Enantioselective, Electrocatalytic Lactonization of Methyl-substituted Diols on a TEMPO-modified Graphite Felt Electrode in the Presence of (–)-Sparteine

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A TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl)-modified graphite felt electrode afforded enantioselective, electrocatalytic lactonized products of (*S*)-(-)-3,4,5,6-tetrahydro-4-methyl-2-pyranone, (*S*)-(-)-4,5-dihydro-4-methyl-2(3*H*)-furanone and (*S*)-(-)-4,5-dihydro-5-methyl-2(3*H*)-furanone from 3-methylpentane-1,5-diol, (*S*)-(-)-2-methylbutane-1,4-diol and racemic pentane-1,4-diol, respectively, in enantiomeric excess more than 95%, in the presence of (-)-sparteine in acetonitrile. The current efficiency and isolated yield of former two lactones were more than 90%.

Optically active substituted lactones have been widey used as building block to synthesize biologically active compounds by taking advantage of their chiral and bifunctional nature.[1] The preparation of optically pure lactones usually involves a complicated process such as 2 step conversion of methyl (*R*)-(-)-3-hydroxy-2-methylpropionate to (*S*)-(-)-3,4,5,6-tetrahydro-4-methyl-2-pyranone (*S*-**1**).[2] On the other hand, a direct oxidative formation of such lactones from 1,ω-diols has succeeded in using enzyme system of microorganisms : optically pure *S*-**1** was obtained from 3-methylpentane-1,5-diol (**4**) in 57% yield after 2 d incubation with *Gluonobactor roseus*.[3] It was known that TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl) oxoammonium salts lactonize 1,ω-diols to lactones in a fairly high yield.[4] In the TEMPO-catalyzed lactonization, enantioselectivity of substituted lactones which are produced from diols having primary hydroxy and/or secondary hydroxy groups in the molecule has not been controlled.

We now report a simple electrocatalytic synthesis of optically pure *S*-**1**, (*S*)-(-)-4,5-dihydro-4-methyl-2(3*H*)-furanone (*S*-**2**) and (*S*)-(-)-4,5-dihydro-5-methyl-2(3*H*)-furanone (*S*-**3**) from prochiral **4**, (*S*)-(-)-2-methylbutane-1,4-diol (*S*-**5**) and racemic pentane-1,4-diol ((±)-**6**), respectively, on a TEMPO-modified graphite felt (GF) electrode in the presence of (-)-sparteine as a chiral deprotonating agent.

The TEMPO-modified electrode was prepared according to our established method.[5] Briefly, GF (National Electric Carbon Corp., WDF) was coated with a ca. 40 nm poly(acrylic acid) (PAA) (MW: 1400000) layer. The PAA layer was reacted with 4-amino-TEMPO (64%), followed by cross-linking with hexamethylenediamine (16%) and by butylation with dibutyl sulfate for blocking the remaining carboxylate groups (20%).[6] The density of TEMPO on the electrode was 24 μmol cm^{-3}.

The cyclic voltammograms (CVs) of 0.2 M (M = mol dm^{-3}) **4** on the TEMPO-modified electrode in 0.8 M (-)-sparteine are shown in Figure 1. In the absence of (-)-sparteine, the oxidation peak current (Figure 1a) was slightly larger than that for blank (Figure 1b, the electrode itself), though the reduction peak current was considerably diminished comparing with that for blank, showing that the oxidation rate of **4** was slow unless (-)-sparteine was present. On the contrary, the peak current (Figure 1c) for **4** with (-)-sparteine was a 4.5 fold larger than that for the blank,

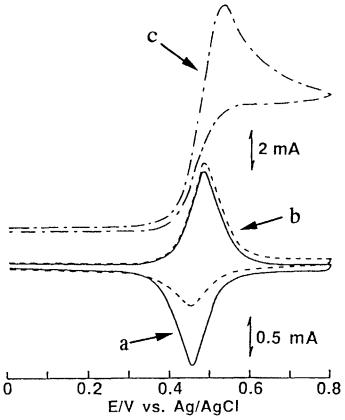


Figure 1. Cyclic voltammograms on TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in 0.2 M $NaClO_4/CH_3CN$. Scan rate of 10 mV s^{-1}. a : in the absence of both **4** and (-)-sparteine, b : in the presence of 0.2 M **4** and in the absence of (-)-sparteine, c: in the presence of 0.2 M **4** and 0.8 M (-)-sparteine.

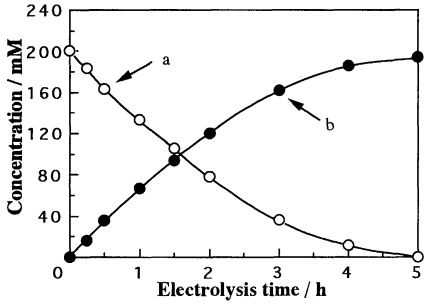
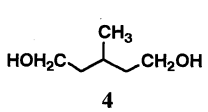
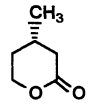
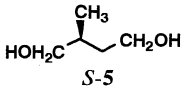
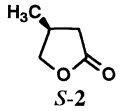
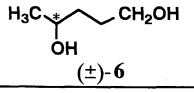
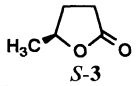


Figure 2. Macroelectrolysis of 0.2 M **4** on TEMPO-modified GF electrode (1.0 x 1.0 x 0.5 cm^3) in the presence of 0.8 M (-)-sparteine. Curve a : **4**, curve b : *S*-**1**.

and no reduction current was observed. The phenomena suggest that **4** is electrocatalytically oxidized in the presence of (-)-sparteine.

A preparative, potential-controlled electrolysis was performed in acetonitrile (CH_3CN) solution, using an H type divided cell separated by cationic-exchange membrane (Nafion 117). The anolyte contained 1 mmol of substrate, 1 mmol of tetralin as a gas chromatographic standard, 4 mmol of base ((-)-sparteine or 2,6-lutidine) and 1 mmol of sodium perchlorate ($NaClO_4$) as a supporting electrolyte in a total volume of 5 ml. The catholyte was 5 ml of CH_3CN solution containing 1 mmol of $NaClO_4$. The electrolysis was carried out at +0.60 V *vs.* Ag/AgCl under nitrogen atmosphere. The size of the modified anode was 1.0 x 1.0 x 0.5 cm^3. During electrolysis, aliquots of anolyte were analyzed by GC and/or HLPC.[7] The consumption of **4** and formation of *S*-**1** are plotted against electrolysis time in Figure 2. In ca. 5 h electrolysis, **4** was almost perfectly converted to *S*-**1**. After complete electrolysis, the anolyte was evaporated

Table1. Enantioselective electrocatalytic lactonization of methyl-substituted diols on a TEMPO-modified GF electrode in the presence of (-)-sparteine

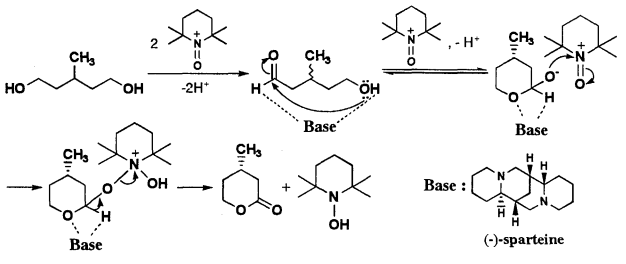
Substrate	Product	Charge passed (C)	Current [a] efficiency (%)	Isolated yield (%)	$[\alpha]_D^{20}$	*R* : *S*	% ee	Turnover number
 **4**	 *S*-**1**	391.0	92.6	93.8	-26.9°[b]	1.0 : 99.0 [e,f]	98.0 [e,f]	307
 *S*-**5**	 *S*-**2**	380.9	97.8	96.5	-24.6°[c]	0 : 100 [e]	100 [e]	316
 (±)-**6**	 *S*-**3**	284.5	65.4	48.2	-29.4°[d]	0.5 : 99.5 [e,f]	99.0 [e,f]	158

[a] The values were calculated based on four electrons process. [b] Lit.[8] $[\alpha]_D^{27}$ -27.6° (*c* 5.6, $CHCl_3$). [c] Lit.[3a] $[\alpha]_D^{20}$ -24.7° (*c* 4, CH_3OH). [d] Lit.[9] $[\alpha]_D^{23}$ -29.6° (*c* 1.29, CH_2Cl_2). [e] Measured by GC (CP-Cyclodextrin-B-2,3,6-M-19, 0.25 mm ϕ x 25 m/raising temp 3 °C min^{-1} from 80 to 150 °C, inj. temp 200 °C, detc. temp 240 °C). [f] Measured by HPLC (CHIRALCEL-OD, 0.46 cm ϕ x 25 cm/column temp 30 °C, flow speed: 0.5 ml min^{-1}, solvent: hexane-isopropanol = 95:5).

and the residue was dissolved in 30 cm^3 ethyl acetate, and the mixture was washed with 0.1 M HCl and H_2O, and dried with sodium sulfate and concentrated. Then, the obtained viscous liquid was fed onto a silica gel column (Wako Gel C-200, 3 cm ϕ x 50 cm) and eluted with a hexane-ethyl acetate mixture (9:1 v/v). The eluted solution was evaporated and distilled. A single product was obtained and identified by conventional methods. The electrolysis gave *S*-**1** in 93.8% of isolated yield, 92.6% of current efficiency, and 98% of enantiomeric excess (ee) (Table 1). On the contrary, the electrolysis on the TEMPO-modified electrode in the presence of 2,6-lutidine afforded optically inactive product of (±)-**1** in 94.6% of isolated yield and 91.8% of current efficiency. A bare GF electrode yielded a poor ee of *S*-**1** (3.0%) even in the presence of 4 mmol of (-)-sparteine and 0.4 mmol of 4-acetylamino-TEMPO in 5 ml of CH_3CN (isolated yield of (±)-**1**: 91.8% and current efficiency: 77.5%). These results show clearly that the enantioselective oxidation of **4** proceeds successfully only on the TEMPO-modified electrode in the presence of (-)-sparteine.

The diol of *S*-**5** was similarly oxidized on the TEMPO-modified electrode in the presence of (-)-spartine to yield 100% ee of *S*-**2** in high current efficiency and isolated yield (Table 1). The use of 2,6-lutidine in place of (-)-sparteine also retained the (*S*)-2-methyl configuration of *S*-**5** to yield *S*-**2** in high current efficiency and isolated yield. Furthermore, racemic **6** was electrolyzed on the TEMPO-modified electrode in the presence of (-)-sparteine (Table 1). In this electrolysis, *S*-**3** was obtained in 48.2% isolated yield and 99.0% ee. Only the *S*-isomer of (±)-**6** was probably oxidized selectively to yield *S*-**3**.

The above lactonization needs four electrons shown in Table 1. For the enantioselective lactonization, we may propose the following mechanism.



Diol, (-)-sparteine and oxoammonium salt of TEMPO interact each other strongly in a suitable size of domain which is formed by the cross-linking of hexamethylenediamine with the PAA backbone structure, and the direction of deprotonations from the diol intermediates may be strongly controlled via hydrogen bonds in the domain by chiral base.

In conclusion, this direct electrocatalytic oxidation on the TEMPO-modified electrode in the presence of chiral base such as (-)-sparteine can be applied for a general synthesis of optically pure lactones from prochiral diols and/or chiral diols. Further study is now underway.

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6 The values were determined by back titration with 0.2 M HCl.

7 The conditions for GC and HPLC are described in Table 1 footnotes of e and f, respectively.

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