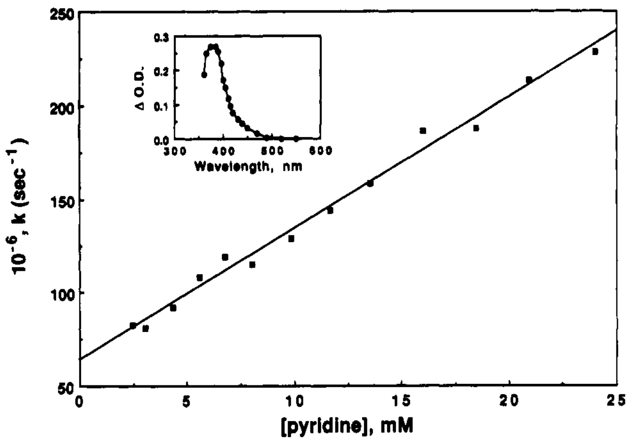

Figure 1. Plot of the observed pseudo-first-order rate constant at 0 °C for growth of ylide absorption at 380 nm vs pyridine concentrations. The slope gives $k_y = 7.01 \times 10^9\ M^{-1}\ s^{-1}$, and the intercept yields $k_i = 6.37 \times 10^7\ s^{-1}$. The insert is the point-by-point absorption spectrum for the pyridinium ylide produced by LFP of diazirine in isooctane containing pyridine.

Table I. Rate Constants for 1,2-Hydrogen Shift for (Phenoxymethyl)chlorocarbene (k_i) and for the Formation of Pyridinium Ylide (k_y)

temp, °C	$k_i \times 10^{-6}$, s^{-1}	$k_y \times 10^{-9}$, $M^{-1}\ s^{-1}$
23.7	114.70 ± 5.98	9.04 ± 0.69
17.8	80.02 ± 4.13	8.64 ± 0.59
10.0	76.91 ± 6.19	7.70 ± 0.64
0.0	63.74 ± 6.19	7.01 ± 0.22
−5.1	54.91 ± 9.47	7.17 ± 0.71
−10.3	59.81 ± 4.34	6.77 ± 0.28

Results and Discussion

LFP of 3-(phenoxymethyl)-3-chlorodiazirine (1) in isooctane (Ar purged) revealed no transient absorptions due to PMCC. The pyridinium ylide method[8] was used to probe the carbene's absolute kinetics. LFP of 1 in isooctane in the presence of pyridine (2–20 mM) gave ylide 2, λ_{max} = 380 nm (Figure 1 insert). This spectrum is similar to the transient spectra of the ylides derived from tBuCCl,[8] $PhCH_2CCl$,[2] alkylchlorocarbenes,[6] and pyridine. A plot (Figure 1) of the observed pseudo-first-order rate constant for growth of ylide 2 vs pyridine is linear. The slope gives the rate constant for the reaction of PMCC with pyridine, k_y, and the intercept, extrapolated to zero pyridine concentration, gives the sum of the rates of all reactions other than trapping. Since the isolated yield for PhOCH=CHCl is 90% and no azine was detected, it is reasonable to assume that the intercept yields the rate constant for 1,2-H shift, k_i. It is true that k_{obsd} has a slight dependence on diazirine concentration,[9,10] but under the conditions of the LFP experiment, [1] ≤ 0.03 M, the correction due to carbene–diazirine reaction is negligible since the azine is undetected under these conditions.

The values of k_y and k_i measured by this method at six temperatures in the −10 to 24 °C range are given in Table I. Within experimental error, the rate constant for ylide formation is diffusion controlled with $E_a = 1.32 \pm 0.18$ kcal mol^{-1} and log $A = 10.90 \pm 0.14\ M^{-1}\ s^{-1}$. Least-squares analysis for log k_i against $1/T$ yields the rate constant for 1,2-H shift in PMCC, $k_i = 10^{10.1\pm0.48} \exp(-2.83 \pm 0.61/RT)$ s^{-1} where R = 1.987 cal K^{-1} mol^{-1} (see Scheme I).

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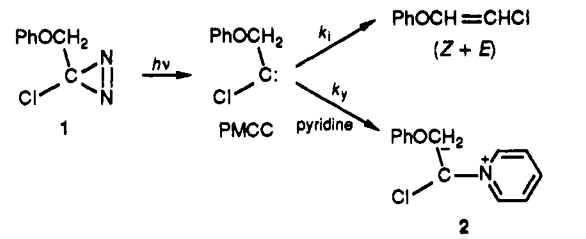
Scheme I



The lifetime of $PhCH_2CCl$ by direct observation[3] of the carbene decay at 24 °C is 18 ns. The lifetimes of CH_3CH_2CCl, $C_2H_5CH_2CCl$, and $(CH_3)_2CHCCl$ have all been *estimated*[6] to be approximately 10 ns (25 °C). If log A = 10, then the activation energies for all these reactions will be ~2.7 kcal mol^{-1}. Data in Table I gave lifetimes of 9 and 17 ns for $PhOCH_2CCl$ at 24 and −10 °C, respectively. It is to be noted that the 9-ns lifetime is approaching the limit of nanosecond laser apparatus. Indeed, PMCC exhibits the largest measured rate constant for 1,2-H shift thus far. Substitution of PhO for Ph in $PhCH_2CCl$ resulted in a lowering of E_a by only ~1 kcal mol^{-1} and produced no significant effect for 1,2-H migration.

Experimental Section

3-(Phenoxymethyl)-3-chlorodiazirine (1) (λ = 333 nm, IR 1580 cm^{-1}) was prepared by Graham oxidation[11] of the corresponding amidine hydrochloride. Photolysis of 1 at 350 nm in isooctane yielded (*Z*)- and (*E*)-1-chloro-2-phenoxyethylene in 90% isolated yield (*Z*/*E* = 2.0). GC analysis using biphenyl as internal standard confirmed this result and revealed that, in the photolysis of 0.03 M 1, no azine was present.

(*Z*)-1-Chloro-2-phenoxyethylene: ^1H NMR δ 5.45 (d, J = 6 Hz, 1 H), 6.78 (d, J = 6 Hz, 1 H), 6.95–7.55 (m, 5 H); MS, m/e 154 (100, M), 119 (36, M − Cl).

(*E*)-1-Chloro-2-phenoxyethylene: ^1H NMR δ 5.95 (d, J = 12 Hz, 1 H), the second doublet is under the aromatic, 6.95–7.55 (m, 5 H); MS, m/e 154 (100, M), 119 (36, M − Cl).

The LFP experiments were carried out in 9 × 6 mm^2 Suprasil quartz cells. Perpendicular 355-nm laser excitation (~8 mJ, pulse width ~ 6 ns) from a Quanta Ray DCR-1 Nd:YAG laser system was used with a 1000-W pulse xenon lamp as the monitoring source.

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Registry No. 1, 104678-42-4; 2, 135284-82-1; PMCC, 104678-23-1; pyridine, 110-86-1; (*Z*)-1-chloro-2-phenoxyethylene, 1850-00-6; (*E*)-1-chloro-2-phenoxyethylene, 1850-01-7.

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Stereoselective Synthesis of 1-*O*-Pivaloyl-β-D-glucopyranuronic Acid

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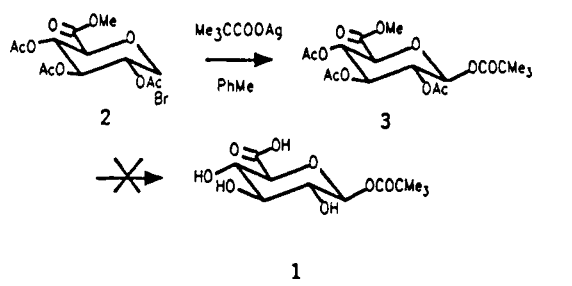
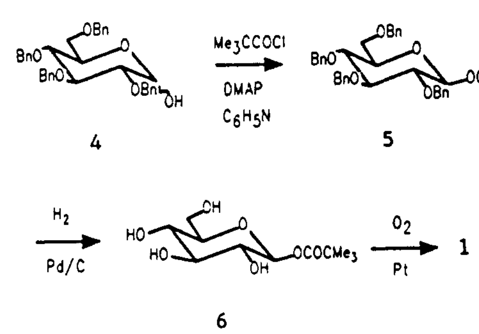
β-D-Glucopyranosiduronic acids are common metabolites of many drugs and endogenous substances.[2] It is often

Scheme I



Scheme II



of vital importance in drug research to be able to identify or analyze these metabolites. This in turn frequently requires the synthesis of reference compounds especially when such metabolites are present in low concentration or difficult to isolate.

1-*O*-Pivaloyl-β-D-glucopyranuronic acid (1) has been identified indirectly as a metbolite of various (pivaloyloxy)alkyl-containing prodrugs[3,4] but has not been synthesized or isolated. In a study of the metabolism of one of our (pivaloyloxy)methyl-containing prodrugs we needed a sample of 1. We here report the synthesis of 1.

Generally, 1-*O*-acylglucuronic acids are prepared by blocking the 2, 3, 4, and 6 positions of glucuronic acid by benzyl or acetal protection groups, establishing the β-glycosidic ester by acylation or nucleophilic displacement, and finally removing the protection groups under mild hydrogenolytic or acidic conditions.[2,5] However, this requires multistep procedures not very suitable for preparing a substantial sample. We therefore considered possible easier routes to 1. Two alternatives were investigated.

On the basis of the fact that pivalic esters are relatively stable toward basic hydrolysis,[6] 1 might be prepared from a 1-pivaloyl derivative of the common glucuronyl donor methyl 2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucopyranuronate (2)[7] by mild hydrolysis (Scheme I). Reacting 2 with silver pivalate in refluxing toluene gave the crystalline β-ester in 66% yield. 3 was formed in more than 10:1 over the α-anomer. This is in agreement with Helferich and Forsthoff, who obtained the β-anomer in the reaction of acetobromoglucose with silver pivalate.[8] However, selective removal of the acetates and the methyl ester in 3 was unsuccessful. When hydrolysis was attempted in $NaHCO_3/Na_2CO_3$-buffered solutions at pH 9.1, 9.9, and 10.8, the pivalic ester was found to cleave in a rate comparable to the acetates. This is possibly due to the higher lability of glycosidic esters.[2] Attempts to selectively deblock using NH_3/MeOH or KCN/EtOH were also unsuccessful.

Another alternative involved preparing 1 from the corresponding glucose derivative (Scheme II); aryl glucopyranosiduronic acids can be prepared in this manner.[9] Starting from commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (4)[10] acylation of the 1-hydroxy group using pivaloyl chloride, pyridine, and DMAP in CH_2Cl_2 gave crystalline 2,3,4,6-tetra-*O*-benzyl-1-*O*-pivaloyl-β-D-glucopyranose (5) in 86% yield; no α-anomer was observed. It was surprising that this reaction was more stereoselective than the nucleophilic displacement of bromide 2 and in fact also more selective than pivalations of 4 carried out via the pseudourea derivative[11] or by using CsF/acyl fluoride.[12] Our pivalation conditions caused a slower reaction than the ones previously published[11,12] requiring overnight reaction to complete, so this was possibly why more selective formation of the kinetic product, the less hindered β-anomer, was observed. Hydrogenation of 5 using palladium on carbon catalyst gave crystalline 1-*O*-pivaloyl-β-D-glucopyranose (6) in 84% yield. 6 has been prepared by direct acylation of glucose;[13] this is simple but gives a low yield and requires chromatography. For both 5 and 6 we found different rotations than cited in the literature;[11,13] however, ^1H NMR data and melting points agree with published values. 6 was reported as a not analytically pure syrup,[13] so a small content of D-glucose could explain the discrepancy in this case; for 5 its less clear. The oxidation of 6 using oxygen over platinum black catalyst gave a 60% yield of crystalline 1. We found that keeping the temperature between 85–90 °C and pH below 8 gave the results, so that byproducts were avoided. However, the pivaloyl ester was stable under the reaction conditions. The reaction tended to be inconveniently slow when scaled up unless a high oxygen flow was ensured. This was done by using a inlet tube with a sintered glass dispenser.

The present synthesis of 1 in three steps from 4 in an overall yield of 43% is the first practical route to this compound. A major advantage is the stereoselectivity, and it is likely this method can be extended to other 1-*O*-acylglucopyranuronic acids.

Experimental Section

General Methods. The NMR spectra were done on a Bruker AC-300 instrument. Tetramethylsilane was used as internal reference in spectra done in $CDCl_3$ and CD_3OD. Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer FE241 instrument. Microanalysis were performed by Leo microanalytical laboatory. Concentrations were performed by rotary evaporation in vacuo at 40 °C.

Methyl 2,3,4-Tri-*O*-acetyl-1-*O*-pivaloyl-β-D-glucopyranuronate (3). Methyl 2,3,4-tri-O-acetyl-1-bromo-1-deoxy-α-D-glucopyranuronate (2[7] 2.63 g, 6.6 mmol) was dissolved in dry toluene (100 mL) under argon, and silver pivalate[14] (2.76 g, 13.2

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mmol) was added. The mixture was refluxed for 3.5 h and then filtered and concentrated. From the resulting residue crystalline **3** was obtained with EtOAc/pentane. Yield: 2.51 g (66%). Mp: 118–119 °C. $[\alpha]_D^{20}$: 10.5° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{18}H_{26}O_{11}$: C, 51.67; H, 6.26. Found: C, 51.75; H, 6.26. Concentration of the mother liquor gave a syrup containing a mixture of **3** and methyl 2,3,4-tri-*O*-acetyl-1-*O*-*pivaloyl*-α-D-glucopyranuronate (0.57 g, ratio 2:1) as seen by NMR. ^1H NMR ($CDCl_3$): δ 5.72 (d, J_{12} = 8 Hz, H-1), 5.32, 5.25, 5.20 (3 t, H-2, H-3, H-4), 4.18 (d, J_{45} = 9 Hz, H-5), 3.74 (s, OMe), 2.02–2.06 (3 s, OAc's), and 1.20 (s, CCH_3's). ^{13}C NMR ($CDCl_3$): δ 176.9 (C=O), 169.6, 169.0, 168.6 (OAc's), 166.4 (C-6), 91.1 (C-1), 72.7, 71.5, 69.6, 68.8 (C-2, C-3, C-4, C-5), 52.6 (OMe), 38.4 (CMe_3), 26.4 (3 C, Me's), 20.2, 20.1, and 20.1 (OAc's).

2,3,4,6-Tetra-*O*-benzyl-1-*O*-pivaloyl-β-D-glucopyranose (5). 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (4) (10.0 g, 18.5 mmol) was dissolved in CH_2Cl_2 (100 mL), and (dimethylamino)pyridine (100 mg), pyridine (10 mL, 124 mmol), and pivaloyl chloride (9.0 g, 74 mmol) were added. The resulting solution was kept at 25 °C for 24 h. More CH_2Cl_2 (200 mL) was added, and the solution was washed with 1 N HCl (200 mL), saturated $NaHCO_3$ solution (200 mL), and H_2O (200 mL). Drying ($MgSO_4$) and concentrating the solution left an oily liquid (15 g). Crystallization from ether/pentane gave **5**. Yield: 9.91 g (86%). Mp: 89–90 °C (lit.[11] mp 87.9–88.5 °C). $[\alpha]^{20}_D$: 20.1° (*c* 1.0, $CHCl_3$) [lit.[11] $[\alpha]^{20}_D$ −14° (*c* 1.0, $CHCl_3$)]. ^1H NMR ($CDCl_3$): δ 7.14–7.35 (m, Phs), 5.62 (d, J_{12} = 8 Hz, H-1), 4.72–4.90 (m, 5 H), 4.48–4.64 (m, 3 H), 3.55–3.81 (m, 6 H), and 1.24 (s, Me's). ^{13}C NMR ($CDCl_3$): δ 176.9 (C=O), 138.0–138.4 (4 C, ipso Ph), 127.6–128.4 (20 C, Ph), 94.3 (C-1), 84.8, 81.0, 77.3 and 75.6 (C-2, C-3, C-4 and C-5), 75.6, 74.9 (2 C) and 73.4 (CH_2Ph's), 66.1 (C-6), 38.7 (CMe_3), and 27.0 (3 C, Me's). Anal. Calcd for $C_{39}H_{44}O_7$: C, 74.98; H, 7.10. Found: C, 75.11; H, 7.20.

1-*O*-Pivaloyl-β-D-glucopyranose (6). **5** (5.0 g, 8 mmol) was dissolved in EtOAc (100 mL) and EtOH (50 mL), and palladium on carbon (10%, 1.0 g) was added. The mixture was hydrogenolyzed (101 kPa) until the expected amount of H_2 had been consumed (5 h). Fitration and concentration left clear syrupy **6** (2.19 g). On addition of ether a white solid was obtained (1.77 g, 84%). Mp: 123–135 °C (lit.[13] syrup). $[\alpha]^{20}_D$: −7.7° (*c* 1.0, dioxane) (lit.[20] $[\alpha]^{20}_D$ 12° (dioxane)]. Anal. Cacd for $C_{11}H_{20}O_7$: C, 49.99; H, 7.63. Found: C, 49.61; H, 7.77. The mother liquor contained 0.27 g (13%) of **6** as syrup; pure as seen from NMR. ^1H NMR (CD_3OD): δ 5.44 (d, J_{12} = 8 Hz, H-1), 3.83 (br d, J_{6a6b} = 12 Hz, H-6a), 3.68 (dd, J_{56b} = 3 Hz, H-6b), 3.33–3.42 (m, H-2, H-3, H-4 and H-5), and 1.23 (s, Me's). ^{13}C NMR (CD_3OD): δ 178.8 (C=O), 95.8 (C-1), 78.8, 78.2, 74.0 and 71.0 (C-2, C-3, C-4 and C-5), 62.3 (C-6), 39.8 (CMe_3), and 27.4 (3 C, Me's).

1-*O*-Pivaloyl-β-D-glucopyranuronic Acid (1). **6** (0.50 g) in H_2O (50 mL) was stirred with platinum black (0.25 g) at 87–88 °C. A stream of O_2 was bubbled through the solution. When necessary, pH was adjusted to 7–8 by addition of 0.5 M $NaHCO_3$ solution (4.5 mL). After 3.5 h, TLC (EtOAc–MeOH (5:1)) showed the absence of starting material. The solution was filtered and treated with 5 mL of ion-exchange resin (Dowex 50W×8, H^+). The resin was filtered off after 15 min, and the filtrate was concentrated to a clear syrup of **1** that crystallized spontaneously (0.32 g, 60%, mp 164–6 °C). $[\alpha]^{20}_D$: −26.7° (*c* 1.0, H_2O). ^1H NMR (D_2O): δ 5.43 (d, J_{12} = 7.6 Hz, H-1), 3.97 (d, J_{45} = 9.6 Hz, H-5), 3.38–3.49 (m, H-2, H-3, H-4), and 1.08 (s, Me's). ^{13}C NMR (D_2O): δ 182.6 (COOH), 174.7 (C=O), 96.4 (C-1), 77.8 (2 C), 74.2, 73.7 (C-2, C-3, C-4 and C-5), 41.3 (CMe_3), and 28.7 (3 C, Me's). Anal. Calcd for $C_{11}H_{18}O_8 \cdot 0.5H_2O$: C, 45.99; H, 6.67. Found: C, 46.06; H, 6.73.

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Registry No. **1**, 98299-37-7; **2**, 21085-72-3; **3**, 135505-23-6; **4**, 38768-81-9; **5**, 82561-63-5; **6**, 80928-26-3; Me_3CCOCl, 3282-30-2; $Me_3CCOOAg$, 7324-58-5.

(14) Silver pivalate was prepared as follows: 0.5 M $AgNO_3$ (100 mL) was slowly added to 1.67 M $Me_3CCOO^-Na^+$ (30 mL). After thorough stirring the precipitate was filtered off and washed with H_2O (4 × 25 mL) and acetone (4 × 25 mL). Overnight drying in a desiccator afforded 6.7 g of $Me_3CCOO^-Ag^+$.

Indirect Electroreduction of 2-Alkyl-2-(bromomethyl)cycloalkanones with Cobaloxime To Form 3-Alkyl-2-alkenones via 1,2-Acyl Migration

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Radical reactions mediated by organocobalt complexes[1,2] have proven to be useful for the construction of carbon[3] and hetero ring systems[4] directed toward the synthesis of bioactive compounds. In particular, carbon radicals, generated by a homolytic carbon–Co bond cleavage of alkylcobalt complexes, are likely to recombine reversibly in a matrix with the released cobalt complex.[5] These aspects are of benefit to the concomitant rearrangement of the carbon skeleton of the radical intermediates and the formation of olefins thereafter via β-elimination of the Co–H moiety.[6] However, few synthetic transformations have been achieved by recyclable cobalt complexes.[4d,7] We report here that 1,2-acyl migration[8–11] of alicyclic 2-alkyl-2-(bromomethyl)alkanones **1** is operative by an indirect electroreduction with (chloropyridine)cobaloxime(III) as a mediator.[12] This method can provide a facile access to α,β-unsaturated ketones[13] by a one-step operation.

External irradiation with a tungsten sunlump and heating at 55–60 °C were applied during the electroreduction in a divided cell in order to facilitate the ensuing carbon–Co bond cleavage of the alkylcobaloxime complexes.[4d] Thus, the electrolysis of 2-hexyl-2-(bromomethyl)cyclopentanone (**1a**) in the presence of cobaloxime (50 mol %) and a small amount of aqueous 50% potassium hydroxide in an MeOH–Et_4NOTs–(Pt) system under a constant applied voltage of 9–15 V (current density: 30 mA/cm^2), 5 F/mol of electricity being charged, gave the desired 3-hexyl-2-cyclohexenone (**2a**) in 74% yield together with minor products such as **3a** (4%), a saturated isomer of **1a**, and 2-hexyl-2-methylcyclopentanone (**4a**, 17%).[14] Similar electrolysis of **1a** in an undivided cell afforded the enone **2a** in 32–34% yield, and the run without use of the cobaloxime resulted in recovery of the starting material (Scheme I).

Authentic samples of **3a** and **4a** were prepared as follows. The compound **3a** was obtained by hydrogenation of the enone **2a** over palladium on carbon and the 2-methylcyclopentanone **4a** was derived from **1a** by exhaustive reduction with lithium aluminum hydride ($LiAlH_4$) followed by oxidation of the resulting cyclopentanol with pyridinium chlorochromate (PCC).[14]

The correlation between yields of **2a**, **3a**, and **4a** under varying the amount of cobaloxime was explored as illustrated in Figure 1 in order to clarify the role of the cobaloxime in this electroreduction. Formation of the enone **2a** is favored in the presence of more than 20 mol % of the cobaloxime. The saturated **3a** yield increases to 14–28% at the expense of **2a** in the range of 5–10 mol % of cobaloxime. The unrearranged product **4a** is produced in about 5–17% yields regardless of the catalyst amount.

The present reaction can be explained by assuming the path shown in Scheme II. The alkyl–Co(III)py complex

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