Combination of ionic liquid [bmim]PF_6 with boron trifluoride etherate as an efficient catalytic system for the glycosylation of α-tocopherol and naphthotocopherol

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The use of a combination of ionic liquid [bmim]PF_6 with boron trifluoride etherate as the catalyst in the glycosylation of α-tocopherol and chromanol of vitamin K_1 (naphthotocopherol) allowed us to obtain β-glycosides in high yield when β-anomer of peracetylated D-glucose was used. In addition, usually inactive α-anomers of peracetylated D-glucopyranose and D-galactopyranose were involved in this reaction.

Key words: ionic liquid, glycosylation, α-tocopherol, naphthotocopherol (chromanol of vitamin K_1), D-glucopyranose and D-galactopyranose pentaacetates.

α-Tocopherol is a structural component of the group E vitamins and is the main lipophilic antioxidant of the mammalian biological membranes. This exerts a positive effect in prevention and treatment of a number of diseases caused by the oxidative stress.[1,2] At the same time, the low stability in an organism, limited absorption, and high extent of accumulation of α-tocopherol in the lipid tissues lead to a reduction of the therapeutic effect and prevents its biocompatibility with other ingredients in the creation of food, pharmaceutical, and cosmetic compositions. In recent years, growing attention has been paid to the hydrophilic α-tocopherol derivatives, modified at the phenolic hydroxy group, among which compounds having biological activity different from that of α-tocopherol itself were found.[3] Earlier, hydrophobic 7,8-benzoannulated analogs of α-tocopherol, *viz.*, cyclic isomer of dihydro derivative of vitamin K_1 (naphthotocopherol), was reported to have high antioxidant activity.[4] In this connection, introduction of a carbohydrate fragment into the α-tocopherol and naphthotocopherol molecules aimed at increasing their polarity and hydrophilicity was of undoubted interest.

Earlier,[5—8] it has been shown that the acid-catalyzed glycosylation of α-tocopherol was complicated due to the formation of by-products (quinones, dimeric spiro derivatives) because of the electronic effects characteristic of 6-hydroxychromanyl system as well as of steric hindrance of the phenolic group created by methyl groups. Therefore, the yields of β-glycosides were low or they partially isomerized to α-anomers.[6] When acetylated sugars were used as the glycosyl donors, boron trifluoride etherate turned out to be the most efficient catalyst out of those studied,[5,6] however, acetates of α-anomers of D-gluco- and D-galactopyranoses did not enter the reaction.

Our quest for the new possibilities in optimization of the synthesis of glycoside conjugates of α-tocopherol was directed to ionic liquids, which in recent years were actively used as the perfect reaction media for the acceleration of various reaction,[9—11] in particular, those proceeding *via* carbocations or acylium ions.[12,13] Ionic liquids have been successfully used as the solvents and catalytic systems in acidic glycosylation of alcohols with benzylated glucopyranosyl fluorides,[14] diethylphosphites,[15] and trichloroacetimidates,[16] as well as with sugars without protecting groups.[17] Ionic liquids were used in O-glycosylation of alcohols with unsaturated sugar derivatives.[18,19] Ionic liquids showed high efficiency in C-glycosylation of phenols and naphthols.[20] At the same time, ionic liquids were not reported to be used in the synthesis of O-glycosides of phenols, in particular, of α-tocopherol and naphthotocopherol.

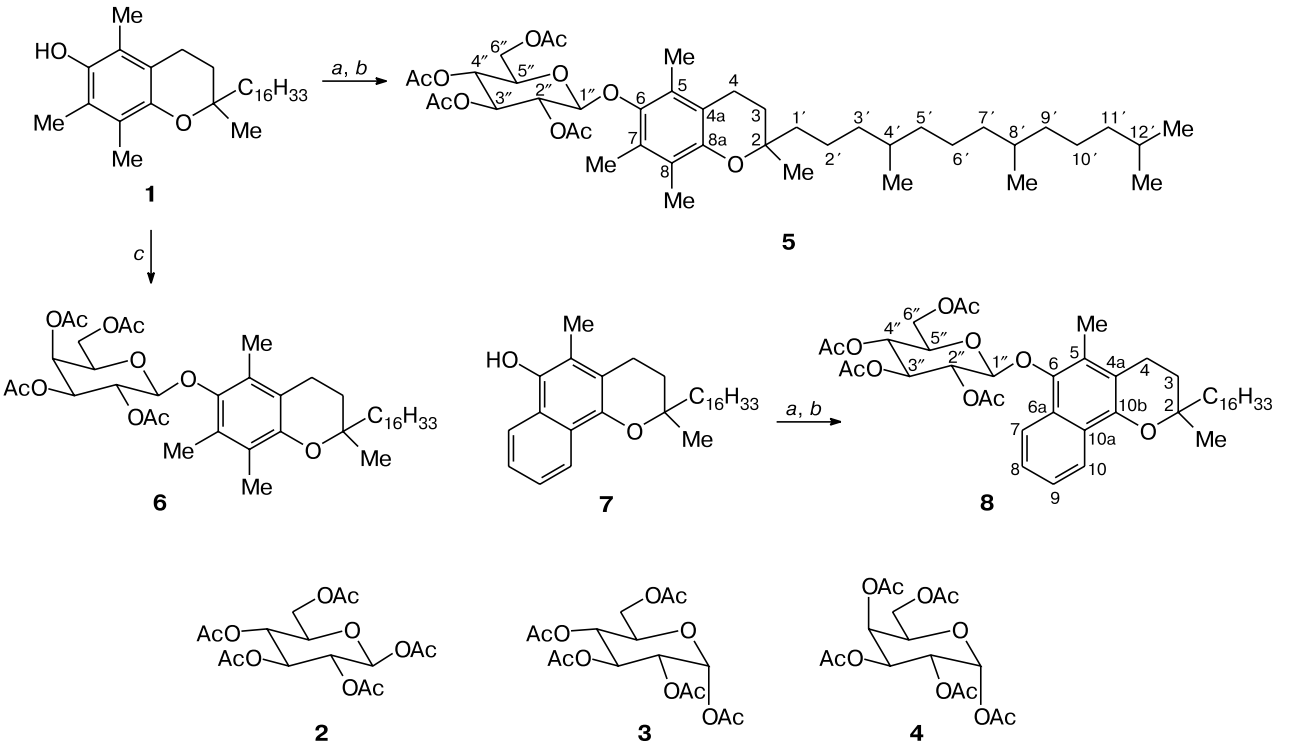
We showed that glycosylation of (*R*,*S*)-α-tocopherol (**1**) upon treatment with β- and α-anomers of D-glucopyranose pentaacetate (**2** and **3**, respectively) and with α-D-galactopyranose pentaacetate (**4**) in dichloromethane in the presence of both [bmim]PF_6 and boron trifluoride etherate proceeds smoothly and leads exclusively to β-glycosides of the corresponding sugars **5** and **6** (Scheme 1).

The highest yields of glycosides were obtained when the molar ratio $BF_3 \cdot OEt_2$: [bmim]PF_6 was 5 : 1. An increase in the content of the ionic liquid (molar ratio

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2401—2404, December, 2007.

1066-5285/07/5612-2487

Scheme 1



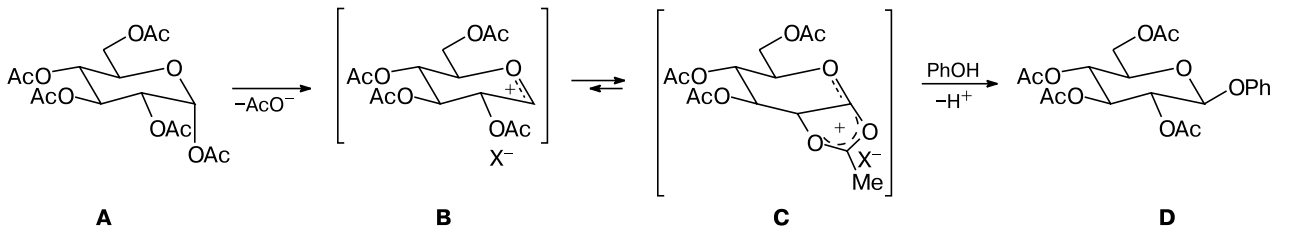
Reagents and condition: *a*. **2**/$BF_3 \cdot OEt_2$—[bmim]PF_6, CH_2Cl_2; *b*. **3**/$BF_3 \cdot OEt_2$—[bmim]PF_6, CH_2Cl_2; *c*. **4**/$BF_3 \cdot OEt_2$—[bmim]PF_6, CH_2Cl_2.

$BF_3 \cdot OEt_2$: [bmim]PF_6 = 1 : 2) causes a decrease in the yields of glycosides. No reaction of α-tocopherol (**1**) occurs in the presence of the ionic liquid alone, without addition of $BF_3 \cdot OEt_2$. A sharp drop in the yield of glycoside **5** was observed when [bmim]PF_6 was used as the solvent (instead of dichloromethane), apparently, because of the low solubility of the reagents and high viscosity of the reaction media.

Similarly to (*R*,*S*)-α-tocopherol (**1**), [bmim]PF_6 as the additive plays a decisive role in the reaction of (*R*,*S*)-naphthotocopherol **7** with β- and α-anomers of D-glucopyranose pentaacetate (**2** and **3**). When boron trifluoride etherate alone was used as the catalyst, naphthotocopherol **7** did not react with α-anomer **3**, whereas its reaction with β-anomer **2** afforded β-glycoside **8** in low yield. At the same time, α-anomer **3** was successfully involved into the reaction under the action of a catalytic system $BF_3 \cdot OEt_2$—[bmim]PF_6, and the reaction with β-anomer **2** afforded β-glycoside **8** in considerably higher yield.

The observed promoting effect of the ionic liquid and the formation of β-glycosides from both anomers of acetylated sugars can be explained by the transformation of glycosyl donor upon treatment with Lewis acids to oxocarbenium ion **B** and further to the more stable 1,2-dioxocarbenium ion **C**, which leads to the corresponding β-glycoside **D** (Scheme 2).[21] An increase in polarity of the

Scheme 2



$X^- = OAc^-, F_6P^-$

solvent and ionic strength of the solution results in acceleration of the reaction,[21—23] which, obviously, is favored by the ionic liquid. In addition, ionic liquid [bmim]PF_6 considerably increases the catalytic activity of $BF_3 \cdot OEt_2$,[12] and its anion (hexafluorophosphate) stabilizes ions **B** and **C**.

In conclusion, a combination of [bmim]PF_6 with boron trifluoride etherate is an efficient catalytic system, exceeding in its activity the earlier known catalysts of glycosylation of α-tocopherol with acetylated sugars. The first synthesis of naphthotocopherol β-glucoside was accomplished in the presence of this catalytic system.

Experimental

IR for neat samples spectra were recorded on a Specord IR-75 spectrometer, UV spectra were recorded on a Specord M-40 spectrometer. ^1H and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Bruker AM-300 spectrometer (^1H, 300.13 MHz; ^{13}C, 75.47 MHz), Me_4Si was used as the internal standard. Optical rotation was determined on a Perkin—Elmer 141 polarimeter, specific rotation is given in deg mL g^{-1} dm^{-1}. Sorbfil plates were used for TLC with *n*-hexane—EtOAc (1 : 1) as the solvent system visualization was done with phosphomolibdic acid and 5% aqueous H_2SO_4. (*R*,*S*)-α-Tocopherol was purchased from Fluka, (*R*,*S*)-naphthotocopherol was obtained by a known procedure,[24] ionic liquid [bmim]PF_6 was synthesized as described earlier.[25]

Glycosylation (general method). A solution of sugar (**2**, **3**, and **4** for **1** or **2** and **3** for **7**) (1 mmol) in CH_2Cl_2 (4 mL) was added to a stirred solution of α-tocopherol (**1**) (1 mmol) or naphthotocopherol (**7**) (1 mmol), $BF_3 \cdot OEt_2$ (2.5 mmol), and [bmim]PF_6 (0.5 mmol) in CH_2Cl_2 (11 mL) (the flask was protected from light, Ar, ~25 °C). The reaction mixture was stirred for 3 h, saturated aq. $NaHCO_3$ was added to make it neutral followed by dilution with CH_2Cl_2 (20 mL). The organic layer was washed with brine (3×10 mL) and dried with $MgSO_4$, the solvent was evaporated. The residue was extracted with hexane—ethyl acetate (5 : 1, 3×10 mL), the combined extracts were concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 (16 g). The starting compounds **1** or **7** were eluted first with *n*-hexane—EtOAc (10 : 1), then glycosides **5**, **6**, and **8** (R_f 0.5) were eluted with *n*-hexane—EtOAc (10 : 3). The yields of glycosides and the results of experiments with other ratios of reagents are given in Table 1.

(*R*,*S*)-α-Tocopheryl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (5), $[\alpha]_D^{18}$ −8.5 (*c* 1.83, CH_2Cl_2) (*cf.* Ref. 5). UV (CH_2Cl_2), λ_{max}/nm (ε): 287 (1772). IR and ^1H and ^{13}C NMR spectra are in agreement with those described.[5,6]

(*R*,*S*)-α-Tocopheryl-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (6), $[\alpha]_D^{20}$ +5.7 (*c* 0.58, $CHCl_3$) (*cf.* Ref. 6). UV (EtOH), λ_{max}/nm (ε): 288 (1786). IR and ^1H and ^{13}C NMR spectra are in agreement with those described.[6]

(*R*,*S*)-Naphthotocopheryl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (8), $[\alpha]_D^{20}$ +2.8 (*c* 1.00, CH_2Cl_2). Found (%): C, 68.83; H, 8.62. $C_{45}H_{66}O_{11}$. Calculated (%): C, 69.03; H, 8.50. IR, ν/cm^{-1}: 1760 (C=O); 1210, 1080, 1060 (C—O). UV (CH_2Cl_2), λ_{max}/nm (ε): 309 (8964), 316 (3796), 330 (3258). ^1H NMR, δ: 0.84—0.88 (m, 12 H, MeC(4′), MeC(8′), 2 MeC(12′)); 1.00—1.79 (m, 23 H, H(1′)—H(12′), H(3)); 1.95, 2.02, 2.04, 2.06 (m, 12 H, MeCO); 2.21 (s, 3 H, MeC(2)); 2.31 (s, 3 H, MeC(5)); 2.71 (t, 2 H, H(4), *J* = 6.5 Hz); 3.50—3.52 (m, 1 H, H(5″)); 4.00 (dd, 1 H, $H(6_b'')$, *J* = 12.2 Hz, *J* = 2.0 Hz); 4.18—4.24 (dd, 1 H, $H(6_a'')$, *J* = 12.2 Hz, *J* = 4.9 Hz); 4.95 (d, H(1″), *J* = 8.0 Hz); 5.18—5.32, 5.45—5.51 (m, 3 H, H(2″), H(3″), H(4″)); 7.27—7.45 (m, 2 H, H(8), H(9)); 8.05, 8.19 (both d, 2 H, H(7), H(10), *J* = 8.1 Hz). ^{13}C NMR, δ: 13.04 (MeC(5)); 19.58, 19.64 (MeC(4′), Me(C(8′)); 20.37 (C(4)); 20.44, 20.52, 20.64 (MeCO); 22.52, 22.61 (2 MeC(12′)); 23.52 (MeC(2)); 23.52 (C(2′)); 24.31, 24.68 (C(6′), C(10′)); 27.34 (C(12′)); 31.0 (C(3)); 32.56, 32.64 (C(4′), C(8′)); 37.17, 37.26 (C(3′), C(5′), C(7′), C(9′)); 39.25 (C(11′)); 39.99 (C(1′)); 61.66 (C(6″)); 68.52 (C(4″)); 71.45 (C(5″)); 71.94 (C(2″)); 73.28 (C(3″)); 75.52 (C(2)); 101.96 (C(1″)); 114.36 (C(5)); 121.06, 122.68, 124.21, 125.44 (C(7)—C(10)); 124.78, 126.79, 127.80 (C(4a), C(6a), C(10a)); 141.43 (C(10b)); 145.80 (C(6)); 169.17, 169.28, 170.24, 170.30 (MeCO).

Table 1. Results of glycosylation of α-tocopherol (**1**) and naphthotocopherol (**7**)

Glycosyl acceptor	Glycosyl donor	A : D : $BF_3 \cdot OEt_2$: [bmim]PF_6[a]	Glycoside	Yield (%)
1	**2**	1 : 1 : 2.5 : 0.5	**5**	93
		1 : 1 : 2.5 : 5	**5**	80
		1 : 1 : 2.5 : 5	**5**	14[b]
		1 : 1 : 0 : 0.5	**5**	0
		1 : 1 : 2.5 : 0	**5**	40[c]
	3	1 : 1 : 2.5 : 0.5	**5**	44
		1 : 1 : 2.5 : 5	**5**	38
		1 : 1 : 2.5 : 0	**5**	0
	4	1 : 1 : 2.5 : 0.5	**6**	48
		1 : 1 : 2.5 : 5	**6**	29
7	**2**	1 : 1 : 2.5 : 0.5	**8**	63
		1 : 1 : 2.5 : 0	**8**	26
	3	1 : 1 : 2.5 : 0.5	**8**	12
		1 : 1 : 2.5 : 0	**8**	0

[a] Molar ratio acceptor : donor : $BF_3 \cdot OEt_2$: [bmim]PF_6.
[b] Solvent-free.
[c] See Ref. 5.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 07-03-00438) and by the Presidium of the Russian Academy of Sciences (Program of Fundamental Research P-08 "Development of Methodology of Organic Synthesis and Creation of Compounds with Valuable Applied Properties").

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Received June 7, 2007;
in revised form September 25, 2007