10b-Chloro-4b,5,6,6a,10b,10c-hexahydrobenzo[3,4]cyclobuta[1,2-*a*]biphenylene (10) and 4b,5,6,6a-Tetrahydrobenzo[3,4]cyclobuta[1,2-*a*]biphenylene (9). To a solution of 5 (2 mM) and pyridine (5 mL) was added $POCl_3$ (6 mM) at 0 °C. The mixture was maintained at ca. 0 °C for 2 h. Upon completion of the reaction (monitored by TLC), the mixture was poured onto ice and was extracted with Et_2O. The extract was washed with 10% aqueous HCl and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by centrifugal TLC on silica gel to give 10: ^1H NMR (CCl_4) δ 0.92–1.42 (m, 4 H, CH_2), 3.03–3.27 (m, 2 H, 2 x C*H*CH_2), 3.92 (d (J = 6 Hz), 1 H, C*H*CHCl), 6.85–7.47 (m, 8 H, Ar H); UV (MeOH) λ (log ε) 262.5 (3.38), 268.5 (3.41), 274.9 (3.38); mp (petroleum ether–ether) 161 °C. Anal. Calcd for $C_{18}H_{15}Cl$: C, 81.04; H, 5.66; Cl, 13.29. Found: C, 81.20; H, 5.65; Cl, 13.08; 9 was obtained once as explained in the text: ^1H NMR (CCl_4) δ 1.50–2.47 (m, 4 H, CH_2), 3.86–4.28 (m, 2 H, benzylic H), 6.67–7.52 (m, 8 H, Ar H).

4b,5,6,6a,10b,10c-Hexahydro-10b-phenylbenzo[3,4]cyclobuta[1,2-*a*]biphenylene (11). To a stirred solution of 5 (Z = H) (2 mM) and benzene (10 mL) were added 3 drops concentrated H_2SO_4. The mixture was refluxed for 3 h. Upon completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, washed with water, and extracted with Et_2O. The extract was dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel to give 11: ^1H NMR (CCl_4) δ 1.06–1.37 (m, 4 H, CH_2), 3.10–3.48 (m, 2 H, C*H*CH_2), 3.97 (d (J = 6 Hz), 1 H, PhC*H*CPh), 6.65–6.90 (m, 1 H, Ar H), 6.90–7.25 (m, 12 H, Ar H); UV (MeOH) λ (log ε) 264.5 (3.24), 269.9 (3.30), 276.2 (3.25); mp (petroleum ether–ether) 180 °C. Anal. Calcd for $C_{24}H_{20}$: C, 93.46; H, 6.53. Found: C, 92.95; H, 6.51.

1-(*p*-Tolulenesulfonyl)-3,4:7,8-dibenzotricyclo[3.3.2.0^{2,6}]decane (12) was prepared in the same manner as 11, but with p-TsOH (1.5 equiv) as the acid instead of H_2SO_4. 12: ^1H, NMR (CCl_4) δ 0.85–1.37 (m, 4 H, CH_2), 2.30 (s, 3 H, CH_3), 2.03–2.40 (m, 2 H, C*H*CH_2), 4.30 (d (J = 6 Hz), 1 H, PhC*H*CHPh), 6.57–7.80 (m, 12 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 21.40 (CH_3), 22.35, 26.27 (CH_2); 43.56, 49.39, 52.56 (C benzylic); 109.29 ($COS(O)_2$); 122.61, 122.84, 123.01, 126.59, 126.62, 127.28, 127.46, 129.07 (Ar CH); 135.49, 138.99, 139.92, 142.72, 143.44, 144.06 (Ar C); UV (MeOH) λ (log ε) 263 (sh); 271.2 (3.12); 277.4 (3.07); mp (EtOAc–ether) 198 °C. X-ray diffraction data were also collected.

8-Hydroxy-3,4:6,7-dibenzobicyclo[6.2.0]decanone (13) was prepared by a method previously described.[4a] 13: IR (KBr) 3500–3100 cm^{-1} (OH), 1650 (C=O); ^1H NMR ($CDCl_3$) δ 1.95–2.40 (m, 4 H, 2 × CH_2), 2.50–2.90 (m, 1 H, OH, exchangable with D_2O), 3.00–3.70 (m, 2 H, benzylic H), 7.10–7.80 (m, 8 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 35.64, 36.43, 41.90 (3 × CH_2); 59.98 (CH); 85.21 (COH); 123.74, 124.45, 127.87, 128.08, 128.81, 129.67, 131.29, 132.37 (Ar CH); 137.23, 139.82, 141.76, 144.98 (Ar C); 206.41 (C=O); UV (MeOH) λ (log ε) 248 (3.31), 271.5 (3.49), 286 (3.27); mp (petroleum ether–ether) 184 °C. Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.49; H, 6.15.

10b,10c-Dihydrobenzo[3,4]cyclobuta[1,2-*a*]biphenylene (14) was prepared by the same method as 10. 14: IR (KBr) 1620 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 3.85 (s, 2 H, benzylic H), 6.35 (s, 2 H, 2 × CH=C), 7.10–7.40 (m, 8 H, Ar H); ^{13}C NMR ($CDCl_3$ δ 50.19 (CH); 113,71 (CH=); 119.56, 122.94, 128.14, 128.54 (Ar CH); 140.82, 144.36, 148.16 (Ar C, PhC=CH); UV (THF) λ (log ε) 214.2 (3.86), 247.2 (3.84), 298.8 (3.30); 355 (3.79); mp (petroleum ether–ether) 142 °C. Anal. Calcd for $C_{18}H_{12}$: C, 94.74; H, 5.26. Found: C, 94.43; H, 5.40.

4b,6a-Bis(acetyloxy)-4b,6a,10b,10c-tetrahydrobenzo[3,4]cyclobuta[1,2-*a*]biphenylene (15) was prepared by a method previously described.[19] 15: IR (KBr) 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.90 (s, 6 H, 2 × CH_3), 4.20 (s, 2 H, benzylic H), 6.35 (s, 2 H, 2 × CH=C), 7.10–7.45 (m, 8 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 21.43 (CH_3); 50.75 (CH); 79.57 (C–O); 122.62, 123.68, 126.61, 128.28, 130.12 (CH=, Ar CH); 144.52, 146.30 (Ar C); 170.23 (C=O); mp (petroleum ether–ether) 220 °C. X-ray diffraction data were also collected.

Compound 16 was prepared in five steps from cycloheptanone. The first transformations (two steps) gave an α-ethylene ketal.[20] Allylic bromination of the ketal[21] and hydrolysis of the resulting bromide gave an allylic alcohol.[22] Compound 16 was obtained by oxidation of the alcohol.[23]

2,3-Benzobicyclo[4.3.0]nonanone-7-spiro-2′-[1,3]dioxolane (17) and 2,3:10,11-dibenzotricyclo[6.3.0.0^{1,9}]undecan-1-ol-7-spiro-2′-[1,3]dioxolane (18 and 19) were prepared by the reaction of the enolate 16 with benzyne. 17: IR (KBr) 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.65–1.85 (m, 1 H, CH), 2.00–2.50 (m, 3 H, CH_2, CH), 2.60–2.85 (m, 2 H, CH_2), 3.00–3.15 (m, 1 H, CH), 3.80–4.10 (m, 5 H, $O(CH_2)_2$, benzylic H), 7.20–7.60 (m, 3 H, Ar H), 8,00 (d, 1 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 25.90, 36.29, 38.91 (CH_2); 42.43, 50.31 (2 × CH); 64.97, 65.31 (OCO, OCH_2CH_2O); 116.02, 125.67, 126.72, 127.68, 132.18 (Ar CH); 133.65, 146.11, 198.49 (Ar C); mp (pentane) 112 °C. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 74.18; H, 6.77. X-ray diffraction data were also collected. 18: IR (KBr) 3500–3300 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 1.60–2.50 (m, 2 × CH_2, 2 × CH), 3.00 (s, 1 H, OH, exchangable with D_2O), 3.80–4.30 (m, $O(CH_2)_2$, CH), 6.90–7.50 (m, 7 H, Ar H), 7.95 (d, 1 H, Ar H); ^{13}C NMR ($CDCl_3$) δ 26.46 (CH_2); 38.17 (CH_2); 39.38, 51.90, 55.20 (3 × CH); 64.42, 64.72 (OCH_2CH_2O); 79.36 (COH); 116.87 (OCO); 120.40, 124.86, 125.37, 126.59, 126.64, 126.98, 128.31, 129.21 (Ar CH); 139.91, 140.10, 142.31, 148.00 (Ar C); UV (MeOH) λ log (ε) 259.5 (2.96), 266.5 (3.09), 273.5 (3.06); mp (ether) 192 °C. Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.44; H, 6.34. X-ray diffraction data were also collected.

Supplementary Material Available: Experimental data for compounds 5, 8, and 19 and ORTEP diagrams of compounds 12, 15, 17, 18, and 19 (8 pages). Ordering information is given on any current masthead page.

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Solvent Effects on the Esterification of 2-Chloroethyl Compounds with Potassium Acetate

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Esters can be prepared by treating alkyl halides with metallic salts of carboxylic acids,[1-4] and the reaction proceeds smoothly in DMF[5] or DMSO.[5,6] The effects of dipolar aprotic solvents and hydrogen bonding on nucleophilic substitution reactions have been reported.[7,8] The reaction of benzyl chloride with sodium[9,10] or potassium acetate[11,12] is catalyzed by phase-transfer catalysts.

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Table I. Effect of Solvent Properties on Second-Order Rate Constant of Esterification[a]

solvent	dielectric constant,[b] D	dipole moment[b]	rate constant, M^{-1} s^{-1}	solubility of AcOK, g L^{-1}
$[(CH_3)_2N]_3PO$	30 (20)[c]	5.37 (25)[c]	15.6×10^{-3}	21.2
CH_3SOCH_3	48.9 (20)	4.3	18.6×10^{-3}	8.6
$HCON(CH_3)_2$	36.7 (25)	3.86 (25)	14.9×10^{-3}	1.3
N-methyl-2-pyrrolidone	32.0 (25)	4.09 (25)	66.4×10^{-4}	2.5
$CH_3CON(CH_3)_2$	37.8 (25)	3.72	10.9×10^{-3}	1.2
CH_3CONH_2	59 (83)	3.44 (30)	30.2×10^{-5}	32.5
$HCONHCH_3$	182 (25)	3.84	27.6×10^{-6}	209.0
$CH_3CONHCH_3$	191 (32)	4.39 (20.1)	48.0×10^{-6}	93.5
$HCON(C_2H_5)_2$			16.1×10^{-4}	2.0
ethylene carbonate	89.6 (40)	4.87 (25)	36.0×10^{-5}	2.8[d]
propylene carbonate	69.0 (23)		80.0×10^{-5}	0.7
o-$C_6H_4Cl_2$	6.83 (25)	2.27 (24)	41.0×10^{-4}	0.07
CH_3CN	37.5 (20)	3.44 (20)	0.0	0.07

[a] The numerical values in parentheses are temperatures. [b] Asahara, T. *Yozai Handbook*; Kodansha Scientific; Tokyo, 1976. [c] Shinoda, K. *Yobai*; Maruzen: Tokyo, 1972. [d] Measured at 80 °C.

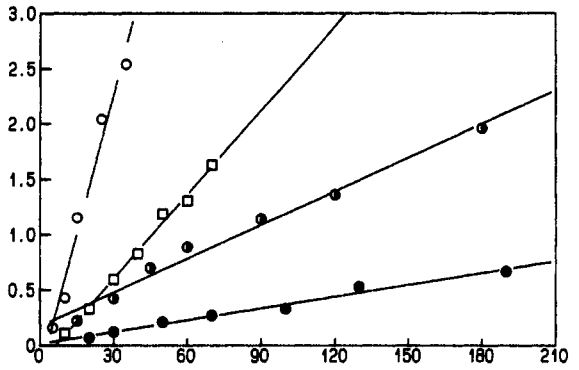

Figure 1. First-order kinetic plots for reaction of DCP and AcOK in various solvents: horizontal axis, reaction time (min); vertical axis, ln $[DCP]_0/[DCP]$; ○, in DMSO; ◑, in *N*-methyl-2-pyrrolidone; ●, in *N*-methylformamide; □, with TEAC in CH_3CN.

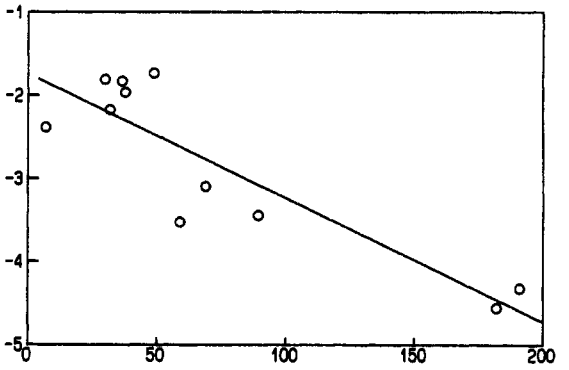

Figure 2. Effect of solvent on reaction rate constant for reaction of DCP and AcOK at 80 °C: horizontal axis, dielectric constant (Debye); vertical axis, log *k*.

The esterification of poly[(chloromethyl)styrene] with salts of carboxylic acids using tetraalkylammonium salts has been reported.[13-16] We wished to study the effects of solvent and molecular structure of the substrate on the rate of esterification of RCH_2CH_2Cl with AcOK.

All reactions were heterogeneous with AcOK partially dissolved. The reaction rate was independent of stirring speed in the range 200–900 rpm, and a stirring speed of 400 rpm was used in the determination of kinetics.

The esterification of 1,3-dichloropropane (DCP) proceeded smoothly in *N*-methylformamide, *N*-methyl-2-pyrrolidone, and DMSO. Figure 1 shows plots of ln $([DCP_0]/[DCP])$ against time; $[DCP]_0$ and [DCP] are the concentrations of DCP at t_0 and t (min). The rate of esterification is first order with respect to [DCP].

Since the solubility of AcOK varies widely in different solvents (Table I), the rate of esterification should depend on the concentration of AcOK. The observed rate constants obtained from the slopes of the straight lines in Figure 1 are a function of the solubility of AcOK in each solvent. If one divides these rate constants by the concentration of AcOK (calculated from its solubility), the specific second-order rate constants are obtained (Table I). The esterification can be described in terms of the following reactions:

Table II. Effect of TEAC on Solubility of AcOK in CH_3CN

temp, °C		solubility, g L^{-1}
25	$(C_2H_5)_4NCl$[a]	15.52
50	$(C_2H_5)_4NCl$[a]	16.26
70		0.07
70	$(C_2H_5)_4NCl$[a]	15.69

[a] Solution contained 3.33 g of TEAC in 100 mL of CH_3CN.

$$(AcOK)_{solid} \rightleftharpoons (AcOK)_{solution} \quad (1)$$

$$AcOK \rightleftharpoons AcO^- + K^+ \quad (2)$$

$$AcO^- + RCl \rightleftharpoons ROAc + Cl^- \quad (3)$$

$$Cl^- + K^+ \rightleftharpoons KCl \quad (4)$$

Reaction 1 defines the solubility of AcOK in a given solvent. Dissolved AcOK dissociates into ions and will be present as both ion pairs and dissociated ions. The dissociated ion AcO^- then reacts with the alkyl chloride to give the product. The equilibrium constants for solubility and for dissociation, as well as the specific second-order rate constant *k*, are functions of the nature of the solvent. Figure 2 is a plot of log *k* against the dielectric constants of solvents and shows a fairly good correlation with a slope of −0.15 (correlation coefficient 0.88). Those solvents that can hydrogen bond to AcO^-, such as some amides, will produce lower reaction rates than polar aprotic solvents that cannot hydrogen bond. Thus the negative slope indicates that a solvent of high dielectric constant reduces the nucleophilicity of AcO^- by solvation. The scatter in Figure 2 undoubtedly arises from the effects of different solvents on eqs 1–3.

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Table III. Second-Order Rate Constants for Esterification of RCH_2CH_2Cl with AcOK at 60 °C and Chemical Shifts for Methylene Protons of Products

R	σ^* [a]	k, M^{-1} s^{-1}		k/k_0		δ, ppm
		DMF	TEAC/CH_3CN	DMF	TEAC/CH_3CN	
CH_2CN	1.3	0.001 29		3.51		1.85–2.11 (m)
CH_2COOCH_3	1.11	0.001 24	0.001 10	3.36	1.86	1.77–2.02 (m)
CH_2Cl	1.05	0.001 26	0.000 81	3.42	1.37	1.92–2.00 (m)
CH_2COCH_3	0.60		0.000 63		1.07	1.70–1.96 (m)
C_6H_5	0.60	0.000 54	0.000 95	1.46	1.62	2.85 (t)
CH_2OCH_3	0.52					1.67–1.92 (m)
CH_2CH_2Cl	0.385	0.000 75	0.000 70	2.02	1.19	1.64–1.91 (m)
$CH_2C_6H_5$	0.215	0.000 59		1.60		1.72–2.00 (m)
CH_3	0.00	0.000 37	0.000 59	1.00	1.00	1.44–1.79 (m)
CH_2CH_3	−0.1	0.000 36	0.000 47	0.98	0.80	1.20–1.69 (m)
$(CH_2)_2CH_3$	−0.115	0.000 36	0.000 63	0.98	1.07	1.47–1.72 (m)
$(CH_2)_3CH_3$	−0.13		0.000 48		0.82	1.46–1.71 (m)
$CH(CH_3)_2$	−0.19	0.000 18	0.000 34	0.50	0.57	1.48 (t)

[a] Newman, M. S. *Steric Effects in Organic Chemistry*; John Wiley & Sons: New York, NY, 1956; p 618.

The reaction of DCP and AcOK was rapid in aprotic polar solvents. It did not proceed in the less polar CH_3CN unless tetraethylammonium chloride (TEAC) was added as a catalyst. Accordingly, we selected DMF and CH_3CN for a detailed study of the esterification.

Starks[17] derived eq 5 from the kinetics of the reaction of 1-chlorooctane and sodium cyanate with a phase-transfer catalyst in aqueous solution. The rate of alkyl

$$\ln \frac{[RCl]}{[RCl]_0} = -k_1[Q]_0 t = -k't \quad (5)$$

halide consumption is first order in [RCl] and pseudo first order in quaternary salt concentration $[Q]_0$ in the organic phase. In a study of the catalytic effect of tertiary amines on the reaction of 1-bromobutane with AcOK, it was found that the catalytic species were the quaternary ammonium salts and that the catalytic effect depended on their reactivity.[18] The equilibrium of eq 6 was assumed, and the reaction rate was first order in [BuBr] (eq 7). In spite of the difference between water–organic solvent and solid–liquid systems, eq 5 is equivalent to eq 7.

$$(C_4H_9)_4N^+Br^- + CH_3CO_2K \rightleftharpoons (C_4H_9)_4N^+\cdot CH_3CO_2^- + KBr \quad (6)$$

$$-\frac{d[BuBr]}{dt} = k_1[BuBr] \quad (7)$$

Table II shows that the solubility of AcOK in CH_3CN is increased by the addition of TEAC and is independent of temperature. It seems reasonable that AcO^- dissolves in CH_3CN as a complex.

$$(C_2H_5)_4N^+\cdot Cl^- + CH_3CO_2K \rightleftharpoons (C_2H_5)_4N^+\cdot CH_3CO_2^- + KCl \quad (8)$$

The plot of first-order kinetics for the esterification of DCP with AcOK in CH_3CN at 60 °C is included in Figure 1. First-order kinetics implies the constant activity of nucleophilic reagents.

With excess AcOK, [AcO^-] depended on [TEAC] and was maintained constant during the reaction. Accordingly, the rate constants obtained from kinetic plots could be used to make corrections to [AcO^-]. The solubility of AcOK in CH_3CN was 25.5 g/L under our conditions. The second-order rate constants are given in Table III. The rate constant for the dichloroalkane was corrected by halving its second-order rate constant. It is reasonable to think that the complex $(C_2H_5)_4N^+\cdot CH_3CO_2^-$ is partially dissociated into $(C_2H_5)_4N^+$ and $CH_3CO_2^-$ in CH_3CN.

Table IV. Activation Parameters for Esterification of RCH_2CH_2Cl with AcOK in DMF

R	E_a, kJ mol^{-1}	ΔH_{333}, kJ mol^{-1}	ΔS_{333}, J K^{-1} mol^{-1}
CH_2CN	92.9	90.1	14.0
CH_2COOCH_3	111	108	64.8
CH_2Cl	82.2	79.5	−19.8
C_6H_5	87.1	84.3	−11.3
CH_2CH_2Cl	76.5	73.7	−40.2
$CH_2C_6H_5$	101	98.1	27.6
CH_3	73.2	70.4	−54.1
CH_2CH_3	79.6	76.8	−36.1
$(CH_2)_2CH_3$	78.5	75.7	−40.3
$CH(CH_3)_2$	93.1	90.3	−1.6

The conductivities in CH_3CN solutions of TEAC and AcOK at various ratios were measured by Rosenthal's procedure.[19] The degree of dissociation was estimated by Kohlraush's square root law as 0.36 under our conditions. The ratio of free ion to ion pair was calculated as 4.9 for 1,4-dichlorobutane; thus the former was the principal promoter of esterification.[20,21] Table III shows the relative rate constant (k/k_0) with respect to the reaction with 1-chloropropane. The rate of esterification was increased by electron-withdrawing groups and decreased by electron-releasing groups.

Linear free energy relationships were found between the relative rate constants and Taft's substituent constants σ^*. The ρ^* values for the reactions in DMF and in CH_3CN were +0.47 and +0.26, respectively. The positive ρ^* values indicate that the esterification is a nucleophilic attack of AcO^- on RCH_2CH_2Cl.

The ^1H NMR spectrum of $RC^aH_2C^bH_2O_2CCH_3$ showed two methylene signals. The chemical shift of the methylene protons (a) on C^a is roughly linear with the electronegativity of R.

Energies, enthalpies, and entropies of activation were determined from the second-order rate constants (Table IV).

Experimental Section

Materials. AcOK and solvents were purchased from the Wako Pure Chemicals Co. 4-Chlorobutyronitrile was prepared from 1-bromo-3-chloropropane and potassium cyanide.[22] 1-Chloro-

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3-methoxypropane was synthesized from 1-bromo-3-chloropropane by modifying the method of Henne and Haeckl.[23] Methyl 3-chloropropionate was prepared from 3-chloropropionic acid.[24] All other reagents were purchased from Tokyo Kasei Kogyo Co. and were used without further purification.

Solubility of AcOK. Solvent containing excess AcOK was placed in a 200-mL round-bottomed flask immersed in a thermostat. The mixture was stirred for 2 h at 70 °C and allowed to stand for 1 h. The supernatant liquid was pipetted off through a wool filter, and the AcOK content was determined by titration with 1 N ethylene glycol/isopropyl alcohol/HCl with thymol blue as an indicator.[25]

Analyses. GC analyses were performed on a Shimadzu GC-8A instrument using 10% PEG 6000 on Celite (60–80 mesh) packed in a stainless steel column (6 m × 4 mm diameter). GC yields were determined with an internal standard and authentic mixtures. For analytical determinations, correction factors for weight ratio/area ratio data were determined with the same standards. ^{1}H NMR spectra were measured on a JEOL JNM-MH-100 spectrometer with tetramethylsilane as internal standard.

Reaction of DCP and AcOK in Various Solvents. A mixture of 50 mL of solvent, 0.14 mol of AcOK, and 0.04 mol of DCP was placed in a 200-mL separable flask fitted with a mechanical stirrer, reflux condenser, and sampling nozzle. The flask was immersed in a thermostat at 80 °C. At regular intervals, 5 mL of samples were taken and poured into water. The aqueous layer was extracted with 5 mL of carbon tetrachloride, and the product was analyzed by GC.

Reaction of RCH_2CH_2Cl and AcOK in DMF. A mixture of 0.1 mol of RCH_2CH_2Cl, 0.3 mol of AcOK, 0.01 mol of toluene (GC standard), and 100 mL of DMF was placed in 500-mL three-necked flask. Unless otherwise stated, the reaction temperature was maintained at 60 °C. Sampling and analyses were carried out as described above.

Reaction of RCH_2CH_2Cl and AcOK in the Presence of TEAC in CH_3CN. The esterification of 0.1 mol of RCH_2CH_2Cl with 0.1 mol of AcOK in the presence of 0.03 mol of TEAC in 100 mL of CH_3CN was performed at 60 °C.

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Synthesis of *cis*-4-(Phosphonooxy)-2-piperidinecarboxylic Acid, an *N*-Methyl-D-aspartate Antagonist

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Excitatory amino acids, aspartate and glutamate, are major neurotransmitters within the mammalian central nervous system.[1-3] One subtype of the glutamate receptor selective for the agonist *N*-methyl-D-aspartate (NMDA) has received a great deal of attention due to its possible involvement in a variety of neuropathologies.[4-6] Therefore, the search for competitive NMDA antagonists has been the focus of considerable investigation and has led to the discovery of *cis*-4-(phosphonomethyl)-2-piperidinecarboxylic acid (CGS 19755) as a potent and selective antagonist at the NMDA site.[7,8] With the exception of *O*-phosphoserine, a phosphate derivative of serine that interacts at the AP4 preferring glutamate site,[9,10] phosphates have not been explored as excitatory amino acid receptor ligands. In order to further investigate the pharmacology of this receptor, we sought to prepare the phosphate analogue *cis*-4-(phosphonooxy)-2-piperidinecarboxylic acid (1). To achieve this allosteric replacement of the methylene group of CGS 19755 for an oxygen atom, we required *cis*-4-hydroxy-2-piperidinecarboxylic acid (2) as our primary synthetic intermediate (Figure 1).

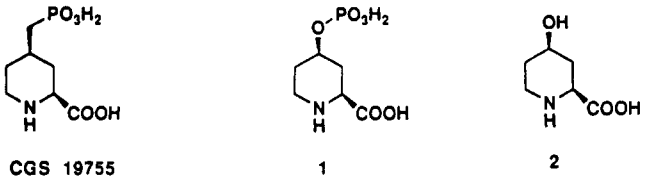
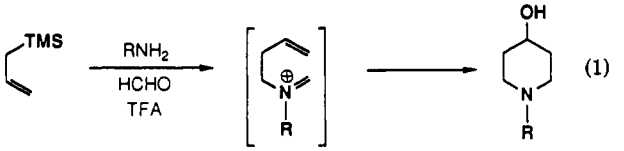


Figure 1.

Amino acid 2 or its derivatives have been synthesized previously by catalytic reduction of 2-carboxy-4-benzoxy- or 4-hydroxypyridines.[11,12] This route suffers from the drawback of erratic yields for the starting pyridine and from the high pressures (70 atm with Rh/Al_2O_3) required for final ring reduction. The preparation of 4-hydroxypipecolic acid has also been studied by Speckamp.[13] In this case, utilization of a Lewis acid catalyzed cyclization of a glycine cation equivalent at low temperature resulted in a moderate (45%) yield of protected 4-hydroxypipecolic acid and recovered starting material.

In 1986, Grieco and co-workers demonstrated that a variety of 4-hydroxypiperidines may be formed under aqueous conditions by an iminium ion cyclization of a homoallylic amine intermediate as shown in eq 1.[14] We



(1)

envisioned that 4-substituted pipecolic acids could be coveniently prepared under the aqueous conditions described by Grieco using an appropriately substituted homoallylamine and glyoxylic acid as precursors. We report here the facile synthesis of methyl *cis*-4-hydroxy-2-piperidinecarboxylate as an intermediate in route to the NMDA antagonist *cis*-4-(phosphonooxy)-2-piperidinecarboxylic acid (1).

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