Racemic and Enantiopure Synthesis and Physicochemical Characterization of the Novel Taste Enhancer *N*-(1-Carboxyethyl)-6-(hydroxymethyl)pyridinium-3-ol Inner Salt

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Convenient syntheses were developed to obtain on a multigram scale the novel taste enhancer *N*-(1-carboxyethyl)-6-(hydroxymethyl)pyridinium-3-ol **1**, called alapyridaine, as a racemic mixture and as pure (+)-(*S*) and (−)-(*R*) enantiomers, respectively. 5-(Hydroxymethyl)-2-furaldehyde was used as key intermediate and was reacted with L-alanine under alkaline conditions to obtain racemic **1**. Alternatively, reductive amination of 5-(hydroxymethyl)-2-furaldehyde with Raney-Ni/hydrogen and L- or D-alanine followed by mild oxidation led to (+)-(*S*)-**1** and (−)-(*R*)-**1**, respectively. Racemization was promoted under alkaline and boiling conditions via a carbanion, the formation of which was facilitated by the electron-withdrawing effect of the iminium cation and the resonance-stabilizing capacity of the pyridinium moiety. Under these conditions, **1** was obtained in a 1:1 mixture of the phenol (**1**) and phenolate (**1-H**) forms as shown by X-ray diffraction. Racemic **1** formed monoclinic crystals of high molecular organization in which the phenol-type (*RS*)-**1**, the phenolate-type (*RS*)-**1-H**, sodium cations, and ethanol molecules are present. The crystal structure of **[Na(1)(1-H)·(C₂H₆O)]** shows one-dimensional μ_2-bridging-oxygen polymers stabilized by a three-dimensional network of ionic, hydrogen bond, and π-stacking interactions with channels occupied by solvent molecules.

KEYWORDS: Maillard reaction; taste enhancer; alapyridaine; crystal structure; pyridinium betaines; X-ray diffraction

INTRODUCTION

The Maillard reaction of reducing sugars and amino acids plays an important role in thermal food processing as a source of color and flavor (*1*, *2*). Although odor-active volatile reaction products have been studied in great detail (*3*−*5*), relatively little has been published on nonvolatile constituents of the Maillard reaction such as taste compounds, for example (*6*−*8*). Recently, however, there has been an increasing number of publications dealing with new structures of taste components generated by the Maillard reaction. As a result, new chemical structures having taste properties, such as bitter (*9*, *10*), cooling (*11*), and umami-like (*12*), have been isolated and identified from Maillard reactions.

Very recently, *N*-(1-carboxyethyl)-6-(hydroxymethyl)pyridinium-3-ol inner salt (**1**, **Figure 1**) has been identified in heated aqueous solutions of D-glucose and L-alanine on the basis of a
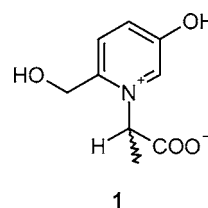
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Figure 1. Structure of *N*-(1-carboxyethyl)-6-(hydroxymethyl)pyridinium-3-ol isolated from a heated aqueous solution of glucose and L-alanine (*13*).

newly developed comparative taste dilution analysis used as a screening procedure that combines instrumental analysis and human taste perception (*13*). This novel Maillard reaction product, also called alapyridaine, is tasteless on its own, but enhances the sweet taste of the sugars glucose and sucrose, the amino acid L-alanine, and the artificial sweetener aspartame (L-Asp-L-Phe-OMe). Depending on the pH value, the detection threshold of glucose was decreased by a factor of 16 in the presence of an equimolar amount of alapyridaine. The (+)-(*S*)-**1** enantiomer has been reported as the physiologically active compound, whereas (−)-(*R*)-**1** did not affect sweetness perception at all (*13*).
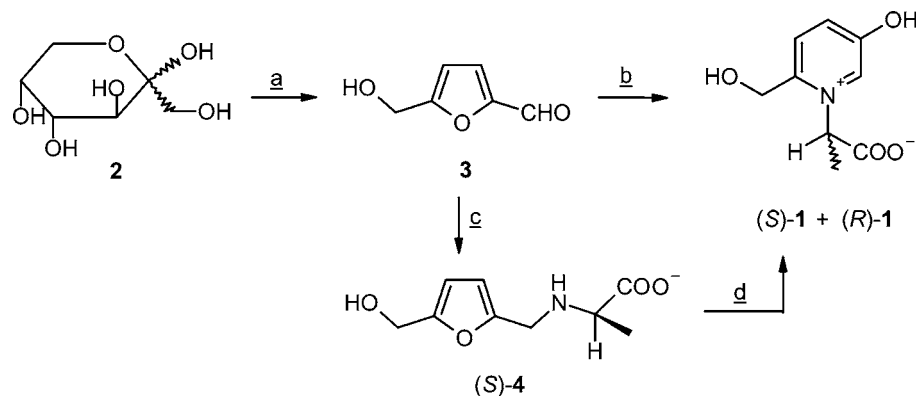
Figure 2. Synthesis of racemic and enantiopure **1**: *a*, Amberlite 15 (H+ resin), NEt₃·HCl, BuOAc/H₂O, reflux under N₂, 2.5 h, 52% yield; *b*, 1.0 equiv of L-alanine, 1.9 equiv of **3**, EtOH/water (1:1), aq NaOH (32%) → pH 9.4, RT (1.5 h) → reflux (72 h), 65% yield (sodium salt); *c*, 1.5 equiv of **3**, 2 equiv of L-alanine, water, aq NaOH (32%) → pH 8.5, Ni/H₂, RT, 5 bar, 48 h, 38% yield (ammonium salt); *d*, 1 equiv of **4** in water, 0 °C, 1.25 equiv of Br₂/MeOH (0.5 h), RT (1 h), 13% yield (ammonium salt). RT, room temperature.

In the course of the study on **1**, we observed racemization of **1** during the synthesis procedure. Also, the target compound could be obtained in crystalline form, which showed a particular three-dimensional structure. In addition, racemization resulted in a lower taste-enhancing activity of the racemate compared to the (+)-(*S*) enantiomer, which needed to be studied in more detail. Therefore, sufficient amounts of highly purified and structurally well-defined alapyridaine were required in order to (i) study the taste-enhancing activity of alapyridaine in food products, (ii) gain an initial insight into the racemization process as induced by thermal treatment, (iii) investigate the biochemical mechanisms of alapyridaine on sweet taste enhancement in human taste buds, and (iv) perform a safety assessment. We now report on convenient syntheses of racemic **1** and its enantiomers on a multigram scale, the racemization process, and the crystal structure observed by X-ray diffraction.

EXPERIMENTAL PROCEDURES

Materials. L-Alanine, D-alanine, alumina (neutral), Amberlite 15, *n*-butyl acetate (BuOAc), D-fructose, 5-(hydroxymethyl)-2-furaldehyde, acetic acid, ammonium formate, silica gel 60, Amberlite IRA-400 (OH⁻), Raney nickel, heavy water (D₂O), sodium 3-trimethylsilyl [2,2,3,3-²H₄]-propionate (TSP), dimethyl sulfoxide (DMSO), and tri-ethylamine hydrochloride (NEt₃·HCl) were from Aldrich/Fluka (Buchs, Switzerland). Ethanol (EtOH), methanol (MeOH), *n*-butanol, sodium hydroxide (NaOH), RP18 reversed phase (LiChroprep, 25−40 μm), formic acid, petroleum ether, and bromine (Br₂) were from Merck (Darmstadt, Germany). Hydrogen (5.0) was from Messer Griesheim GmbH (Krefeld, Germany).

High-Resolution Gas chromatography (HRGC). A Carlo Erba Mega 2 series chromatograph was used equipped with a cold on-column injector and a flame ionization detector (FID). The column was a 30 × 0.32 mm i.d., 0.25 μm, DB-Wax (J&W Scientific, Folsom, CA). The temperature was programmed as follows: 35 °C (2 min), 40 °C/min to 50 °C, 6 °C/min to 180 °C, and 10 °C/min to 240 °C (10 min).

High-Pressure Liquid Chromatography—Diode Array Detection (HPLC-DAD). HPLC was performed with an apparatus from Jasco (Gross-Umstadt, Germany) composed of an HPLC pump system (PU 1580) with an in-line degasser (DG-1580-53), a low-pressure gradient unit (LG-1580-02), and a diode array detector (MD 1515). Analytical (250 × 4.6 mm) or semipreparative scale (250 × 10 mm) RP-18 columns (ODS-Hypersil, 5 μm) from Phenomenex (Aschaffenburg, Germany) were used. Operating at a flow rate of 0.8 mL/min (analytical) or 3.2 mL/min (semipreparative), the mobile phase was a mixture of aqueous ammonium formate (10 mmol, pH 8.2) and methanol or formic acid (0.1%, pH 2.5) and methanol. The injection volume was 10−100 μL. Software used included Jasco Borwin v1.50 and Jasco-PDA v1.50.

Liquid Chromatography—Mass Spectrometry (LC-MS). An analytical HPLC column Nucleosil 100-5C18 (Macherey and Nagel, Düren, Germany) was coupled to an LCQ-MS (Finnigan MAT, Bremen, Germany) using positive (ESI⁺) and negative (ESI⁻) electrospray ionization. After injection of the sample (2−20 μL), compounds were chromatographed using the conditions described above.

Nuclear Magnetic Resonance (NMR) Spectroscopy. The samples for NMR spectroscopy were prepared in Wilmad 528-PP 5 mm Pyrex NMR tubes, using deuterated water (0.7 mL) as solvent. The NMR spectra were acquired on a Bruker AC-250 or AM-360 spectrometer (Rheinstetten, Germany), equipped with a quadrinuclear 5 mm probe head, at 250/360 MHz for ¹H and at 41.7/90 MHz for ¹³C NMR. One-dimensional ¹H NMR, ¹³C NMR, and distortionless enhancement by polarization transfer (DEPT-135) spectra were acquired as described earlier using standard conditions (*14*). The chemical shifts were referenced to TSP or ethanol (residual solvent) as an internal standard. Measurements were performed at room temperature (298 K). The following abbreviations are used to describe multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The spectra were interpreted using MestRe-C 2.3 software.

Infrared (IR) Spectroscopy. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR apparatus (Norwalk, CT).

Polarimetry. Measurements were performed on a Perkin-Elmer 241 MC polarimeter with a sodium lamp at 589 nm and a slit of 1 mm. The cuvette length was 100 mm.

X-ray Diffraction. Light brown prisms 0.21 × 0.21 × 0.24 mm were mounted on a quartz fiber with protection oil. Cell dimensions and intensities were measured at 200 K on a Stoe IPDS diffractometer with graphite-monochromated Mo[Kα] radiation ($\lambda = 0.71073$ Å); θ_{max} = 25.8°; 19655 measured reflections, 4213 independent reflections (R_{int} = 0.072) of which 1819 had |Fo| > 4 σ (Fo). Data were corrected for Lorentz and polarization effects and for absorption (*T* min, max = 0.9703, 0.9839). The structure was solved by direct methods using SIR97 (*15*); all other calculations were performed with XTAL system (*16*) and ORTEP (*17*) programs. Full-matrix least-squares refinement based on *F* using the weight of $1/[\sigma^2(\text{Fo}) + 0.00015(\text{Fo}^2)]$ gave final values of $R = 0.039$, $\omega R = 0.038$, and $\text{GOF}(F) = 1.46(3)$ for 352 variables and 2037 contributing reflections. Maximum shift/error = 0.0003, max/min residual electron density = 0.61/−0.48 eÅ⁻³. Hydrogen atoms were observed and refined with a fixed value of their isotropic displacement parameter.

Syntheses. Following the synthetic sequence shown in **Figure 2**, 5-(hydroxymethyl)-2-furaldehyde (**3**), obtained by acid-catalyzed dehydration of D-fructose (**2**), was reacted with L-alanine under alkaline conditions, resulting in racemic **1**. Enantiopure **1** was prepared by reductive amination of **3** in the presence of L- or D-alanine, followed by mild oxidation of the intermediary furfurylamine derivative (**4**) to (+)-(*S*)-**1** and (−)-(*R*)-**1**, respectively.

5-(Hydroxymethyl)-2-furaldehyde (3). In a flask equipped with a reflux condenser, D-fructose (10.0 g, 55 mmol), strong acid resin

Table 1. Synthesis of 5-(Hydroxymethyl)-2-furaldehyde (**3**) from D-Fructose

trial	reaction time (h)	temp (°C)	solvent(s)	purification	yield of **3**[a] (%)	ref
1	16	100	DMSO	none	32	nr[b]
2	2	150	DMSO	chromatography	24	24
3	40	50	H₂O/EtOAc H⁺, H₂O	none	0	nr
4	1	300		distillation	6	25
5	2.5	100	BuOAc, resin H⁺, H₂O	chromatography	52	nr

[a] Yields of **3** were determined by HR/GC (FID detector). [b] Not reported.

Table 2. ¹H NMR Data of Racemic N-(1-Carboxyethyl)-6-(hydroxymethyl)pyridinium-3-ol (**1**) before and after Refluxing under Alkaline Conditions in D₂O

	1 at pD 4.7			**1** after 24 h reflux at pD 9.5		
proton	δ (ppm)	mult[a]	J (Hz)	δ (ppm)	mult[a]	J (Hz)
CH₃	1.73	d	7.2	1.55	s	
CH₂OH	4.68	s				
CH	5.31	q	7.2			
H-4	7.42	dd	9.0, 2.5	7.15	d	9.0
H-5	7.52	d	9.0	7.30	d	9.0
H-2	7.83	d	2.5			

[a] Multiplicity of signals: s, singlet; d, doublet; dd, double-doublet; q, quartet.

Amberlite 15 (10.0 g), and NEt₃·HCl (2.0 g) were stirred in a mixture of *n*-butyl acetate (150 mL) and water (5 mL) and then heated at 100 °C under a nitrogen atmosphere for 2.5 h. After cooling to room temperature, the mixture was decanted, and the organic layer was concentrated under reduced pressure to yield **3** (3.3 g, 26 mmol, yield = 52%, purity > 80%, GC) as an amorphous solid after filtration over neutral alumina using a mixture of petroleum ether and ethyl acetate (3:2, v/v) as the solvent.

Racemic 1. A solution of L-alanine (1.0 equiv) and **3** (1.2 equiv) in EtOH/water (50:50, v/v) was adjusted to pH 9.4 with an aqueous NaOH solution (32%). After stirring at room temperature for 1.5 h, the mixture was refluxed for 24 h and then cooled to room temperature. This procedure was repeated twice after the addition of 0.4 and 0.3 equiv of **3**. The sample was then concentrated under reduced pressure and purified by chromatography on silica gel 60 with a solvent mixture composed of butanol, water, and acetic acid (2:2:1, v/v/v). Finally, chromatography on RP18 reversed phase material with aqueous formic acid (0.5% in water) and subsequent recrystallization from absolute ethanol furnished racemic **1** in 65% yield with a purity of >98% (NMR): mp (absolute ethanol), 91 °C; $[\alpha]_D^{20} = 0°$ (*c* 1.0, Millipore water, pH 4.7, Na⁺ salt); ¹³C NMR (90 MHz, D₂O, pD 4.7) δ 174.6 (s), 160.9 (s), 142.8 (s), 133.8 (d), 133.1 (d), 128.6 (d), 65.5 (d), 59.7 (t), 18.5 (q); IR (KBr) $\nu = 3417, 3090, 3080, 3040, 2798, 1616$ cm⁻¹; UV–vis (ammonium formate, 10 mmol/L, pH 8.2), λ_{max} 248, 326 nm; UV–vis (formic acid, 0.1% in water, pH 2.5), λ_{max} 300 nm; LC-MS (ESI⁺), *m/z* (%) 198 (21, [M + 1]⁺), 220 (10, [M + Na]⁺), 395 (100, [2M + 1]⁺), 417 (29, [2M + K]⁺), 592 (53, [3M + 1]⁺); crystal data, light brown monoclinic prism, (C₉H₁₁NO₄) (C₉H₁₀NO₄)⁻ Na⁺ (C₂H₆O), M$_r$ = 462.5; μ = 0.12 mm⁻¹, d_x = 1.359 g·cm⁻³, P 2₁/c, Z = 4, a = 7.1705(3), b = 22.7540(16), c = 13.8627(7) Å, β = 91.635(6)°, V = 2260.9(2) Å³.

(S)-N-(1-Carboxyethyl)-2-(hydroxymethyl)-5-(methylamino)furan [(S)-4]. A solution of **3** (30 mmol) and L-alanine (60 mmol) in water (30 mL) was adjusted to pH 8.5 with an NaOH solution (32% in water) and was stirred in a hydrogenation vessel at room temperature for 30 min. After the addition of Raney nickel (0.75 g), the mixture was stirred under a hydrogen atmosphere at 5 bar for 48 h. Another aliquot of **3** (10 mmol) was added, and hydrogenation was continued for an additional 48 h. After filtration of the catalyst and a wash with methanol, the filtrate was concentrated in vacuo. The residue was dissolved in ammonium formate (10 mmol/L, pH 8.2) and applied on a water-cooled 30 × 4 cm glass column filled with a slurry of RP-18 (LiChroprep, 25–40 μm) in a mixture (99:1, v/v) of ammonium formate (10 mmol/L, pH 8.2) and methanol. By using the same solvent mixture as the mobile phase and monitoring the effluent at 220 nm, the fractions eluting between 210 and 330 mL were collected to obtain (S)-**4** (15.0 mmol) after freeze-drying in 38% yield: ¹H NMR (250 MHz, D₂O, TSP) δ 1.43 (d, J = 7.3 Hz, 3H), 3.57 (q, J = 7.3 Hz, 1H), 4.18 (d, J = 2.4 Hz, 2H), 4.56 (s, 2H), 6.39 (d, J = 3.4 Hz, 1H), 6.51 (d, J = 3.4 Hz, 1H); ¹³C NMR (41.7 MHz, D₂O, TSP) δ 173.7 (s), 157.7 (s), 148.9 (s), 115.4 (d), 112.1 (d), 59.7 (d), 58.5 (t), 44.7 (t), 18.5 (q); LC-MS (ESI⁺), *m/z* (%) 421 (100, [2 M + Na]⁺), 399 (95, [2 M + H]⁺), 222 (42, [M + Na]⁺), 200 (49, [M + H]⁺); UV–vis (ammonium formate, 10 mmol/L, pH 8.2), λ_{max} 210 nm.

(+)-(S)-1. A solution of bromine in methanol (6.0 mmol in 10 mL) was added dropwise to a cooled (0 °C) solution of (S)-**4** (7.5 mmol) in

water (35 mL) over a period of 30 min. After 1 h of stirring, the resulting mixture was neutralized by adding a strongly basic ion-exchange resin [Amberlite IRA-400 (OH⁻)] and filtered, and the filtrate was freed from solvent in vacuo. The residue was dissolved in a formic acid solution (0.1% in water) and applied to a 30 × 3 cm water-cooled glass column filled with RP-18 (LiChroprep, 25–40 μm) in a formic acid solution (0.1% in water). Using the same solvent as the mobile phase and monitoring the effluent at 300 nm, (+)-(S)-**1** was eluted between 150 and 290 mL. Chromatography was repeated using ammonium formate (10 mmol/L, pH 8.2) as the mobile phase, and the fraction containing the target compound was freeze-dried twice to obtain the (+)-(S)-**1** inner salt (0.76 mmol) in 13% yield: ¹H NMR (360 MHz, D₂O, pD 7.1, TSP) δ 1.86 (d, J = 6.8 Hz, 3H), 4.84 (s, 2H), 5.42 (q, J = 6.8 Hz, 1H), 7.70 (dd, J = 2.3, 8.6 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 8.08 (d, J = 2.3 Hz, 1H); LC-MS (ESI⁺), *m/z* (%) 198 (100, [M + 1]⁺), 220 (57, [M + Na]⁺); UV–vis (Millipore water, 12.5 mmol/L, pH 7.1), λ_{max} 248, 326 nm; $[\alpha]_D^{20}$ +40.2° (*c* 0.01, Millipore water, pH 7.0, NH₄⁺ salt).

(−)-(R)-1. Following the procedure described for the preparation of (S)-**4** and (+)-(S)-**1**, (−)-(R)-**1** was synthesized using D-alanine. LC-MS and NMR data were identical to those obtained for (+)-(S)-**1**: $[\alpha]_D^{20}$ −38.6° (*c* 0.01, Millipore water, pH 7.0, NH₄⁺ salt).

RESULTS AND DISCUSSION

Syntheses. As shown in **Figure 2**, the synthesis of racemic and enantiopure **1** is based on 5-(hydroxymethyl)-2-furaldehyde **3** as the common intermediate. The synthesis of **3** was studied in more detail, as it is a rather unstable and expensive material. It has mainly been prepared from the readily available D-fructose **2** by dehydration using Brønsted and Lewis acids as catalysts (*18−20*). In general, the yields were low and strongly dependent on the reaction conditions such as time and temperature as well as the solvent used. The methods described for its production so far suffered from the disadvantage that it was obtained in aqueous or polar media from which isolation was a challenging task.

To overcome these problems, we applied a phase transfer procedure with *n*-butyl acetate/water using the strong acid resin Amberlite 15 and ammonium salts as catalyst, thus resulting in ∼50% yield after chromatographic workup (**Table 1**, trial 5). This procedure could easily be scaled up to 100 g without decreasing the yield. Another advantage was the feasibility of recovering the catalyst and solvents. Purification was achieved by dry chromatography on alumina with petroleum ether/EtOAc as eluent.

Alternatively, **3** was obtained at ∼30% yield without purification using DMSO as solvent (trial 1). However, a much longer reaction time was required compared to trial 5. Increasing the reaction temperature to 150 °C led to lower yields (trials 2 and 4). This is most likely due to polymerization reactions, which we observed in most of the samples shown in **Table 1**, known to be favored at high temperatures and in highly
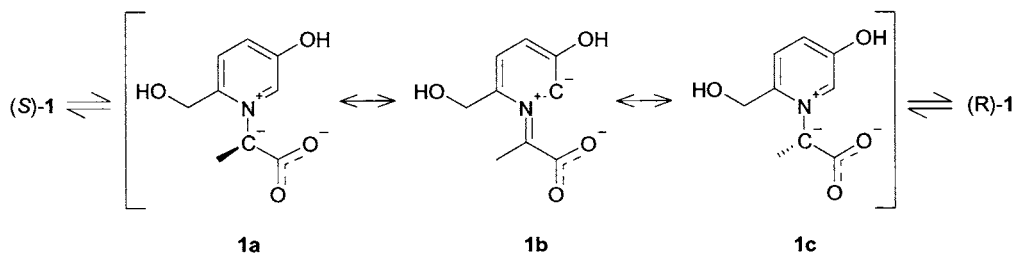
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Figure 3. Racemization of **1** in an aqueous alkaline solution under reflux conditions showing the delocalization of the negative charge in the mesomeric forms **1a**, **1b**, and **1c**.

concentrated samples. Lowering the temperature to 50 °C, on the other hand, did not yield **3** at all (trial 3). In general, purification was required to separate the brown polymeric substances prior to reaction with alanine. Distillation did not give satisfactory results; total polymerization of **3** occurred at 80 °C and 0.02 mbar pressure.

Reaction of **3** with L-alanine in alkaline aqueous solutions on a 100 g scale gave rise to racemic **1**, as indicated by polarimetry, in a 65% yield after purification (**Figure 2**). Reactant **3** was added in three to five portions and in an overall excess (alanine to **3**, 1:2 equivalent) to improve the yields by limiting polymerization reactions of **3** and also by entirely consuming the amino acid. The latter facilitated separation of the target **1** from residual alanine, which in general is a challenging task. Purification of **1** was achieved by column chromatography on silica gel using a ternary eluent composed of butanol, water, and acetic acid. If very pure material is required, additional chromatography on an RP18 column using aqueous formic acid as the eluent is suitable. However, precipitation from ethanol was found to be a convenient procedure for purifying multigram amounts of racemic **1**. The overall yield of **1** was 30% on the basis of D-fructose as the starting material.

Enantiopure **1** was prepared by adapting the procedure described for *N*-alkyl pyridinium betaines (*23*) to alapyridaine (**Figure 2**). Reductive amination of **3** and L-alanine with Raney nickel/hydrogen resulted in the corresponding furfurylamine derivative (*S*)-**4**, (*S*)-*N*-(1-carboxyethyl)-2-(hydroxymethyl)-5-(methylamino)furan. The latter was converted into the target pyridinium betaine compound by mild oxidation with bromine in water/methanol to yield (+)-(*S*)-**1**. Similarly, the reaction with D-alanine resulted in (−)-(*R*)-**1**. Purification was performed by column chromatography using an RP18 column and aqueous formic acid as mobile phase, monitoring the target compound at 300 nm. Optical rotation of +40.2° and −38.6° indicated the presence of (*S*)-**1** and (*R*)-**1**, respectively.

Racemization. Despite the use of enantiopure alanine as the starting material, **1** was obtained as a racemate under reflux conditions in alkaline aqueous solutions. To study the racemization process, L-alanine or racemic **1** was refluxed in D_2O at pD 9.5 for 24 h. No proton−deuterium exchange was observed for L-alanine by ^1H NMR (data not shown). This is in agreement with previously published data, indicating that more severe conditions are required for racemization of amino acids (*24*, *25*).

However, the data obtained for racemic **1** indicated the disappearance of the enantiotopic α-proton (**Table 2**). Compared to L-alanine, the acidity of the proton at the chiral center is increased by the pyridinium moiety. Abstraction of the α-proton results in the formation of a carbanion at the asymmetric carbon, which can be stabilized by delocalization of the negative charge through the aromatic pyridinium moiety, thus facilitating the racemization step via the iminium mesomeric form **1b** upon
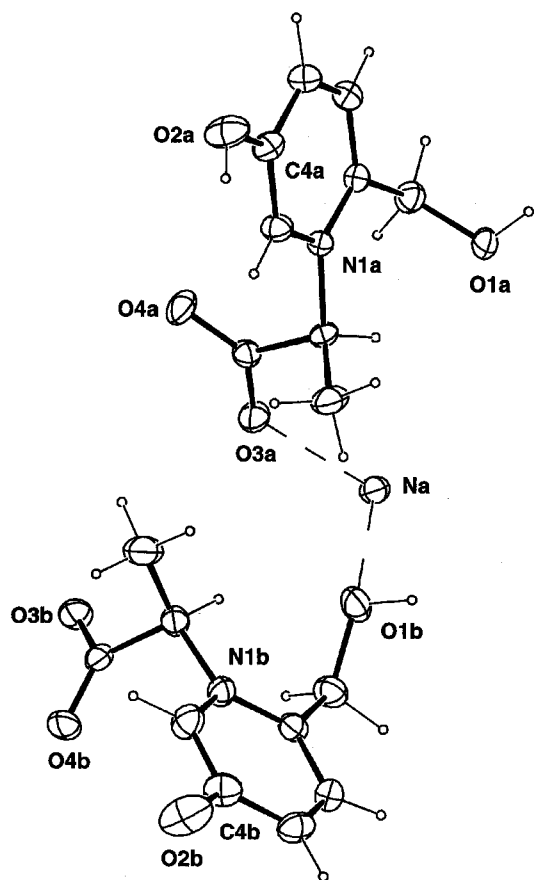

Figure 4. ORTEP view of the asymmetric unit of racemic **[Na(1)(1-H)·(C₂H₆O)]** (solvent molecule omitted) showing the phenol (labeled a) and phenolate (labeled b) forms. Ellipsoids are represented with 40% probability. Selected interatomic distances: C4a–O2a = 1.338(4) Å, C4b–O2b = 1.308(4) Å, Na···O3a = 2.376(3) Å, Na···O1b = 2.352(3) Å.

reprotonation (**Figure 3**). At present, however, it is not yet clear if the racemization process is due to the formation mechanism or the consequence of the long thermal treatment during the synthesis procedure of **1**.

Three-Dimensional Structure Characterization of Racemic 1. Suitable crystals for X-ray diffraction of racemic **1** were obtained by crystallization in absolute ethanol. An analysis of the crystal structure shows that the asymmetric unit (**Figure 4**) is composed of one molecule of **1** (phenol form), one deprotonated molecule at the alcohol function (phenolate form, **1-H**) compensating for the positive charge of one sodium cation, and one molecule of ethanol. Due to the absence of residual electron density around O2b and the shorter observed C−O bond distance, the localization of the negative charge was attributed to this atom. Moreover, the three other hydroxyl groups are involved as donors in hydrogen bond interactions with two distinct carboxylates and O2b as acceptors.
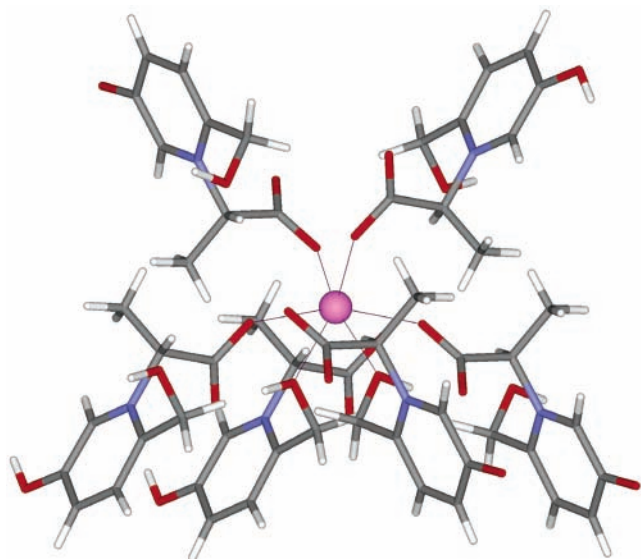
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Figure 5. Perspective view of **[Na(1)(1-H)]** crystal structure showing the three phenol and three phenolate forms involved in the distorted octahedral coordination of Na⁺.

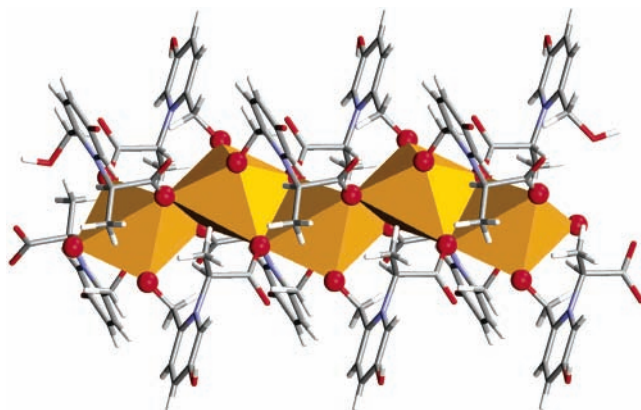**Figure 6.** View of the crystal structure of **[Na(1)(1-H)]** showing the one-dimensional μ_2-bridging-oxygen polymer with the edge-linked *cis*-chain of octahedra running along the [100] direction.

The coordination of the sodium atom (**Figure 5**) is strongly distorted from octahedral: four oxygen donor atoms of the carboxylate ligands coordinate the sodium with average Na−O distances of 2.47 Å, and two oxygen donors of the alcohol functions show much stronger interactions with Na⁺ (average distance = 2.34 Å). The average O−Na−O angles are 90.3° (with a large dispersion) and 161.6°.

An analysis of the molecular packing reveals that two oxygen atoms (O3a and O3b) of the carboxylates act as bridging ligands to form one-dimensional μ_2-polymers along the [100] direction. The polymeric chains show a *cis*-edge-linked sequence of octahedra (**Figure 6**) with alternate Na···Na interatomic distances of 3.721(2) and 3.826(2) Å. Inside a polymeric chain, two hydrogen bonds were observed: O1a···O4a′ = 2.635 Å and O1a−H01a···O4a′ = 179(3)°; O1b···O4b′ = 2.599(4) Å and O1b−H01b···O4b′ = 167(3)° (primed atoms in equivalent position *x* + 1, *y*, *z*). The cohesion between the polymeric chains is fixed by π-stacking interactions between pyridinium moieties through 2-fold screw axes (mean interplane distances = 3.29 Å; mean interplane angles = 6.0°) and one strong hydrogen bond interaction involving the phenolate as acceptor: O2a···O2b$_{(1-x,1-y,2-z)}$ = 2.481Å, O2a−H02a···O2b$_{(1-x,1-y,2-z)}$ = 171-(4)°. The interstices between the polymeric chains form chan-

nels parallel to [100] in which the ethanol molecules are located.

In conclusion, we have developed convenient synthetic approaches to obtain on a multigram scale the novel, foodborne taste enhancer **1** as a racemic mixture and also its enantiomers, required for extended sensorial evaluation of alapyridaine in food products as well as for safety assessment. Under alkaline and boiling conditions, racemization occurred via an intermediary carbanion, the formation of which was facilitated by the electron-withdrawing effect of the iminium cation and the resonance-stabilizing capacities of the pyridinium moiety. Racemic **1** formed monoclinic crystals in which (*RS*)-**1** (phenol), (*RS*)-**1-H** (phenolate), sodium cations, and ethanol molecules are assembled as **[Na(1)(1-H)·(C₂H₆O)]** in one-dimensional μ_2-bridging-oxygen polymers stabilized by a three-dimensional network of ionic, hydrogen bond, and π-stacking interactions with channels occupied by solvent molecules.

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