Anal. Calcd for $C_{30}H_{30}O_{10}$: C, 65.49; H, 5.50. Found: C, 65.48; H, 5.58. This compound was a white solid with mp 153–154 °C.

5-*C*-(4,5,8-Triacetoxy-2-naphthyl)-1,2:3,4-bis-*O*-(1-methylethylidene)-L-arabinopyranose (16): ^{1}H NMR ($CDCl_3$) δ 7.327 (s, 1 H), 7.270 (d, 1 H, J = 9.0 Hz), 7.255 (s, 1 H), 7.084 (d, 1 H, J = 8.1 Hz), 5.730 (d, 1 H, J = 4.8 Hz), 4.997 (s, 1 H), 4.731 (dd, 1 H, J = 2.1, 7.8 Hz), 4.476 (d, 1 H, J = 7.8 Hz), 4.420 (dd, 1 H, J = 2.1, 4.8 Hz), 2.441 (s, 3 H), 2.374 (s, 6 H), 1.581 (s, 3 H), 1.434 (s, 3 H), 1.332 (s, 3 H), 1.276 (s, 3 H); IR (oil) 1763, 1614, 1460 cm^{-1}; MS m/e 530, 488, 446, 404, 346, 204, 113,85, 59; HRMS m/e for $C_{27}H_{30}O_{11}$ calcd 530.178 82, measured 530.178 85; TLC (1:1 H-EA) R_f = 0.42. Anal. Calcd for $C_{27}H_{30}O_{11}$: C, 61.17; H, 5.70. Found: C, 61.16; H, 5.84. This compound was a white solid with mp 234–235 °C.

C-Allylation of L-Ascorbic Acid under Palladium(0) Catalysis

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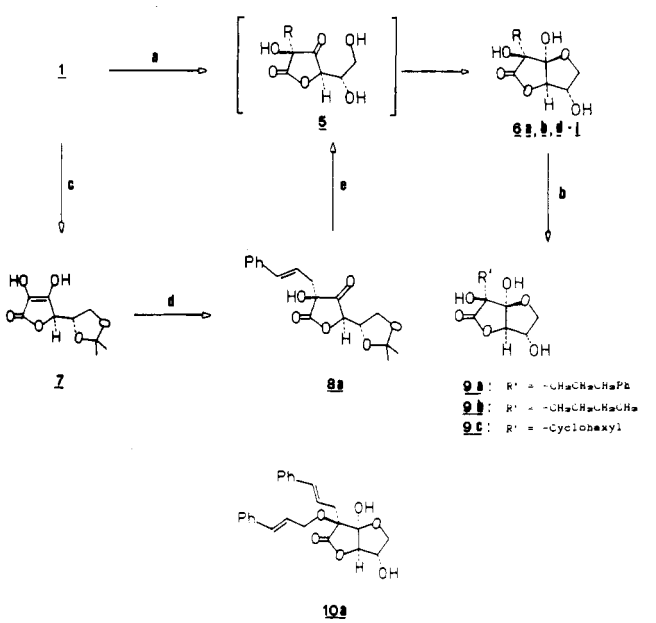
L-Ascorbic acid (1) is efficiently allylated at C-2 with primary and secondary allylic substrates by using palladium(0) catalysis. Hydrogenation of the resulting allylated compounds **6** affords L-ascorbic acid derivatives with saturated chains at C-2.

Some attention has been directed to the chemistry of L-ascorbic acid (vitamin C) (1) with the aim of preparing derivatives with biological activity but resistant to air oxidation.[1] However, despite the enormous biological and industrial importance of L-ascorbic acid, its chemistry has not been developed as it could be thought due to its inherent difficulties. Thus, in relation with reactivity at the active oxygen atoms some confusion has arisen concerning the site of alkylation, and in the review by Tolbert et al.[1] published in 1975 it has been stated that "ascorbic acids derivatized at the 2-O position have often been called 3-O derivatives, and early work should be critically evaluated". Recently the problem of noncrystallographic differentiation of O-2 and O-3 acyl derivatives of L-ascorbic acid has been approached.[2] Moreover, no general methods to alkylate L-ascorbic acid at C-2 have been reported.

L-Ascorbic acid is a fully enolic and strongly acidic β-dicarbonyl compound with a pK_a value of 4.85 in ethanol–water.[3] It is well known that compounds sharing these features present great difficulties for alkylation at the activated carbon atom under kinetically controlled conditions, the oxygen atoms being the preferred sites for reaction. To the best of our knowledge only two reports dealing with direct C-alkylations of L-ascorbic acid have appeared in the chemical literature. Thus, Jackson and Jones[4a] reported the reaction of sodium L-ascorbate with benzyl chloride to afford mixtures of benzylated products at C-2 and O-3. More recently Poss et al. have described the C-alkylation of potassium L-ascorbate with some allylic and propargylic halides.[4b]

Many familiar carbon–carbon bond formation processes such as the aldol and the Michael reactions occur under thermodynamic control, thus eluding the carbon–oxygen bond formation which is the kinetically favored alternative. Therefore, it is not surprising that some recently reported reactions of L-ascorbic acid forming a carbon–carbon bond at C-2 can be cataloged as aldol[5a,b] or Michael reactions.

Scheme I[a]



[a] (a) See Table I; (b) H_2/10% Pd-C/EtOH; (c) MeCOCl/acetone; (d) **4a**/Pd(acac)$_2$/PPh$_3$/THF/reflux, 15 h; (e) 2 N HCl/MeOH.

In the last case the Michael acceptor can be a conventional one[6a–d] or of the quinone methide type,[7a,b] one particular case being the reactions leading to ascorbigens.[8a–c]

Additional evidence of the recently renewed interest on the chemistry of L-ascorbic acid is provided by the paper by Kato et al. on the synthesis of 2-*O*-alkylascorbic acids for testing as scavengers of active oxygen species[9] and by

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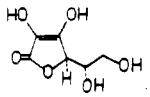
Table I.[a] Allylations of L-Ascorbic Acid (1)

run	3 or 4	catal/L[b]	1:3 or 4:Pd:L:base[c]	t, h	product (%)
1	PhCH=CHCH$_2$OAc, **3a**	Pd(dba)$_2$/DPPE	1.0:1.2:0.05:0.1:1.0	5	**6a** (28)
2	PhCH=CHCH$_2$OAc, **3a**	Pd(acac)$_2$/PPh$_3$	1.0:1.2:0.05:0.2:1.0	3	**6a** (23)
3	PhCH=CHCH$_2$OCOOEt, **4a**	Pd(dba)$_2$/DPPE	1.0:1.2:0.05:0.1:–	5	–
4	PhCH=CHCH$_2$OCOOEt, **4a**	Pd(acac)$_2$/PPh$_3$	1.0:2.0:0.05:0.2:–	3.5	**6a** (41)
5	MeCH=CHCH$_2$OCOOEt, **4b**	Pd(acac)$_2$/PPh$_3$	1.0:1.2:0.05:0.2:–	4.5	**6b** (28)
6	CH$_2$=CHCH(Me)OAc, **3c**	Pd(acac)$_2$/PPh$_3$	1.0:1.0:0.05:0.2:1.0	2	–
7	CH$_2$=CHCH(Me)OCOOEt, **4c**	Pd(acac)$_2$/PPh$_3$	1.0:1.2:0.05:0.2:–	4	**6b** (57)
8	Me(CH$_2$)$_4$CH(CH=CH$_2$)OAc, **3d**	Pd(dba)$_2$/DPPE	1.0:1.2:0.05:0.1:1.0	5	**6d**[d] (23)
9	CH$_2$=CHCH$_2$OCOOEt, **4e**	Pd(acac)$_2$/PPh$_3$	1.0:1.2:0.05:0.2:–	4	**6e** (70)
10	CH$_2$=C(Me)CH$_2$OCOOEt, **4f**	Pd(acac)$_2$/PPh$_3$	1.0:1.2:0.05:0.2:–	2	**6f** (48)
11	Me$_2$C=CHCH$_2$OAc, **3g**	Pd(dba)$_2$/DPPE	1.0:1.2:0.05:0.1:1.0	8	–
12	Me$_2$C=CHCH$_2$OCOOEt, **4g**	Pd(acac)$_2$/PPh$_3$	1.0:1.2:0.05:0.2:–	4	**6g** (38)
13	MeCH=CHCH(Me)OAc, **3h**	Pd(dba)$_2$/DPPE	1.0:1.0:0.05:0.1:1.0	22	**6h**[e] (5)
14	MeCH=CHCH(Me)OCOOEt, **4h**	Pd(acac)$_2$/PPh$_3$	1.0:1.2:0.05:0.2:–	5	**6h**[e] (55)
15	2-cyclohexenyl-OAc, **3i**	Pd(acac)$_2$/PPh$_3$	1.0:2.0:0.05:0.2:1.0	4	–
16	2-cyclohexenyl-OCOOEt, **4i**	Pd(dba)$_2$/DPPE	1.0:1.0:0.05:0.1:–	20	–
17	2-cyclohexenyl-OCOOEt, **4i**	Pd(acac)$_2$/PPh$_3$	1.0:1.1:0.05:0.2:–	12	**6i**[e] (48)

[a] Refluxing in THF for the indicated time. Yields of isolated products. In runs in which Pd(acac)$_2$ was used variable amounts of C-allylated pentane-2,4-diones were isolated. [b] Ligand. DPPE = 1,2-bis(diphenylphosphino)ethane. [c] DBU when present. [d] Radical R in **6d**: Me(CH$_2$)$_4$CH=CHCH$_2$. [e] Diastereomeric mixture.

a letter dealing with the double alkylation at O-2 and O-3 in a synthesis of the L-talonic lactone.[10]

Palladium(0) chemistry offers many possibilities for carbon–carbon bond formation.[11] We have recently reported the regioselective C-allylation of highly enolic and acidic carbo- and heterocyclic β-dicarbonyl compounds under thermodynamically controlled conditions which involve catalysis by palladium(0) species. Both the mechanistic[12,13] features and the synthetic scope[12,14] of the novel alkylation method have been extensively studied. It is noteworthy that the C-allylation procedure can be applied to tetronic acid[14] (**2**) (pK_a 3.76) containing the basic carbon



1

2

skeleton of L-ascorbic acid. The resulting C-allylic derivatives can be selectively hydrogenated at the introduced chain thus all together affording an excellent alkylation method for the activated carbon atom.

Results

Our results are collected in Table I and Scheme I. L-Ascorbic acid can be reasonably C-allylated by several allylic acetates **3** and mixed ethyl carbonates **4** (Table I) under palladium(0) catalysis. This includes the introduction of both primary and secondary radicals. Four different combinations of allylating agent, catalyst precursor, and stabilizing phosphine were studied. The best results were observed working with carbonates **4**, bis(pentanedionato)palladium(II) and triphenylphosphine (runs 4, 5, 7, 9, 10, 12, 14, and 17). However, the combination of carbonates **4** with Pd(dba)$_2$ and 1,2-bis(diphenylphosphino)ethane was useless in two experiments (runs 3 and 16). Intermediate results were obtained with the rest of the combinations shown in Table I. One equivalent of a base, DBU, was added to the reaction media in the experiments with acetates **3**, but this was omitted when working with carbonates **4** because 1 equiv of the strongly basic ethoxide anion is released during the process.[15]

In no case were products **5** isolated. Instead the cyclized hemiketals **6** were spontaneously formed under the reaction conditions as evidenced by spectroscopic means. Thus, the isolated compounds presented only a carbonyl stretching in the range 1770–1798 cm^{-1} (KBr or film) corresponding to the lactone group. The ^{13}C NMR spectra of these compounds were also very informative since they exhibited only one carbonyl carbon absorption in the range δ 174.0–175.9 and one peak in the range δ 107.5–108.8 for the hemiketal carbon atoms at C-3. Absorptions corresponding to C-2 appear in the range δ 85.6–88.1. For compounds **6h** and **6i** two close absorptions were observed for many carbon atoms, thus indicating the presence of two diastereoisomers originated by the formation of a new chiral center at C-1′ of the incorporated radical.

Several features need to be pointed out: (i) The reactions were regioselective with respect to the allylic derivative, allylations occurring at the less substituted terminus of the allylic system. Thus, both isomeric carbonates **4b** and **4c** afforded the same final compound **6b** (runs 5 and 7). Also, the reaction of the branched acetate **3d** produced compound **6d** possessing a linear chain at C-2 (run 8). Nevertheless, allylic derivatives giving rise to allylpalladium complexes substituted at both termini were active as evidenced in runs 14 and 17 for the secondary carbonates **4h** and **4i**. (ii) Allylation of dioxolane **7** with **4a** (Scheme I) in the presence of bis(pentane-2,4-dionato)palladium(II) afforded the C-allylation compound **8a** in 68% yield. However, the overall yield from **1** to **6a** through **8a** (25%) is lower than that obtained by direct allylation of **1** (run 4) in Table I. (iii) No attention was paid to the stereochemistry of the double bond of the hydrocarbon chain at C-2 of compounds **6** apart from **6a** for which stereochemistry *E* was evident on the basis of a coupling constant of 15 Hz. (iv) A small quantity of product **10a** from double allylation at C-2 and O-2 was isolated in run 4.

X-ray diffraction studies have shown that aldol[5] and Michael reactions at C-2[6a,d,7b] occur from the less hindered face of **1**. Compound **6e** has been previously prepared by

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Poss and Belter[4b] who determined its stereochemistry by chemical means (Wacker oxidation of the allyl chain to acetonyl and intramolecular hemiketal formation with the OH at C-3). Their close spectroscopic behavior and in particular the similarity of their ^{13}C NMR spectra allows us to attribute the same stereochemistry to all compounds **6**.

Experimental Section

General. All melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 80 and 20 MHz, respectively, in acetone-d_6 unless otherwise stated using TMS as internal standard. Acetates **3** were prepared by treating the corresponding alcohols with acetic anhydride and pyridine in dichloromethane at room temperature followed by conventional workup and fractional distillation of the dichloromethane and **3**, or by treatment with acetyl chloride and pyridine at 70 °C followed by workup. Similarly, alkyl ethyl carbonates **4** were prepared by reaction of equimolar amounts of ethyl chlorocarbonate, the corresponding alcohol, and pyridine in ether at 0–10 °C. Bis(dibenzylideneacetone)palladium(0),[16] mp 146–148 °C, and 5,6-isopropylidene-L-ascorbic acid (**7**),[17] mp 195 °C, were prepared by described procedures. Solvent THF was anhydrous and transferred via syringes under argon pressure. Specific rotations at 20 °C were measured with a sodium D lamp in methanol (concentration in g/100 mL given for each compound). The solvents used in column chromatographies were, in order of increasing polarity: petroleum ether, dichloromethane, and ethyl acetate.

(*E*)-2-(3-Phenylallyl)-3-oxo-L-gulonolactone 3,6-Hemiketal (6a) (Run 4, Table I). General Procedure. A solution of bis(pentane-2,4-dionato)palladium(II) (0.123 g, 0.4 mmol) and triphenylphosphine (0.419 g, 1.6 mmol) in THF (20 mL) was poured under argon atmosphere into a magnetically stirred mixture of L-ascorbic acid (**1**) (1.409 g, 8.0 mmol) and THF (20 mL). Cinnamyl ethyl carbonate (3.364 g, 16.0 mmol) in THF (10 mL) was then added, and the mixture was refluxed for 3.5 h. The solvent was evaporated, and the residue was chromatographed through silica gel to afford in elution order: 3,3-dicinnamylpentane-2,4-dione (92% yield with respect to bis(pentane-2,4-dionato)palladium(II)) which was compared with an authentic sample.[18] 2-(3-Phenylallyl)-2-((3-phenylallyl)oxy)-3-oxo-L-gulonolactone 3,6-hemiketal (**10a**) (0.511 g, 16%): mp 147–148 °C (dichloromethane); IR (KBr) 3398 (br), 1787, 970 cm^{-1}; ^1H NMR δ 2.7 (d, J = 6 Hz, 2 H), 4.0–4.8 (m, 6 H), 6.1–6.9 (m, 4 H), 7.35 (m, 10 H); ^{13}C NMR δ 38.9, 71.3, 73.6, 79.3, 82.9, 85.3, 108.2, 123.9, 126.4, 127.0, 127.2, 127.3, 128.1, 128.5, 129.2, 129.4, 134.8, 137.6, 138.3, 175.0; MS m/e (relative intensity) 291 (1), 117 (100), 116 (22), 115 (78), 91 (28); $[\alpha]_D$ = +68° (c 1.0). Anal. Calcd for $C_{24}H_{24}O_6$: C, 70.57; H, 5.88. Found: C, 70.14; H, 5.89. **6a**: mp 146–147 °C (benzene); IR (KBr) 3543 (br), 3332 (br), 1771, 969 cm^{-1}; ^1H NMR δ 2.7 (d, J = 6 Hz, 2 H), 4.0–4.8 (m, 5 H), 6.3 (dt, J = 6 and 15 Hz, 1 H), 6.6 (d, J = 15 Hz, 1 H), 7.4 (m, 5 H); ^{13}C NMR δ 38.8, 75.4, 75.7, 79.3, 87.4, 108.3, 123.8, 126.9, 128.0, 129.3, 134.8, 138.1, 175.4; MS m/e (relative intensity) 292 (M, 5), 117 (100), 115 (66), 91 (46), 45 (20); $[\alpha]_D$ = +47° (c = 2.0). Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.40; H, 5.56. Triphenylphosphine oxide (0.134 g).

Preparation of 6a through 7 and 8a. 2-Cinnamyl-5,6-isopropylideneascorbic acid (**8a**) was prepared from **7** by the above procedure in 68% yield. Product **8a** was an oil difficult to purify and was directly treated (1.802 g, 2.7 mmol) in methanol (8 mL) with 2 N HCl (4 mL) under stirring at room temperature for 6 h. The solvent was evaporated to afford crude **6a** (1.805 g, 46%) compared with the sample obtained in run 4 as above described.

2-(2-Buten-1-yl)-3-oxo-L-gulonolactone 3,6-Hemiketal (6b) (Run 7, Table I). Product **6b** was prepared from carbonate **4c** by the same procedure as **6a** under the experimental conditions indicated in Table I. Product **6b**: mp 107–108 °C (lit.[4b] mp 88–89.5 °C); IR (KBr) 3553, 3528, 3484, 3429, 1778, 981 cm^{-1}; ^1H NMR δ 1.6 (d, J = 4 Hz, 3 H), 2.5 (m, 2 H), 4.0–4.7 (m, 4 H + 1 H (OH)), 5.6 (m, 2 H); ^{13}C NMR δ 18.0, 38.4, 75.3, 75.6, 79.2, 87.3, 108.2, 124.5, 130.6, 175.6; MS m/e (relative intensity) 230 (M, 1), 119 (30), 102 (28), 85 (100), 84 (22), 55 (83); $[\alpha]_D$ = +28° (c 1.0) (lit.[4b] $[\alpha]_D$ = +27° under the same experimental conditions).

2-(2-Octen-1-yl)-3-oxo-L-gulonolactone 3,6-Hemiketal (6d) (Run 8, Table I). Product **6d** was prepared from acetate **3d** by the same procedure as **6a** under the experimental conditions indicated in Table I. Product **6d**: oil; IR (film) 3400 (br), 1785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7–1.5 (m, 11 H), 2.0 (m, 2 H), 2.5 (d, J = 2.5 Hz, 2 H), 4.0–4.6 (m, 4 H), 5.1–5.9 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 28.8, 31.3, 32.5, 37.6, 74.1, 75.4, 78.7, 85.6, 107.5, 120.5, 138.0, 175.4; MS m/e (relative intensity) 177 (21), 176 (20), 119 (21), 116 (34), 111 (26), 110 (23), 102 (21), 85 (70), 71 (21), 69 (100), 67 (21), 55 (80), 54 (23), 43 (50); $[\alpha]_D$ = +21° (c 2.0). Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.35; H, 8.07.

2-Allyl-3-oxo-L-gulonolactone 3,6-Hemiketal (6e) (Run 9, Table I). Product **6e** was prepared by the same procedure as **6a** under the experimental conditions indicated in Table I. Product **6e**: oil. The spectroscopic data were coincident with those previously reported:[4b] IR (film) 3259 (br), 1792, 997 cm^{-1}; ^1H NMR δ 2.5 (m, 2 H), 4.0–4.5 (m, 4 H + 1 H (OH)), 5.0–5.3 (m, 2 H), 5.5–6.2 (m, 1 H); ^{13}C NMR δ 39.5, 75.2, 75.6, 78.9, 87.2, 108.1, 119.5, 132.3, 175.3; MS m/e (relative intensity) 152 (32), 119 (46), 102 (32), 85 (72), 77 (72), 69 (22), 51 (67); $[\alpha]_D$ = +29° (c 2.0) (lit.[4b] $[\alpha]_D$ = +29.2° under identical experimental conditions).

2-(2-Methylallyl)-3-oxo-L-gulonolactone 3,6-Hemiketal (6f) (Run 10, Table I). Product **6f** was prepared from carbonate **4f** by the same procedure as **6a** under the experimental conditions indicated in Table I. Product **6f**: mp 120–121 °C (chloroform) (lit.[4b] mp 115–117 °C); IR (KBr) 3532, 3329 (br), 1771 cm^{-1}; ^1H NMR δ 1.68 (s, 3 H), 2.56 (s, 2 H), 4.00–4.56 (m, 4 H + 1 H (OH)), 4.84 (br s, 2 H); ^{13}C NMR δ 23.9, 42.7, 75.3, 76.1, 79.7, 87.1, 108.4, 115.7, 141.5, 174.9; MS m/e (relative intensity) 230 (M, <1), 129 (21), 119 (20), 102 (41), 85 (100), 84 (22), 83 (41), 71 (23), 56 (31), 55 (71); $[\alpha]_D$ = +6° (c 2.0) (lit.[4b] $[\alpha]_D$ = +7.1 under identical experimental conditions).

2-(3-Methyl-2-buten-1-yl)-3-oxo-L-gulonolactone 3,6-Hemiketal (6g) (Run 12, Table I). Product **6g** was prepared from carbonate **4g** by the same procedure as **6a** under the experimental conditions indicated in Table I. Product **6g**: oil; IR (film) 3448 (br), 1789 cm^{-1}; ^1H NMR δ 1.6 (s, 3 H), 1.7 (s, 3 H), 2.5 (d, J = 7.5 Hz, 2 H), 4.0–4.5 (m, 4 H), 5.1–5.4 (m, 1 H); ^{13}C NMR δ 17.9, 26.0, 34.1, 75.4, 75.6, 78.9, 87.4, 108.2, 117.6, 136.3, 175.9; MS m/e (relative intensity) 244 (M, 1), 176 (39), 85 (42), 69 (100); $[\alpha]_D$ = +29° (c 2.0). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.85; H, 6.79.

2-(3-Penten-2-yl)-3-oxo-L-gulonolactone 3,6-Hemiketal (6h) (Run 14, Table I). Compound **6h** was prepared from carbonate **4h** by the same procedure as **6a** under the experimental conditions indicated in Table I. Product **6h** (mixture of diastereoisomers): oil which crystallized spontaneously upon standing, mp 118–119 °C; IR (film) 3420 (br), 1799, 1782, 972 cm^{-1}; ^1H NMR (methanol-d_4) δ 1.2 (d, J = 6 Hz, 3 H), 1.8 (d, J = 5 Hz, 3 H), 2.5–3.0 (br, 1 H (OH)), 3.6–4.6 (m, 4 H), 5.2–6.0 (m, 2 H); ^{13}C NMR δ 14.7, 18.1, 41.1, 75.1, 75.2, 75.6, 80.6, 87.3, 87.7, 108.5, 108.8, 128.8, 128.9, 131.2, 131.7, 174.8, 175.9; MS m/e (relative intensity) 176 (11), 85 (22), 69 (100), 43 (33), 41 (55). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.72; H, 6.98.

2-(2-Cyclohexen-1-yl)-3-oxo-L-gulonolactone 3,6-Hemiketal (6i) (Run 17, Table I). Compound **6i** was prepared from carbonate **4i** by the same procedure as **6a** under the experimental conditions indicated in Table I. Compound **6i** (mixture of diastereoisomers): mp 137–139 °C (dichloromethane); IR (KBr) 3504, 3360 (br), 1790 cm^{-1}; ^1H NMR (methanol-d_4) δ 1.1–2.3 (m, 6 H), 2.6–3.0 (m, 1 H), 3.9–5.1 (m, 4 H + 2 H (OH)), 5.7–6.2 (m, 2 H); ^{13}C NMR δ 22.0, 22.6, 23.3, 24.5, 25.3, 25.5, 41.1, 74.7, 75.1, 75.5, 75.7, 80.2, 80.3, 87.5, 88.1, 108.2, 125.6, 131.4, 131.7, 174.0, 174.5; MS m/e (relative intensity) 256 (M, <1), 176 (20), 81 (100), 79 (20). Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.34; H, 6.24.

2-(3-Phenylpropyl)-3-oxo-L-gulonolactone 3,6-Hemiketal (9a). A strongly stirred mixture of **6a** (0.200 g, 0.68 mmol), 10% Pd/C (0.020 g), and ethanol (50 mL) was treated with hydrogen

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at atmospheric pressure and room temperature for 20 min. The catalyst was filtered off through Celite, and the filtrate was evaporated to afford 0.193 g (96%) of compound **9a**: mp 141–142 °C (chloroform); IR (KBr) 3523 (br), 3342 (br), 1772 cm^{-1}; ^1H NMR δ 1.7–2.0 (m, 4 H), 2.5–2.7 (m, 2 H), 4.0–4.5 (m, 4 H), 4.8 (s, 1 H (OH)), 5.7 (s, 1 H (OH)), 7.2 (s, 5 H); ^{13}C NMR δ 25.4, 34.4, 36.5, 75.4, 75.9, 78.6, 87.3, 108.5, 126.4, 129.0, 129.1, 142.9, 175.7; MS *m/e* (relative intensity) 294 (M, 3), 129 (27), 119 (33), 117 (21), 104 (66), 91 (100); $[\alpha]_D$ = +36° (*c* 1.0). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 60.85; H, 6.21.

2-Butyl-3-oxo-L-gulonolactone 3,6-Hemiketal (9b). Compound **9b** was prepared in 91% yield from **6b** by the same procedure as **9a**. Compound **9b**: mp 89–90 °C (spontaneous crystallization); IR (KBr) 3423 (br), 1785 cm^{-1}; ^1H NMR δ 0.8–1.9 (m, 9 H), 3.9–4.7 (m, 4 H); ^{13}C NMR δ 14.1, 23.5, 25.5, 34.5, 75.4, 75.9, 78.7, 87.3, 108.5, 175.8; MS *m/e* (relative intensity) 232 (M, <1), 119 (53), 102 (40), 101 (21), 85 (100), 57 (34); $[\alpha]_D$ = +29° (*c* 1.5). Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.88; H, 7.08.

2-Cyclohexyl-3-oxo-L-gulonolactone 3,6-Hemiketal (9i). Compound **9i** was prepared in 96% yield from **6i** by the same procedure as **9a**. Compound **9i**: mp 148–149 °C (chloroform); IR (KBr) 3504, 3382 (br), 1788 cm^{-1}; ^1H NMR δ 1.0–2.0 (m, 11 H), 4.0–4.6 (m, 4 H + 1 H (OH)), 4.8 (br s, 1 H (OH)); ^{13}C NMR δ 26.6, 26.9, 27.6, 42.9, 75.0, 75.9, 80.6, 87.9, 108.6, 175.4; MS *m/e* (relative intensity) 258 (M, <0.5), 119 (25), 102 (28), 85 (68), 81 (100), 71 (25), 55 (82), 41 (62); $[\alpha]_D$ = +40° (*c* 1.0). Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.65; H, 7.08.

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Registry No. 1, 50-81-7; **3a**, 21040-45-9; **3c**, 6737-11-7; **3d**, 2442-10-6; **3g**, 1191-16-8; **3h**, 10500-12-6; **3i**, 14447-34-8; **4a**, 106625-69-8; **4b**, 121725-70-0; **4c**, 106625-68-7; **4e**, 1469-70-1; **4f**, 70122-91-7; **4g**, 116504-03-1; **4h**, 121740-92-9; **4i**, 119825-50-2; **6a**, 127855-06-5; **6b**, 117383-61-6; **6d**, 127855-07-6; **6e**, 117383-59-2; **6f**, 117383-60-5; **6g**, 127855-08-7; **6h** (isomer 1), 127855-09-8; **6h** (isomer 2), 127855-10-1; **6i** (isomer 1), 127855-11-2; **6i** (isomer 2), 127855-12-3; **7**, 15042-01-0; **9a**, 127855-13-4; **9b**, 127820-02-4; **9i**, 127820-03-5; **10a**, 127880-39-1; 3,3-dicinnamylpentane-2,4-dione, 106536-22-5.

Cerium(IV)-Mediated Halogenation at C-5 of Uracil Derivatives

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Treatment of protected uracil nucleosides **1** or **2** with elemental iodine or metal halogenides and ceric ammonium nitrate (CAN) at 80 °C gave the corresponding protected 5-halouracil nucleosides **3a–f** in excellent yields. Treatment of the resulting crude **3a–f** with 0.1 M NaOMe/MeOH at ambient temperature gave the corresponding 5-halouridines **4a–f** in high overall yields from **1** or **2**. Further, 5-halouracils **9a–f** were prepared in good yields by treatment of 1,3-dimethyluracil (**7**) or uracil (**8**) with elemental iodine, metal halogenides, or hydrochloric acid and CAN. Halouridines **4a–e** also were obtained in good yields by treatment of unprotected uracil nucleosides **5** or **6** with halogen sources as above and CAN.

Halogen-substituted nucleosides and related compounds have been shown to exhibit interesting chemotherapeutic, biochemical, and biophysical properties.[1] A number of 5-substituted uracil derivatives, especially 2′-deoxyuridines, have been investigated extensively for the experimental and clinical treatment of neoplastic and viral diseases.[2] In addition, they have been utilized as intermediates for a variety of synthetic transformations of related compounds of biological interest.[3-5] Recently, it has been shown that 5-iodouracil derivatives undergo high-yield coupling with terminal alkynes to give 5-alkynyluracil nucleosides with antiviral activity,[6] and such products can be transformed into fluorescent 5-substituted compounds for automated DNA sequencing.[7] Therefore, new methods for the convenient synthesis of 5-halouracil derivatives are of current interest in nucleoside chemistry.

Halogenated pyrimidine and purine nucleosides have been prepared by direct reaction with halogens. Iodination of pyrimidine bases takes place under vigorous conditions. For example, Prusoff and co-workers described the first 5-iodination of uridine and 2′-deoxyuridine using an iodine/nitric acid system.[8] Dale et al. have effected iodination of ill-defined 5-mercuriuridine derivative mixtures in aqueous alcohol.[9] *N*-Iodosuccinimide has been utilized for iodination of pyrimidine nucleosides.[10] Iodine monochloride has been found to give high yields of 5-iodo-

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