H each, t, CH_3CH_2), 2.50, 2.58 (2 H each, q, CH_3CH_2 of pyrroline ring), 2.93, 3.06 (2 H each, t, $CH_2CH_2CO_2$), 3.27, 3.37 (3 H each, s Me), 3.59, 3.66 (3 H each, s, CO_2Me), 3.85 (4 H, q, Et), 3.94, 4.06 (2 H each, t, $CH_2CH_2CO_2$), 8.92, 9.00 (1 H each, s, methine α,β), 9.46, 9.67 (1 H each, s, methine γ, δ), −2.62 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 643 nm (46 900), 614 (4000), 590 (4200), 522 (2900), 494 (14 200), 490 (14 200), 392 (198 000).

13,17-Bis[2-(methoxycarbonyl)ethyl]-12,13-dihydroxy-12,18-dimethyl-2,3,7,8-tetraethylchlorin (4b): NMR δ 1.80 (12 H, m, Et), 2.14 (3 H, s, 12-Me), 2.50 (2 H, t, 13-$CH_2CH_2CO_2$), 3.15, 3.32 (2 H each, t, $CH_2CH_2CO_2$), 3.37 (3 H, s, Me), 3.51, 3.66 (3 H each, s, CO_2Me), 3.85 (8 H, m, Et), 4.08 (2 H, t, 17-$CH_2CH_2CO_2$), 8.98, 9.04 (1 H each, s, methine α,β), 9.62, 9.69 (1 H each, s, methine γ, δ), −2.60 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 643 nm (44 000), 615 (3600), 590 (3900), 521 (2600), 494 (13 700), 490 (13 700), 392 (19 300).

13,17-Bis[2-(methoxycarbonyl)ethyl]-3,3,7,8,12,18-hexamethyl-2-oxochlorin (5a) and 13,17-Bis[2-(methoxycarbonyl)ethyl]-2,2,7,8,12,18-hexamethyl-3-oxochlorin (6a). Perchloric acid (70%, 1 mL) was added to a methylene chloride solution (60 mL) of **3a** (150 mg, 0.25 mmol). The mixture was allowed to stir at room temperature for $^1/_2$ h before being extracted with water (3×, 60 mL each). The CH_2Cl_2 layer contained the mixture of **5a** and **6a**, which were separated on preparative TLC plates (silica gel, CH_2Cl_2/1% MeOH), yielding 60 mg (42%) each of the oxochlorins. The structure assignment for the slower moving **5a** and the faster moving **6a** was achieved via NOE measurements.

5a: NMR δ 2.09 (6 H, s, Me), 3.12, 3.15 (2 H each, t, $CH_2CH_2CO_2$), 3.37, 3.43, 3.46, 3.49 (3 H each, s, Me), 3.57, 3.59 (3 H each, s, CO_2Me), 4.15, 4.30 (2 H each, t, $CH_2CH_2CO_2$), 9.02 (1 H, s, methine α), 9.70 (1 H, s, methine β), 9.75 (1 H, s, methine γ), 9.84 (1 H, s, methine δ), −3.06, −2.86 (1 H, each, br s, NH); mass spectrum, m/e 582.2838 (calcd for $C_{34}H_{38}N_4O_5$ 582.2844); mp 265–266 °C; UV–vis λ_{max} (ϵ_M) 642 nm (32 400), 585 (6000), 546 (12 000), 508 (9500), 490 (6200), 404 (169 000).

6a: NMR δ 2.00 (6 H, s, Me), 3.13, 3.18 (2 H each, t, $CH_2CH_2CO_2$), 3.39, 3.44, 3.46, 3.50 (3 H each, s, Me), 3.59 (6 H, s, CO_2Me), 4.16, 4.32 (2 H each, t, $CH_2CH_2CO_2$), 9.07 (1 H, s, methine β), 9.74 (1 H, s, methine α), 9.79 (1 H, s, methine γ), 9.80 (1 H, s, methine δ), −3.12 (2 H, br s, NH); mass spectrum, m/e 582 (M^+); mp 266–268 °C; UV–vis λ_{max} (ϵ_M) 642 nm (32 300), 585 (5500), 546 (11 300), 508 (8500), 490 (5600), 404 (151 000). Anal. Calcd: C, 70.07; H, 6.58; N, 9.62. Found: C, 70.18; H, 6.66; N, 9.57.

13,17-Bis[2-(methoxycarbonyl)ethyl]-12,18-dimethyl-3,3,7,8-tetraethyl-2-oxochlorin (5b) and 13,17-Bis[2-(methoxycarbonyl)ethyl]-12,18-dimethyl-2,2,7,8-tetraethyl-3-oxochlorin (6b). The dihydroxychlorin **3b** (50 mg, 0.076 mmol) in CH_2Cl_2 was treated with perchloric acid (70%, 1 mL), and the reaction was worked up in the same manner as described above to afford 19 mg of each (40%) of the isomeric oxochlorins.

5b (slower component on TLC): NMR δ 0.38 (6 H, t, Et), 1.86 (4 H, q, Et), 2.75 (4 H, q, Et), 3.20, 3.24 (3 H each, t, $CH_2CH_2CO_2$), 3.48, 3.59 (3 H each, s, Me), 3.65, 3.66 (3 H each, CO_2Me), 4.00, 4.06 (3 H each, q, Et), 4.25, 4.40 (2 H each, t, $CH_2CH_2CO_2$), 9.13 (1 H, s, methine α), 9.84 (1 H, s, methine β), 9.85 (1 H, s, methine δ), 9.95 (1 H, s, methine δ, −2.91, −2.78 (1 H each, br s, NH); UV–vis λ_{max} (ϵ_M) 642 nm (34 700), 586 (5900), 546 (11 800), 508 (9600), 490 (6300), 406 (173 000).

6b (first band on TLC): NMR δ 0.38 (6 H, t, Et), 1.85 (6 H, t, Et), 2.76 (4 H, q, Et), 3.21, 3.28 (3 H each, t, $CH_2CH_2CO_2$), 3.48, 3.58 (3 H, s, Me), 3.67, 3.68 (3 H each, s, CO_2Me), 4.06 (4 H, q, Et), 4.25, 4.41 (2 H each, t, $CH_2CH_2CO_2$), 9.13 (1 H, s, methine β), 9.84 (1 H, s, methine α), 9.88 (1 H, s, methine γ), 9.93 (1 H, s, methine δ), −2.90 (2 H, br s, NH); UV–vis λ_{max} (ϵ_M) 642 nm (35 000), 586 (5700), 546 (11 800), 508 (9000), 490 (6000), 406 (162 000).

13,17-Bis[2-(methoxycarbonyl)ethyl]-2,2,7,8,12,18-hexamethyl-3-methylenechlorin (7). The methyl ester groups of oxochlorin **6a** (100 mg, 0.18 mmol) were hydrolyzed in a mixture of equal volume of THF and 2 N aqueous KOH. The mixture was stirred for 12 h before the THF solvent was removed in a rotorvap. The remainder of the aqueous solution was acidifed with HCl, and the precipitated oxochlorin diacid was collected by filtration, washed with water, and dried.

To a suspension of Ph_3PCH_3Br (614 mg, 1.72 mmol) in dry THF (20 mL) was added an equivalent amount of *n*-butyllithium (1.6 M solution in hexane) under nitrogen. The resultant orange suspension was allowed to stir at room temperature for 30 min before being added to a solution of the oxochlorin diacid (95 mg, 0.172 mmol) in dry THF (25 mL) at 0 °C. The mixture was allowed to stir at room temperature for 12 h, after which time the reaction was quenched with water. The solvent was evaporated, and the residue was esterified in dry methanol (50 mL), saturated with HCl gas, and left overnight. The solvent was again evaporated, and the residue was taken in CH_2Cl_2, washed with water, and chromatographed on silica gel (CH_2Cl_2). The methylenechlorin **7** (68 mg, 71% yield), migrating in front of the unreacted **6a** (20 mg), was further purified by crystallization from CH_2Cl_2/hexane: NMR δ 2.03 (6 H, s, *gem*-Me), 3.17, 3.20 (2 H each, t, $CH_2CH_2CO_2$), 3.41 (6 H, s, Me), 3.45, 3.49 (3 H each, s, Me), 3.66, 3.67 (3 H each, s, CO_2Me), 4.19, 4.33 (2 H each, t, $CH_2CH_2CO_2$), 5.81, 6.78 (1 H each, s, $=CH_2$), 8.86, 9.38 (1 H each, methine α,β), 9.65, 9.71 (1 H each, s, methine γ, δ), −2.54 (2 H, br s, NH); mass spectrum, m/e 580.3049 (calcd for $C_{35}H_{40}N_4O_4$ 580.3052); UV–vis λ_{max} (ϵ_M) 656 nm (36 000), 600 (4400), 534 (13 000), 506 (9600), 498 (9600), 400 (136 000).

13,17-Bis[2-(methoxycarbonyl)ethyl]-2,2,3,7,8,12,18-heptamethylchlorin or 2,4,4-Trimethyldeuterochlorin Dimethyl Ester (8). The above chlorin **7** (10 mg) was dissolved in formic acid (88%, 8 mL), to which a small amount of Adams catalyst (PtO_2, 5 mg) was added. A gentle stream of hydrogen was passed into the mixture for 5 min. A distinct color change was observed. The hydrogenated product was obtained almost quantitatively by evaporating the formic acid and purified by passing through a short silica gel pad with CH_2Cl_2: NMR δ 1.83, 2.01 (3 H each, s, *gem*-Me), 1.98 (3 H, d, tertiary Me), 3.17, 3.20 (2 H each, t, $CH_2CH_2CO_2$), 3.41, 3.42, 3.47, 3.50 (3 H each, s, ring Me), 3.67 (6 H, s, CO_2Me), 4.20, 4.33 (2 H, t, $CH_2CH_2CO_2$), 4.55 (1 H, q, tertiary H), 8.81, 8.85 (1 H each, s, methine α,β), 9.68, 9.70 (1 H each, s, methine γ, δ), −2.42 (2 H, br s, NH); mass spectrum, m/e 582.3200 (calcd for $C_{35}H_{42}N_4O_4$ 582.3208); UV–vis λ_{max} (ϵ_M) 643 nm (36 900), 614 (3700), 589 (4200), 524 (4000), 497 (9900), 490 (9800), 392 (141 000).

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Registry No. **3a**, 98821-76-2; **3b**, 98821-78-4; **4a**, 98821-77-3; **4b**, 98821-79-5; **5a**, 98821-80-8; **5b**, 98821-81-9; **6a**, 98838-34-7; **6a** (diacid), 98821-83-1; **6b**, 98821-82-0; **7**, 98821-84-2; **7** (diacid), 98821-86-4; **8**, 98821-85-3; Ph_3PCH_3Br, 1779-49-3; 2,4-dimethyldeuteroporphyrin dimethyl ester, 78986-42-2; dimethyl 5,8-dimethyl-1,2,3,4-tetraethylporphine-6,7-dipropionate, 66145-61-7.

A New Convenient Method for Esterification Using the Ph_3P/CCl_4 System

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In connection with one of our ongoing projects, well-established esterification methods,[1-3] such as the reaction of metal salts of carboxylic acids with alkyl halides, were not successful due to competing side reactions. Other

(1) Hasam, E. *Tetrahedron* **1980**, *36*, 2409.
(2) Rao, C. G. *Org. Prep. Proced. Int.* **1980**, *12*, 225.
(3) Wagner, R. B.; Zook, H. D. "Synthetic Organic Chemistry"; Wiley: New York, 1953.

0022-3263/85/1950-4991$01.50/0

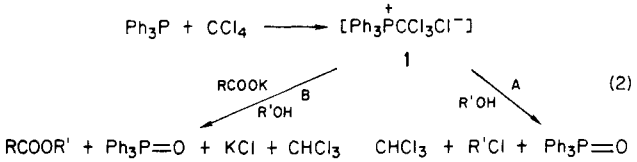
Table I. Preparation of Esters from the Ph_3/CCl_4 System

entry	ester	yield, %
	PhCOOR', R'	
1	CH_3CH_2	88
2	$PhCH_2$	65
3	CH_2=$CHCH_2$	65
4	$(CH_3)_3SiCH_2CH_2$	54
5		54
6		68
7		82
8	$EtOOC(CH_3)CH$	65
9	$NC(CH_3)CH$	60
10	$CH_3(CH_2)_5(CH_3)CH$	70
11	$CH_3CO_2CH_2Ph$	60
12	PhCH=CHCOOCH$_2$CH$_3$	75
13	4-pyridyl-$COOCH_3$	91
14	4-pyridyl-$COOCH_2C_6H_5$	64
15	p-NO_2-$C_6H_4COOCH(CH_3)_2$	85

methods that involve mixed anhydrides,[4] heterocyclic bases,[5] and thio esters[6] were considered to be unsuitable for our purpose. Because of mild conditions and reliability, the Mitsunobu reaction[7,8] (eq 1) was considered, but its use was precluded for large-scale synthesis due to the high cost of diethyl azodicarboxylates.

$$\mathrm{RCOOH + R'OH \xrightarrow[Ph_3P]{EtOOCN=NCOOEt} RCOOR' + Ph_3P{=}O + EtOOCNH{-}NHCOOEt} \quad (1)$$

Phosphonium salts 1,[9] in which a Cl^- ion acts as a nucleophile in an S_N2 fashion have been regarded as intermediates for the preparation of a variety of alkyl halides (eq 2A). Use of another nucleophile, which competes with



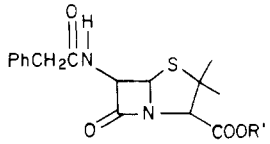
(2)

the halide ion already present in this reaction system, has not been common. The literature indicates that in nonpolar solvents, the few attempted competitive nucleophiles have not produced preparatively useful products; dipolar aprotic solvents, such as DMF or Me_2SO, have been found to be useful with cyanides and azides.[10]

In this context, recent reports[11,12] utilizing the Ph_3P/CCl_4 system for the preparation of cyclic ethers prompted us to report our results.

It was reasoned that if a nucleophile, e.g., a carboxylate anion along with an inorganic electrophile such as alkaline metal cation, was introduced into the reaction (eq 2B) in a suitable nonpolar solvent system, the halide ion might be removed out of the reaction site as insoluble metal halide. The carboxylate ion might then have the opportunity to displace triphenylphosphine oxide to give the corresponding ester. Indeed, the reaction of ethanol with potassium benzoate in the presence of carbon tetrachloride and triphenylphosphine at 55 °C produced ethylbenzoate in 88% yield.

Table II. Preparation of Pen-G Esters



entry	R'	yield, %
1	CH_2=$CHCH_2$	9
2	CH_2=$C(CH_3)CH_2$	15
3	CCl_2=$CClCH_2$	20
4	$ClCH_2CH_2$	10
5	$PhCH_2$	25

This method works well with aromatic, heteroaromatic, α,β-unsaturated and aliphatic acids, giving esters in good to excellent yields as indicated in Table I. The reaction conditions are very mild, and as a result, acid and base sensitive functionalities are unaffected. Furthermore, the reagents are inexpensive and are readily available, and more important, one set of reaction conditions is suitable for a variety of esters. It is noteworthy that there is no added solvent other than a small excess of carbon tetrachloride. Primary and secondary alcohols reacted equally well, but tertiary alcohols such as *tert*-butyl alcohol failed to give any product with potassium benzoate. Not unexpectedly, trichloroethanol did not produce an ester with potassium benzoate.

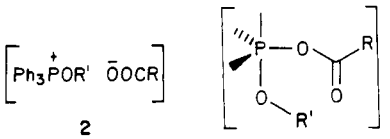
In spite of the success with a large number of functional groups, the preparation of Pen-G ester by this method resulted in very low yields (Table II). Actual yields, as judged by TLC, appears to be higher than isolated yields. The purification was difficult because of a major side product[13] which eluted along with desired ester under many chromatographic systems. Finally, intramolecular esterification[14] was achieved in low yields (<10%) with potassium 12-hydroxydodecanoate by heating at 50–60 °C for 48 h. Normally macrolide syntheses are conducted under high-dilution conditions.[15,16] The present lactone synthesis may be significant since this reaction was conducted in high concentration (4 equiv of carbon tetrachloride per mol of hydroxy acid).

For conversion of secondary alcohols to the corresponding chlorides by the Ph_3P/CCl_4 system, inversion at the secondary carbon atom is often predominant or total.[9] To investigate the stereochemical integrity of the present system *l*-(−)-ethyl lactate was esterified with potassium benzoate in a 65% yield (entry 8, Table I). The $[\alpha]^{22}_D$ (*c* 0.01 mg/mL, $CHCl_3$) of the corresponding ester was −2.65°. However, the same alcohol when esterified under standard conditions (pyridine, PhCOCl, CH_2Cl_2), gave an ester whose $[\alpha]^{22}_D$ (*c* 0.013 g/mL, $CHCl_3$) was +14.04°, thus indicating that the Ph_3P/CCl_4 system proceeded with inversion and racemization. We considered the possibility of racemization during or after completion of the reaction due to the acidic nature of the secondary proton of ethyl lactate, but ruled out this possibility since similar results, i.e., inversion and racemization, were observed with the

(4) Liu, H. J.; Chan, W. H.; Lee, S. P. *Tetrahedron Lett.* **1978**, 4461.
(5) Kim, S.; Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, 3365.
(6) Endo, T.; Ikenaga, S.; Mukaiyama, T. *Bull. Chem. Chem. Jpn.* **1970**, *43*, 2633.
(7) Mitsunobu, O. *Synthesis* **1981**, 1.
(8) Amos, R. A.; Emblidge, R. W.; Havens, N. *J. Org. Chem.* **1983**, *48*, 3598.
(9) Castro, B. R. *Org. React. (N.Y.)* **1983**, *29*, 1.
(10) Hata, Y.; Yamamoto, I.; Sekine, M. *Chem. Lett.* **1975**, 977.
(11) Robinson, P. L.; Barry, C. N.; Bass, S. W.; Jervis, S. E.; Evans, S. A., Jr. *J. Org. Chem.* **1983**, *48*, 5396.
(12) Barry, C. N.; Evans, S. A., Jr. *Tetrahedron Lett.* **1983**, 661.
(13) The nature of this product is being investigated.
(14) Kurihama, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455.
(15) Nicolau, K. C. *Tetrahedron* **1977**, *33*, 683.
(16) Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

ester (entry 10, Table I) prepared from (−)-2-octanol and potassium benzoate;[17] under present reaction conditions $[\alpha]^{22}_D$ (c 0.013 g/mL, $CHCl_3$) was +3.8°. The possibility of partial or double inversion via an intermediate alkyl chloride has been eliminated since ethyl 2-chloropropionate in carbon tetrachloride with potassium benzoate did not produce any significant amounts of the corresponding ester. A carbonium ion mechanism was considered to be unreasonable due to the nonpolar nature of the reaction medium and also due to the observed inversion with racemization. Also ruled out is the possibility of carboxylic acid activation[20] mechanism because the observed product does not retain the configuration.

Although a definitive mechanism awaits further study, the esterification is assumed to proceed initially via 1 and then 2, which could either be a tight ion pair[9] or a pentacoordinate species such as 3 in which the carboxylate group is either equatorial or apical.[18,19] This species, via



2 3

a four-atom or six-atom cyclic transition state (concerted or nonconcerted fashion), could lead to either retention or inversion, respectively. Molecular models appear to indicate the latter possibility is preferential if not exclusive. However, the tight ion pair mechanism, which is well accepted with oxyphosphonium salts, cannot be excluded.

In analogy to the Mitsunobu and related reactions, (alcohol activation), other heteroatom nucleophiles, e.g., N and O react in a similar manner to give amines and ethers.[21–23] However, sulfur nucleophiles such as potassium salt of ethylxanthic acid did not give desired product.

Experimental Section

IR spectra were obtained on a Perkin-Elmer 598 infrared spectrometer using either thin films or Nujol mulls on NaCl plates. NMR spectra were obtained on an EM360A spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. Analytical and preparative TLC were performed with silica plates from Analtech. All reagents were used as received. Aldrich's IR and NMR spectra were referred to when available and others were obtained from authentic samples prepared by literature procedures.

Preparation of Benzyl Acetate. Potassium acetate (0.20 g), carbon tetrachloride (0.76 g), triphenylphosphine (0.588 g), and benzyl alcohol (0.21 g) were placed in a round-bottomed flask fitted with an efficient water condenser and the semisolid mixture was heated at 55–60 °C for 4 h with stirring. The solvent ($CHCl_3$ and excess CCl_4) was then removed on a rotary evaporator and 10 mL of hexane was added; the mixture was stirred for 15 min and then filtered. The hexane solution was concentrated to give an oil, which was then distilled (Kugelrohr) under reduced pressure [110 °C (2 mm)] to give 0.18 g of benzyl acetate, 60% yield.

Preparation of 4-[(Benzoyloxy)methyl]-1,3-dioxolan-2-one. Triphenylphosphine (0.55 g), carbon tetrachloride (0.91 g), glycerol carbonate (0.24 g), and potassium benzoate (0.35 g) were heated with stirring at 55–60 °C for 5.5 h. During this period, the reaction mixture underwent solidification. After the reaction was complete, the residue was dissolved in chloroform and filtered to remove potassium chloride. The solvent from the filtrate was removed, and the residue was dissolved in a small amount of chloroform and then chromatographed over silica gel with hexane/ether (95:5) to give 0.28 g of the dioxolanone: 68% yield; mp 68–69 °C; NMR ($CDCl_3$) δ 4.5 (4 H), 5.05 (1 H), 7.3 (3 H), 8.05 (2 H).

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Registry No. PhCOOK, 582-25-2; H_3CCOOK, 127-08-2; PhCH=CHCOOK, 16089-48-8; 4-$O_2NC_6H_4COOK$, 15922-01-7; $PhCOOCH_2CH_3$, 93-89-0; $PhCOOCH_2Ph$, 120-51-4; $PhCOOCH_2CH{=}CH_2$, 583-04-0; $PhCOO(CH_2)_2Si(CH_3)_3$, 98760-24-8; (±)-$PhCOOCH(CH_3)COOCH_2CH_3$, 1020-09-3; (±)-$PhCOOCH(CH_3)CN$, 98777-16-3; (±)-$PhCOOCH(CH_3)(CH_2)_5CH_3$, 98819-31-9; CH_3COOCH_2Ph, 140-11-4; $PhCH{=}CHCOOCH_2CH_3$, 103-36-6; 4-$O_2NC_6H_4COOCH(CH_3)_2$, 13756-40-6; $(CH_3)_3Si(CH_2)_2OH$, 2916-68-9; (−)-$CH_3CH(OH)COOCH_2CH_3$, 7699-00-5; (±)-$CH_3CH(OH)CN$, 42492-95-5; (−)-$CH_3(CH_2)_5CH(CH_3)OH$, 5978-70-1; $CH_2{=}C(CH_3)CH_2OH$, 513-42-8; $CCl_2{=}C(Cl)CH_2OH$, 3266-39-5; $ClCH_2CH_2OH$, 107-07-3; Ph_3P, 603-35-0; CCl_4, 56-23-5; 4-pyridinecarboxylic acid potassium salt, 25108-37-6; (±)-oxiranylmethyl benzoate, 98760-25-9; (±)-[(benzoyloxy)methyl]-1,3-dioxolan-2-one, 98760-26-0; (±)-4-[(benzoyloxy)methyl]-2,2-dimethyl-1,3-dioxolane, 98760-27-1; methyl 4-pyridinecarboxylate, 2459-09-8; benzyl 4-pyridinecarboxylate, 21182-01-4; (±)-oxiranemethanol, 61915-27-3; (±)-4-(hydroxymethyl)-1,3-dioxolan-2-one, 63121-19-7; (±)-4-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane, 22323-83-7; Pen-G allyl ester, 80127-23-7; Pen-G 2-methylallyl ester, 65590-78-5; Pen-G 2,3,3-trichloro-2-propenyl ester, 98760-28-2; Pen-G 2-chloroethyl ester, 98760-29-3; Pen-G benzyl ester, 1254-56-4; Pen-G potassium salt, 113-98-4.

(17) Complete inversion $[\alpha]^{22}_D$ is +34.4°.[8]
(18) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1970**, *35*, 1627.
(19) Weiss, R. G.; Snyder, E. I. *J. Org. Chem.* **1971**, *36*, 403.
(20) One of the reviewers suggested to include this alternate reaction pathway to explain the lack of stereocontrol.
(21) E.g., with present procedure, methyl lactate was reacted with potassium 2,6-dichlorophenoxide to give methyl 2-(2,6-dichlorophenoxy) propionate in 80% yield. Similarly reacted potassium phthalimide.
(22) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026.
(23) Garcia, J.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1984**, 4841.

Acetylative Cleavage of (Arylsulfonyl)ureas to *N*-Acetylarenesulfonamides and Isocyanates

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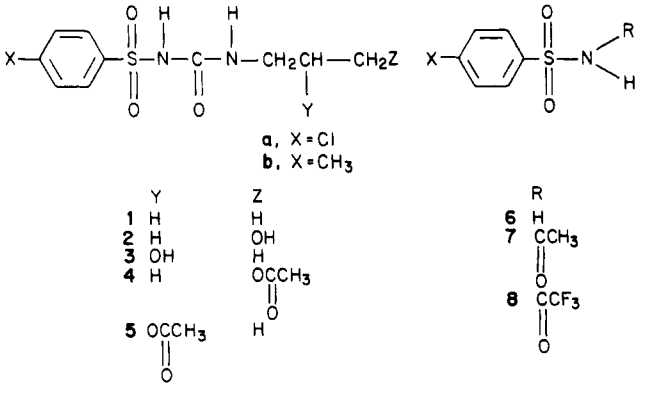
Oral hypoglycemic agents of the class exemplified by 1-[(4-chlorophenyl)sulfonyl]-3-(*n*-propyl)urea (chlorpropamide, **1a**) are known to be metabolized by man[1] and rodents[2] by hydroxylation on the aliphatic side chain. In



a, X = Cl
b, X = CH_3

	Y	Z
1	H	H
2	H	OH
3	OH	H
4	H	$OCCH_3$ (O)
5	$OCCH_3$ (O)	H

	R
6	H
7	CCH_3 (O)
8	CCF_3 (O)

(1) Taylor, J. A. *Clin. Pharmacol. Ther. (St. Louis)* **1972**, *13*, 710.