2×1 H), 2.00–2.15 (m, 2×2 H), 7.14–7.42 (m, 2×5 H); ¹³C NMR $(CDCl_3)$ 29.4₂, 30.1₉, 32.7₉, 33.1₈, 33.7₅, 35.7₂, 35.7₇, 36.8₈, 37.6₆, 69.4₁, 69.4₇, 125.3₇, 125.4₆, 125.9₇, 128.1₉, 128.2₈ ppm.

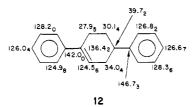
1,4-Dimethyl-4-phenylcyclohexene (10). The epimeric alcohol mixture (10 g) was mixed with 10 g of powdered KHSO₄ in a 100-mL round-bottom flask equipped with a Kugelrohr receiver bulb and placed in the Kugelrohr heater. The flask was heated at 150 °C for ca. 1 h which caused water droplets to collect in the receiver. The receiver was changed and aspirator vacuum applied to distill the olefin [bp 150–160 $^{\circ}\mathrm{C}$ (20 mm)]. The product thus collected was redistilled to yield 8.67 g (95%) of olefin 10: MS, m/e 186, 118, 117, 91; ¹H NMR (CDCl₃) δ 1.24 (s, 3 H), 1.58-1.60 (d, J = 3 Hz, 3 H), 1.68-1.81 (m, 2 H), 1.85-1.98 (m, 2 H), 2.02-2.15 (m, 1 H), 2.41-2.83 (m, 1 H), 5.39-5.45 (m, 1 H), 7.11-7.18 (br t, 1 H), 7.23-7.38 (m, 4 H); ¹³C NMR (CDCl₃), see Table I.

1,c-4-Dimethyl-r-1-phenylcyclohexane (6) and 1,t-4-Dimethyl-r-1-phenylcyclohexane (7). The olefin 10 (6.5 g, 35 mmol) was dissolved in 50 mL of absolute ethanol in a hydrogenation bottle, 900 mg of 10% Pd on carbon was added, and the mixture was shaken under hydrogen (initial pressure 45 psi) in a Parr apparatus for 1 h. Filtering through a Celite pad, removing the solvent, and distillation of the residue [bp 140-145 °C (20 mm)] in a Kugelrohr yielded 6.1 g (92%) of 6 and 7 in a ratio of ca. 3:2 as shown by GC. This mixture was separated by preparative GLPC using an Apiezon-L column at 170 °C. Compound 6 emerged first followed by 7.

cis-Isomer 6: MS, m/e 188, 173, 131, 118, 105, 91, and 32. Anal. Calcd for $C_{14}H_{20}$: M⁺, 188.157. Found: M⁺, 188.157. ¹H NMR $(CDCl_3) \delta 0.76-0.82 (d, J = 7 Hz, 3 H), 0.96-1.04 (m, 1 H), 1.14$ (s, 3 H), 1.2-1.62 (m, 6 H), 2.22-2.50 (m, 2 H), 7.1-7.4 (m, 5 H); ¹³C NMR, see Table I.

trans-Isomer 7: MS, m/e 188, 173, 131, 118, 105, 91. Anal. Calcd for $C_{14}H_{20}$: M⁺, 188.157. Found: M⁺, 188.157. ¹H NMR (CDCl₃) δ 0.96–1.00 (d, J = 7 Hz, 3 H), 1.1–1.9 (m, 9 H), 1.28 (s, 3 H), 7.2-7.44 (m, 5 H); ¹³C NMR, see Table I.

Alternate Synthesis of cis- (2) and trans-1,4-Diphenylcyclohexane (11). The epimeric alcohol mixture of t-1,c-4-diphenyl-r-1-cyclohexanol and t-1,t-4-diphenyl-r-1-cyclohexanol⁸ was heated with KHSO4 as described above for 10 to yield 1,4diphenylcyclohex-1-ene (12) in ca. 90% yield, mp 101–103 °C (lit.¹⁴ mp 102 °C) after vacuum distillation in a Kugelrohr: ¹H NMR δ 1.96-2.22 (m, 2 H), 2.3-2.7 (m, 4 H), 2.8-3.0 (m, 1 H), 6.18-6.30 (m, 1 H, olefinic), 7.2–7.5 (m, 10 H, Ph); ^{13}C NMR (CDCl₃) (in ppm)



Catalytic reduction of 12 in absolute ethanol at 45 psi initial hydrogen pressure with 10% by weight of 10% Pd-C yielded cis-1,4-diphenylcyclohexane (2) of ca. 95% purity as an oil. However, hydrogenation in 95% ethanol using the same catalyst at atmospheric pressure yielded a mixture of 2 and 11.15 From the cis-trans mixture the trans (11) compound crystallizes from ethanol, mp 171-172 °C (lit.¹⁶ mp 170-172 °C; ¹³C NMR of 2 and 11; see Table I.

cis-(1,4-Diphenylcyclohexane)chromium Tricarbonyl (1). cis-1,4-Diphenylcyclohexane (2) (0.294 g, 1.24 mmol) and Cr(CO)₆ (0.824 g, 4.12 mmol) in 20 mL of dioxane were heated at reflux in an argon atmosphere for 20 h. Removal of solvent at reduced pressure left a yellow-green solid, which was dissolved in anhydrous ether and filtered through a filter-aid pad to remove the

excess chromium hexacarbonyl. Evaporation of ether at reduced pressure left a residue (0.833 g), which was loaded onto a column of silica gel HF-254 packed in 20% ethyl acetate in hexane. Elution with the same solvent gave complexation product 1 (0.193)g, 42% yield) as a yellow-green oil: IR (CCl₄) 1980, 1910, 1550, 650, 630 cm⁻¹; ¹H NMR ($\tilde{C}Cl_4$) δ 1.80 (m, 8 H), 2.55 (br m, 1 H), 2.87 (br m, 1 H), 5.11 (s, 5 H), 7.14 (s, 5 H). ¹³C NMR, see Table T 17

Chromium tricarbonyl complexes 3 and 5 were prepared similarly and were characterized by ¹³C NMR spectroscopy (Table I).¹⁷

Acknowledgment. Part of this work was supported by NSF Grant CHE-802088.

Registry No. 1, 98859-22-4; 2, 21072-41-3; 3, 98859-23-5; 4, 828-45-5; 5, 98859-24-6; 6, 98859-17-7; 7, 98859-18-8; 8, 98859-19-9; 9, 98859-20-2; 10, 98859-21-3; 11, 21072-42-4; 12, 10470-07-2; 4-methyl-4-phenylcyclohexanone, 18932-33-7; t-1,c-4-diphenylr-1-cyclohexanol, 93783-02-9; t-1,t-4-diphenyl-r-1-cyclohexanol, 93783-03-0.

A Facile Procedure for Oxidative Cleavage of Enolic Olefins to the Carbonyl Compounds with Ruthenium Tetraoxide (RuO_4)

Sigeru Torii,* Tsutomu Inokuchi, and Kazumi Kondo

Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama 700, Japan

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Oxidative cleavage of a carbon-carbon double bond to the corresponding carbonyl compounds is an essential operation in organic synthesis.¹ Ozonolysis is accepted as the most general method for this purpose, but this technique involves the tedious feature that the reaction is carried out at low temperature by bubbling an excess amount of ozone.² On the other hand, among the high valent metal salts suitable for the oxidative cleavage of olefins,³ ruthenium tetraoxide (RuO_4) is promising with respect to its high efficiency⁴ and is already employed in the conversion of simple olefins to the carbonyl compounds.⁵ However, to date no systematic study of this application to an enolic system has appeared except for one case attempted in the cleavage of C=C bond of steroidal enamines.⁶ In this paper, we disclose a versatile procedure for the oxidative cleavage of enolic olefins including enol ethers, enol acetates, and enamines to give

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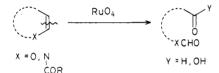
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Table I. Oxidative Cleavage of Enolic Olefins with RuO-NaIO

RuO_2 -NaiO ₄				
entry	substrate	NaIO ₄ (mmol)	time (h)	product (yield, %) ^b
1	- 0 1	2.1	40	COOH CCHO 2 (53) CCHO (27)
2	1	4	50	ССНО 3 (2/)
3	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	4	10	СООН осно 6 (93)
4	OAc AcO	4	10	ACO OCHO 8 (97) OAc
5	7	6	40	OAc ACO COOH 9 (96) OAc
6	40T 10	4	20	ОСНО 11 (35)
7	200 12	6	10	соон осно 13 (96)
8	↓ ↓ ↓ 15	5	30	16 (45)
9	CO ₂ Et	ц	10	COOH NCHO 18 CO2Et
10	Ac 19	4	10	

^aOxidations 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 $RuO_4 \cdot 2H_2O$ (4 mg, 0.024 mmol) and $NaIO_4$ under vigorous stirring. ^b Yields based on isolated products.

the corresponding carbonyl compounds with RuO_4 under mild conditions.

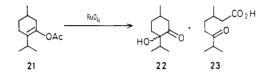


The oxidation of enolic olefins was carried out in carbon tetrachloride-water (1:1) in which sodium metaperiodate $(NaIO_4)$ was used as a stoichiometric oxidant for the regeneration of RuO_4 from RuO_2 present only in a catalytic amount.⁷ A number of cyclic enol ethers and enamines were subjected to 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 $NaIO_4$ (entry 1), while oxidation of the same substrate 1 with 4 equiv of $NaIO_4$ 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

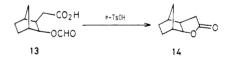
the highest oxidation state. The exhaustive oxidation of α -D-glucal triacetate 7 with RuO₄ in the presence of a large excess amount of NaIO₄, however, produced keto acid 9, exclusively. Formation of 9 can be understood in terms of overoxidation of the formyloxy carboxylic acid 8, since the treatment of 8 with RuO_4 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 RuO_4 in the presence of 3 equiv of $NaIO_4$ afforded a mixture of α -hydroxy ketone 22 (53%) and the keto acid



23 (44%), while treatment of the hydroxy ketone 22 with RuO_4 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 RuO_2 (2 equiv) and $NaIO_4$ (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 RuO_4 . 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-2H-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-2H-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 RuO**₄. 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 (Na_2SO_4) 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: $[\alpha]_D^{17}$ +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: $[\alpha]_D^{17}$ –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 RuO_4 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 RuO_4 . 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[†]

Jacob S. Tou* and Billy D. Vineyard

Monsanto Company, Nutrition Chemicals Division, St. Louis, Missouri 63167

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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-Laspartate 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*, 96095*h*).