impurities. (*E*) and (*Z*)-4-bromo-4-octene were prepared by literature methods.[13,14] Diethyl ether, THF, and benzene were distilled from sodium/benzophenone. 4-Octyne, CH_2Cl_2, hexane, and TMEDA were distilled from CaH_2.

Competition Experiments. A solution of the test substrate (3 equiv, 1.5 M), a standard (3 equiv, 1.5 M), an internal standard (mesitylene, 1 equiv), AIBN (0.12 equiv), tributyltin hydride (1 equiv, added last), and dry, degassed benzene was placed under an N_2, and the mixture was heated at 80 °C for 4 h. An aliquot was removed and diluted, and the yield of reduced products was measured by GC. Experiments conducted at ambient temperature were initiated by irradiation with an Ace-Hanovia 450-W high-pressure quartz mercury vapor lamp.

Calculation of Rate Constants. Absolute rate constants were calculated using an equation provided by Beckwith:[2b]

$$k_X = \frac{(k_Y) \log ([R^1X]/[R^1X]_o)}{\log ([R^2Y]/[R^2Y]_o)}$$

where k_X is the rate constant for atom (group) abstraction of the test substrate, k_Y is the rate constant for atom (group) abstraction of the standard, $[R^1X]$ and $[R^1X]_o$ are the final and initial concentrations of the test substrate, and $[R^2Y]$ and $[R^2Y]_o$ are the final and initial concentrations of the standard. The final concentrations were determined by subtracting the yields of reduced products from the starting concentrations.

Benzyl Chloroacetate. A solution of dry CH_2Cl_2 (55 mL), benzyl alcohol (4.5 mL, 43 mmol), and pyridine (3.5 mL, 43 mmol) was cooled to 0 °C with stirring, and chloroacetyl chloride (3.4 mL, 43 mmol) was slowly added dropwise. The reaction was then stirred at 25 °C for 15 min and then quenched in cold water. The two phases were separated, and the aqueous layer extracted twice with CH_2Cl_2. The organic extracts were combined and washed with water and then with brine. The CH_2Cl_2 solutions were dried over $MgSO_4$, filtered, and concentrated. The product was purified by vacuum distillation (bp 79–81 °C at 0.65 mmHg) to give 6.88 g (0.037 mol, 86%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 5,20 (s, 2 H), 4.08 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 134.93, 128.66, 128.46, 67.86, 40.89; IR (neat film) 1736, 1498, 1455, 1377, 1168, 749, 698 cm^{-1}; MS *m/e* 184, 108, 91, 77, 65, 51; HRMS for $C_9H_9ClO_2$ calcd 184.0291, found 184.0291.

Malonic Esters 12 and 13. NaH (12 mmol, 1.2 equiv) was suspended in dry THF at 0 °C, diethyl methylmalonate (10 mmol, 1.0 equiv) was added dropwise, and the reaction was stirred at 25 °C for 1 h. An alkylating agent (11 mmol, 1.1 equiv, 1,2-dibromo-2-propene for **12**, or 1,3-dibromo-1-propene for **13**) was added, and the reaction stirred at 25 °C for 7 h. The reaction was quenched in ice water and extracted several times with ether. Ether extracts were washed with water and then with brine. The ether solution was dried over $MgSO_4$, filtered, and concentrated. Products were purified by flash chromatography on silica in 8:1 hexane/ethyl acetate.

Diethyl (2-Bromo-1-prop-2-enyl)methylmalonate (12). The yield was 1.74 g (70%): ^1H NMR ($CDCl_3$) δ 5.6 (s, 1 H), 5.3 (t, J = 2 Hz, 1 H), 4.16 (q, J = 7 Hz, 4 H), 3.1 (d, J = 3 Hz, 2 H), 1.44 (s, 3 H), 1.21 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.3, 127.5, 121.7, 61.6, 53.1, 45.9, 19.3, 13.9; IR (neat film) 2940, 1731, 1625, 1448, 1266, 1297, 1206, 1023, 898, 860 cm^{-1}; MS *m/e* 247, 231, 219, 213, 201, 185, 175, 157, 139, 111, 67; HRMS for $C_{11}H_{17}O_4Br$ calcd 291.9970, found 246.9970 (M - OEt).

Diethyl (1-Bromo-3-prop-1-enyl)methylmalonate (13). The yield was 2.92 g (99%, mixture ~2/3 of cis and trans): ^1H NMR ($CDCl_3$) δ 6.25 (dd, J = 6, 1.5 Hz, 1 H, *Z*), *E*, 6.06 (m, 2 H, *E*; 1 H, *Z*), 4.14 (q, J = 7 Hz, 8 H), 2.72 (dd, J = 1 Hz, J = 1.6 Hz, 2 H, *E*), 2.51 (t, J = 3 Hz, 2 H, *Z*), 1.36 (s, 3 H, *E*), 1.33 (s, 3 H, *Z*), 1.19 (t, J = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.6 (*E*), 171.4 (*Z*), 132.4 (*Z*), 129.4 (*E*), 111.1 (*E*), 108.6 (*Z*), 61.5 (*E* and *Z*), 53.2 (*Z*), 52.9 (*E*), 39.6 (*Z*), 35.8 (*E*), 19.9 (*E* and *Z*), 14.0 (*E* and *Z*); IR (neat film) 1737, 1622, 1449, 1366, 1334, 1296, 1023, 953, 860, 710, 664 cm^{-1}; MS *m/e* 292, 249, 213, 185, 139, 111, 69; HRMS for $C_{11}H_{17}O_4Br$ calcd 292.0310, found 292.0310.

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4-*tert*-Butyl-1-bromocyclohex-1-ene (14).[15] 4-*tert*-Butylcyclohexanone tosylhydrazone[16] (9.67 g, 30 mmol) was added to a three-neck flask and placed under N_2 atmosphere. Dry TMEDA (190 mL) was added via cannula, and the resulting suspension was cooled to −45 °C with vigorous stirring. A 1.6 M solution of *n*-butyllithium in hexanes (75 mL, 120 mmol) was added dropwise via an addition funnel, and the reaction was stirred at −45 °C for 30 min and then at 25 °C for 3 h. The reaction was cooled to 0 °C, and 1,2-dibromoethane (11 mL, 128 mmol) was added dropwise. The reaction was stirred at 25 °C for 1.5 h, quenched in 10% $NaHSO_4$(aq), and extracted several times with pentane. The pentane extracts were washed with 5% $NaHSO_4$(aq), water, saturated $CuSO_4$ (2×), and brine. The pentane solution was dried over $MgSO_4$, treated with decolorizing carbon, filtered through a pad of neutral alumina, and concentrated. The crude product was purified by vacuum distillation (bp 41–42 °C at 0.7 mmHg) to give 1.35 g (6.2 mmol, 21%) of a colorless oil: ^1H NMR ($CDCl_3$) δ 5.99 (t, J = 3 Hz, 1 H), 2.44 (q, J = 2 Hz, 2 H), 1.83 (dd, J = 3 Hz, 2 H), 1.31 (m, 2 H), 1.23 (m, 1 H), 0.84 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 128.9, 121.9, 42.9, 36.5, 32.2, 29.1, 27.2, 26.0; IR (neat film) 2901, 2842, 1655, 1478, 1434, 1394, 1046, 976, 906, 705 cm^{-1}; MS *m/e* 216, 201, 160, 137, 81, 69, 57; HRMS for $C_{10}H_{17}Br$ calcd 216.0514, found 216.0514.

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Registry No. 1, 3972-65-4; 2, 696-62-8; 3, 104-92-7; 4, 2398-37-0; 5, 578-57-4; 6, 99-90-1; 7, 2142-63-4; 8, 2142-69-0; 9, 623-00-7; 10, 6952-59-6; 11, 2042-37-7; 12, 137256-13-4; (*Z*)-13, 137256-14-5; (*E*)-13, 137256-15-6; 14, 23525-05-5; 15, 24291-80-3; 16, 24291-81-4; Bu_3SnH, 688-73-3; dimethyl methylmalonate, 609-08-5; 1,3-dibromo-1-propene, 627-15-6; 1,2-dibromo-2-propene, 513-31-5; 4-*tert*-butylcyclohexanone tosylhydrazone, 41780-53-4; benzyl chloroacetate, 140-18-1; 1-bromooctane, 111-83-1.

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Acidity of Imidodicarbonates and Tosylcarbamates in Dimethyl Sulfoxide. Correlation with Yields in the Mitsunobu Reaction

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Unsubstituted imidodicarbonates $R_1OCO-NH-COOR_2$, such as **1–13**, are useful phthalimide substitutes[1-3] in Gabriel[4] and Mitsunobu[5] reactions, and a tosylcarbamate **15** has also recently been applied to the latter context.[6] In connection with the synthesis of protected chiral alanine derivatives directly from lactate esters using the Mitsunobu reaction,[7] we noticed that some imidodicarbonates,[8] related to amino-protecting groups used in peptide synthesis,[9] reacted poorly, whereas others, probably more acidic ones, and, particularly, a few tosylcarbamates gave the expected products in much higher yields. To the best of our knowledge, no relevant acidity measurements of imidodicarbonates and tosylcarbamates have been reported in the literature so far. Therefore, the present investigation was undertaken with the goal of determining whether any correlation exists between the pK_a values of these NH acids and the yields[7] obtained in the Mitsunobu reactions.

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Table I. Equilibrium Acidities of Imidodicarbonates and Tosylcarbamates in Dimethyl Sulfoxide

entry	acid	pK_a	Mitsunobu yields (%)
control	Ac_2NH	17.9 (17.9[18])	nd[a]
1	*t*-BuOC(O)NHC(O)O-*t*-Bu (Boc_2NH)	16.9	<5
control	$PhSO_2NH_2$	16.0 (16.1[18])	nd
2	1-Adamantyl-OC(O)NHC(O)O-Bzl (AdocNHZ)	15.6	13
3	9-(Fluorenemethyl)-OC(O)NHC(O)O-Bzl (FmocNHZ)	15.4	0[7]
control	Succinimide	14.7 (14.6[18])	nd
4	*t*-BuOC(O)NHC(O)O-Bzl (BocNHZ)	14.4	16
5	4-$CH_3OC_6H_4CH_2OC(O)NHC(O)$-O-Bzl [Z(OMe)NHZ]	14.3	30
6	Bzl-OC(O)NHC(O)O-Bzl (Z_2NH)	14.2	42
7	4-$ClC_6H_4CH_2OC(O)NHC(O)O$-Bzl	14.0	45
8	2-$ClC_6H_4CH_2OC(O)NHC(O)O$-Bzl	13.8	55
9	CH_2=$CHCH_2OC(O)NHC(O)O$-Bzl (AlocNHZ)	13.8	31
	phthalimide	13.4	
10	4-$NO_2C_6H_4CH_2OC(O)NHC(O)O$-Bzl [Z($NO_2$)NHZ]	13.3	66
11	$CCl_3C(Me)_2OC(O)NHC(O)O$-Bzl	13.3	73
12	4-$NC_5H_4CH_2OC(O)NHC(O)O$-Bzl (PocNHZ)	13.2	50
13	$CCl_3CH_2OC(O)NHC(O)O$-Bzl (TrocNHZ)	12.7	83
14	Bzl-SC(O)NHC(O)O-Bzl	12.5	90
ref	AcOH	12.3[18]	
standard	PhCOOH	11.0	nd
15	Tos-NHC(O)O-*t*-Bu (TosNHBoc)	8.5	93
16	Tos-NHC(O)O-Bzl (TosNHZ)	7.5	91
17	Tos-NHC(O)$OCH_2C_6H_4$-4-NO_2 [TosNHZ(NO_2)]	7.0	93
ref	saccharin	4.0[18]	
	$(CF_3CO)_2NH$	2.3	nd

[a] nd, not determined.

Results and Discussion

The results of the determinations of the pK_a values of 14 imidodicarbonates and three tosylcarbamates together with a few controls and reference substances in dimethyl sulfoxide are given in Table I. Also, the yields obtained with these substances in Mitsunobu reactions with ethyl (*S*)-lactate in THF in the presence of triphenylphosphine and diethyl azodicarboxylate as given in ref 7 are listed for comparison. Among the 13 imidodicarbonates 1–13, not unexpectedly the only one (1) containing two *aliphatic* groups (*tert*-butyl) is the least acidic, 2.5 log orders less so than the benzyl *tert*-butyl derivative 4 which has roughly the same acidity as the succinimide standard. It should be noted that derivatives of 1 are extremely labile to acid and that one of their Boc groups can be removed selectively.[10] The pK_a values for the various benzyl imidodicarbonates 2–13 are distributed around that (14.2) of the bisbenzyl derivative 6 and cover the range 14.2 ± 1.5, with AdocNHZ (2) being least acidic. FmocNHZ (3) is only slightly more acidic than 2. The pK_a of 5 is essentially identical to that of 4. When used as an N-protecting group, Z(OMe)[11] is normally cleaved off using the same conditions as for Boc. Compounds 7 and 8 have somewhat lower pK_a values than 6 and also contain slightly more acid-stable protecting groups[12] than this compound. The values for 9,[13] 10,[14] 11,[15] 12,[16] and 13[17] decrease further down to a minimum of 12.7 for the Troc derivative 13. Compounds 9–13 all contain an amino-protecting group of high acid stability.

It should also be noted that the substitution of a sulfur atom for an oxygen one in 6, resulting in 14, lowers the pK_a from 14.2 to 12.5. Compound 14 is thus slightly more acidic than 13, and its pK_a approaches that of acetic acid (12.3[18]). Benzoic acid in DMSO has a pK_a of 11.0 (see the Experimental Section).

The tosylcarbamates (15–17) are all considerably more acidic than the above imidodicarbonates. Whereas 6 is 0.2 units more acidic than 4, this difference between 16 and 15 is larger, i.e., 1.0 unit. On the other hand, the difference is somewhat smaller between 17 and 16 (0.5 units) than between 10 and 6 (0.9 units). Compound 17 has approximately the same acidity in DMSO as benzenesulfinic acid (pK_a = 7.1[18]), whereas all three sulfonimides (15–17) studied by us are somewhat weaker NH acids than saccharin (pK_a = 4.0[18]) or $CF_3CH_2SO_2NHPh$ (pK_a = 5.7[18]).

Inspection of Table I demonstrates that the acidities of the NH acids studied in the present work and the yields in the Mitsunobu reactions roughly run parallel with each other. Actually, only two compounds, 9 and 12, deviate from the general trend, and in both cases the yields are significantly lower than those expected from the pK_a values. We therefore tentatively conclude that, in order to obtain a high yield with imidodicarbonates and lactate esters in the Mitsunobu reaction, the pK_a of the former in DMSO should be below 13.5. As seen in Table I, this is also in line with extensive previous successful work using phthalimide.[5a] On the other hand, when this value exceeds 14.5, the yields become rather insignificant. Wada and Mitsunobu[19] noticed long ago that benzamide and 4-

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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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