Synthesis of α-tocopherol analogs with unsaturated side chain and their transformation into the corresponding chromans with ω-functionalized side chain

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α-Tocopherol analogs with double bond-containing side chains were synthesized by condensation of trimethylhydroquinone with optically active (3*R*/*S*,4*S*)-3,4,8-trimethylnona-1,7-dien-3-ol and linalool in the presence of the zeolite-containing Tseokar-10 aluminosilicate. Ozonolysis of these compounds gave the corresponding chromans with ω-formyl or (after hydride reduction) ω-hydroxyl groups in the side chain.

Key words: α-tocopherol analogs, trimethylhydroquinone, isoprenoid vinylcarbinols, condensation, catalysis, aluminosilicates, ozonolysis, hydride reduction.

In view of the intensive search for biologically active analogs of vitamin E with a modified side chain,[1] we investigated the possibility of synthesizing its analogs with shortened functionalized side chains.[2] These compounds present interest as objects of biological studies and as building blocks for the synthesis of other vitamin E analogs.

The first step used in this work was acid-catalyzed coupling of trimethylhydroquinone (TMHQ) with allylic isoprenoid alcohols.[3] The usual catalysts are unsuitable for reactions of tertiary vinylcarbinols with unsaturated isoprenoid groups because in this case, the reaction is complicated by side cyclization resulting in tricyclic esters.[4,5]

We have reported previously the use of the Tseokar-10 aluminosilicate for the synthesis of optically active analogs of α-tocopherol with a saturated isoprenoid side chain.[2] The AShNTs-3 and Tseokar-2 aluminosilicates have been used for TMHQ condensation with isophytol and dihydrolinalool.[6] In this work, we have studied the capacity of the aluminosilicate catalyst Tseokar-10 in the synthesis of chromanols with an isoprenoid side chain containing a terminal isopropylidene group. (3*R*/*S*,4*S*)-3,4,8-Trimethylnona-1,7-dien-3-ol (**1**) (a 1 : 1 mixture of (3*R*,4*S*)-*erythro*- and (3*S*,4*S*)-*threo*-diastereomers, *ee* ~50%) and linalool (**2**) served as the allyl isoprenoid alcohols for the condensation with TMHQ.

It was found that the reaction of TMHQ with **1** in boiling heptane* in the presence of the Tseokar-10 aluminosilicate gives a mixture of diastereomeric optically active chromanols **3** in 54% yield (*erythro*/*threo* ~1 : 1, GLC data, *ee* ~50%, as in the initial **1**, see Ref. 2). The diastereomer mixture **3** was transformed into a mixture of the corresponding acetates **4** and characterized.

Under the same conditions, the condensation of TMHQ with **2** is less selective, resulting in the formation of a considerable amount of tricyclic isomer **6** besides the target chromanol **5**. Compounds **5** and **6** were separated and characterized as the corresponding acetates **7** and **8**. The best yield of the target chromanol **5** is obtained by performing the reaction in heptane (the **5** : **6** ratio is 2 : 1),* while the reaction in aromatic solvents (benzene, toluene) gives a nearly equimolar mixture of compounds **5** and **6**, and the reaction in dioxane does not proceed at all.

The difference between the selectivities observed in the reactions of TMHQ with **1** and **2** may be due to easy cyclization of intermediate **9** (see Refs. 7 and 8), whereas in the reaction of TMHQ with **1**, the cyclization of the similar intermediate to compound **10** containing a seven-membered ring is hampered.

The ozonolysis of olefins **4** and **7** in a CH_2Cl_2—MeOH mixture with subsequent reduction of the peroxide products by Me_2S [9] yields the corresponding aldehydes and their acetals in a total yield of no more than 35%. The oxidative cleavage of chromanols **4** and **7** was carried out using the procedure of ozonolysis[10] in aqueous acetone in the presence of $Ba(OH)_2$, which gave aldehydes **11** and **12** in 52 and 80% yields, respectively, in one step. The hydride reduction of **11** and **12** yielded the corresponding alcohols **13** and **14**. Compounds **11**—**14** can serve as synthons for various α-tocopherol analogs.

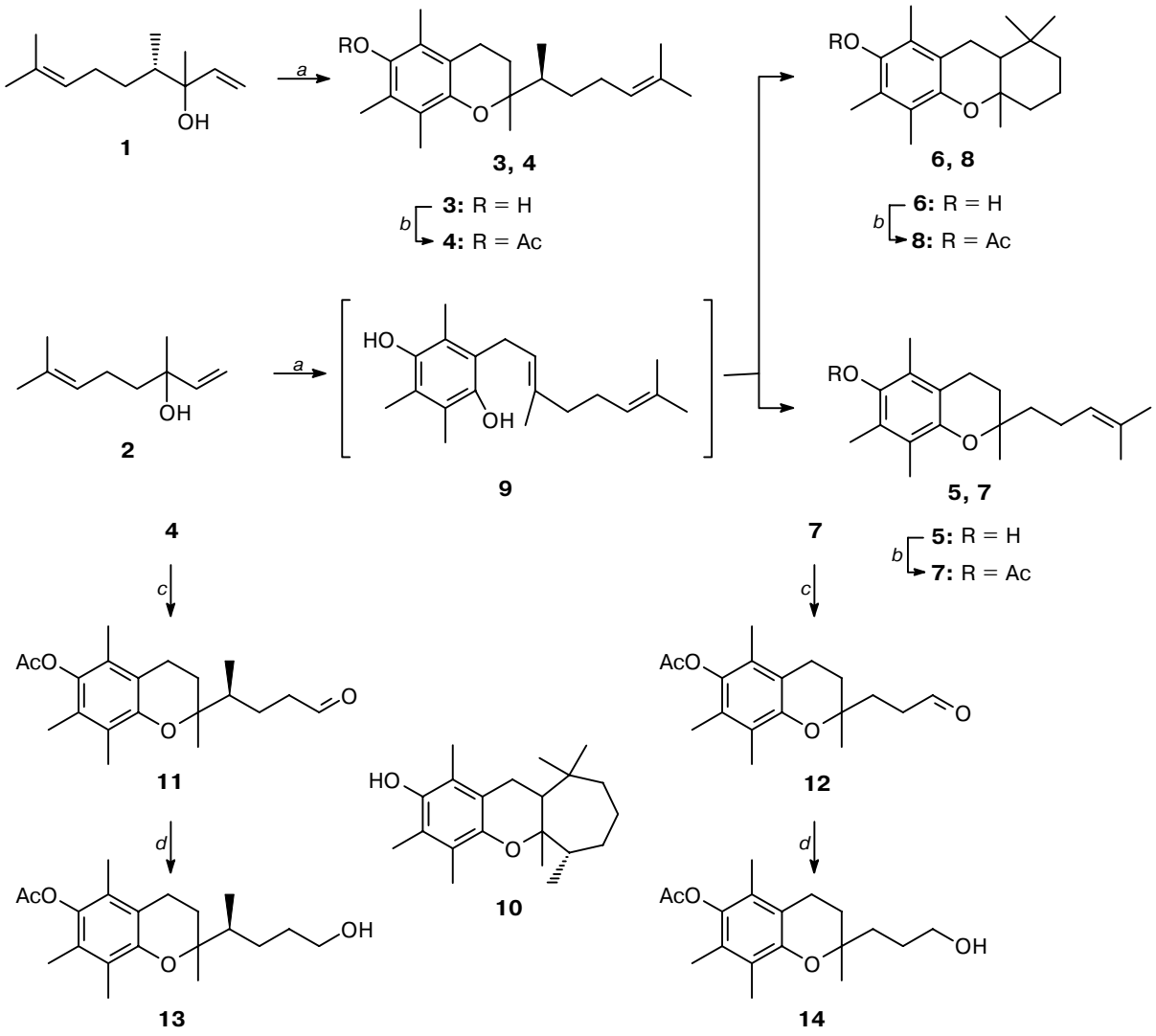
The ^{13}C NMR spectra of aldehydes **11** and alcohols **13**, like those of compounds **3** and **4**, exhibit double sets of signals (Table 1) for atoms that experience the influ-

* Under more drastic conditions (in boiling nonane), the selectivity of the reaction is much lower and a complex mixture of products is obtained.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2127—2130, November, 2001.

1066-5285/01/5011-2227 $25.00

Scheme 1



Reagents and conditions: *a*. TMHQ/Tseokar 10, *n*-C_7H_{16}; *b*. Ac_2O/Py; *c*. $O_3/Me_2CO/Ba(OH)_2$; *d*. $NaBH_4$/MeOH.

ence by the chiral 2- and 1′-centers, which is typical of diastereomer mixtures.[2,11] The presence of two doublets of equal intensities corresponding to the protons of the methyl group bound to C(1′) in the region of δ 0.92—1.02 in the ^1H NMR spectra of compounds **3**, **4**, **11**, and **13** implies that these products are equimolar mixtures of (2*R*,1′*S*)-*erythro*- and (2*S*,1′*S*)-*threo*-diastereomers.

Experimental

IR spectra were recorded on a Specord 75-IR spectrometer (in thin film). UV spectra were measured using a Specord M-40 instrument. ^1H and ^{13}C NMR spectra were run on a Bruker AM-300 spectrometer (300.13 and 75 MHz for ^1H and ^{13}C, respectively) in $CDCl_3$. The chemical shifts are given in the δ scale relative to Me_4Si (internal standard). GLC analysis was performed using a Chrom-5 chromatograph (a 2400×4 mm column with the Chromaton N-AW-DMCS and SE-30 (5%) stationary phase at a temperature of 50—300 °C (8 K min^{-1}) using helium as the carrier gas). The preparative resolution of acetates **7** and **8** was carried out using a Carlo Erba chromatograph (a 6000×6 mm column) with the SE-30 stationary phase, a thermostat temperature of 300 °C, and helium as the carrier gas. Optical rotation was measured using a Perkin—Elmer-141 polarimeter.

6-Hydroxy-2,5,7,8-tetramethyl-2-[2*S*-(6-methylhept-5-en-2-yl)]chromans (3). A mixture (prepared by a known procedure[2]) of alcohols **1** (2.5 g, 13.74 mmol) was added dropwise (Ar, 98 °C) to a suspension of TMHQ (1.04 g, 6.87 mmol) and the powdered Tseokar-10 catalyst (2.4 g) (a zeolite-containing aluminosilicate catalyst for the cracking of petroleum fractions, manufactured at the Salavatnefteorgsintez plant) in 30 ml of dry *n*-heptane. The reaction mixture was refluxed for 5 h, cooled to ~20 °C, and filtered. The filtrate was concentrated and the residue was chromatographed on SiO_2. Elution first with *n*-hexane and then with an *n*-hexane—Et_2O mixture

Table 1. ^{13}C NMR spectral data (δ) for compounds **3**, **4**, **7**, **8**, **11—14**

C atom, group	**3**	**4**	**7**	**8**	**11**	**12**	**13**	**14**
C(2)	75.57	77.20	74.71	75.92	76.84	73.59	77.55	74.49
		77.57			77.00		77.61	
C(3)	29.73	28.63	30.99	47.99	28.46	30.80	28.39	30.67
	30.24	29.12			28.98		29.22	
C(4)	21.00	20.27	20.45	33.37	19.78	20.06	20.24	20.28
					19.83		20.30	
C(5)	118.04	124.63	124.79	125.12	124.54	124.75	124.83	124.71
C(6)	145.88	149.20	149.21	148.90	148.45	148.46	149.07	148.92
					148.54		149.16	
C(7)	123.05	126.59	126.54	126.58	126.34	126.54	126.67	126.42
C(8)	121.76	122.97	122.90	122.85	122.51	122.62	122.99	122.69
	121.80							
C(9)	145.06	140.52	140.46	140.73	140.22	140.49	140.57	140.37
C(10)	119.10	117.55	117.19	118.82	116.97	116.74	117.53	117.07
	119.21				117.06		117.56	
C(1′)	39.53	39.57	37.90	41.72	42.16	38.12	39.61	35.87
	39.79	39.81			42.25			
C(2′)	31.40	31.63	22.15	32.08	27.67	59.96	26.70	26.59
	32.30	32.71			27.88		27.42	
C(3′)	26.05	25.52	124.34	40.01	65.38	202.01	31.21	62.64
	26.16	25.60					31.33	
C(4′)	125.28	125.75	131.27	29.75	202.03		63.04	
	125.42				202.32		63.15	
C(5′)	131.66	131.26	25.56					
	131.95	131.48						
C(6′)	27.02	26.42						
2-Me	19.94	19.63	25.56	21.81	19.09	13.83	20.40	23.65
	20.38	20.08			20.07		20.45	
Me—Ar	11.70	11.77	11.70	11.93	11.43	11.52	11.75	11.59
	12.22	11.96	11.96	12.16	11.63	11.72	11.99	11.81
	12.28	12.59	12.82	12.97	12.50	12.58	12.85	12.67
	12.65							
1′-Me	18.05	13.37			13.66		13.55	
	18.13	14.15			14.84		14.26	
4′-Me			17.42	19.35				
				20.01				
5′-Me	14.77	17.59						
Ac								
CO		169.57	169.57	169.73	169.23	169.28	169.67	169.80
CH_3		20.39	20.39	20.59	20.07	20.13	20.45	20.17

(10 : 1) gave 1.16 g (54%) of chromans **3**; according to GLC, this was a 1 : 1 mixture of *erythro*- and *threo*-diastereomers; $[\alpha]_D^{20}$ −2.0° (*c* 3.0, $CHCl_3$). UV ($CHCl_3$), λ_{max}/nm (ε): 296 (3780) (*cf.* Ref. 4). ^1H NMR, δ: 1.02 (d, 1.5 H, C(1′)CH_3, J = 6.7 Hz); 1.08 (d, 1.5 H, C(1′)CH_3, J = 6.8 Hz); 1.22 (s, 3 H, C(2)CH_3); 1.6—2.1 (m, 7 H, H(3), H(1′), H(2′), H(3′)); 1.66, 1.70, 1.72, 1.80 (all s, 6 H, C(5′)CH_3, H(6′)); 2.18 (s, 3 H, ArCH_3); 2.22 (s, 3 H, ArCH_3); 2.24 (s, 3 H, ArCH_3); 2.68 (t, 2 H, H(4), J = 6.6 Hz); 4.50 (s, 1 H, OH); 5.13 (t, 0.5 H, H(4′), J = 7.5 Hz); 5.26 (t, 0.5 H, H(4′), J = 7.5 Hz).

6-Acetoxy-2,5,7,8-tetramethyl-2-[2*S*-(6-methylhept-5-en-2-yl)]chromans (4). A solution of chroman mixture **3** (0.5 g, 1.58 mmol) in 4 mL of Ac_2O and 5 mL of anhydrous Py was kept for 0.5 h at ~20 °C and then poured into 20 mL of ice water and extracted with EtOAc. The extract was washed with 3 *M* HCl, a saturated solution of $NaHCO_3$, and H_2O, dried with $MgSO_4$, and concentrated to give 0.5 g (88.3%) of a mixture of *erythro*- and *threo*-diastereomers of **4**; $[\alpha]_D^{20}$ −5.7° (*c* 0.34, $CHCl_3$). Found (%): C, 77.27; H, 9.63. $C_{23}H_{34}O_3$. Calculated (%): C, 77.10; H, 9.50. IR, ν/cm^{-1}: 1740 (C=O). UV (EtOH), λ_{max}/nm (ε): 285 (2400). ^1H NMR, δ: 0.97 (d, 1.5 H, C(1′)CH_3, J = 7.0 Hz); 1.03 (d, 1.5 H, C(1′)CH_3, J = 7.0 Hz); 1.99 (s, 3 H, C(2)CH_3); 1.6—2.0 (m, 7 H, H(3), H(1′), H(2′), H(3′)); 1.62, 1.75 (both s, 6 H, C(5′)CH_3, H(6′)); 2.02 (s, 3 H, ArCH_3); 2.06 (s, 3 H, ArCH_3); 2.18 (s, 3 H, ArCH_3); 2.38 (s, 3 H, OAc); 2.60 (t, 2 H, H(4)); 5.17 (t, 1 H, H(4′), J = 6.7 Hz).

6-Acetoxy-2,5,7,8-tetramethyl-2-(4-methylpent-3-en-1-yl)chroman (7) and 7-acetoxy-1,1,4a,5,6,8-hexamethyl-1,2,3,4-tetrahydro-9*H*-xanthene (8). Alcohol **2** (1.63 g, 10.56 mmol) was added dropwise (Ar, 98 °C) to a suspension of TMHQ (0.8 g, 5.28 mmol) and the powdered Tseokar-10 catalyst (1.8 g) in 24 mL of boiling anhydrous *n*-heptane. The reaction mixture was refluxed for 6 h, cooled to ~20 °C, and filtered. The filtrate was concentrated and the residue (1.9 g)

was chromatographed on SiO_2 as described above in the synthesis of **3** to give a mixture of chromanols **5** and **6** (1.12 g) (2 : 1, GLC data, retention times 20.89 and 22.02 min, respectively). The mixture of **5** and **6** was dissolved in 11 mL of anhydrous Py and 8.5 mL of Ac_2O was added with stirring. The mixture was kept for 0.5 h at ~20 °C and poured into 25 mL of ice water, the products were extracted with EtOAc, washed with 3 *M* HCl, a solution of $NaHCO_3$, and H_2O, and dried with $MgSO_4$ to give 1.20 g (68.9%) of a mixture of acetates **7** and **8** (2 : 1, GLC data, retention times 21.45 and 22.76 min, respectively). The mixture was resolved by preparative GLC.

Acetate 7. IR, ν/cm^{-1}: 1740 (C=O). UV (EtOH), λ_{max}/nm (ε): 285 (1900), (*cf.* Ref. 6). ^{1}H NMR, δ: 1.30 (s, 3 H, C(2)CH_3); 1.65, 1.73 (both s, 6 H, C(4′)CH_3, H(5′)); 1.70—1.95 (m, 6 H, H(3),H(1′), H(2′)); 2.02, 2.08, 2.15 (all s, 9 H, ArCH_3)); 2.38 (s, 3 H, CH_3CO); 2.68 (t, 2 H, H(4), *J* = 6.7 Hz); 5.19 (t, 1 H, H(3′), *J* = 7.0 Hz).

Acetate 8. m.p. 138—139 °C. IR, ν/cm^{-1}: 1740 (C=O). UV (EtOH), λ_{max}/nm (ε): 285 (1700) (*cf.* Ref. 6). ^{1}H NMR, δ: 0.95, 1.03 (both s, 6 H, C(4′)CH_3); 1.19 (s, 3 H, C(2)CH_3); 1.3—1.8 (m, 6 H, H(1′), H(2′), H(3′)); 2.10 (m, 1 H, H(3)); 2.01, 2.03, 2.10 (all s, 9 H, ArCH_3); 2.38 (s, 3 H, OAc); 2.61 (dd, 2 H, H(4), *J* = 5.1 and *J* = 16.0 Hz) (*cf.* Ref. 7).

6-Acetoxy-2,5,7,8-tetramethyl-2-[(2*S*-(5-oxopent-2-yl)]chroman (11). An ozone—oxygen mixture was passed for 8 min through a mixture of acetates **4** (0.5 g, 1.4 mmol), $Ba(OH)_2$ (0.48 g, 2.8 mmol), H_2O (0.12 mL), and acetone (5 mL) at ~20 °C at a velocity of 30 L h^{-1} (1.45 mmol of O_3). After the reaction was completed, the precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in 10 mL of Et_2O, dried with $MgSO_4$, and concentrated. The residue was chromatographed on SiO_2 using an *n*-hexane—Et_2O mixture (10 : 1) as the eluent to give 0.24 g (52%) of aldehyde **11**, $[\alpha]_D^{20}$ −5.9° (*c* 0.54, $CHCl_3$). Found (%): C, 72.47; H, 8.50. $C_{20}H_{28}O_4$. Calculated (%): C, 72.26; H, 8.49. IR, ν/cm^{-1}: 1710 and 1740 (C=O). UV ($CHCl_3$), λ_{max}/nm (ε): 280 (1400), 288 (1600). ^{1}H NMR, δ: 0.92, 0.98 (both d, 3 H, C(1′)CH_3, *J* = 6.9 Hz, *J* = 6.7 Hz); 1.15 (s, 3 H, C(2)CH_3); 1.6—2.0 (m, 5 H, H(3), H(1′), H(2′)); 1.98, 2.00, 2.10 (all s, 9 H, ArCH_3); 2.30 (s, 3 H, CH_3CO); 2.58 (m, 4 H, H(4), H(3′)); 9.80 (s, 1 H, H(4′)).

6-Acetoxy-2,5,7,8-tetramethyl-2-(3-oxopropyl)chroman (12). An ozone—oxygen mixture was passed for 15 min through a mixture of acetates **7** and **8** (0.8 g) (the content of **7** in the mixture was 0.48 g (1.45 mmol)), $Ba(OH)_2$ (0.87 g, 5.04 mmol), H_2O (0.2 mL), and acetone (8 mL) at ~20 °C at a velocity of 30 L h^{-1} (2.05 mmol of O_3). The reaction mixture was worked-up as described in the previous experiment to give 0.35 g (80%) of aldehyde **12** and 0.25 g of compound **8**.

Aldehyde 12. IR, ν/cm^{-1}: 1710 and 1740 (C=O). UV ($CHCl_3$), λ_{max}/nm (ε): 278 (1600), 287 (1800). ^{1}H NMR, δ: 1.20 (s, 3 H, C(2)CH_3); 1.75 (m, 4 H, H(3), H(1′)); 1.95, 2.0, 2.03 (all s, 9 H, ArCH_3); 2.10 (s, 3 H, CH_3CO); 2.58 (m, 4 H, H(4), H(2′)); 9.75 (s, 1 H, H(3′)).

6-Acetoxy-2-[2*S*-(5-hydroxypent-2-yl)]-2,5,7,8-tetramethylchroman (13). $NaBH_4$ (0.017 g, 0.42 mmol) was added in one portion to a solution of aldehyde **11** (0.14 g, 0.4 mmol) in 2 mL of MeOH. The reaction mixture was stirred for 12 h and then the solvent was removed *in vacuo*. The residue was dissolved in EtOAc, washed with 3 *M* HCl, a saturated solution of $NaHCO_3$, and brine, and dried with $MgSO_4$. The solution was concentrated and the residue was chromatographed on SiO_2 using a 10 : 1 hexane—EtOAc mixture as the eluent to give 0.08 g (58%) of alcohol **13,** $[\alpha]_D^{20}$ −5.8° (*c* 0.37, $CHCl_3$). Found (%): C, 71.97; H, 8.90. $C_{20}H_{30}O_4$. Calculated (%): C, 71.82; H, 9.04. IR, ν/cm^{-1}: 3400 (OH), 1740 (C=O). UV ($CHCl_3$), λ_{max}/nm (ε): 280 (2100), 288 (2500). ^{1}H NMR, δ: 0.94, 1.0 (both d, 3 H, C(1′)CH_3, *J* = 6.5 Hz); 1.15 (s, 3 H, C(2)CH_3); 1.6—2.0 (m, 7 H, H(3), H(1′), H(2′), H(3′)); 2.0, 2.07, 2.13 (all s, 9 H, ArCH_3); 2.34 (C, 3 H, CH_3CO), 2.58 (t, 2 H, H(4), *J* = 6.6 Hz); 3.60, 3.65 (both t, 2 H, H(4′), *J* = 6.1 Hz).

6-Acetoxy-2-(3-hydroxypropyl)-2,5,7,8-tetramethylchroman (14). The reaction of aldehyde **12** (0.32 g, 1.04 mmol) and $NaBH_4$ (0.04 g, 1.04 mmol) in 3 mL of MeOH carried out as described above gave 0.18 g (58%) of alcohol **14**. IR, ν/cm^{-1}: 3400 (OH), 1740 (CH_3CO). UV ($CHCl_3$), λ_{max}/nm (ε): 280 (1500), 287 (1700). ^{1}H NMR, δ: 1.25 (s, 3 H, C(2)CH_3); 1.65 (m, 4 H, H(1′), H(2′)); 1.78 (m, 2 H, H(3)); 1.98, 2.02, 2.10 (all s, 9 H, ArCH_3); 2.32 (s, 3 H, CH_3CO); 2.59 (t, 2 H, H(4), *J* = 6.6 Hz); 3.60 (m, 3 H, H(3′), OH).

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Received March 7, 2001;
in revised form April 24, 2001