nitrobenzamide did not undergo a similar reaction and attributed this fact to their low acidity. Benzamide has a pK_a in DMSO of 23.35.[18]

In summary, the present work demonstrates that in DMSO the pK_a's of compounds 1-17 vary widely and span an interval of 10 powers of 10. Furthermore, it provides a rationale of the previously made observations.[7] Obviously, steric factors are not the major reasons for the low reactivity of compounds 1, 2, and 4 under the conditions studied.

Experimental Section

The syntheses of all imidodicarbonates and tosylcarbamates studied in this paper have previously been described in papers originating from the Uppsala laboratory or elsewhere (1,[1,2] 2 and 3,[8] 4,[3,8] 5,[8] 6,[8,20] 7 and 8,[7] 9-11,[8] 12,[7] 13,[8] 14,[7] 15,[6,7] and 16 and 17.[7]

The pK_a determinations were performed at 25 °C using potentiometric titration of the NH acids with a solution of Bu_4NOH in a mixture of benzene and *i*-PrOH (4:1). The detailed description of the technique was given previously.[21-24]

The calibration of the glass electrode (filled with mercury)[25] was done using as reference points the pK_a values of benzoic acid (11.0[18]) and 2,6-dinitrophenol (4.9[18]). Within the experimental errors the slope of the calibration plot in coordinates E (mV) vs p_aH did not differ from the theoretical value as predicted by the Nernst equation. The procedure used for calculation of the pK_a values was also described previously.[21-23] For each acid the titration was repeated 3-4 times and the corresponding arithmetic mean is given as the pK_a value in Table I (the reliability interval was ±0.1-0.2 pK_a unit).

The purification of DMSO, benzene, i-PrOH and preparation of the solution of Bu_4NOH were described earlier.[22,23]

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Registry No. 1, 51779-32-9; 2, 120542-14-5; 3, 120542-17-8; 4, 120542-13-4; 5, 120542-10-1; 6, 69032-13-9; 7, 136667-56-6; 8, 136667-57-7; 9, 120542-15-6; 10, 120542-11-2; 11, 136667-58-8; 12, 136667-59-9; 13, 120542-16-7; 14, 136667-60-2; 15, 18303-04-3; 16, 18303-10-1; 17, 136667-61-3; $(CF_3CO)_2NH$, 407-24-9; phthalimide, 85-41-6; (*S*)-ethyl lactate, 687-47-8.

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Total Synthesis of (-)-Citreoviridin and (+)-Citreoviral

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The investigation of the toxicity of "yellowed rice" produced by a variety of *Penicillium* fungi led Hirata and co-workers to the isolation and subsequent structural elucidation of a potent mycotoxin, citreoviridin (1).[2] Recently a series of structurally related α-pyrone mycotoxins (2-4) have been isolated,[3] most of which are known to be potent inhibitors of mitochondrial ATPase and oxidative phosphorylation.[4] As shown in Scheme I, we envisioned that an ideal synthetic approach to these metabolites would utilize a common advanced intermediate such as **5**. The latter, for example, has been converted into (+)-verrucosidin (3).[5] Herein we describe a successful bifurcation of **5a** into (-)-citreoviridin (1) and (+)-citreoviral (2).[6,7]

Treatment of the epoxy ester **5a**, $[\alpha]^{28}_D = -44°$ (*c* 0.9, $CHCl_3$),[5a] with aqueous $HClO_4$ in THF gave stereoselectively diol **6** in 54% yield (based on 50% conversion) (Scheme II).[8] The stereochemistry of the diol **6** was secured by its conversion to citreoviral (2),[6,9] which direct comparison of ^1H NMR spectra showed to be identical with the natural material.[10] Similarly, a bis-silylated derivative **7** of citreoviral (2) was also prepared in 80% overall yield.

The pyrone phosphonate **10** was readily prepared by the iterative Wittig olefination of (triphenylphosphoranylidene)acetaldehyde with the known and readily available pyrone aldehyde 8,[11] followed by standard transformations of the resulting dienal **9**. The final union of the two segments was then achieved in 75% yield by treatment of the phosphonate **10** with *n*-BuLi, followed by addition of aldehyde **7** at -78 °C. Use of other bases gave uniformly inferior results. Finally, the silyl group was

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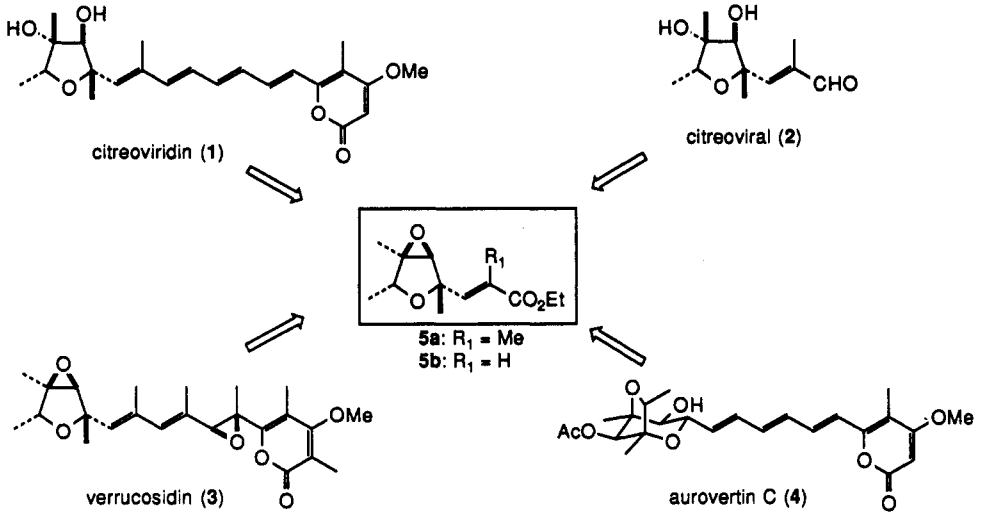
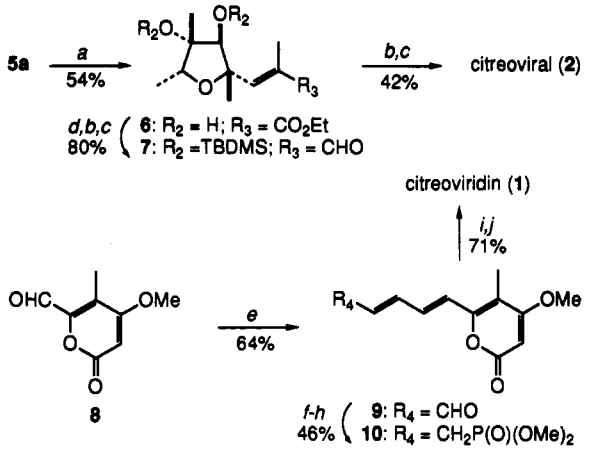
Scheme I

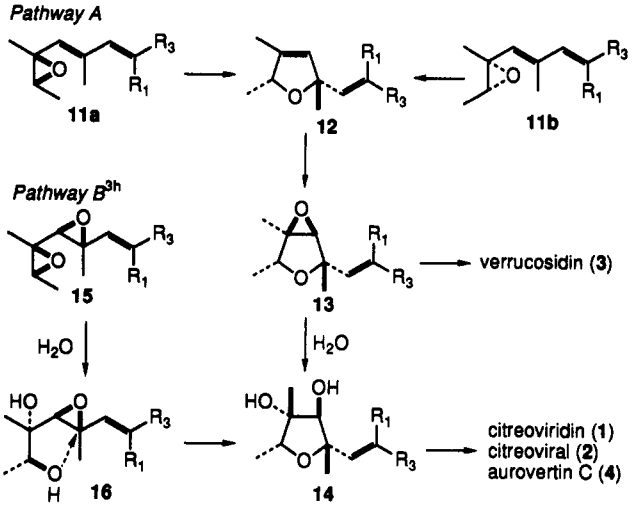


Scheme II[a]



[a] (a) Aqueous $HClO_4$, THF, 3 h; (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) MnO_2, ether, 1 h; (d) 4 equiv of TBDMSOTf, 4 equiv of 2,6-lutidine, CH_2Cl_2, 8 h; (e) 1.2 equiv of $Ph_3P{=}CHCHO$, PhH, 2 h; 1.1 equiv of $Ph_3P{=}CHCHO$, $CHCl_3$, 48 h; (f) $NaBH_4$, MeOH, 0 °C, 1 h; (g) CBr_4, Ph_3P, CH_2Cl_2, −23 °C, 2 h; (h) $(MeO)_3P$, toluene, reflux, 40 h; (i) *n*-BuLi, THF, −78 °C; addition of **7**; (j) *n*-Bu_4NF, THF, 0 °C, 20 min.

Scheme III. Biosynthetic Hypotheses



deprotected (95%) with *n*-Bu_4NF in THF to afford (−)-citreoviridin (**1**). The synthetic substance was found to be identical in every aspect with the natural material.[12]

It is interesting to speculate that the biosynthesis of these mycotoxins could involve the common intermediacy of epoxide **13** and subsequent ring opening to diol **14**. The latter process mirrors closely the pivotal transformation of our common synthetic intermediate **5a** to diol **6**. As shown in Scheme III, epoxide **13** in turn might be derived biosynthetically from the rearrangement of epoxide **11** and subsequent monooxygenase epoxidation of the resulting dihydrofuran **12** (pathway A).[13] Our biosynthetic postulate, which accounts for the biogenesis of verrucosidin (**3**) as well, is somewhat different from that of Vleggaar, which involves bisepoxide **15** (→ **16** → **14**; pathway B).[3h]

In summary, we have developed an efficient synthesis of citreoviridin (**1**) and citreoviral (**2**), as well as verrucosidin (**3**), from the common synthetic intermediate **5a**. Further synthetic and biosynthetic studies of these α-pyrone mycotoxins will be reported in due course.

(12) Kindly furnished by Professor Burchard Franck (W. Germany).
(13) Similarly, the epoxide ring opening of **5b**, followed by epoxidation and subsequent ring opening, would lead to aurovertin C (**4**) as well.

Experimental Section

(+)-(2*S*,3*S*,4*S*,5*R*)-2-(2-Carbethoxy-1(*E*)-propenyl)-3,4-dihydroxy-2,4,5-trimethyltetrahydrofuran (6). To a solution of epoxy ester **5a** (60 mg, 0.25 mmol) in THF (10 mL) and water (3 mL) was added 70% perchloric acid (3.3 mL). The reaction mixture was stirred at room temperature for 3 h and neutralized with saturated sodium bicarbonate solution. The mixture was saturated with sodium chloride and extracted with ethyl acetate (4 × 10 mL). The extracts were washed with brine, dried ($MgSO_4$), and concentrated. The resulting oil was purified with chromatography on silica gel to give 30 mg of the recovered starting material (**6**) and 16 mg (54% based on the consumed SM) of diol ester **6**: $[\alpha]^{25}_D$ = +23° (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 3450, 1694, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (d, 3 H, *J* = 6.4 Hz), 1.20 (s, 3 H), 1.27 (t, 3 H, *J* = 7.2 Hz), 1.34 (s, 3 H), 1.95 (d, 3 H, *J* = 1.2 Hz), 3.80 (q, 1 H, *J* = 6.4 Hz), 3.94 (s, 1 H), 4.16 (m, 2 H), 6.94 (br s, 1 H); ^{13}C NMR (100 MHz) δ 12.2, 13.5, 14.2, 17.6, 20.2, 60.9, 77.7, 80.5, 84.0, 85.2, 127.3, 147.2, 168.5.

Citreoviral (2). To a stirred solution of ester **6** (17 mg, 0.07 mmol) in anhydrous CH_2Cl_2 (5 mL) at −78 °C was added dropwise 0.26 mL of a 1.5 M solution of diisobutylaluminum hydride in hexane. After 6 h at −78 °C, the reaction mixture was treated sequentially with a few drops of methanol and water, allowed to warm to room temperature, diluted with 10 mL of ethyl acetate, and dried ($MgSO_4$). Removal of the solvents and a short-column silica gel chromatography gave the allylic alcohol (10 mg, 83%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, 3 H, *J* = 6.3 Hz), 1.18 (s, 3 H), 1.32 (s, 3 H), 1.78 (d, 3 H, *J* = 1.1 Hz), 3.79 (q, 1 H, *J* = 6.3 Hz), 3.90 (s, 1 H), 3.93 (s, 2 H), 5.72 (q, 1 H, *J* = 1.1 Hz).

To a stirred solution of the resulting allylic alcohol (30 mg, 0.07 mmol) in anhydrous ether (2 mL) at 0 °C was added in one portion

20 mg (0.23 mmol) of manganese dioxide. After 1 h at room temperature, the reaction mixture was filtered through Celite and washed sequentially with ether (10 mL) and ethyl acetate (10 mL). Concentration of the filtrate in vacuo yielded a pale yellow oil, which was purified by preparative TLC on silica gel. Elution with 1:1 hexane/ethyl acetate afforded 15 mg of citreoviral **2** as a pale yellow oil: $[\alpha]^{25}_D$ = +23.3° (*c* 0.12, $CHCl_3$) [lit.[6a] $[\alpha]^{25}_D$ = +21.1° (*c* 2.5, $CHCl_3$); lit.[6b] $[\alpha]^{25}_D$ = +18.7° (*c* 0.65, $CHCl_3$)]; IR ($CHCl_3$) 3423, 1679, 1635 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, 3 H, *J* = 6.4 Hz), 1.25 (s, 3 H), 1.41 (s, 3 H), 1.87 (d, 1 H, *J* = 1.2 Hz), 3.88 (q, 1 H, *J* = 6.2 Hz), 3.94 (d, 1 H, *J* = 3.8 Hz), 6.68 (br s, 1 H), 9.36 (s, 1 H); ^{13}C NMR (100 MHz) δ 195.4, 159.4, 137.4, 85.1, 84.3, 80.5, 77.9, 20.1, 17.9, 12.2, 10.1.

(+)-(2*S*,3*S*,4*S*,5*R*)-3,4-Bis(*tert*-butyldimethylsilyl)-2-(2-formyl-1(*E*)-propenyl)-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran (7). To a stirred solution of **6** (41 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C were added sequentially 2,6-lutidine (0.07 mL, 0.64 mmol) and (*tert*-butyldimethylsilyl)trifluoromethanesulfonate (0.15 mL, 0.64 mmol). The reaction mixture was stirred for an additional 0.5 h at 0 °C and then at room temperature for 8 h. The mixture was diluted with ether (10 mL) and washed with saturated aqueous sodium bicarbonate (1 × 3 mL) and water (3 × 5 mL). The aqueous layer was extracted with ether (1 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification with silica gel chromatography gave 70 mg (95%) of the bis-silylated diol ester as a colorless oil: HRMS ($M^+ - C_4H_9$) 429.2493 calcd for $C_{21}H_{41}O_5Si_2$, found 429.2491.

To a stirred solution of the resulting ester (37 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (10 mL) at −78 °C was added dropwise 0.24 mL of 1.0 M solution of diisobutylaluminum hydride in hexane. After 1 h at −78 °C, the reaction mixture was treated sequentially with a few drops of methanol and water, allowed to warm to room temperature, diluted with 10 mL of ethyl acetate, and dried ($MgSO_4$). Removal of the solvents gave the allylic alcohol (30 mg, 90%), which was used for the next step without further purification.

To a stirred solution of the allylic alcohol (30 mg, 0.07 mmol) in anhydrous ether (2 mL) at room temperature was added in one portion 60 mg (0.69 mmol) of manganese dioxide. After 1 h at room temperature, the reaction mixture was filtered through Celite and washed sequentially with ether (10 mL) and ethyl acetate (10 mL). Concentration of the filtrate in vacuo yielded 30 mg of white, crystalline **7**: mp 68–70 °C; $[\alpha]^{25}_D$ = +11.6° (*c* 0.28, $CHCl_3$); IR ($CHCl_3$) 1693, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.02 (s, 3 H), 0.05 (s, 3 H), 0.11 (s, 3 H), 0.12 (s, 3 H), 0.80 (s, 9 H), 0.92 (s, 9 H), 1.13 (d, 3 H, *J* = 6.2 Hz), 1.20 (s, 3 H), 1.30 (s, 3 H), 1.84 (d, 3 H, *J* = 0.9 Hz), 3.79 (q, 1 H, *J* = 6.2 Hz), 3.87 (s, 1 H), 6.57 (br s, 1 H), 9.31 (s, 1 H); ^{13}C NMR (100 MHz) δ −3.9, −3.7, −1.7 (2 C's), 10.1, 13.3, 18.2, 18.5, 19.8, 21.8, 26.0 (6 C's), 80.2, 84.3, 85.4, 86.0, 135.8, 161.4, 195.9.

6-[4-Formylbuta-1(*E*),3(*E*)-dienyl]-4-methoxy-5-methyl-2*H*-pyran-2-one (9). To a stirred solution of pyrone **8** (114 mg, 0.576 mmol) in anhydrous benzene (10 mL) at room temperature was added (triphenylphosphoranylidene)acetaldehyde (210 mg, 0.69 mmol). After 2 h at room temperature, an additional 193 mg (0.64 mmol) of (triphenylphosphoranylidene)acetaldehyde, followed by 15 mL of chloroform, was added. The reaction mixture was then stirred at room temperature for 48 h. Evaporation of the solvents and purification by silica gel chromatography with hexane/ethyl acetate (1:1) as eluant gave 96 mg (64%) of the diene aldehyde **9** as a yellow solid: mp 187–190 °C; IR ($CHCl_3$) 1703, 1689, 1680, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (s, 3 H), 3.83 (s, 3 H), 5.56 (s, 1 H), 6.33 (dd, 1 H, *J* = 7.8 and 14.6 Hz), 6.80 (d, 1 H, *J* = 14.1 Hz), 7.15–7.33 (m, 2 H), 9.62 (d, 1 H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.2, 56.4, 90.7, 112.0, 127.7, 132.0, 134.0, 149.0, 152.3, 162.6, 169.9, 193.0.

Dimethyl [5-(4-Methoxy-5-methyl-2-oxo-2*H*-pyranyl)-2(*E*),4(*E*)-pentadienyl]phosphonate (10). To a stirred solution of $NaBH_4$ (180 mg, 4.75 mmol) in 10 mL of methanol at 0 °C was added a solution of pyrone **9** (210 mg, 0.95 mmol) in methanol (5 mL). After 1 h at 0 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. Methanol was removed under reduced pressure. The residue was then extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by silica gel chromatography with hexane/ethyl acetate (1:2) as eluant gave 170 mg (80%) of the alcohol as a yellow solid: mp 133–136 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (s, 3 H), 3.81 (s, 3 H), 4.24 (d, 2 H, *J* = 5.1 Hz), 5.47 (s, 1 H), 5.98 (dt, 1 H, *J* = 5.2 and 15.2 Hz), 6.30–6.46 (m, 2 H), 7.15 (dd, 1 H, *J* = 11.0 and 15.1 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.8, 56.1, 62.8, 88.8, 108.1, 119.4, 129.3, 135.1, 138.1, 154.1, 163.7, 170.6.

To a stirred solution of the resulting alcohol (132 mg, 0.60 mmol) in anhydrous CH_2Cl_2 (20 mL) at −23 °C were added carbon tetrabromide (395 mg, 1.20 mmol) and triphenylphosphine (312 mg, 1.20 mmol). After 2 h at −23 °C, the reaction mixture was allowed to warm to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography using hexane/ethyl acetate (1:2) as eluant to afford 112 mg (66%) of the corresponding bromide as a yellow solid: mp 115–117 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (s, 3 H), 3.84 (s, 3 H), 4.04 (d, 2 H, *J* = 7.8 Hz), 5.49 (s, 1 H), 6.12 (dt, 1 H, *J* = 7.8 and 15.2 Hz), 6.41 (d, 1 H, *J* = 15.1 Hz), 6.43 (dd, 1 H, *J* = 10.9 and 15.2 Hz), 7.10 (dd, 1 H, *J* = 10.9 and 15.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.8, 32.9, 56.1, 89.1, 108.9, 121.1, 133.5 (2 C), 133.7, 153.5, 163.2, 170.3.

To a stirred solution of the resulting bromide (112 mg, 0.40 mmol) in anhydrous toluene (3 mL) at room temperature was added trimethyl phosphite (1 mL, 6 mmol). After 40 h at reflux, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography using hexane/ethyl acetate (1:3) followed by ethyl acetate as eluant to afford 107 mg (87%) of phosphonate **10** as a yellow oil: IR 1708, 1664, 1630, 1251; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.91 (s, 3 H), 2.70 (dd, 2 H, *J* = 7.7, 23.2 Hz), 3.71 (d, 6 H, *J* = 10.9 Hz), 3.78 (s, 3 H), 5.45 (s, 1 H), 5.87 (m, 1 H), 6.36–6.26 (m, 2 H), 7.08 (dd, 1 H, *J* = 11.4 and 14.9 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 8.8, 30.2 (d, *J* = 139.7 Hz), 52.8 (d, 2 C, *J* = 6.7 Hz), 56.1, 88.9, 108.9, 119.4 (d, *J* = 4.5 Hz), 127.5 (d, *J* = 13.1 Hz), 134.1 (d, *J* = 14.8 Hz), 134.7 (d, *J* = 5.1 Hz), 153.9, 163.4, 170.5; HRMS (M^+ + H) 315.0998 calcd for $C_{14}H_{20}O_6P$, found 315.1001.

Bis(*tert*-butyldimethylsilyl)-Protected Citreoviridin. To a stirred solution of phosphonate **10** (45 mg, 0.14 mmol) in anhydrous THF (0.5 mL) was added at −78 °C 0.14 mL of 1.5 M *n*-BuLi in hexane. The mixture was stirred at −78 °C for an additional 0.5 h. Room illumination was removed except for a red "safe" light, and the reaction vessel was wrapped completely in aluminum foil. To the resulting deep-purple solution was added dropwise a solution of aldehyde **7** (28 mg, 0.063 mmol) in anhydrous THF (1 mL). The reaction mixture was allowed to slowly warm to room temperature, stirred for 8 h, and treated with saturated aqueous NH_4Cl solution. The mixture was diluted with EtOAc (10 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The organic extracts were combined, washed with brine, and dried ($MgSO_4$). Evaporation of the solvent and purification by silica gel chromatography with hexane/ethyl acetate (2:1) as eluant gave 27 mg (75%) of bissilyl-protected citreoviridin as a yellow oil: $[\alpha]^{25}_D$ = −41.1° (*c* 0.9, $CHCl_3$); IR 1712, 1628, 1538; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.12 (s, 6 H), 0.83 (s, 9 H), 0.93 (s, 9 H), 1.14 (d, 3 H, *J* = 6.2 Hz), 1.20 (s, 3 H), 1.27 (s, 3 H), 1.94 (s, 3 H), 1.96 (s, 3 H), 3.74 (q, 1 H, *J* = 6.2 Hz), 3.82 (s, 1 H), 3.91 (s, 3 H), 5.46 (s, 1 H), 5.75 (s, 1 H), 6.18–6.40 (m, 4 H), 6.52 (dd, 1 H, *J* = 14.8 and 9.8 Hz), 7.22 (dd, 1 H, *J* = 14.8 and 11.1 Hz); ^{13}C NMR (100 MHz) δ −4.0, −3.8, −1.7, −1.6, 8.8, 13.3, 13.6, 18.1, 18.5, 20.4, 22.8, 26.0 (6 C), 56.1, 77.2, 79.9, 84.1, 84.8, 87.3, 88.5, 107.4, 118.1, 126.1, 130.4, 132.2, 136.2, 139.1, 142.4, 142.8, 154.7, 163.7, 170.6; HRMS (M^+ + H) 631.3850 calcd for $C_{35}H_{59}O_6Si_2$, found 631.3854.

Citreoviridin (1). Room illumination was removed except for a red "safe" light, and the reaction vessel was wrapped completely in aluminum foil. To a stirred solution of bis(*tert*-butyldimethylsilyl)-protected citreoviridin (20 mg, 0.035 mmol) in THF (2 mL) was added at 0 °C 0.1 mL of a 1.0 M tetra-*n*-butylammonium fluoride solution in THF. After 20 min at 0 °C, the reaction mixture was diluted with 20 mL of ethyl acetate, washed with a saturated aqueous sodium chloride solution (2 × 5 mL), and dried ($MgSO_4$). Evaporation of the solvent and silica gel chromatography of the residue using hexane/ethyl acetate (1:2) as eluent gave 13.3 mg (95%) of **1** as a yellow solid: mp 103 °C]lit. mp 105–107 °C;[2c] 107–111 °C;[2b] 108–110 °C[2d]]; $[\alpha]^{25}_D$ = −87.8°

(c 0.18, $CHCl_3$) {lit.[2b] $[\alpha]^{25}_D = -68.9°$; lit.[2c] $[\alpha]^{19}_D = -107.8°$ (c 1, $CHCl_3$); lit.[6b] $[\alpha]^{23}_D = -77.0°$ (c 0.1, $CHCl_3$)}; IR ($CHCl_3$) 3420, 1686, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (d, 3 H, J = 6.3 Hz), 1.19 (s, 3 H), 1.35 (s, 3 H), 1.90 (s, 3 H), 1.94 (s, 3 H), 3.79 (q, 1 H, J = 6.3 Hz), 3.80 (s, 3 H), 3.96 (s, 1 H), 5.46 (s, 1 H), 5.87 (s, 1 H), 6.38–6.20 (m, 4 H), 6.49 (dd, 1 H, J = 9.1 and 14.8 Hz), 7.18 (dd, 1 H, J = 11.0 and 15.0 Hz); ^{13}C NMR (50 MHz) δ 8.8, 12.3, 13.4, 17.2, 21.3, 56.1, 77.0, 80.8, 84.7, 85.8, 88.6, 107.8, 118.6, 127.2, 131.1, 134.3, 136.1, 138.6, 140.7, 141.1, 154.6, 163.8, 170.7; HRMS (M^+ + H) 403.2121 calcd for $C_{23}H_{31}O_6$, found 403.2103.

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Supplementary Material Available: $^1H/^{13}C$ NMR spectra for key intermediates (12 pages). Ordering information is given on any current masthead page.

Asymmetric Reduction of Chlorinated 4-Oxopentanoates with Bakers' Yeast. Synthesis of Optically Active γ-Butyrolactones and Useful Chiral Building Blocks

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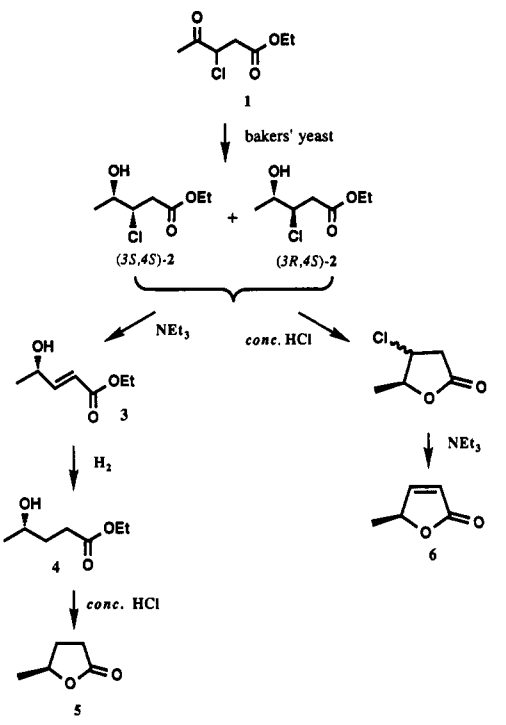
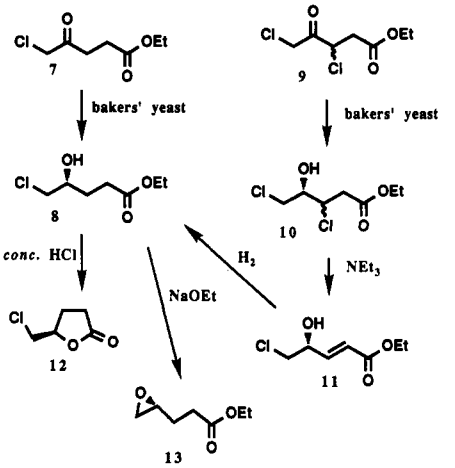
The asymmetric reduction of carbonyl groups by bakers' yeast (Saccharomyces) is a well-known reaction that is widely applied for the preparation of chiral building blocks.[1] It has been published by many groups that α-halo ketones are easily reduced with bakers' yeast to give chiral halo hydrins.[2] Most of these studies are concerned with the reductions of β-keto esters. Recently we reported the syntheses of chiral epoxides, key intermediates of natural products, by the reduction of 3-chloro-2-oxoalkanoates with bakers' yeast.[3,4] Here we describe the results of asymmetric reductions of chlorinated 4-oxopentanoates with bakers' yeast, which gives versatile chiral building blocks. Ethyl 3-chloro-4-oxopentanoate (1) can be easily obtained by the chlorination of ethyl 4-oxopentanoate.[5] Treatment of 1 with bakers' yeast in the presence of glucose for 3 days gave a mixture of ethyl (3*S*,4*S*)-3-chloro-4-hydroxypentanoate (2) and (3*R*,4*S*)-2 with a ratio of 1:1 in 75% yield. Although the isomers could not be separated by any chromatographic procedures, their existence was recognized by ^{13}C NMR analysis. Dehydrochlorination of the mixture of (3*S*,4*S*)-2 and (3*R*,4*S*)-2 with triethylamine gave ethyl (*S*)-(+)-4-hydroxy-2-pentenoate (3) in 71% yield, and the subsequent hydrogenation afforded ethyl (*S*)-4-hydroxypentanoate (4) in 76% yield. Hydrolysis of 4 with concd HCl gave (*S*)-5-methyltetrahydro-2-furanone (5).[6]

Scheme I



Scheme II



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