Diastereoselective Electrosynthesis of (±)-(2*R*,4*S*,6*R*)-6-[(*Z*)-1′-Bromo-2′-phenylethenyl]-2,4-dimethyltetrahydropyran-2,4-diol

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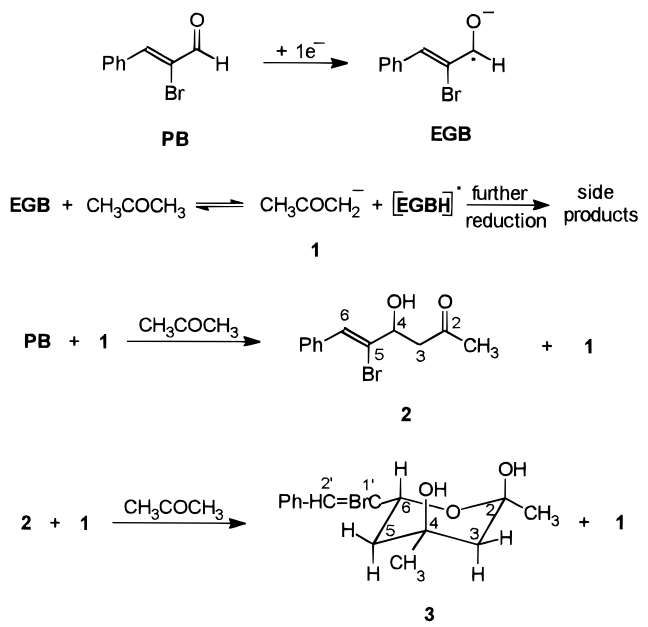
A number of common inorganic and organic reagents can be generated *in situ* electrochemically. Electrochemical generation offers advantages over conventional methods when, for instance, it is necessary to add the reagent at extremely low concentration or when the reagent may be unstable, hazardous, or cumbersome to use on a large scale. A particular case in this field is the electrochemical generation of acids or bases in organic synthesis.

In previous papers we reported the electrosynthesis of 4-aryl-2-methylfurans[1] and 1-phenyl-2,3,4-tribenzoyl-1-cyclopentanols[2] by cathodic reduction. In these processes the electrogenerated anions act as *electrogenerated bases* (**EGBs**).

In this paper, we report the cathodic reduction of α-bromo-*cis*-cinnamaldehyde (*probase*, **PB**) in dry acetone and anhydrous lithium perchlorate on mercury cathode. The major reaction product obtained corresponds to a cyclic structure formed by the addition of two molecules of acetone to a molecule of substrate. The process can be summarized as outlined in Scheme 1.

Scheme 1



Results and Discussion

The first step of the synthetic route involves the transfer of one electron and the formation of the radical anion, **EGB**. This **EGB** reacts in solution with a molecule of acetone by abstracting one proton to give the corresponding **[EGBH]·** and the enolate **1**. Collaterally, the radical **[EGBH]·** undergoes further reduction to give small amounts of other materials, which were studied by MS and ^{1}H NMR and were identified as condensation products from cinnamaldehyde and molecules of acetone. The enolate **1** adds to the carbonyl group of another molecule of substrate to give **2**, which was identified as racemic 5-bromo-4-hydroxy-6-phenyl-5(*Z*)-hexen-2-one. The ketone **2** reacts again with another enolate **1** to give a new anion which finally undergoes an intramolecular cyclization to give **3**, (±) (2*R*,4*S*,6*R*)-6-[(*Z*)-1′-bromo-2′-phenylethenyl]-2,4-dimethyltetrahydropyran-2,4-diol, as main product.

Preliminary structural elucidation, based on the ^{1}H, ^{13}C, and DEPT NMR spectra, in combination with ^{1}H−^{13}C correlation (HETCOSY) NMR experiment, allowed one to establish the structure of the pyranoid ring of compound **3**. Its ^{1}H NMR spectrum ($CDCl_3$) showed a proton adjacent to the oxygen atom H6 at δ 4.78 (ddd, $^3J_{aa}$ = 11.6 Hz, $^3J_{ae}$ = 2.4 Hz, $^4J_{ally}$ = 0.9 Hz) and the *equatorial* hydrogens (H5e and H3e) were found at δ 2.01 and 1.89, respectively. This assignment was confirmed by the W coupling constant ^4J_w = 2.3 Hz between these protons. The *axial* protons, as a general rule in tetrahydropyrans,[3] were found to resonate at higher field δ 1.65 (H5a) and 1.61 (H3a). The relative stereochemistry at carbons 2 and 4 was delineated by a series of NOE measurements.[4] The observed NOE enhancements agreed with a *cis* periplanar position of the hydroxyl groups. The most significant NOE effects were observed for the protons of both OH groups upon irradiation of H6. Furthermore, great similarity between the chemical shift of the carbons for the methyl groups, δ 29.49 and 30.70, confirmed the same disposition for both substituents on the ring.[5] The ^{1}H and ^{13}C NMR data of compound **3** are summarized in Table 1.

Upon standing under inert atmosphere for 24 h at room temperature, compound **3** converts to an unsaturated derivative, 7-bromo-1,4-dimethyl-8-phenyl-3(*E*),5(*E*),7(*Z*)-octatrien-2-one.

Although several attempts to obtain **3** by a conventional procedure were carried out (reaction of starting material with a strong base in acetone as solvent), all results were unsuccessful.

This synthesis is a new, efficient, and stereoselective route to prepare 2,4-dihydroxy-2,4-dimethyltetrahydropyrans. The generality of this unusual reaction is now under active investigation and will be the subject of future reports. Tetrahydropyrans are the main structural feature of polyether antibiotics and biologically active natural products.[6,7]

Experimental Section

General Methods. The electrolysis was carried out using an Amel potenstiostat Model 552 with an electronic integrator Amel Model 721. Mass spectra were determined at an ionizing voltage of 70 eV. IR spectra were obtained using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz,

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Table 1. NMR Spectral Data of Compound 3 in $CDCl_3$

pos		δ_H (mult, J (Hz))	δ_C
2			97.7
	OH	4.40 (brs)	
	CH_3	1.48 (s)	30.7
3	a	1.61 (d, 14.0)	44.7
	e	1.89 (dd, 14.0, 2.3)	
4			71.9
	OH	3.09 (brs)	
	CH_3	1.29 (s)	29.5
5	a	1.65 (dd, 13.5, 11.6)	42.8
	e	2.01 (td, 13.5, 2.4, 2.3)	
6		4.78 (ddd, 11.6, 2.4, 0.9)	69.8
1′		x	126.5
2′		7.15 (brs, 0.9)	129.1
aromatics		7.25−7.59 (m)	127.9
			128.0
			128.2
			135.4

respectively, with TMS (^{1}H) or $CDCl_3$ (^{13}C) as internal standard. Chemical shifts are expressed in ppm and J values in hertz. Melting points were determined on a Reichter Thermovar microhot-stage apparatus and are uncorrected. Elemental analysis was performed on a Perkin-Elmer Model 240-B analyzer. Reagents and solvent were obtained from commercial suppliers and were purified by usual laboratory techniques.

Electrosynthesis and Isolation. Anode: Pt.Anolite: anhydrous $LiClO_4$ (4 mmol) in dry acetone (15 mL). Cathode: Hg pool. Catholite: anhydrous $LiClO_4$ (6 mmol) in dry acetone (15 mL). The electrolysis cell was a divided cell maintained at 15 °C and equipped with a magnetic stirrer containing a piece of glass tubing with a glass frit of medium porosity at one end (anode compartment). Anhydrous sodium carbonate (2.0 g) was added to the anode compartment for *in-situ* neutralization of the perchloric acid generated.

A solution of α-bromo-*cis*-cinnamaldehyde (5 mmol in 20 mL of dry acetone) was added into the cathodic compartment, and a potential of −1.5 V vs ECS was applied. The reaction time was 50 min. The cathode solution was worked up by evaporation of the solvent to dryness at 30 °C under reduced pressure. The residue was extracted with ether and washed with water (2 × 50 mL) to remove inorganic salts. The extract was dried (anhydrous Na_2SO_4) and then evaporated to dryness under reduced pressure. The crude reaction products were chromatographed on silica gel using CH_3Cl:CH_2Cl_2:EtOAc (2:2:1) as eluent to give **3** (0.670 g, 41%) and **2** (0.160 g, 12%).

Racemic 5-bromo-4-hydroxy-6-phenyl-5(*Z*)-hexen-2-one (2): IR (KBr) 3429, 1710, 1232, 1159, 1075, 699 cm^{-1}; CI-MS m/z (rel int) 271 ($M^+ + 3$, 1.5), 269 ($M^+ + 1$, 1.5), 253 (35), 251 (35), 189 (20), 129 (100); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.22 (s, 3H), 2.90 (dd, J = 8.5, 17.5 Hz, 1H), 2.98 (dd, J = 3.5, 17.5 Hz, 1H), 3.29 (d, J = 4.3 Hz, 1H, OH), 4.78 (m, J = 0.9, 3.5, 4.3, 8.5 Hz, 1H), 7.16 (brs, 1H), 7.58−7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.9, 48.7, 73.2, 126.9 (C5), 128.1, 128.2, 128.3, 129.1 (C6), 134.9, 208.2. Anal. Calcd for $C_{12}H_{13}O_2Br$: C, 53.55; H, 4.87. Found: C, 53.63; H, 4.83.

(±)-(2*R*,4*S*,6*R*)-6-[(*Z*)-1′-Bromo-2′-phenylethenyl]-2,4-dimethyltetrahydropyran-2,4-diol (3): mp 96−98 °C; IR (KBr) 3421, 3254, 1377, 1189, 1098, 1041, 915, 696 cm^{-1}; CI-MS m/z (rel int) 329 ($M^+ + 3$, 9), 327 ($M^+ + 1$, 9), 294 (15), 293 (100), 292 (18), 291 (100), 213 (14), 211 (25); ^{1}H and ^{13}C NMR Table 1. Anal. Calcd for $C_{15}H_{19}O_3Br$: C, 55.06; H, 5.85. Found: C, 55.11; H, 5.82.

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