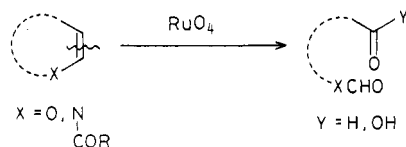


Table I. Oxidative Cleavage of Enolic Olefins with RuO₂-NaIO₄^a

entry	substrate	NaIO ₄ (mmol)	time (h)	product (yield, %) ^b
1		2.1	40	(53%) (27%)
2	1	4	50	(96%)
3		4	10	(93%)
4		4	10	(97%)
5	7	6	40	(96%)
6		4	20	(35%)
7		6	10	(96%)
8		5	30	(45%)
9		4	10	(96%)
10		4	10	(51%)

^a Oxidations were carried out by using 1.0 mmol of the substrate in a suspension of CCl₄ (10 mL) and H₂O (10 mL) in the presence of RuO₄·2H₂O (4 mg, 0.024 mmol) and NaIO₄ under vigorous stirring. ^b Yields based on isolated products.

the corresponding carbonyl compounds with RuO₄ under mild conditions.

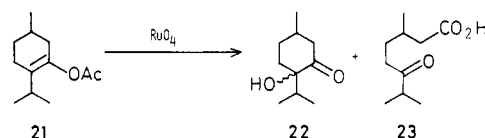


The oxidation of enolic olefins was carried out in carbon tetrachloride-water (1:1) in which sodium metaperiodate (NaIO₄) was used as a stoichiometric oxidant for the regeneration of RuO₄ from RuO₂ present only in a catalytic amount.⁷ A number of cyclic enol ethers and enamines were subjected to the oxidation with RuO₄ and the results are summarized in Table I. In general, the cleaved products are obtained in excellent yields.

The product selectivity of this reaction is strongly dependent on the amount of NaIO₄ used as a cooxidant. For example, a mixture of aldehyde 3 (27%) and carboxylic acid 2 (53%) was obtained when dihydropyran 1 was oxidized with 2.1 equiv of NaIO₄ (entry 1), while oxidation of the same substrate 1 with 4 equiv of NaIO₄ for an extended period afforded the lactone 4 in 96% yield, presumably as a result of the cyclization of the corresponding γ -formyloxy carboxylic acid 2 under slightly acidic conditions (entry 2). These results demonstrate that it is difficult to produce the initially formed aldehyde selectively. Therefore, oxidation was performed by taking prolonged reaction times with an excess amount of NaIO₄ in order to ensure complete conversion to the product in

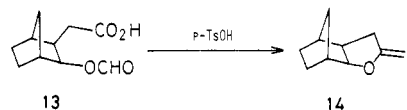
the highest oxidation state. The exhaustive oxidation of α -D-glucal triacetate 7 with RuO₄ in the presence of a large excess amount of NaIO₄, however, produced keto acid 9, exclusively. Formation of 9 can be understood in terms of overoxidation of the formyloxy carboxylic acid 8, since the treatment of 8 with RuO₄ under the conditions of entry 5 afforded 9 in 90% yield (entries 4 and 5). By analogy, *N*-acyl enamines 17 and 19 were also oxidized to the corresponding carbonyl compounds 18 and 20, respectively, in good yields.

It is interesting to note that the oxidation of enol acetate 21 with RuO₄ in the presence of 3 equiv of NaIO₄ afforded a mixture of α -hydroxy ketone 22 (53%) and the keto acid



23 (44%), while treatment of the hydroxy ketone 22 with RuO₄ in the same manner as above resulted in a mixture of 23 (9%) and the unchanged 22 (89%). However, the oxidation of 21 in a stoichiometric manner employing an excess amount of RuO₄ pregenerated from a mixture of RuO₂ (2 equiv) and NaIO₄ (4 equiv) provided 23 in 80% yield along with 22 in 16% yield.¹³ The formation of 23 from 21 is explained by assuming that 23 may be produced by the direct cleavage of the C=C bond of 21 with RuO₄. On the other hand, it is plausible that the conversion of 21 into 22 would occur by an oxidizing reagent which lies between octavalent and tetravalent oxidation states as ruthenium oxides.¹⁴

Finally, the γ -formyloxy carboxylic acid 13 was converted into the γ -lactone 14 on heating with *p*-toluene-



sulfonic acid (*p*-TsOH) in benzene. The present γ -lactone synthesis constitutes a viable alternative method to the reported one, since the starting 3,4-dihydro-2*H*-pyrans are easily accessible from olefins and α,β -unsaturated aldehyde by the hetero-Diels-Alder reaction.⁹

Experimental Section

Melting point ranges are uncorrected and boiling point ranges are indicated by an air-bath temperature without correction. IR spectra were recorded with a JASCO IRA-1 grating spectrometer. Unless otherwise noted, ¹H NMR spectra were determined at 60 MHz with a Hitachi R-24 spectrometer. Optical rotations were taken on a JASCO DIP-140 digital polarimeter in chloroform. Elemental analyses were performed in our laboratory.

Materials. According to the reported methods,⁹ 2,3-disubstituted 3,4-dihydro-2*H*-pyrans 5, 10, and 12 were prepared by the hetero-Diels-Alder reaction of α,β -unsaturated aldehydes with olefins. Bicyclic enol ether 15¹⁰ and enamine 19¹¹ were prepared by the reported procedures. *N*-Acyl enamine 17 was obtained by the electrochemical methoxylation of the carbamate followed

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by the demethoxylation with ammonium bromide.¹²

General Procedure for the Oxidative Cleavage of Enol Ethers with RuO₄. To a suspension of α -D-glucal triacetate 7 (270 mg, 1 mmol) dissolved in CCl₄ (10 mL) and NaIO₄ (857 mg, 4 mmol) dissolved in water (10 mL) was added RuO₂·2H₂O (4 mg, 0.024 mmol). After vigorous stirring for about 10 h, the reaction was quenched with isopropyl alcohol. The organic layer was separated and the aqueous layer was extracted several times with AcOEt. The combined extracts were dried (Na₂SO₄) and the concentrated residue was purified by column chromatography (SiO₂, hexane-AcOEt, 1/1) to give 299 mg (97%) of 8: mp 128–129 °C: [α]_D¹⁷ +29.18° (c 2.45); IR (Nujol) 3280–2600 (COOH), 1768, 1755, 1748, 1730, 1700 (ester C=O), 1380, 1260, 1240, 1202, 1145, 1110, 1062, 1040, 950, 928, 845, 760 cm⁻¹; ¹H NMR (CDCl₃) δ 2.09, 2.14, 2.19 (s, 9, CH₃C=O), 4.27 (m, 2, CH₂O), 5.27–5.83 (m, 3, CHO), 8.05 (s, 1, OCHO), 8.36 (br s, 1, COOH). Anal. Calcd for C₁₂H₁₆O₁₀: C, 45.01; H, 5.04. Found: C, 44.96; H, 5.09.

Similar treatment of 7 with a mixture of RuO₂·2H₂O (4 mg, 0.024 mmol) and NaIO₄ (1286 mg, 6 mmol) for 40 h provided keto acid 9 (276 mg, 96%) which was characterized after esterification with CH₂N₂: (Me ester of 9) mp 56–57 °C: [α]_D¹⁷ -10.31° (c 6.00); IR (neat) 1750 (ester C=O), 1375, 1220, 1070 cm⁻¹; ¹H NMR (CDCl₃) δ 2.15 (s, 6, CH₃COO), 2.17 (s, 3, CH₃COO), 3.75 (s, 3, OCH₃), 4.85 (d, *J* = 2 Hz, 2, CH₂O), 5.59 (d, *J* = 2.5 Hz, 1, OCHCO), 5.73 (d, *J* = 2.5 Hz, 1, OCHCOO). Anal. Calcd for C₁₂H₁₆O₉: C, 47.38; H, 5.30. Found: C, 47.31; H, 5.33.

Conversion of 8 into 9. A mixture of 8 (160 mg, 0.5 mmol), RuO₂·2H₂O (3 mg, 0.02 mmol), and NaIO₄ (642 mg, 3.0 mmol) was added to CCl₄ (10 mL) and H₂O (10 mL). The resulting suspension was vigorously stirred for 45 h and the products were taken up in AcOEt. Usual workup followed by column chromatography (SiO₂, hexane-AcOEt, 1/1) gave 130 mg (90%) of 9.

Results of the oxidation of enolic olefins with RuO₄ are given in Table I and physical properties along with spectral data of products are as follows.

6: bp 139–141 °C (1 mm); IR (neat) 3600–2400 (COOH), 1720 (C=O), 1410, 1180, 1085 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (m, 3, CH₃), 1.10–2.75 (m, 10, CH₂), 5.05 (m, 1, CHO), 8.09 (s, 1, OCHO). Anal. Calcd for C₉H₁₆O₄: C, 57.43; H, 8.57. Found: C, 57.52; H, 8.51.

11: bp 128–130 °C (2 mm); IR (neat) 1740 (C=O), 1715 (C=O), 1405, 1355, 1210, 1170, 965 cm⁻¹; ¹H NMR (CDCl₃) δ 1.00–1.75 (m, 7, CH₂, CH), 1.90–2.75 (m, 4, CH₂, CH), 2.13 (s, 3, CH₃C=O), 4.85 (d, *J* = 6 Hz, 1, CHO), 7.95 (s, 1, OCHO). Anal. Calcd for C₁₁H₁₆O₃: C, 67.32; H, 8.22. Found: C, 67.30; H, 8.27.

13: bp 144–146 °C (2 mm); IR (neat) 3400–2300 (COOH), 2640 (CHO), 1720 (C=O), 1695 (COOH), 1460, 1405, 1300, 1245, 1170, 900, 680 cm⁻¹; ¹H NMR (CDCl₃) δ 1.00–2.50 (m, 11, CH₂, CH), 4.90 (m, CHO), 7.98 (s, 1, OCHO), 10.48 (s, 1, COOH). Anal. Calcd for C₁₀H₁₄O₄: C, 60.59; H, 7.12. Found: C, 60.62; H, 7.19.

16: mp 54–55 °C; IR (Nujol) 1715 (C=O), 1697 (C=O), 1455, 1378, 1255, 1060, 1010, 1000 cm⁻¹; ¹H NMR (CDCl₃) δ 0.96 (d, *J* = 7 Hz, 6, CH₃), 1.10–2.00 (m, 4, CH₂, CH), 2.00–2.80 (m, 6, CH₂), 3.47–4.55 (m, 2, CH₂O). Anal. Calcd for C₁₁H₁₈O₃: C, 66.64; H, 9.15. Found: C, 66.59; H, 9.16.

18: bp 146–150 °C (2 mm); IR (neat) 3640–2400 (COOH), 1732 (C=O), 1705 (C=O), 1690 (C=O), 1320, 1270, 1230, 1185, 1012, 772 cm⁻¹; ¹H NMR (CDCl₃) δ 1.13–1.50 (m, 6, CH₃), 1.80–2.50 (m, 4, CH₂), 4.07–4.74 (m, 3, CH₂, CH), 9.21 (br s, 2, CHO, COOH). Anal. Calcd for C₉H₁₅O₅: C, 49.76; H, 6.96. Found: C, 49.76; H, 6.86.

20: bp 139–142 °C (2 mm); IR (neat) 1740 (C=O), 1712 (C=O), 1695 (C=O), 1385, 1372, 1247, 1178, 1170, 1045, 920, 732 cm⁻¹; ¹H NMR (CDCl₃) δ 1.02 (d, *J* = 6 Hz, 3, CH₃), 1.55–2.84 (m, 11, CH₂, CH), 2.38 (s, 3, CH₃C=O), 3.70–4.03 (m, 2, CH₂NC=O). Anal. Calcd for C₁₂H₁₉NO₃: C, 63.98; H, 8.50. Found: C, 63.90; H, 8.52.

Cleavage of Enol Acetate 21 with a Stoichiometric Amount of RuO₄. To a cooled (0 °C) solution of menthone enol acetate 21 (196.3 mg, 1 mmol) in CCl₄ (10 mL) was added dropwise a yellow solution of RuO₄ generated from RuO₂·2H₂O (338 mg, 2 mmol) and NaIO₄ (856 mg, 4 mmol) in CCl₄ (50 mL). The mixture was stirred for 1 h at 0–5 °C and the reaction was quenched with isopropyl alcohol (1 mL). The mixture was freed from RuO₂ by filtration under reduced pressure and the filtrate was concentrated to give a mixture of 22¹³ (29 mg, 16%) and 23

(160 mg, 80%) after purification on column chromatography (SiO₂, hexane-AcOEt, 4/1).

Treatment of 22 with RuO₄ Regenerated from RuO₂·2H₂O (Catalytic) and NaIO₄ (Stoichiometric). Hydroxy ketone 22 (100 mg, 0.66 mmol), NaIO₄ (561 mg, 2.62 mmol), and RuO₂·2H₂O (3 mg, 0.02 mmol) were placed in CCl₄ (10 mL) and H₂O (10 mL). The mixture was stirred vigorously for 1 h at 0–5 °C and quenched with 2-propanol (0.5 mL). Extractive workup followed by column chromatography (SiO₂, hexane-AcOEt, 2/1) gave 89 mg (89%) of 22 and 10 mg (9%) of 23.¹³

Lactonization of Formyloxy Carboxylic Acid. A solution of 13 (66 mg, 0.33 mmol) and a catalytic amount of *p*-TsOH in benzene (1 mL) was heated to reflux for 30 min. The mixture was washed with aqueous NaHCO₃ and dried (Na₂SO₄). Evaporation followed by column chromatography (SiO₂, hexane-AcOEt, 1/1) gave 41.6 mg (82%) of lactone 14: bp 105–107 °C (1 mm); IR (neat) 1775 (lactone C=O), 1460, 1415, 1365, 1310, 1215, 1175, 1115, 1045, 1030, 890, 875, 785, 685 cm⁻¹; ¹H NMR (CDCl₃) δ 1.00–2.90 (m, 11, CH₂, CH), 4.48 (m, 1, OCH). Anal. Calcd for C₉H₁₂O₂: C, 71.03; H, 7.95. Found: C, 70.96; H, 7.97.

Registry No. 1, 2270-61-3; 2, 94924-63-7; 3, 64833-76-7; 4, 1679-47-6; 5, 60443-97-2; 6, 94924-64-8; 7, 2873-29-2; 8, 94924-61-5; 9, 98919-96-1; 9 (methyl ester), 98839-00-0; 10, 98838-97-2; 11, 98838-98-3; 12, 69486-16-4; 13, 98838-99-4; 14, 5963-22-4; 15, 94924-57-9; 16, 94924-51-3; 17, 94924-59-1; 18, 94924-54-6; 19, 94924-60-4; 20, 94924-55-7; 21, 20144-45-0; 22, 74219-28-6; 23, 589-60-6; RuO₄, 20427-56-9.

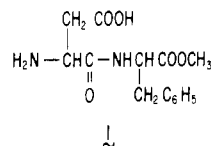
An *N*-Carboxyanhydride (NCA) Route to Aspartame[†]

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α -L-Aspartyl-L-phenylalanine methyl ester 1 (aspartame) is a nutritive sweetener approximately 200 times as sweet as sucrose.¹ Since the discovery in 1969, much effort has been directed toward an efficient synthesis.²



The selective formation of a peptide bond in the α -position of the L-aspartic acid moiety poses a major challenge to the synthesis of aspartame. It has been shown that the ring-opening reaction of *N*-substituted L-aspartic anhydride 2 with L-phenylalanine or its methyl ester 3 gives a mixture of α - and β -adducts 4 and 5, with a predominance of the α -isomer² (Scheme I). Therefore, a separation/recovery step is required.² On the other hand, several regioselective routes to the α -dipeptide have also been reported by either enzymatic^{3a,b} or chemical methods.^{3c} For example, the approach by Vinick^{3c} et al. involves the coupling of L-phenylalanine methyl ester 3 and L-aspartic acid *N*-thiocarboxyanhydride (NTA) 6, which was prepared from L-aspartic acid and methyl ethyl xanthate followed by PBr₃ cyclization.

We now wish to report our discovery of a simple and regioselective synthesis of aspartame from β -methyl-L-aspartate *N*-carboxyanhydride 7 (NCA) (Scheme II). This

[†] After this work had been completed in our laboratory, a similar but independent result was recently reported in a patent application (Chem. Abstr. 1985, 102, 96095h).