Electroorganic Chemistry. 120. New Patterns of Anodic Oxidation of Amides. Synthesis of α-Amino Aldehyde Acetals and Pyrrolidines from Amines

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Abstract: Anodic oxidation of *N*-alkyltosylamides **1** in methanol containing KX (X = Br, I) gave two types of products, α-(tosylamino) aldehyde acetals **2** and pyrrolidine derivatives **3**, and each of the products could selectively be formed by modifying the reaction conditions when the alkyl group on the nitrogen of **1** was not branched at its α-position. Namely, anodic oxidation of *N*-(α-unbranched alkyl)tosylamides **1a-g** in methanol containing NaOMe and KI at −10 °C followed by further anodic oxidation at 25 °C afforded **2** in good yields, while that of **1** in a two-layer system consisting of cyclohexane and water containing KOH and KBr under heating yielded solely **3**. On the other hand, *N*-(α-branched alkyl)tosylamides **1h-j** gave always **3**. Two types of reaction routes leading to each of the products were proposed.

Recently, electrochemical oxidation and reduction have clearly been shown to be unique and promising tools for the functionalization of a variety of organic compounds.[1] One such typical reaction is the anodic functionalization of carbamates or amides at their position α to the nitrogen. As it has already been well known, the direct oxidation of amines is not an effective method for the transformation of amines, even in the case of the anodic oxidation since the first intermediate formed in such oxidation is generally not stable.[2] Hence, the protection of amino nitrogen atoms by N-carbomethoxylation or N-acylation is essential to make such oxidations useful, especially in organic synthesis. The α-functionalization of carbamates or amides using the usual chemical oxidizing agents is, however, not always easy, whereas the usefulness of the anodic method in α-functionalization has clearly been shown in our previous studies which are represented by the anodic α-methoxylation of carbamates.[3] The versatility of the α-methoxylated carbamates as starting materials in organic synthesis has also been shown in these studies.

On the other hand, the structure of the acid moiety of an amide can have a large influence on the reactivity of the amide. Tosylamides are generally less reactive than carbamates or carboxamides in the direct anodic oxidation.[4]

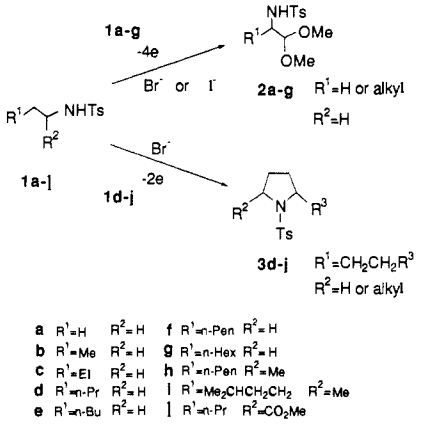
We have found in the present study, however, that the anodic oxidation of N-monoalkyltosylamides **1** in the presence of halide ions under basic conditions resulted in an unprecedented pattern of reaction. Namely, the products were α-(tosylamino) aldehyde acetals **2** and pyrrolidine derivatives **3** (Scheme I), and the control of the reaction conditions made it possible to form each of the products selectively.

Formation of these two types of products is interesting from synthetic and mechanistic viewpoints since **2** and **3** are completely different types of products from those obtained so far in the anodic oxidation of carbamates or amides and since the preparation of these products is not always facile by the conventional chemical methods.

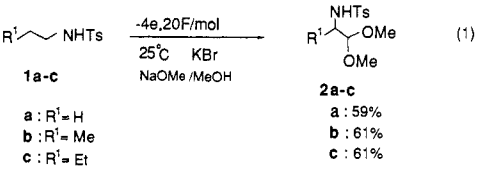
Results and Discussion

Selective Synthesis of α-(Tosylamino) Aldehyde Acetals 2. In the presence of NaOMe and NaBr (or KBr), the anodic oxidation

Scheme I

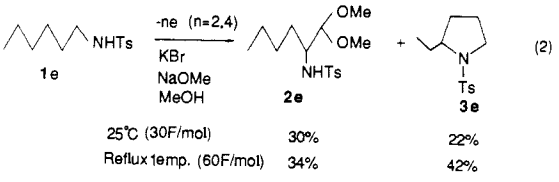


of tosylamides **1a-c** in which the R^1 group is a two-carbon chain or is shorter than a two-carbon chain at 25 °C gave the rearranged compounds **2a-c** as the sole product (eq 1).



(1)

On the other hand, when the R^1 group is longer than a two-carbon chain, the reaction carried out under the same reaction conditions was not selective and a mixture of **2** and **3** was obtained as the product. The anodic oxidation of *N*-hexyltosylamide **1e**, for example, in methanol containing NaOMe and KBr at room temperature gave **2e** and **3e** in the yields shown in eq 2.



(2)

The selective formation of each of these products, **2** and **3**, with high yields is desirable from a synthetic viewpoint. Accordingly, the reaction conditions were scrutinized on the basis of the proposed working hypothesis that is shown in the following section, and those leading to the selective formation of **2** were found. The key point was the use of KI instead of KBr. Thus, the anodic

(1) For examples: Baizer, M. M.; Lund, H., Eds. *Organic Electrochemistry*, 2nd ed.; Marcel Dekker: New York, 1983. Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer-Verlag: New York, 1984. Weinberg, N. L., Ed. *Technique of Electroorganic Synthesis*; John Wiley: New York, 1974-1982; Vols. 1-3.

(2) Smith, P. J.; Mann, C. K. *J. Org. Chem.* **1969**, *34*, 1821. Portis, L. C.; Klug, J. T.; Mann, C. K. *J. Org. Chem.* **1974**, *39*, 3488.

(3) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264. Shono, T.; Tsubata, K.; Matsumura, Y. *Org. Synth.* **1985**, *63*, 206.

(4) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K.; Kanazawa, T.; Tsuda, K. *J. Org. Chem.* **1984**, *49*, 3711.

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Table I. Anodic Oxidation of **1b–j** in MeOH Containing NaOMe and KI

run	cmpd **1**	electricity (F/mol) −10 °C[a]	electricity (F/mol) 25 °C[b]	products **2**	yields (%)
1	**1b**	13	5	**2b**	87
2	**1c**	10	6	**2c**	96
3	**1d**	13	6	**2d**	88
4	**1e**	16	6	**2e**	82
5	**1f**	14	6	**2f**	85
6	**1g**	12	6	**2g**	74
7	**1h**	10	10	*d*	
8	**1i**	10	10	*d*	
9	**1j**	10	10	*d*	
10	**1c**	-	20[c]	**2c**	64
11	**1e**	-	20[c]	**2e**	48

[a] The electricity shown on this column was passed at −10 °C as the first oxidation. [b] The elecricity shown on this column was passed at 25 °C as the second oxidation. [c] The whole electrolysis was carried out at 25 °C. [d] Starting material was recovered.

oxidation of **1e** in methanol containing NaOMe and KI at −10 °C (16 F/mol) followed by further anodic oxidation at 25 °C (6 F/mol) gave **2e** as the sole product in 82% yield. The other results (**1b–i**) obtained under similar reaction conditions are summarized in Table I.

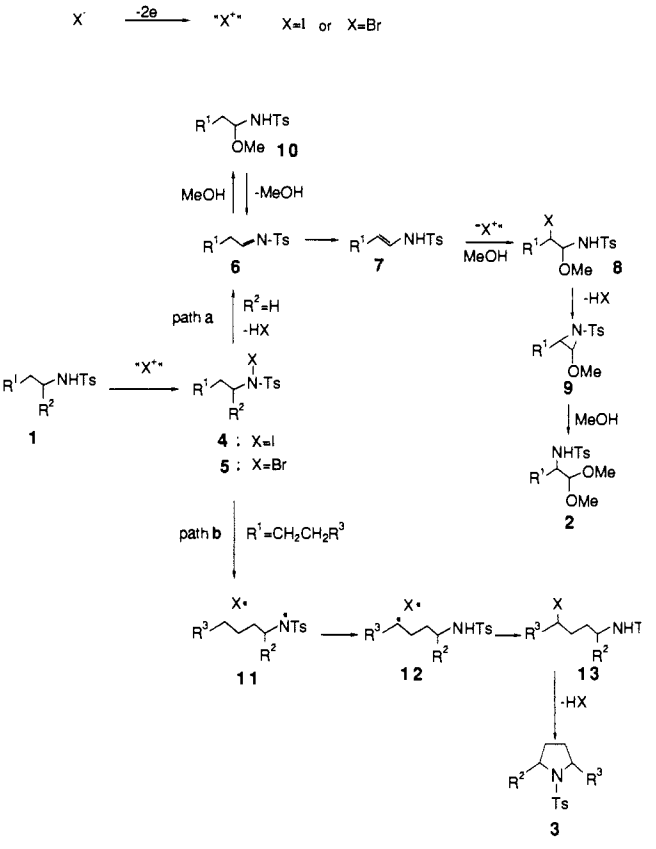
This new rearrangement generally took place when the alkyl group located on the nitrogen of the sulfonamides was not branched at its α-position (runs 1–6 in Table I), whereas N-(α-branched alkyl)tosylamides such as **1h–j** were actually not oxidizable under the same reaction conditions (runs 7–9 in Table I).

Furthermore, it was found that the yield of product **2** was considerably influenced by the reaction temperature. When **1** was anodically oxidized at 25 °C from the beginning, the yield of **2** decreased as exemplified by **2c** (64%) and **2e** (48%) (runs 10 and 11 in Table I). These decreases may be explained in terms of the instability of the product **2** under the reaction conditions. In fact, **2e** was gradually consumed when it was exposed to anodic oxidation under the same conditions.

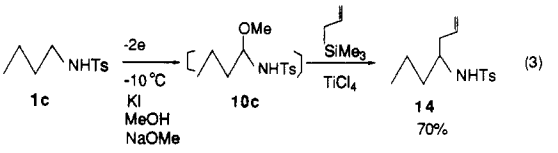
Reaction Route for the Formation of 2. The formation of **2** is reasonably explained by the following working hypothesis (path a in Scheme II). Namely, the electrochemically generated positive halogen active species "X^+" (X = I)[5] attacks **1** to form a first intermediate **4** (X = I).[6] The base-induced elimination of HX from **4** gives imine **6**.[7] After **6** spontaneously rearranges to *N*-(α,β-unsaturated alkyl)tosylamide **7**, the electrophilic addition of "X^+" (X = I) on **7** followed by methanolysis affords **8**. The final product **2** is formed through the intermediary formation of an aziridine **9** by the reaction of **8** with a base.[8]

Although the detection or isolation of the intermediates **6–9** was not possible, it was found by a careful inspection of the anodic oxidation of **1c** carried out with using KI that compound **10c** was formed as a relatively stable intermediate at −10 °C. Although the intermediate was not able to be purified, its H^1 NMR spectrum observed in CD_3OD showed a triplet signal (1 H) at 4.51 ppm which corresponded to the hemiacetal proton (NC*H*O) of **10c**. The structure of **10c** was also supported by the fact that Lewis acid treatment of the intermediate corresponding to **10c** with

Scheme II



allyltrimethylsilane gave the allylated product **14** in a reasonable yield (eq 3).



Furthermore, in spite of the fact that anodic oxidation of **1c** in the presence of KI at −10 °C almost stopped at the stage of the formation of **10c**, the anodic oxidation of **10c** in the presence of KI at 25 °C gave **2c** in more than 80% yield. All of these results suggest that **10** is formed prior to the formation of **7** at −10 °C, compound **10** is fairly stable toward anodic oxidation at −10 °C, and compound **10** is transformed to **7** at 25 °C.

Since the final product **2** was not always stable to anodic oxidation as described in the previous section, shortening the time of exposure of **2** to anodic oxidation by carrying out the anodic oxidation at −10 °C in the first stage and then at 25 °C would make the yield of **2** much better than that obtained in the reaction which was carried out entirely at 25 °C.

Although product **2** was also formed when X was Br as shown in eq 2, the selectivity of the formation of **2** was much less than the reaction using I as X. The reason why the formation of **2** was achieved more selectively by using KI than by using KBr is explained in the following sections.

Reaction Route for the Formation of 3. The reaction route for the formation of **3** seems to be analogus to the Hofmann–Loffler reaction.[9] Thus, four consecutive reactions, namely, homolytic fission of the N–Br bond of **5** to yield a radical **11** and Br•, subsequent abstraction of a δ-hydrogen of **11**, δ-halogenation of **12**, and base-induced ring closure of δ-halo intermediate **13** yield the product **3** (path b in Scheme II).

Since path b competes with path a, both types of products **2** and **3** are formed when the R^1 group is longer than a two-carbon chain, while only the formation of product **2** is possible in the case

(5) "X^+" denotes a positive halogen active species.

(6) The cathodic reduction of "X^+" to X^- and the formation of X_2 from "X^+" would take place as the main competitive reactions with the formation of *N*-halo amides (**4** and **5**) since the reaction was carried out without using a diaphragm. It is rather unreasonable that the formation of **4** and **5** is sufficiently faster than the above mentioned two competitive reactions. Hence, the current efficiency of **4** and **5** was decreased.

(7) Formation of **6** from **1** by direct anodic oxidation is unlikely since a competitive anodic reaction between **1c** (*n*-BuNHTs) and the corresponding *N*-methoxycarbonyl compound **1'c** (*n*-BuNHCO$_2$Me) in methanol containing NaOMe and KI resulted in the recovery of almost all of **1'c** with formation of **2c** (70% yield) from **1c** in spite of the fact that carbamates such as **1'c** are more susceptible to direct anodic oxidation than sulfonamides such as **1c**.[4]

(8) It has been reported that α-methoxyaziridines are easily converted by methanolysis to α-amino acetals; Duhamel, L.; Poirier, J.-M. *Bull. Soc. Chim. Fr.* **1975**, 329.

(9) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55.

Table II. Anodic Oxidation of **1** To Give **3**

run	cmpd	KX	reaction systems[a]	electricity (F/mol)	products **3**	yields (%)
1	**1e**	KBr	A	24	**3e**	92
2	**1g**	KBr	A	25	**3g**	96
3	**1h**	KBr	A	33	**3h**	100
4	**1h**	KBr	B	12	**3h**	92
5	**1i**	KBr	B	16	**3i**	86
6	**1j**	KBr	B	34	**3j**	52
7	**1e**	KI	A	72	**3e**	97

[a]System A: KX (0.8 equiv), KOH (0.2 equiv), cyclohexane (15 mL)/H_2O (15 mL), reflux. System B: KBr (0.5 equiv), NaOMe (0.5 equiv), methanol (20 mL), reflux.

of **1a–c** since the R^1 groups of **1a–c** do not possess the δ-hydrogen to be abstracted.

Although the reason why **3** was not formed in the anodic oxidation of **1** with KI is not always consistently explained, one of the explanations is that the homolytic fission of the N–I bond of **4** in path b may be less favorable than that of the N–Br bond of **5**,[10] and hence path a predominantly takes place.

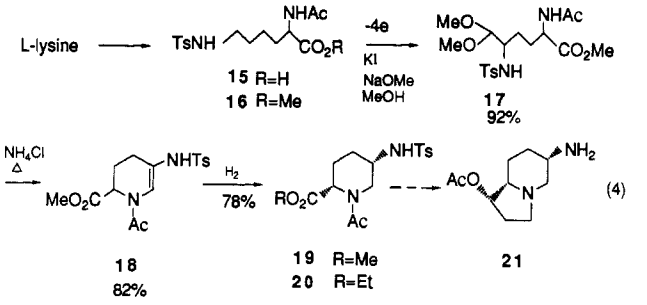
Selective Synthesis of Pyrrolidine Derivative 3. Provided that path b is really reasonable for the formation of **3**, the yield of **3** will be improved by modifying the reaction conditions favorable for the homolytic fission of the N–Br bond of **5**. Several attempts for this purpose have been tried, and the results are shown in eq 2 and in Table II.

Raising the reaction temperature of the anodic oxidation is one of the methods for increasing the ratio of **3**/**2** (eq 2). Satisfactory selectivity for the formation of **3** was obtained by carrying out the anodic oxidation of **1** in a two-layer system consisting of cyclohexane and water containing KOH and KBr. The results are shown in runs 1–3 in Table II.[13,14]

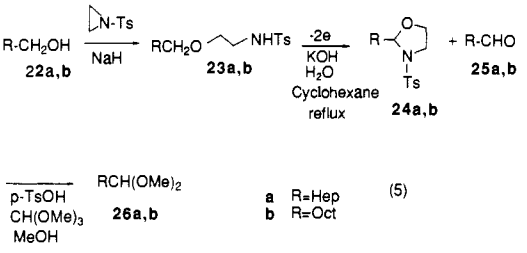
In this two-layer system, the base-induced elimination of HX from **5** to give **6** (path a) may be suppressed since almost all of **5** is located in the cyclohexane layer where base is absent.[15] Although the use of KI instead of KBr in this two-layer system also gave **3e** in a good yield, an excess of charge was required (run 7 in Table II).[16]

In contrast to **1a–g**, the anodic oxidation of *N*-(α-branched alkyl)tosylamides **1h–j** predominantly gave the corresponding pyrrolidines **3h–j** under conditions using KBr in refluxing methanol (runs 4–6 in Table II). In these cases, path a may be inhibited by a steric factor at the step from **5** to **6** even in a polar solvent such as methanol.

Application to Some Organic Synthesis. The anodic transformation of **1** to **2** is synthetically very interesting since **2** is an useful intermediate for the synthesis of a variety of nitrogen heterocycles.[17] In addition, this reaction was applicable to the synthesis of slaframine (**21**), a fungal toxin produced by *Rhizoctonia leguminicola*. Although a variety of methods for the synthesis of **21** have been exploited so far,[18,19] they require many steps and/or often involve rather difficult processes. On the other hand, our synthetic route (eq 4) is simple and can start from L-lysine, which is known to be the starting compound in the biogenetic formation of **21**.[20] Namely, the anodic oxidation of α-*N*-acetyl-ε-*N*-tosyl-L-lysine methyl ester (**16**)[21] in the presence of KI gave the expected rearranged product **17** in a good yield, though it was a racemic compound.[22] The acid-catalyzed intramolecular cyclization of **17** followed by hydrogenation gave a methyl ester **19**. The stereochemistry of **19** was confirmed to be cis by converting **19** to the known compound **20**.[18] The conversion of **20** to **21** has already been reported.[18]



The anodic method of the formation of pyrrolidines was also applicable to the oxidation of primary alcohols **22** to aldehyde acetals **26** (eq 5). Transformation of **22** to **23** followed by anodic oxidation of **23** in the two-layer system gave a mixture of **24** (**24a**, 47%; **24b**, 38%) and aldehydes **25** (**25a**, 39%; **25b**, 15%). The treatment of the mixture with an acidic methanolic solution of trimethyl orthoformate afforded **26** (**26a**, 91%; **26b**, 92%).



Experimental Section

IR spectra were taken with a Hitachi 215 spectrometer. ^1H NMR spectra were recorded on Varian Associates EM-390 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL IMSDX-300 mass spectrometer. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University. Melting points are uncorrected. Electrochemical oxidation was carried out by using a DC power supply (GP 050-2) of Takasago Seisakusho, Ltd. An undivided cell was used for electrolyses. Cooling (−10 °C) was achieved by using a low-temperature thermostat (EC-30) of Tokyo Rikakikai, Ltd.

Preparation of *N*-Alkyltosylamides 1. Tosylamides **1a–c**,[23] **1e**,[24] **1g**,[25] **1h**,[26] **1i**,[27] and **1j**[28] are known compounds. Tosylamides **1d** and **1f** were

(10) It has been known that homolytic benzylic halogenation of toluene is easily achieved by *N*-bromosuccinimide but with difficulty by *N*-iodosuccinimide (NIS),[11] though the homolytic cleavage of the N–I bond of NIS may not always be denied.[12]

(11) Djerassi, C.; Lenk, C. T. *J. Am. Chem. Soc.* **1953**, *75*, 3493.

(12) Taneja, S. C.; Dhar, K. L.; Atal, C. K. *J. Org. Chem.* **1978**, *43*, 997.

(13) The yield of **3** monotonously increased with the increase of amount of electricity.

(14) The reason why the formation of **3** (path b, two-phase system) requires larger amount of electricity than that of **2** (path a, one-phase system) is the difference of the reaction conditions. Namely, in the case of the two-phase system, the active species "X^+" is generated in the aqueous phase, while the N-halogenation takes place in the organic phase. Hence, the formation of **4** and **5** in the two-phase system is less efficient than that in the one-phase system. Since the two competitive reactions described in ref 6 take place in the aqueous phase, the current efficiency of the formation of **3** (path b, two-phase system) is made lower than that of **2** (path a, one-phase system).

(15) The electrochemical reduction of **4** and **5** on the cathode seems minimum since almost all of **4** and **5** exist in the organic phase and electric current does not pass through the organic phase.

(16) The difference of the current efficiency between N–Br and N–I compounds is mainly explained by the inefficiency of the formation of the latter compound from **1**.

(17) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2185. Shono, T.; Matsumura, Y.; Katoh, S.; Inoue, K.; Matsumoto, Y. *Tetrahedron Lett.* **1986**, *27*, 6083.

(18) Schneider, M. J.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3681.

(19) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065 and references cited therein.

(20) Clevenstine, E. C.; Broquist, H. P.; Harris, T. M. *Biochemistry* **1979**, *18*, 3658 and references cited therein.

(21) Woolley, D. W.; Hershey, J. W. B.; Jodlowski, H. A. *J. Org. Chem.* **1963**, *28*, 2012.

(22) α-*N*-Acetyl-L-lysine derivatives have been known to be easily racemized, for example, under basic conditions.[21]

(23) Goldstein, M.; Russell, M. A.; Willis, H. A. *Spectrochim. Acta, Part A* **1969**, *25*, 1275.

(24) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

(25) White, E. H.; Lewis, C. P.; Ribi, M. A.; Ryan, T. J. *J. Org. Chem.* **1981**, *46*, 552.

(26) Barluenga, J.; Jimenez, C.; Najera, C.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 721.

(27) Hutchins, R. O.; Kandasamy, D.; Dux, F., III; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259.

prepared in almost quantitative yields in a similar way to the synthesis of *N*-methyltosylamide.[29]

1d: IR (film) 3290, 2970, 2940, 2875, 1600, 1500, 1480, 1460, 1430, 1330, 1310, 1165, 1100, 820, 710, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (2 H, d, J = 8.5 Hz), 7.17 (2 H, d, J = 8.5 Hz), 4.96 (1 H, t, J = 6.5 Hz), 2.86 (2 H, q, J = 6.5 Hz), 2.38 (3 H, s), 1.53–0.90 (6 H, m), 0.80 (3 H, t, J = 4.5 Hz). Anal. Calcd for $C_{12}H_{19}NO_2S$:C, 59.72; H, 7.94; N, 5.80; S, 13.28. Found: C, 59.89; H, 8.02; N, 5.86; S, 13.43.

1f: IR (film) 3300, 2960, 2940, 2855, 1600, 1500, 1470, 1460, 1420, 1330, 1310, 1160, 1100, 815, 710, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (2 H, d, J = 8.0 Hz), 7.26 (2 H, d, J = 8.0 Hz), 4.53 (1 H, t, J = 6.0 Hz), 2.88 (2 H, q, J = 6.0 Hz, 2.30 (3 H, s), 1.70–0.90 (10 H, m), 0.83 (3 H, t, J = 5.0 Hz). Calcd. for $C_{14}H_{23}NO_2S$: C, 62.42; H, 8.61; N, 5.20; S, 11.90. Found: C, 62.28; H, 8.63; N, 5.24; S, 11.98.

General Procedure for Anodic Oxidation of 1a–c,e in the Presence of Br^- at Room Temperature. A solution of **1** (2 mmol) in methanol (20 mL) containing NaOMe (54 mg, 1 mmol) and KBr (119 mg, 1 mmol) was placed in an electrolysis cell equipped with two platinum electrodes (2 cm × 2 cm), a thermometer, and a magnetic bar. Anodic oxidation was carried out under conditions of constant current (50 mA/cm^2) with cooling by means of a water bath. The temperature of the solution was maintained at 25 °C. After the charge shown in eqs 1 and 2 was passed, the reaction mixture was poured into an aqueous solution of Na_2CO_3 and $Na_2S_2O_3$ (50 mL). The organic portion was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic solution was dried over anhydrous $MgSO_4$. The residue obtained by evaporation of the solvent was column chromatographed (SiO_2/CH_2Cl_2) to give **2** or a mixture of **2** and **3** in the yields shown in eqs 1 and 2. α-(Tosylamino) aldehyde acetals **2a**,**c**[17] are known compounds.

2b: mp 53.0–54.0 °C; IR (KBr) 3300, 3000, 2950, 2850, 1600, 1500, 1430, 1350, 1330, 1160, 1120, 1100, 1070, 820, 720, 710, 680, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.0 Hz), 7.18 (2 H, d, J = 8.0 Hz), 4.72 (1 H, d, J = 7.0 Hz), 4.03 (1 H, d, J = 4.0 Hz), 3.53–3.20 (1 H, m), 3.27 (6 H, s), 2.38 (3 H, s), 1.02 (3 H, d, J = 6.5 Hz). Anal. Calcd for $C_{12}H_{19}NO_4S$: C, 52.73; H, 7.01; N, 5.12; S, 11.73. Found: C, 52.62; H, 7.22; N, 5.05; S, 11.68.

2e: IR (film) 3300, 2960, 2940, 2870, 1600, 1500, 1470, 1455, 1420, 1335, 1165, 1130, 1100, 1080, 820, 710, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (2 H, d, J = 8.0 Hz), 7.22 (2 H, d, J = 8.0 Hz), 4.75 (1 H, d, J = 8.5 Hz), 4.20 (1 H, d, J = 3.0 Hz), 3.47–3.07 (1 H, m), 3.28 (3 H, s), 3.22 (3 H, s), 2.38 (3 H, s), 1.76–0.60 (6 H, m), 0.77 (3 H, b t, J = 5.0 Hz). Anal. Calcd for $C_{15}H_{25}NO_4S$: C, 57.12; H, 7.99; N, 4.44; S, 10.16. Found: C, 56.83; H, 7.97; N, 4.41; S, 10.15.

3e: mp 72.0 °C; IR (KBr) 2970, 2940, 2875, 1600, 1500, 1465, 1345, 1305, 1200, 1160, 1095, 995, 815, 710, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (2 H, d, J = 8.0 Hz), 7.29 (2 H, d, J = 8.0 Hz), 3.82–3.05 (3 H, m), 2.42 (3 H, s), 2.29–1.22 (6 H, m), 0.90 (3 H, t, J = 7.0 Hz). Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53; S, 12.65. Found: C, 61.35; H, 7.34; N, 5.38; S, 12.67.

General Procedure for Anodic Oxidation of 1 in the Presence of I^- at −10 °C Followed by Further Anodic Oxidation at 25 °C. A solution of **1** (2 mmol), NaOMe (54 mg, 1 mmol), and KI (166 mg, 1 mmol) in methanol (20 mL) was placed in an electrolysis cell equipped with two platinum electrodes (2 cm × 2 cm), a thermometer, and a magnetic bar. Anodic oxidation was carried out under conditions of constant current (50 mA/cm^2), with the temperature of the reaction mixture being maintained at −10 °C. After the charge shown in Table I was passed, the electrolyzed solution was warmed up to room temperature and subjected to further electrolysis (constant current, 50 mA/cm^2) until the charge shown in Table I was passed. The electrolyte was poured into an aqueous solution of Na_2CO_3 and $Na_2S_2O_3$, the organic portion was extracted with CH_2Cl_2 (3 × 50 mL), and the extract was dried over anhydrous $MgSO_4$, successively. The residue obtained by evaporation of the solvent was column chromatographed (SiO_2/CH_2Cl_2) to give **2** in the yields shown in Table I.

2d: IR (film) 3300, 2970, 2945, 2880, 1600, 1500, 1460, 1335, 1160, 1100, 820, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (2 H, d, J = 8.0 Hz), 7.27 (2 H, d, J = 8.0 Hz), 4.86 (1 H, d, J = 8.5 Hz), 4.06 (1 H, d, J = 2.5 Hz), 3.53–2.97 (1 H, m), 3.26 (6 H, m), 2.42 (3 H, s), 1.73–0.83 (4 H, m), 0.77 (3 H, b t, J = 4.0 Hz). Anal. Calcd for $C_{14}H_{23}NO_4S$: C, 55.79; H, 7.69; N, 4.65; S, 10.64. Found: C, 55.65; H, 7.71; N, 4.68; S, 10.72.

2f: IR (film) 3300, 2970, 2940, 2880, 1600, 1500, 1460, 1340, 1170, 1100, 820, 710, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.5 Hz), 7.21 (2 H, d, J = 8.5 Hz), 4.60 (1 H, d, J = 8.0 Hz), 4.04 (1 H, d, J = 5.5 Hz), 3.47–3.03 (1 H, m), 3.27 (3 H, s), 3.25 (3 H, s), 2.39 (3 H, s), 1.73–0.53 (8 H, m), 0.80 (3 H, b t, J = 6.0 Hz). Anal. Calcd for $C_{16}H_{27}NO_4S$: C, 58.33; H, 8.26; N, 4.25; S, 9.73. Found: C, 58.31; H, 8.52; N, 4.26; S, 9.74.

2g: IR (film) 3300, 2970, 2940, 2860, 1600, 1500, 1475, 1455, 1340, 1170, 1100, 1080, 990, 820, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.0 Hz), 7.22 (2 H, d, J = 8.0 Hz), 4.72 (1 H, d, J = 8.5 Hz), 4.06 (1 H, d, J = 3.5 Hz), 3.58–3.01 (1 H, m), 3.28 (3 H, s), 3.25 (3 H, s), 2.39 (3 H, s), 1.72–0.58 (10 H, m), 0.83 (3 H, b t, J = 4.5 Hz). Anal. Calcd for $C_{17}H_{29}NO_4S$: C, 59.45; H, 8.51; N, 4.08; S, 9.33. Found: C, 59.15; H, 8.55; N, 4.14; S, 9.59.

^1H NMR Measurement and Allylation of 10c. Electrolysis of **1c** (455 mg, 2 mmol) was carried out at −10 °C in methanol containing NaOMe (54 mg, 1 mmol) and KI (166 mg, 1 mmol). After 10 F/mol of charge was passed, the electrolyte was poured into an aqueous solution of Na_2CO_3 and $Na_2S_2O_3$ (50 mL). The organic portion was extracted with CH_2Cl_2 (3 × 50 mL) and dried over anhydrous $MgSO_4$. After removal of the drying agent, the solvent was evaporated off in vacuo (5 mm Hg) to give a crude **10c**. This crude **10c** was subjected to the ^1H NMR measurement and to α-allylation without purification since the contact of this crude product with silica gel or alumina brought about the decomposition of **10c**.

10c: ^1H NMR (CD_3OD) δ 7.82 (2 H, d, J = 8.0 Hz), 7.41 (2 H, d, J = 8.0 Hz), 4.51 (1 H, t, J = 7.0 Hz), 2.47 (3 H, s), 1.90–1.03 (4 H, m), 0.83 (3 H, t, J = 5.5 Hz).

The crude product **10c** obtained from **1c** (455 mg, 2 mmol) was dissolved in dry CH_2Cl_2 (20 mL) under an atmosphere of nitrogen, and the solution was cooled to −72 °C. To the cooled solution, titanium(IV) chloride (0.22 mL, 2 mmol) was added with vigorous stirring. After the solution stood for 30 min at that temperature, allyltrimethylsilane (0.64 mL, 4 mmol) was added to the solution, which was stirred overnight at room temperature. The resulting solution was poured into aqueous Na_2CO_3 (50 mL), and the organic portion was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic solution was dried, evaporated, and column chromatographed (SiO_2/CH_2Cl_2) to give **14** (376 mg, 70%).

14: mp 83.3–84.9 °C; IR (KBr) 3290, 3080, 2975, 2950, 2880, 1650, 1610, 1500, 1450, 1430, 1330, 1310, 1170, 1100, 820, 710, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (2 H, d, J = 8.0 Hz), 7.21 (2 H, d, J = 8.0 Hz), 5.90–4.54, (4 H, m), 3.54–2.87 (1 H, m), 2.39 (3 H, s), 2.08 (2 H, t, J = 6.0 Hz), 1.54–0.97 (4 H, m), 0.77 (3 H, b t, J = 4.5 Hz). Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24; S, 11.99. Found: C, 62.90; H, 7.91; N, 5.17; S, 12.16.

General Procedure for Anodic Oxidation of 1 in the Presence of Br^- in Methanol under Heating (Reaction System B). A solution of **1** (4 mmol); NaOMe (108 mg, 2 mmol), and KBr (238 mg, 2 mmol) in methanol (20 mL) was placed in a three-necked electrolysis cell equipped with two platinum electrodes (1 cm × 2 cm), a reflux condenser, and a magnetic bar. Anodic oxidation was carried out while being heated externally at 60 °C under conditions of constant current (100 mA/cm^2). After the charge shown in Table II was passed, the solution was poured into an aqueous solution of Na_2CO_3 and $Na_2S_2O_3$ (50 mL). The organic portion was extracted with CH_2Cl_2 (3 × 50 mL), and then the combined organic solution was dried over anhydrous $MgSO_4$. The residue obtained by evaporation of the solvent was column chromatographed (SiO_2/CH_2Cl_2) to give a mixture of **2e** and **3e** from **1e**, and **3h–j** from **1h–j**, respectively, in the yields shown in eq 2 and Table II. Mixtures of stereoisomers were obtained in the case of **3h–j**. Since it was difficult to isolate each of the stereoisomers, the measurement of spectra and elemental analyses was carried out for the mixtures.

3h: IR (film) 2970, 2930, 2875, 1605, 1500, 1470, 1340, 1305, 1210, 1160, 1095, 815, 710, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (2 H, d, J = 8.0 Hz), 7.17 (1.2 H, d, J = 8.0 Hz), 7.13 (0.8 H, d, J = 8.0 Hz), 4.17–3.23 (2 H, m), 2.36 (3 H, s), 2.18–1.00 (8 H, m), 1.25 (1.8 H, d, J = 6.0 Hz), 1.10 (1.2 H, d, J = 6.0 Hz), 0.92 (3 H, b t, J = 6.0 Hz). Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98; S, 11.39. Found: C, 63.89; H, 8.27; N, 4.97; S, 11.49.

3i: mp 50–63 °C; IR (KBr) 2970, 2880, 1600, 1500, 1330, 1300, 1215, 1155, 1090, 820, 710, 670, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (2 H, d, J = 8.5 Hz), 7.20 (1.1 H, d, J = 8.5 Hz), 7.12 (0.9 H, d, J = 8.5 Hz), 4.30–4.20 (2 H, m), 2.40 (3 H, s), 2.20–1.00 (5 H, m), 1.32 (1.65 H, d, J = 3.0 Hz), 1.22 (1.35 H, d, J = 3.0 Hz), 1.01, 0.92, 0.84, 0.61 (6 H, d, J = 3.8 Hz, d, J = 3.8 Hz, d, J = 6.5 Hz, d, J = 6.5 Hz). Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98; S, 11.39. Found: C, 64.08; H, 8.51; N, 4.84; S, 11.35.

3j: IR (film) 2975, 2950, 2900, 1760, 1600, 1470, 1450, 1440, 1350, 1310, 1200, 1160, 1100, 820, 710, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (2 H, d, J = 8.5 Hz), 7.26 (2 H, b d, J = 8.5 Hz), 4.50–3.77 (1 H, m), 3.71 (1.65 H, s), 3.62 (1.35 H, s), 3.50–3.10 (1 H, m), 2.42 (3 H, s), 2.40–1.07 (4 H, m), 1.33 (1.65 H, d, J = 6.5 Hz), 1.20 (1.35 H, d, J = 6.5 Hz). Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S,

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10.78. Found: C, 56.28; H, 6.50; N, 4.55; S, 10.49.

General Procedure for Anodic Oxidation of 1 in Two-Layer System (Reaction System A). A solution of **1** (5 mmol), KOH (85%, 66 mg, 1 mmol), and KBr (476 mg, 4 mmol) in cyclohexane (15 mL)/distilled water (15 mL) was placed in a three-necked electrolysis cell equipped with two platinum electrodes (1 cm × 2 cm), a reflux condenser, and a magnetic bar. Anodic oxidation was carried out while being heated externally at 90 °C under conditions of constant current (50 mA/cm^2). After the charge shown in Table II was passed, the organic portion was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic solution was dried over anhydros $MgSO_4$. The residue obtained by evaporation of the solvent was column chromatographed (SiO_2/CH_2Cl_2) to give **3** in the yields shown in Table II.

3g: IR (film) 2970, 2930, 2870, 1600, 1500, 1460, 1350, 1160, 1095, 820, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (2 H, d, J = 8.0 Hz), 7.23 (2 H, d, J = 8.0 Hz), 3.90–2.92 (3 H, m), 2.40 (3 H, s), 2.12–1.00 (10 H, m), 0.90 (3 H, b t, J = 5.0 Hz). Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98; S, 11.39. Found: C, 63.97; H, 8.38; N, 4.91; S, 11.35.

Synthesis of Slaframine (21) from L-Lysine. α-Acetyl-ϵ-tosyl-L-lysine (**15**)[21] prepared from L-lysine was converted to the methyl ester **16** by adding dry hydrogen chloride into a solution of **15** (10 mmol) in methanol (200 mL); quantitative yield; $[\alpha]^{30}_D$ +11.126° (c 11.091, $CHCl_3$).

16: IR (film) 3300, 2950, 1750, 1660, 1540, 1330, 1160, 1100, 820, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.0 Hz), 7.22 (2 H, d, J = 8.0 Hz), 6.80 (1 H, d, J = 8.0 Hz), 5.80 (1 H, t, J = 6.0 Hz), 4.18 (1 H, m), 3.67 (3 H, s), 2.87, (2 H, m), 2.42 (3 H, s), 2.00 (3 H, s), 1.90–1.20 (6 H, m). Anal. Calcd for $C_{16}H_{24}N_2O_5S$: C, 53.91; H, 6.79; N, 7.86; S, 9.00. Found: C, 53.83; H, 6.93; N, 7.65; S, 8.81.

The anodic oxidation of **16** was carried out according to the procedure described above; **16** (1.741 g, 4.88 mmol) in methanol (30 mL) containing KI (0.406 g, 2.44 mmol) and NaOMe (0.14 g, 2.44 mmol); 12 F/mol at −10 °C and then 17 F/mol at 25 °C. **17**: 1.867 g (4.49 mmol); 92% yield.

17: IR (film) 3300, 2950, 1740, 1660, 1450, 1330, 1160, 1100, 820, 730, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.0 Hz), 7.23 (2 H, d, J = 8.0 Hz), 6.45 (1 H, b d, J = 8.0 Hz), 5.30 (1 H, m), 4.50 (1 H, m), 3.93 (1 H, m), 3.65 (3 H, s), 3.60 (6 H, s), 2.40 (3 H, s), 2.00 and 1.97 (3 H, s and s), 2.00–1.20 (4 H, m). Anal. Calcd for $C_{18}H_{28}N_2O_7S$: C, 51.91; H, 6.78; N, 6.73. Found: C, 51.49; H, 6.91; N, 6.47.

Heating **17** (359 mg, 0.863 mmol) in the presence of NH_4Cl (100 mg) at 130 °C under a reduced pressure (20 mmHg) for 3 h followed by purification of the residue gave **18** (249 mg, 0.708 mmol; 82% yield).

18: IR (film) 3270, 2970, 1750, 1660, 1460, 1340, 1160, 1100, 820, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.83 (2 H, d, J = 8.0 Hz), 7.42 (2 H, d, J = 8.0 Hz), 6.75 (1 H, s), 5.23 (1 H, m), 3.70 (3 H, s), 3.60–3.80 (1 H, m), 2.47 (3 H, s), 2.63–1.80 (4 H, m), 2.13 (3 H, s). Anal. Calcd for $C_{16}H_{20}N_2O_5S$: C, 54.53; H, 5.72; N, 7.95; S, 9.10. Found: C, 54.78; H, 5.80; N, 7.60; S, 8.98.

Both **17** and **18** did not show any optical rotation.

Hydrogenation of **18** (120 mg, 0.34 mmol) was carried out in acetic acid (8 mL) in the presence of PtO_2 (50 mg). After the hydrogenation (10 atm), the solution was added to aqueous sodium bicarbonate. Extraction with CH_2Cl_2 (3 × 50 mL) followed by purification on column chromatography gave methyl ester **19** (94 mg, 0.27 mmol, 78% yield), which was identified as the corresponding ethyl ester **20** by comparison with reported data (^{1}H, ^{13}C, and IR spectra).[18] The conversion of **19** to **20** was achieved by passing dry hydrogen chloride into a solution of **19** in ethanol (77% yield). The synthesis of **21** from **20** has already been reported.[18]

Preparation of 23 from 22. To a suspension of NaH (60%, 1.20 g, 30 mmol) in dry THF (5 mL) was added dropwise a dry THF solution of alcohol **22a** (2.99 g, 23 mmol, 10 mL) while being cooled by a water bath. After the completion of hydrogen evolution, a THF solution of *N*-tosylethylenimine[30] (4.925 g, 25 mmol) was added with stirring followed by standing for 2 days at room temperature. The resulting reaction mixture was poured into brine (50 mL), the organic portion was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic solution was dried over $MgSO_4$, successively. From the solution obtained by removal of the drying agent, the solvent was evaporated off. Unreacted **22a** was recovered by bulb-to-bulb distillation (1.05 g, 8 mmol, 35%), and from the residue, the product **23a** was isolated by column chromatography (3.69 g, 11 mmol, 49%, 75% based on consumed **22a**). Similarly product **23b** was obtained from **22b** (50%, 63% based on consumed **22b**).

23a: IR (film) 3290, 2930, 2860, 1605, 1465, 1325, 1165, 1120, 1100, 820, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.75 (2 H, d, J = 8.0 Hz), 7.29 (2 H, d, J = 8.0 Hz), 4.84 (1 H, b t, J = 6.0 Hz), 3.49–2.98 (6 H, m), 2.42 (3 H, s), 1.74–1.09 (12 H, m), 0.83 (3 H, b t, J = 6.0 Hz). Anal. Calcd for $C_{17}H_{29}NO_3S$: C, 62.35; H, 8.93; N, 4.28; S, 9.79. Found: C, 62.13; H, 9.03; N, 4.19; S, 9.93.

23b: IR (film) 3285, 2940, 2860, 1605, 1475, 1335, 1170, 1125, 1100, 815, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (2 H, d, J = 8.0 Hz), 7.25 (2 H, d, J = 8.0 Hz), 4.83 (1 H, b t, J = 6.0 Hz), 3.53–2.92 (6 H, m), 2.42 (3 H, s), 1.80–1.00 (14 H, m), 0.88 (3 H, b t, J = 5.0 Hz). Anal. Calcd for $C_{18}H_{31}NO_3S$: C, 63.31; H, 9.15; N, 4.10; S, 9.39. Found: C, 63.54; H, 9.40; N, 3.93; S, 9.27.

Anodic Oxidation of 23. Anodic oxidation of **23a** (327 mg, 1 mmol) was carried out under the conditions of reaction system A, described above. After the electrolysis, the organic portion was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic solution was dried, evaporated, and column chromatographed (SiO_2/CH_2Cl_2) to give **24a** (91 mg, 28%, 47% based on consumed **23a**) and **25a** (30 mg, 23%, 39% based on consumed **23a**) with **23a** (131 mg, 40%). Treatment of the mixture of **24a** and **25a** with a solution of methanol (3 mL) and trimethyl orthoformate (9 mL) containing *p*-TsOH (50 mg) for a day gave **26a** in 91% GLC yield. Similarly, products **24b** (38%), **25b** (15%), and **26b** (92%) were obtained from **23b**.

24a: IR (film) 2960, 2930, 2860, 1600, 1470, 1355, 1170, 1095, 815, 705, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.79 (2 H, d, J = 9.0 Hz), 7.38 (2 H, d, J = 9.0 Hz), 5.13 (1 H, t, J = 5.5 Hz), 3.99–3.22 (4 H, m), 2.47 (3 H, s), 2.04–1.08 (12 H, m), 0.89 (3 H, b t, J = 5.5 Hz). Anal. Calcd for $C_{17}H_{27}NO_3S$: C, 62.74; H, 8.36; N, 4.30; S, 9.85. Found: C, 62.52; H, 8.49; N, 4.14; S, 9.86.

24b: IR (film) 2950, 2925, 2850, 1595, 1495, 1470, 1350, 1305, 1165, 1090, 810, 705, 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.72 (2 H, d, J = 8.0 Hz), 7.28 (2 H, d, J = 8.0 Hz), 5.06 (1 H, t, J = 5.0 Hz), 3.96–3.12 (4 H, m), 2.41 (3 H, s), 1.99–1.06 (14 H, m), 0.87 (3 H, b t, J = 5.0 Hz). Anal. Calcd for $C_{18}H_{29}NO_3S$: C, 63.68; H, 8.61; N, 4.13; S, 9.44. Found: C, 63.51; H, 8.77; N, 3.96; S, 9.25.

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