}$Me, CHC$\underline{H}_3$); 1.41—1.58 (m, 4 H, C$\underline{H}_2$($CH_2)_{12}$Me); 1.73—1.89 (m, 2 H, C$\underline{H}Me_2$); 2.11—2.36 (m, 4 H, C$\underline{H}_2CH_2$($CH_2)_{12}$Me); 2.38—2.42 (m, 4 H, CHC$\underline{H}_2$); 3.15—4.50 (m, 38 H, CH, C(2)H—C(5)H, C(6)H_2); 4.70—4.90 (m, 6 H, C(1)H); 5.15—5.40 (m, 14 H, C(2)OH, C(3)OH, C(6)OH); 6.98—7.22 (m, 8 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 14.5 (Me); 19.0 (CH$\underline{C}H_3$); 22.5 (Me_2); 22.9, 24.9, 29.7, 32.1, 33.7 (($\underline{C}H_2)_{14}$Me, $\underline{C}$HMe_2); 60.4 (C(6)); 63.8 (C(6′)); 69.5 (C(5′)); 71.9—74.3 (C(2), C(3), C(5)); 82.7 (C(4)); 99.1 (C(1′)); 102.5 (C(1)); 127.0—140.6 (Ar); 173.3 ($CH_2\underline{C}$(O)); 174.5 (Ar$\underline{C}$(O)). Found (%): C, 61.93; H, 8.20. $C_{94}H_{152}O_{34}$. Calculated (%): C, 61.82; H, 8.39.

References

1. R. A. Rajewski, V. J. Stella, *J. Pharm. Sci.*, 1996, **85**, 1142.
2. K. Uekama, F. Hirayama, T. Irie, *Chem. Rev.*, 1998, **98**, 2045.
3. M. E. Davis, M. E. Brewster, *Nature Rev., Drug Discovery*, 2004, **3**, 1023.
4. R. Challa, A. Ahuja, J. Ali, R. K. Khar, *AAPS PharmSciTech*, 2005, **6**, Arcticle 43, E329; http://www. aapspharmscitech.org.

5. E. Memisoglu, A. Bochot, M. Sen, D. Charon, D. Duchêne, A. A. Hincal, *J. Pharm. Sci.*, 2002, **91**, 1214; E. Memisoglu, A. Bochot, M. Oezalp, M. Sen, D. Duchêne, A. A. Hincal, *Pharm. Res.*, 2003, **20**, 117; A. Geze, S. Aous, I. Baussanne, J. L. Putaux, J. Defaye, D. Wouessidjewe, *Int. J. Pharm.*, 2002, **242**, 301; M. Roux, B. Perly, F. Djedaïni-Pilard, *Eur. Biophys. J.*, 2007, **36**, 861; E. Bilensoy, *J. Biomed. Nanotech.*, 2008, **4**, 293; R. H. de Rossi, O. F. Silva, R. V. Vico, C. J. Gonzalez, *Pure Appl. Chem.*, 2009, **81**, 755; H. Parrot-Lopeza, F. Perreta, B. Bertino-Ghera, *Ann. Pharm. Franc.*, 2010, **68**, 12.
6. I. Javierre, M. Nedyalkov, V. Petkova, J.-J. Benattar, S. Weisse, R. Auzely-Velty, F. Djedaïni-Pilard, B. Perly, *J. Colloid Interface Sci.*, 2002, **254**, 120; S. Moutard, B. Perly, P. Gode, G. Demailly, F. Djedaïni-Pilard, *J. Inclusion Phenom. Macr. Chem.*, 2003, **44**, 317.
7. B. Perly, S. Moutard, F. Djedaïni-Pilard, *PharmaChem.*, 2005, **4**, 4.
8. M. K. Grachev, S. V. Sipin, L. O. Kononov, E. E. Nifant´ev, *Izv. Akad. Nauk*, *Ser. Khim.*, 2009, 221 [*Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 223].
9. T. Kida, T. Ohe, H. Higashimoto, H. Harada, Y. Nakatsuji, I. Ikeda, M. Akashi, *Chem. Lett.*, 2004, **33**, 258.
10. K. Kobayashi, K. Kajikawa, H. Sasabe, W. Knoll, *Thin Solid Films*, 1999, **349**, 244.
11. N. Badi, N. Jarroux, P. Guegan, *Tetrahedron Lett.*, 2006, **47**, 8925; A. Benkhaled, H. Cheradame, O. Fichet, D. Teyssie, W. Buchmann, P. Guegan, *Carbohydr. Polym.*, 2008, **73**, 482.
12. J. Szejtli, *Chem. Rev.*, 1998, **98**, 1743.
13. H. Parrot-Lopez, F. Djedaïni, B. Perly, A. W. Coleman, H. Galons, M. Miocque, *Tetrahedron Lett.*, 1990, **31**, 1999; F. Djedaïni-Pilard, J. Désalos, B. Perly, *Tetrahedron Lett.*, 1993, **34**, 2457; M. K. Hristova-Kazmierski, P. Horan, P. Davis, H. I. Yamamura, T. Kramer, R. Horvath, W. M. Kazmierski, F. Porreca, V. J. Hruby, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 831; K. Uekama, K. Minami, F. Hirayama, *J. Med. Chem.*, 1997, **40**, 2755; K. Minami, F. Hirayama, K. Uekama, *J. Pharm. Sci.*, 1998, **87**, 715; S. Tavornvipas, H. Arima, F. Hirayama, K. Uekama, T. Ishiguro, M. Oka, K. Hamayasu, H. Hashimoto, *J. Inclusion Phenom. Macr. Chem.*, 2002, **44**, 391.
14. G. I. Kurochkina, N. A. Kudryavtseva, M. K. Grachev, S. A. Lyssenko, L. K. Vasyanina, E. E. Nifant´ev, *Zh. Obshch. Khim.*, 2007, **77**, 477 [*Russ. J. Gen. Chem.* (*Engl. Transl.*), 2007, **77**, 442]; G. I. Kurochkina, N. A. Kudryavtseva, M. K. Grachev, S. A. Lyssenko, E. E. Nifant´ev, *Zh. Obshch. Khim.*, 2007, **77**, 485 [*Russ. J. Gen. Chem.* (*Engl. Transl.*), 2007, **77**, 450]; M. K. Grachev, A. A. Charaev, G. I. Kurochkina, L. K. Vasyanina, V. N. Shmeleva, E. E. Nifant´ev, *Zh. Obshch. Khim.*, 2010, **80**, 1494 [*Russ. J. Gen. Chem.* (*Engl. Transl.*), 2010, **80**, 1812].
15. T. A. Batalova, V. A. Dorovskikh, A. A. Sergievich, M. L. Plastinin, M. K. Grachev, G. I. Kurochkina, S. A. Lyssenko, *Dal´nevost. Med. Zh.* [*Far Eastern Medical Journal*], 2008, 105 (in Russian); T. A. Batalova, V. A. Dorovskikh, G. I. Kurochkina, M. K. Grachev, A. A. Sergievich, M. L. Plastinin, *Byul. Eksperim. Biol. Med.* [*Experimental Biological Medical Bulletin*], 2011, 642 (in Russian); T. A. Batalova, V. A. Dorovskikh, M. K. Grachev, G. I. Kurochkina, A. A. Charaev, M. L. Plastinin, A. A. Sergievich, *Voprosy Biol., Med. Farm. Khim.* [*Problems of Biology, Medical Pharmaceutical Journal*], 2011, No. 1, 42 (in Russian).
16. Pat. RF No. 2363473, 2008; *Byul. Izobr.* [*Invention Bulletin*], 2009, 22; Pat. RF No. 2428205, 2010; *Byul. Izobr.* [*Invention Bulletin*], 2011, 25; Pat. RF. No. 2429017, 2010; *Byul. Izobr.* [*Invention Bulletin*], 2011, 26; A. A. Sergievich, M. K. Grachev, G. I. Kurochkina, T. A. Batalova, M. L. Plastinin, *Yakutsk. Med. Zh.* [*Yakutsk Medical Journal*], 2011, No. 1,101 (in Russian).
17. A. E. Glazyrin, A. N. Syrtsev, G. I. Kurochkina, L. O. Kononov, M. K. Grachev, E. E. Nifant´ev, *Izv. Akad. Nauk*, *Ser. Khim.*, 2003, 225 [*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 237].
18. M. K. Grachev, A. V. Edunov, G. I. Kurochkina, A. V. Popkov, I. I. Levina, E. E. Nifant´ev, *Zh. Org. Khim.*, 2011, **41**, 290 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2011, **47**, 284].
19. M. K. Grachev, A. V. Edunov, G. I. Kurochkina, I. I. Levina, E. E. Nifant´ev, *Zh. Obshch. Khim.*, 2011, **81**, 222 [*Russ. J. Gen. Chem.* (*Engl. Transl.*), 2011, **81**, 322].
20. K. Takeo, H. Mitoh, K. Uemura, *Carbohydr. Res.*, 1989, **187**, 203; H. H. Baer, Ya. Shen, F. S. González, A. V. Berenguel, J. I. García, *Carbohydr. Res.*, 1992, **235**, 129; S. Hanessian, A. Benalil, C. Laferrière, *J. Org. Chem.*, 1995, **60**, 4786; D. Rong, V. T. D´Souza, *Tetrahedron Lett.*, 1990, **31**, 4275.
21. A. Harada, A. Hashidzume, Y. Takashima, *Adv. Polym. Sci.*, 2006, **201**, 1.
22. P. Fügedi, *Carbohydr. Res.*, 1989, **192**, 366.
23. W. Zhang, M. J. Robins, *Tetrahedron Lett.*, 1992, **33**, 1177.
24. K. Takeo, K. Uemura, H. Mitoh, *J. Carbohydr. Chem.*, 1988, **7**, 293.

Received March 16, 2011;
in revised form November 2, 2011