

New Halogenation Reagent Systems Useful for the Mild One-Step Conversion of Alcohols into Iodides or Bromides[†]

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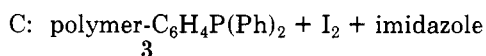
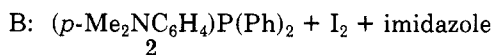
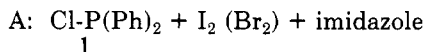
Introduction

Alkyl halides, especially iodides and bromides, are used for ionic or radical carbon-carbon coupling reactions. They are often the intermediates of choice in substitution reactions, eliminations, and rearrangements. Alcohols are also easily transformed into the deoxy derivatives via the halides. Alkyl halides are readily available from the corresponding alcohols by different procedures. For the direct conversion of alcohols into alkyl bromides or iodides, phosphorus-based reagents are the most commonly used.

Rydon et al., in the 1950s, introduced triphenyl phosphite based reagents such as methyltriphenoxyphosphonium iodide and iodotriphenoxyphosphonium iodide for the iodination of alcohols.¹ These reagents have now generally been replaced by triphenylphosphine in combination with a halogen source such as carbon tetrabromide,² *N*-bromosuccinimide or *N*-iodosuccinimide.³ Recently triphenylphosphine together with triiodoimidazole, or iodine and imidazole, or tribromoimidazole, have been used, giving high yields coupled with selectivity for polyhydroxy compounds.⁴ All of these systems generally require elevated temperatures and long reaction times. A major difficulty experienced with these reagent systems is due to the fact that triphenylphosphine and its oxide are difficult to remove from the reaction mixture by means other than precipitation and/or chromatography, which besides being cumbersome results in reduced yield. This is especially inconvenient in large-scale synthesis.

The aim of this work was to find new iodination and bromination reagent systems in which the phosphorus-based reagents and products could be removed from the organic phase by extraction. Two halogenation reagent systems were designed with this requirement. They consist of iodine (or bromine), imidazole and one of the following reagents: A, chlorodiphenylphosphine (CDP) (1); or B, [*p*-(dimethylamino)phenyl]diphenylphosphine⁵ [(*p*-Me₂NC₆H₄)P(Ph)₂] (DAPDP) (2). Halogenation of alcohols with these systems gives products in high yields under mild conditions, and the phosphorus-containing products are extracted from the organic phase into a basic (for A) or acidic (for B) aqueous phase during workup.

halogenation reagent systems



Polymer-bound triphenylphosphine⁶ (3), which together with its oxide is removed from the reaction mixture by filtration, was also examined with use of similar reaction

conditions as earlier described for triphenylphosphine, iodine, and imidazole.⁴ Yields were found to be comparable to those previously obtained.

Results and Discussion

The halogenations examined deal with the syntheses of iodides from alcohols, using different carbohydrates as substrates. To establish the extension of the halogenation reagent systems for the preparation of bromides, some selected brominations were also carried out. The halogenations are generally performed in toluene, which is nonpolar and appears to promote reactivity by destabilizing the charged phosphonium halide intermediate, thus favoring decomposition to uncharged alkyl halide and phosphorus product. With toluene as solvent a two phase liquid-liquid reaction system is generally obtained. The amount of toluene used in these experiments can be substantially reduced without adverse effects.⁷ Other solvents such as acetonitrile, dichloromethane, or pyridine were also examined, but these solvents give lower yields.

In previous work on halogenations using triphenylphosphine, the addition of imidazole was shown not only to neutralize liberated halogen acids but also to enhance reactivity.⁴ Imidazole was therefore used in the present study. Other bases such as triethylamine or pyridine were also examined, but lower yields were generally obtained. Imidazole has the additional advantage of being only sparingly soluble in toluene but freely soluble in water and is thus extracted from the toluene phase by using either acidic or basic aqueous workup.

Halogenation Reagent System A: Chlorodiphenylphosphine (CDP), Iodine (or Bromine), and Imidazole. This reagent system appears to be the most reactive and versatile. Primary alcohols are converted into alkyl iodides or alkyl bromides at room temperature in less than 10 min and in essentially quantitative yields. Secondary alcohols react at 40-90 °C in 0.5-2 h. After completion of the reaction the resulting diphenylphosphonic acid is extracted into saturated aqueous sodium carbonate or aqueous sodium hydroxide, yielding an organic phase essentially devoid of phosphorus-containing compounds. It has been shown that 1-substituted *n*-alkyl diphenylphosphinites react with halogens to produce alkyl halides with inversion of configuration.⁸ We have compared the reactivity of chlorodiphenylphosphine and 1-(diphenylphosphino)imidazole⁹ and found that essentially identical yields of alkyl halides are obtained under similar reaction conditions. In order to study halogenations using CDP, reactions were followed by ³¹P NMR spectroscopy. CDP in toluene gives a peak at 81.9 ppm. When 3 equiv of imidazole are added at room temperature, 1-(diphenyl-

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[†]Dedicated to Prof. E. J. Corey on the occasion of his 60th birthday.

Table I

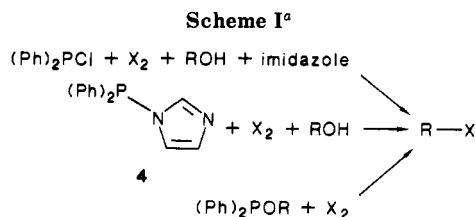
formula	substrate	product	halogenation reagent systems (isolated yields, %)		
			A	B	C
	6: R = OH	7: R = I 8: R = Br	98 91	92	91
	9: R = OH	10: R = I 11: R = Br	95 90	90	84
	12: R = OH	13: R = I	91	88	89
	14: R ¹ = OH; R ² = H	15: R ¹ = H; R ² = I	67	62	45
	16: R ¹ = OH; R ² = H	17: R ¹ = H; R ² = I	86	81	68
	18: R ¹ = OH; R ² = H	19: R ¹ = H; R ² = I		69	78
	20: R ¹ = OH; R ² = H	21: R ¹ = H; R ² = I		63	75
	22: R ¹ = R ² = OH	23: R ¹ = I; R ² = OAc		81	67
	24: R ¹ = R ² = OH	25: R ¹ = I; R ² = OAc		67	61
	26: R ¹ = R ² = OH	27: R ¹ = I; R ² = OAc		72	64

phosphino)imidazole is formed (~25%, -5.2 ppm), and when 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (1.4 equiv) is added, a mixture of CDP (~50%), 1-(diphenylphosphino)imidazole (~20%), and diphenyl phosphinite (~30%, 20.1 ppm) is obtained. It is evident from these results that the main reactive intermediate is generated after the addition of iodine (bromine) and that it is formed equally well from CDP, 1-(diphenylphosphino)imidazole, or the diphenyl phosphinite as is shown in Scheme I.

The chloride present in chlorodiphenylphosphine does not give rise to competitive chlorination, as no incorporation of chlorine in the reaction products was observed within the detection limits of NMR and combustion analysis.

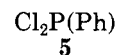
CDP is commercially available and inexpensive, making large-scale halogenations using this reagent system especially attractive.

Acid-sensitive groups such as triphenylmethyl ethers, acetals, and glycosidic linkages are stable under the reaction conditions. The CDP, iodine (or bromine), imidazole system was unsuitable for substrates having a free amino group and also for unprotected polyhydroxy compounds, which gave complicated reaction mixtures.



^aX = I or Br.

Dichlorophenylphosphine **5** was also investigated as a halogenating reagent with iodine and imidazole in toluene. After completion of reaction the phosphorus-containing products were removed from the toluene phase by a basic aqueous wash.



Also with this reagent system, no incorporation of chloride into products during iodination was observed. A major limitation of the dichlorophenylphosphine reagent system is, however, that yields are consistently low.

Halogenation Reagent System B, [*p*-(Dimethylamino)phenyl]diphenylphosphine (DAPDP) (2), Iod-

ine (or Bromine), and Imidazole, and Halogenation Reagent System C, Polymer-Bound Triphenylphosphine (3), Iodine (or Bromine), and Imidazole. The reactivity of these two reagent systems resembles those with triphenylphosphine.⁴ They show good reactivity and give high yields of halogenated products but require, compared to the CDP system, longer reaction times and higher temperatures. [*p*-(Dimethylamino)phenyl]diphenylphosphine (2) and its oxide are conveniently removed from the toluene phase by extraction with aqueous hydrochloric acid (pH ≈ 1). Substance 2 is not commercially available, but is a crystalline compound prepared in a single step from CDP.⁵ Polystyrene polymer supported phosphine resin used in reagent system C is commercially available. The phosphorus component of the reagent system is removed from the reaction mixture by filtration. The reaction mechanism for these two reagent systems appears to be similar to that proposed for the triphenylphosphine, iodine, and imidazole system,⁴ which has been studied by ³¹P NMR.¹⁰

Experimental Section

General Methods. Melting points are corrected. Concentrations were performed under diminished pressure (1–2 kPa) at a bath temperature not exceeding 40 °C. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. NMR spectra were recorded at 25 °C unless otherwise stated, with a JEOL JNM FX-100 or a JEOL GSX-270 instrument. Chemical shifts are given in ppm downfield from tetramethylsilane. ³¹P NMR spectra were recorded in a 10-mm tube with a JEOL FX 400 spectrometer operating at 161.70 MHz. Chemical shifts are reported relative to 2% phosphoric acid in D₂O (inner tube). NMR spectra for all compound were in accordance with the postulated structure, and only selected data are reported. Thin-layer chromatography was carried out with precoated silica gel plates (F 250 Merck), and the spots were detected by UV light and/or charring with 80% aqueous sulfuric acid. All reactions were monitored by TLC. Column chromatography was performed on silica gel 60 (0.04–0.063 mm Merck). The loadings were in the range 1/25–1/100. Organic solutions were dried over anhydrous magnesium sulfate. The yields given below are for purified products. Chlorodiphenylphosphine was obtained from Aldrich Chemical Co. and distilled (bp 130 °C at 0.5 mmHg) before use. Polymer-bound triphenylphosphine was obtained from Aldrich Chemical Co., and [*p*-(dimethylamino)phenyl]diphenylphosphine was prepared according to the literature procedure.⁵

Workup Procedure a: For Halogenation Reagent System

A. The reaction mixture was poured at room temperature into an equal volume of saturated aqueous sodium carbonate or aqueous sodium hydroxide in a separating funnel. The funnel was shaken for 5 min during portionwise addition of iodine, until the toluene phase remained iodine-colored. The aqueous phase was separated, and the organic phase was washed with aqueous sodium thiosulfate to remove the excess iodine and then washed with water, dried, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate–toluene, 1:3) to obtain analytically pure compounds.

Workup Procedure b1: For Halogenation Reagent System

B and Products Soluble in Toluene. The reaction mixture was cooled and poured into an equal volume of saturated aqueous sodium hydrogen carbonate in a separating funnel. The funnel was shaken for 5 min during portionwise addition of iodine, until the toluene phase remained iodine-colored. The aqueous phase was separated, and the organic phase was washed with aqueous sodium thiosulfate to remove the excess iodine. The organic phase was washed with aqueous hydrochloric acid (pH ≈ 1) until all [*p*-(dimethylamino)phenyl]diphenylphosphine oxide was removed from the toluene. The organic phase was washed with water, dried, and concentrated. Silica gel column chromatography (ethyl acetate–toluene, 2:1) yield the pure product.

Workup Procedure b2: For Halogenation Reagent System B and Products Soluble in Water. The reaction mixture was cooled and transferred to a separating funnel and extracted repeatedly with water. The combined aqueous phase was concentrated, and water was removed by codistillation with toluene. The residue was acetylated at room temperature in acetic anhydride–pyridine (1:1), concentrated, and partitioned between toluene and water. The organic phase was washed with water, dried, and concentrated. Silica gel column chromatography (ethyl acetate–toluene, 4:1) yielded the pure product.

Workup Procedure c1: For Halogenation Reagent System C and Products Soluble in Toluene. The reaction mixture was cooled and filtered through Celite, and the Celite layer was washed with toluene. The filtrate was washed with saturated aqueous sodium hydrogen carbonate and water, dried, and concentrated. Silica gel column chromatography (ethyl acetate–toluene, 2:1) yielded the pure product.

Workup Procedure c2: For Halogenation Reagent System C and Products Soluble in Water. The reaction mixture was cooled and filtered through Celite, and the celite layer was washed with water followed by methanol. The combined aqueous methanol phase was concentrated, and water was removed by codistillation with toluene. The residue was acetylated at room temperature with acetic anhydride–pyridine (1:1), concentrated, and partitioned between toluene and water. The organic layer was washed with water, dried, and concentrated. Silica gel column chromatography (ethyl acetate–toluene, 4:1) yielded the pure product.

Methyl 5-Deoxy-5-iodo-2,3-O-isopropylidene-β-D-ribofuranoside¹¹ (7). Halogenation Reagent System A. To a solution of methyl 2,3-O-isopropylidene-β-D-ribofuranoside (6) (0.50 g, 2.45 mmol), chlorodiphenylphosphine (0.70 g, 3.19 mmol), and imidazole (0.37 g, 5.39 mmol) in toluene (40 mL) was added iodine (0.81 g, 3.19 mmol) portionwise at room temperature. After 5 min, the TLC indicated that the reaction was complete. Workup (procedure a) yielded the title compound (0.75 g, 98%), [α]²²_D –71° (c 1.0, CHCl₃) [lit.¹¹ [α] –68° (CHCl₃)].

Halogenation Reagent System B. A mixture of methyl 2,3-O-isopropylidene-β-D-ribofuranoside (6) (0.50 g, 2.45 mmol), [*p*-(dimethylamino)phenyl]diphenylphosphine (0.97 g, 3.19 mmol), imidazole (0.50 g, 7.35 mmol), and iodine (0.81 g, 3.19 mmol) in toluene (30 mL) was stirred at 50 °C for 3 h. Workup (procedure b1) yielded the title compound (0.71 g, 92%).

Halogenation Reagent System C. A mixture of methyl 2,3-O-isopropylidene-β-D-ribofuranoside (6) (0.50 g, 2.45 mmol), polymer-bound triphenylphosphine (1.76 g, 5.39 mmol), imidazole (0.42 g, 6.13 mmol), and iodine (0.81 g, 3.19 mmol) in toluene (50 mL) was stirred at 50 °C for 4 h. Workup (procedure c1) yielded the title compound (0.70 g, 91%).

Methyl 5-Bromo-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside³ (8). Halogenation Reagent System A. Bromine (0.51 g, 3.19 mmol) was added dropwise at room temperature to a solution of methyl 2,3-O-isopropylidene-β-D-ribofuranoside (6) (0.50 g, 2.45 mmol), chlorodiphenylphosphine (0.70 g, 3.19 mmol), and imidazole (0.37 g, 5.39 mmol) in toluene (40 mL). After 10 min, TLC indicated that the reaction was complete. Workup (procedure a) yielded the title compound (0.60 g, 91%), [α]²²_D –78° (c 1.0, CHCl₃) [lit.³ [α] –80° (CHCl₃)].

6-Deoxy-6-iodo-1,2,3,4-di-O-isopropylidene-α-D-galactopyranose¹² (10). Halogenation Reagent System A. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (9) (0.50 g, 1.92 mmol) was reacted in the same way as for 7. Workup (procedure a) yielded the title compound (0.68 g, 95%); mp 66 °C (crystallized from ligroin); [α]²²_D –53° (CHCl₃) [lit.¹² mp 72 °C; [α] –50° (1,1,2,2-tetrachloroethane)].

Halogenation Reagent System B. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (9) (0.20 g, 0.77 mmol) was reacted in the same way as for 7. Workup (procedure b1) yielded the title compound (0.26 g, 90%).

Halogenation Reagent System C. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (9) (0.20 g, 0.77 mmol) was reacted in the same way as for 7. Workup (procedure c1) yielded

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the title compound (0.25 g, 84%).

6-Bromo-6-deoxy-1,2,3,4-di-O-isopropylidene- α -D-galactopyranose¹³ (11). Halogenation Reagent System A. 1,2,3,4-Di-O-isopropylidene- α -D-galactopyranose (9) (0.60 g, 2.30 mmol) was reacted in the same way as for 8. Workup (procedure a) yielded the title compound (0.67 g, 90%), $[\alpha]_D^{25} -51^\circ$ (c 1.0, CHCl₃) [lit. $[\alpha] -58.9^\circ$ (CHCl₃)].

1,2,3,4-Tetra-O-acetyl-6-deoxy-6-iodo- β -D-glucopyranose¹⁴ (13). Halogenation Reagent System A. Iodine (0.28 g, 1.12 mmol) was added at room temperature to a mixture of 1,2,3,4-tetra-O-acetyl- β -D-glucopyranose (12) (0.30 g, 0.86 mmol), chlorodiphenylphosphine (0.25 g, 1.12 mmol), and imidazole (0.13 g, 1.89 mmol) in toluene (40 mL), and the reaction mixture was stirred at 50 °C for 1 h when TLC indicated that the reaction was complete. Workup (procedure a) yielded the title compound (0.36 g, 91%): mp 149 °C; $[\alpha]_D^{25} +15^\circ$ (c 1.0, CHCl₃) [lit.¹⁴ mp 148 °C; $[\alpha] +9.5^\circ$ (CHCl₃)].

Halogenation Reagent System B. A mixture of 1,2,3,4-tetra-O-acetyl- β -D-glucopyranose (12) (0.20 g, 0.57 mmol), [*p*-(dimethylamino)phenyl]diphenylphosphine (0.26 g, 0.86 mmol), imidazole (0.12 g, 1.71 mmol), and iodine (0.17 g, 0.68 mmol) in toluene (30 mL) was stirred at 50 °C for 4 h. Workup (procedure b1) yielded the title compound (0.23 g, 88%).

Halogenation Reagent System C. A mixture of 1,2,3,4-tetra-O-acetyl- β -D-glucopyranose (12) (0.20 g, 0.57 mmol), polymer-bound triphenylphosphine (0.41 g, 1.25 mmol), imidazole (0.12 g, 1.72 mmol), and iodine (0.19 g, 0.74 mmol) in toluene (30 mL) was stirred at 50 °C for 5 h. Workup (procedure c1) yielded the title compound (0.24 g, 89%).

3-Deoxy-3-iodo-1,2,5,6-di-O-isopropylidene- α -D-allofuranose¹⁵ (15). Halogenation Reagent System A. A mixture of 1,2,5,6-di-O-isopropylidene- α -D-glucopyranose (14) (0.30 g, 1.15 mmol), chlorodiphenylphosphine (0.51 g, 2.31 mmol), imidazole (0.59 g, 8.68 mmol), and iodine (0.24 g, 3.46 mmol) in dry toluene (50 mL) was stirred at 90 °C for 2 h when TLC indicated that the reaction was complete. Workup (procedure a) yielded the title compound (0.29 g, 67%), $[\alpha]_D^{25} +65^\circ$ (c 2.0, CHCl₃) [lit.¹⁵ $[\alpha] +66^\circ$ (CHCl₃)].

Halogenation Reagent System B. A mixture of 1,2,5,6-di-O-isopropylidene- α -D-glucopyranose (14) (0.30 g, 1.15 mmol), [*p*-(dimethylamino)phenyl]diphenylphosphine (0.70 g, 2.31 mmol), imidazole (0.31 g, 4.60 mmol), and iodine (0.59 g, 2.31 mmol) in toluene (30 mL) was stirred under reflux at a bath temperature of 120 °C overnight. Workup (procedure b1) yielded the title compound (0.27 g, 62%).

Halogenation Reagent System C. A mixture of 1,2,5,6-di-O-isopropylidene- α -D-glucopyranose (14) (0.20 g, 0.77 mmol), polymer-bound triphenylphosphine (0.50 g, 1.54 mmol), imidazole (0.13 g, 1.92 mmol), and iodine (0.25 g, 0.99 mmol) in toluene (20 mL) was stirred under reflux at a bath temperature of 120 °C overnight. Workup (procedure c1) yielded the title compound (0.12 g, 45%).

Methyl 4-Deoxy-4-iodo-2,3-di-O-methyl-6-O-(triphenylmethyl)- α -D-galactopyranoside (17). Halogenation Reagent System A. To a mixture of methyl 2,3-di-O-methyl-6-O-(triphenylmethyl)- α -D-glucopyranoside¹⁶ (16) (0.40 g, 0.86 mmol), chlorodiphenylphosphine (0.38 g, 1.72 mmol), and imidazole (0.18 g, 2.59 mmol) in toluene (50 mL) was added iodine (0.44 g, 1.72 mmol) portionwise at room temperature. The reaction mixture was then stirred at 60 °C for 2 h. Workup (procedure a) yielded the title compound (0.43 g, 86%): $[\alpha]_D^{25} +85^\circ$ (c 2.8, ethanol); ¹³C NMR (100 MHz, CDCl₃) δ 39.5 (C-4), 55.0, 56.5, 59.2 (3 OCH₃), 67.4, 68.3, 77.3, 79.8, 87.0, 97.9 (C-1). Anal. Calcd for C₂₈H₃₁O₅: C, 58.2; H, 5.41. Found: C, 58.3; H, 5.40.

Halogenation Reagent System B. A mixture of methyl 2,3-di-O-methyl-6-O-(triphenylmethyl)- α -D-glucopyranoside (16) (0.20 g, 0.43 mmol), [*p*-(dimethylamino)phenyl]diphenylphosphine (0.19 g, 0.65 mmol), imidazole (0.09 g, 1.29 mmol), and iodine (0.13 g, 0.52 mmol) in toluene (20 mL) was stirred under reflux at a bath temperature of 120 °C for 6 h. Workup (procedure b1)

yielded the title compound (0.20 g, 81%).

Halogenation Reagent System C. A mixture of methyl 2,3-di-O-methyl-6-O-(triphenylmethyl)- α -D-glucopyranoside (16) (0.20 g, 0.43 mmol), polymer-bound triphenylphosphine (0.31 g, 0.94 mmol), imidazole (0.09 g, 1.29 mmol), and iodine (0.14 g, 0.56 mmol) in toluene (20 mL) was stirred under reflux at a bath temperature of 120 °C for 8 h. Workup (procedure c1) yielded the title compound (0.17 g, 68%).

Methyl 4,6-O-Benzylidene-3-deoxy-3-iodo- β -D-allopyranoside (19). Halogenation Reagent System B. A mixture of methyl 4,6-O-benzylidene- β -D-glucopyranoside (18) (0.20 g, 0.70 mmol), [*p*-(dimethylamino)phenyl]diphenylphosphine (0.49 g, 1.61 mmol), imidazole (0.19 g, 2.80 mmol), and iodine (0.36 g, 1.40 mmol) in toluene (30 mL) was stirred at 50 °C for 3 h. Workup (procedure b1) yielded the title compound (0.19 g, 69%): mp 151–152 °C; $[\alpha]_D^{25} +1.62^\circ$ (c 2.22, CHCl₃); ¹³C NMR (270 MHz, CDCl₃) δ 38.9 (C-3), 57.6 (OCH₃), 67.2, 68.6, 69.0, 76.1, 101.6 (PhCO), 104.0 (C-1); ¹H NMR (270 MHz, CDCl₃) δ 2.94 (1 H, dd, $J_{1,2} = 7.6$ Hz, $J_{2,3} = 3.6$ Hz, H-2), 3.05 (1 H, dd, $J_{3,4} = 3.4$ Hz, $J_{4,5} = 9.3$ Hz, H-4), 3.55–3.57 (3 H, m, OCH₃), 3.87 (1 H, t, $J_{5,6} = J_{6,6'} = 10.1$ Hz, H-6'), 4.01 (1 H, m, H-5), 4.38 (1 H, dd, $J_{5,6'} = 4.8$ Hz, $J_{6,6'} = 10.1$ Hz, H-6''), 4.60 (1 H, d, $J_{1,2} = 7.6$ Hz, H-1), 4.89 (1 H, t, $J_{2,3} = J_{3,4} = 3.5$ Hz, H-3), 5.67 (1 H, s, PhCH), and 7.26–7.54 (5 H, m, Ar). Anal. Calcd for C₁₄H₁₇O₅: C, 42.6; H, 4.3. Found: C, 42.5; H, 4.3.

Halogenation Reagent System C. A mixture of methyl 4,6-O-benzylidene- β -D-glucopyranoside (18) (0.20 g, 0.70 mmol), polymer-bound triphenylphosphine (0.69 g, 2.12 mmol), imidazole (0.14 g, 2.12 mmol), and iodine (0.23 g, 0.90 mmol) in toluene (50 mL) was stirred at 70 °C for 6 h. Workup (procedure c1) yielded the title compound (0.22 g, 78%).

Methyl 4,6-O-(4-Methoxybenzylidene)- β -D-glucopyranoside (20). A solution of methyl β -D-glucopyranoside (5.0 g, 25.8 mmol), 4-methoxybenzaldehyde dimethyl acetal (7.0 g, 38.4 mmol), and *p*-toluenesulfonic acid monohydrate (0.091 g, 0.48 mmol) in dimethylformamide (30 mL) was rotated under aspirator pressure at 50 °C for 2.5 h. The temperature was raised to 70 °C, and solvent was distilled off until about 10 mL remained, after which the solution was poured into a stirred mixture of ice (13 g) in saturated aqueous sodium hydrogen carbonate (30 mL) and diethyl ether (30 mL). After 0.5 h the solid residue was filtered off, washed successively with petroleum ether and water, and dried in a vacuum to give the title compound (6.80 g, 85%): mp 171–173 °C (crystallized from ethyl acetate); $[\alpha]_D^{25} -8.8^\circ$ (c 6.35, methanol); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 55.0, 56.2 (2 OCH₃), 56.2, 65.7, 72.8, 80.5, 100.5, (PhCO), 104.4 (C-1). Anal. Calcd for C₁₅H₂₀O₇: C, 57.7; H, 6.5; O, 35.9. Found: C, 57.6; H, 6.5; O, 36.0.

Methyl 4,6-O-(4-Methoxybenzylidene)-3-deoxy-3-iodo- β -D-allopyranoside (21). Halogenation Reagent System B. Methyl 4,6-O-(4-methoxybenzylidene)- β -D-glucopyranoside (20) (0.40 g, 1.28 mmol) was reacted in the same way as for 19. Workup (procedure b1) yield the title compound (0.34 g, 63%): $[\alpha]_D^{25} -27^\circ$ (c 0.89, CHCl₃); ¹³C NMR (270 MHz, CDCl₃) δ 39.2 (C-3), 55.4, 57.5 (2 OCH₃), 67.2, 68.4, 68.8, 75.9, 101.4 (PhCO), 103.9 (C-1); ¹H NMR (270 MHz, CDCl₃) δ 2.93 (1 H, m, $J_{1,2} = 7.4$ Hz, $J_{2,3} = 3.8$ Hz, H-2), 3.02 (1 H, dd, $J_{3,4} = 3.6$ Hz, $J_{4,5} = 8.7$ Hz, H-4), 3.56, 3.80 (6 H, s, s, 2 OCH₃), 3.85 (1 H, t, $J_{5,6} = J_{6,6'} = 10.1$ Hz, H-6'), 3.98 (1 H, dd, $J_{5,6'} = 4.9$ Hz, $J_{6,6'} = 10.1$ Hz, H-6''), 4.59 (1 H, d, $J_{1,2} = 7.4$ Hz, H-1), 4.87 (1 H, t, $J_{3,4} = J_{3,4} = 3.7$ Hz, H-3), 5.63 (1 H, s, PhCH), and 6.88–7.42 (4 H, m, Ar). Anal. Calcd for C₁₅H₁₉O₆: C, 42.4; H, 4.5. Found: C, 42.7; H, 4.6.

Halogenation Reagent System C. Methyl 4,6-O-(4-methoxybenzylidene)- β -D-glucopyranoside (20) (0.40 g, 1.28 mmol) was reacted in the same way as for 19. Workup (procedure c1) yielded the title compound (0.41 g, 75%).

Methyl 2,3,4-Tri-O-acetyl-6-deoxy-6-iodo- α -D-glucopyranoside¹⁷ (23). Halogenation Reagent System B. A mixture of methyl α -D-glucopyranoside (22) (0.20 g, 1.03 mmol), [*p*-(dimethylamino)phenyl]diphenylphosphine (0.47 g, 1.54 mmol), imidazole (0.15 g, 2.26 mmol), and iodine (0.36 g, 1.44 mmol) in toluene (20 mL) was vigorously stirred at 70 °C for 3 h. Workup (procedure b2) yielded the title compound (0.36 g, 81%): mp 151–152 °C (crystallized once from ethanol); $[\alpha]_D^{25} +115^\circ$ (c 1.0,

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CHCl_3) [lit.¹⁷ mp 150–151 °C; $[\alpha] +116^\circ$ (CHCl_3)].

Halogenation Reagent System C. A mixture of methyl α -D-glucopyranoside (**22**) (0.40 g, 2.06 mmol), polymer-bound triphenylphosphine (1.0 g, 3.09 mmol), imidazole (0.31 g, 4.53 mmol), and iodine (0.73 g, 2.88 mmol) in toluene (50 mL) was vigorously stirred at 70 °C for 4 h. Workup (procedure c2) yielded the title compound (0.60 g, 67%).

Methyl 2,3,4-Tri-O-acetyl-6-deoxy-6-iodo- β -D-glucopyranoside¹⁸ (25). **Halogenation Reagent System B.** Methyl β -D-glucopyranoside (**24**) (0.20 g, 1.03 mmol) was reacted in the same way as for **23**. Workup (procedure b2) yielded the title compound (0.30 g, 67%): mp 113–114 °C (crystallized once from ethanol); $[\alpha]^{22}_D +2^\circ$ (c 3.0, CHCl_3) [lit.¹⁸ mp 114–115 °C; $[\alpha] +1^\circ$ (methanol)].

Halogenation Reagent System C. Methyl β -D-glucopyranoside (**24**) (0.40 g, 2.06 mmol) was reacted in the same way as for **23**. Workup (procedure c2) yielded the title compound (0.54 g, 61%).

Methyl 2,3,4-Tri-O-acetyl-6-deoxy-6-iodo- α -D-mannopyranoside¹⁹ (27). **Halogenation Reagent System B.** Methyl α -D-mannopyranoside (**26**) (0.20 g, 1.03 mmol) was reacted in the same way as for **23**. Workup (procedure b2) yielded the title compound (0.32 g, 72%): mp 90–91 °C (crystallized once from ethanol); $[\alpha]^{22}_D +48^\circ$ (c 1.2, CHCl_3) [lit.¹⁹ mp 91–92 °C; $[\alpha] +37^\circ$ (CHCl_3)].

Halogenation Reagent System C. Methyl α -D-mannopyranoside (**26**) (0.40 g, 2.06 mmol) was reacted in the same way as for **23**. Workup (procedure c2) yielded the title compound (0.57 g, 64%).

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Registry No. 1, 1079-66-9; 2, 739-58-2; 6, 4099-85-8; 7, 38838-06-1; 8, 38838-05-0; 9, 4064-06-6; 10, 4026-28-2; 11, 38838-08-3; 12, 13100-46-4; 13, 7468-48-6; 14, 582-52-5; 15, 67337-61-5; 16, 51016-10-5; 17, 117560-27-7; 18, 71117-37-8; 19, 117605-32-0; 20, 117605-33-1; 21, 117560-28-8; 22, 709-50-2; 23, 6304-96-7; 24, 709-50-2; 25, 7511-38-8; 26, 617-04-9; 27, 50692-55-2.

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Irreversible and Highly Enantioselective Acylation of 2-Halo-1-arylethanol in Organic Solvents Catalyzed by a Lipase from *Pseudomonas fluorescens*

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In recent years enzymatic catalysis in organic solvents has been the subject of extensive investigations.¹ Lipases have been successfully used as transesterification catalysts for stereoselective acylation² and kinetic resolution of

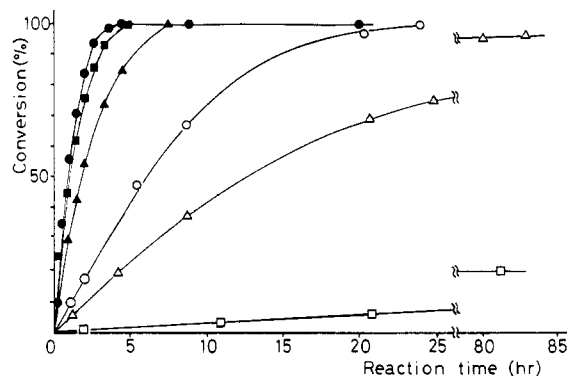
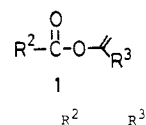


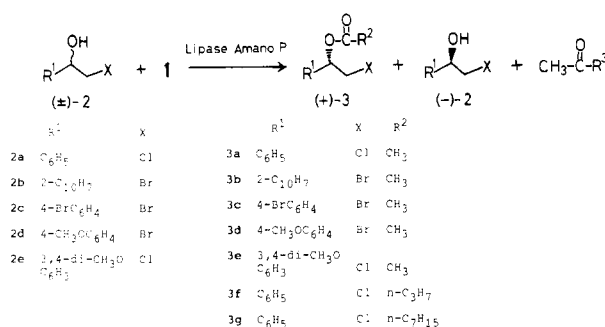
Figure 1. Lipase-catalyzed transesterification of 1-hexanol with vinyl acetate (●), isopropenyl acetate (○), vinyl butyrate (▲), vinyl octanoate (●), 2,2,2-trichloroethyl acetate (Δ), and ethyl acetate (□). Conditions: 1-hexanol (10 mmol), enol esters 1 (10.5 mmol), lipase Amano P (500 mg), dry diisopropyl ether (20 mL), 25 °C. Detection: GC (2% XE-60, 2 m, 70 °C, ethyl benzene as internal standard).

Scheme I



- 1a CH₃ H
1b CH₃ CH₃
1c n-C₃H₇ H
1d n-C₇H₁₅ H

Scheme II



alcohols.³ The enzymatic process, however, is reversible and often requires long reaction times and a large excess of esters as the acyl donor in order to achieve a reasonable degree of conversion.^{2,3b,4}

Recent application of vinyl or isopropenyl esters as the acylating agent to a lipase-catalyzed esterification⁵ appears to offer an effective solution to this problem because the enol, product, is immediately transformed irreversibly into acetaldehyde or acetone. However, not all of the commercially available lipases are necessarily effective for transesterification with enol esters; moreover, the irreversibility (equilibrium) has not yet been clearly demonstrated, although high reactivity (reaction rate) of enol

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