Stereospecific radical addition of isopropanol and *n*-butanal to (5*R*)-(*l*-menthyloxy)furan-2(5*H*)-one

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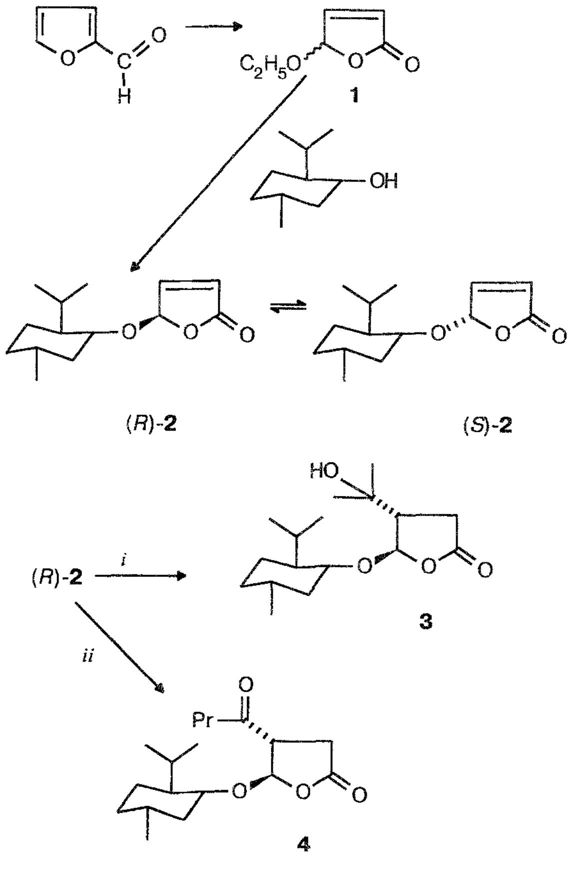
The radical addition of Pr^iOH and *n*-butanal to (5*R*)-5-(*l*-menthyloxy)furan-2(5*H*)-one occurs regio- and diastereospecifically at position 4 of the furanone ring.

Key words: diastereoselectivity, regioselectivity, radical addition, (5*R*)-5-(*l*-menthyloxy)furan-2(5*H*)-one, 2-propanol, *n*-butanal, ^1H, ^{13}C NMR spectra.

The formation of C—C bonds as a result of radical addition of addends at C=C bonds is extensively used in organic synthesis.[1] The use of unsaturated substrates with a chiral group in the side chain allows one to carry out highly efficient asymmetrical reactions with the formation of C—C and/or C—H (C—Hal) bonds.[1,2] Recently, the stereochemistry of the Bu_3SnH reduction of radical adducts formed upon addition of $R^{\cdot}$ to the C=C bond in the chiral Ni^{II} complex of the Schiff's base derived from dehydroalanine and (*S*)-*N'*-(*N*-benzylprolyl)aminobenzophenone has been studied in our laboratory, and it was shown for the first time that the spatial direction of the hydrogen atom transfer to the radical adduct, which determines the configuration of the final product, coincides with the direction of the attack of a proton at a carbanion center existing in the same chiral environment.[3]

In recent years, the readily available (5*R*)-5-(*l*-menthyloxy)furan-2(5*H*)-one has been widely used as a versatile chiral reagent in nucleophilic substitution[4—9] and cycloaddition[10,11] reactions. The addition was shown to occur stereospecifically to give *trans*-products. At the same time, the stereochemistry of radical addition to this substrate has not been studied. Therefore, in the present work we studied the addition of 2-propanol and *n*-butanal to (5*R*)-5-(*l*-menthyloxy)furan-2(5*H*)-one.

Scheme 1



i. Me_2CHOH, $(Bu^tO)_2$, *hv*.
ii. PrCHO, $(Bu^tO)_2$, *hv*.

Results and Discussion

We used 5-ethoxy-2(5*H*)-furanone (**1**) prepared by oxidation of furfural with H_2O_2 according to a modification of the known procedure[12] as the starting compound. An alternative route for the synthesis of **1** is the photochemical oxidation of furfural by singlet oxygen.[13] To synthesize (5*R*)-5-(*l*-menthyloxy)furan-2(5*H*)-one [(*R*)-**2**], we developed a method consisting of transetherification of ethyl ether **1** with *l*-menthol and separation of (*R*)-**2** from the mixture of diastereomeric *l*-menthyl ethers, (*R*)-**2** and (*S*)-**2**, (Scheme 1) by crys-

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tallization followed by epimerization of the mixture enriched in (*S*)-**2** in the mother liquor and repeated crystallization.

The radical addition of 2-propanol and *n*-butanal to (*R*)-**2** is initiated by photochemical decomposition of *tert*-butyl peroxide (TBP) at 25 °C. The reactions occur quantitatively with high regio- and diastereoselectivities to give adducts **3** and **4**, respectively (Scheme 1). No alternative regio- and diastereoisomers were detected by ^1H and ^{13}C NMR spectroscopy. Compound **3** slowly decomposes during storage to liberate *l*-menthol (this was confirmed by GLC), which is probably due to intra- or intermolecular transacetalization.

The absolute configurations of **3** and **4** were determined by comparing the spin-spin coupling constants of protons with the values of these constants obtained by molecular mechanics calculations using the MMX program. 4-(2-Hydroxy-2-propyl)- and 4-butyryl-5-isopropyloxy-γ-butyrolactone (**5** and **6**, respectively) were chosen as model compounds for calculations, since their structures are the most similar to those of compounds **3** and **4** synthesized. The experimental and calculated spin-spin coupling constants are given in Table 1. This comparison indicates that the values for the spin-spin coupling constants of compounds **3** and **4** are in good agreement with the values calculated for model compounds *trans*-**5** and *trans*-**6**, respectively. At the same time, the constants calculated for *cis*-**5** and *cis*-**6** differ substantially from those for compounds **3** and **4**. In other words, the substituents in positions 4 and 5 of the products of radical addition are *trans*-arranged with respect to one another.

Thus, the data presented indicate that (*R*)-**2** is generally attacked by a radical species from the side that is opposite to the *l*-menthyloxy group as has been observed for the majority of reactions of (*R*)-**2**.[4—11]

Table 1. The spin-spin coupling constants of the protons (Hz) at C-3, C-4, and C-5 in 4,5-disubstituted γ-buryrolactones **3—6**

Compound	$J_{3a,4}$	$J_{3b,4}$	$J_{4,5}$
3	6.0	10.0	3.0
4	6.2	9.5	3.5
trans-**5***	7.3	11.0	5.0
trans-**6***	7.1	11.0	5.4
cis-**5***	1.0	7.2	8.8
cis-**6***	1.0	7.3	8.8

* Model compounds: **5** is 4-(2-hydroxy-2-propyl)-5-isopropyloxy-γ-butyrolactone, **6** is 4-butyryl-5-isopropyloxy-γ-butyrolactone. The values of the constants were calculated by molecular mechanics using the MMX program. The total energies are: *trans*-**5** 17.9 kcal mol^{-1}, *cis*-**5** 23.0 kcal mol^{-1}, *trans*-**6** 17.2 kcal mol^{-1}, *cis*-**6** 19.8 kcal mol^{-1}.

Experimental

^1H NMR spectra were recorded on a Bruker WP 200 instrument (200 MHz). The chemical shifts are given in the δ scale (with respect to HMDS as the internal standard) and spin-spin coupling constants are in Hz.

"Chemically pure" grade reagents were used. The reaction mixtures were analyzed on an LKhM-8M chromatograph (katharometer) with temperature programming. Optical rotation was determined on a Perkin-Elmer 241 polarimeter.

5-Ethoxyfuran-2(5*H*)-one (1). 30 % H_2O_2 (180 mL) was added with stirring at 40 °C to a mixture of furfural (69 g, 0.72 mol), V_2O_5 (0.9 g, $5 \cdot 10^{-4}$ mol), and water (550 mL). The mixture was kept at 50—55 °C for 3 h. The water was evaporated at 40—45 °C *in vacuo*, and the residue was diluted with ethanol (100 mL) and benzene (100 mL), boiled at reflux with a Dean—Stark distillation head until separation of water was over, cooled, poured in a saturated solution of $NaHCO_3$ (40 mL), and extracted with ether or benzene. The extract was dried with $MgSO_4$ and distilled. The yield of **1** was 28.1 g (22%), b. p. 62—65 °C (4 Torr), n_D^{20} 1.4508 (*cf.* Ref. 13). ^1H NMR ($CHCl_3$), δ: 1.3 (t, 3 H, Me); 3.85 (m, 2 H, CH_2); 5.9 (dd, *J* = 1.2 Hz, 1.2 Hz, 1 H, H-5); 6.2 (dd, *J* = 6 Hz, 1.2 Hz, 1 H, H-4); 7.2 (dd, *J* = 6 Hz, 1.2 Hz, 1 H, H-3).

(5*R*)-5-(*l*-Menthyloxy)-2(5*H*)-furanone ((*R*)-2). Furanone **1** (27.3 g, 0.213 mol), *l*-menthol (39.9 g, 0.256 mol), and benzene (300 mL) were boiled in a flask equipped with a rectifying column. The azeotrope (C_6H_6/EtOH = 68/32, b.p. 68 °C) was collected for 20 h. Accumulation of the reaction product was monitored by GLC. The reaction mixture was washed with a saturated solution of $NaHCO_3$ and then with H_2O, and dried with $MgSO_4$. The benzene was evaporated, and the residue was distilled to give 11.3 g (22.3 %) of a mixture of diastereomers of **2** (60:40) with b.p. 125—170 °C (11 Torr) (*cf.* Ref. 11). This mixture was recrystallized from hexane to give 5.9 g (11.6 %) of diastereomer (*R*)-**2**, m. p. 79—81 °C, $[\alpha]_D^{20}$ −129.0 (*c* 1, 95% EtOH) (*cf.* Ref. 11). The mother liquors were concentrated, and the residue was boiled with 0.02 g of TsOH in 30 mL of C_6H_6. Evaporation of benzene and recrystallization from hexane gave an additional 2 g of (*R*)-**2**. The overall yield was 15.5%. ^1H NMR (C_6D_6), δ: 0.7—2.2 (m, 18 H, menthyl-H); 3.5 (m, 1 H, menthyl-H); 5.5 (s, 1 H, H-5); 5.65 (d, 1 H, H-4, *J* = 6 Hz); 6.5 (d, 1 H, H-3, *J* = 6 Hz). ^{13}C NMR ($CHCl_3$), δ: 170.61 (C-2); 150.78 (C-3); 124.67 (C-4); 100.34 (C-5); 78.83 (C-1'); 47.66 (C-2'); 40.22 (C-6'); 34.08 (C-4'); 31.36 (C-5'); 25.21 (C-7'); 23.03 (C-3'); 22.10 (C-10'); 20.73 and 15.66 (C-8' and C-9').

The reaction of (*R*)-2 with 2-propanol. A solution of furanone (*R*)-**2** (0.2 g, 0.84 mmol) in 2.6 mL of a 0.25 % v/v isopropanol solution of TBP (0.084 mol) was placed in a test tube of molybdate glass with a stopper and irradiated with a PRK-4 lamp for 4 h at 25 °C without removing air. The consumption of the starting (*R*)-**2** was monitored by GLC. The reaction mixture was concentrated to dryness, and the residual glassy solid mass was dried *in vacuo* to give 0.23 g (99 %) of **3**. Recrystallization from *n*-hexane afforded small colorless crystals, m.p. 65 °C, $[\alpha]_D^{25}$ −145.4 (*c* 1, $CHCl_3$), $[\alpha]_D^{25}$ −151.3 (*c* 10, 90% EtOH). Found (%): C, 68.36; H, 9.56. $C_{17}H_{30}O_4$. Calculated (%): C, 68.41; H, 10.15. ^1H NMR ($CDCl_3$), δ: 0.9—2.1 (m, 18 H, H-menthyl); 1.1 (s, 3 H, Me); 1.15 (s, 3 H, Me); 2.3 (m, 1 H, H-4); 2.5 (dd, 1 H, H_a-3, *J* = 6 and 18 Hz); 2.7 (dd, 1 H, H_b-3, *J* = 10 and 18 Hz);

3.6 (m, 1 H, H-menthyl); 5.75 (d, 1 H, H-5, J = 3 Hz). ^{13}C NMR ($CDCl_3$), δ: 176.37 (C-2); 102.09 (C-5); 77.21 (C-1'); 69.83 (C-6); 51.75 (C-4); 47.74 (C-2'); 39.76 (C-6'); 34.24 (C-4'); 31.30 (C-5'); 30.03 (C-5'); 27.79 and 27.61 (C-7 and C-8); 25.32 (C-7'); 23.02 (C-3'); 22.19 (C-10'); 20.03 and 15.60 (C-8' and C-9').

The reaction of (*R*)-2 with *n*-butanal was carried out as described in the previous experiment with butanal taken instead of 2-propanol. 0.2 g (0.84 mmol) of furanone (*R*)-**2** gave 0.23 g (99 %) of compound **4**, m.p. 65°C, $[\alpha]_D^{25}$ −164.3 (c 1, $CHCl_3$). Found (%): C, 69.46; H, 9.98. $C_{18}H_{30}O_4$. Calculated (%): C, 69.68; H, 9.68. ^{1}H NMR ($CDCl_3$), δ: 0.8—1.0 (m, 21 H, H-menthyl and Me); 1.4 (m, 2 H, CH_2Me); 1.9 (m, 2 H, $COCH_2Et$); 2.3 (dd, 1 H, H_a-3, J = 9.5 and 17.5 Hz); 2.5 (dd, 1 H, H_b-3, J = 6.2 and 17.5 Hz); 2.8 (m, 1 H, H-4); 3.4 (m, 1 H, H-menthyl); 5.5 (m, 1 H, H-5, J = 3.5 Hz).

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