Decarbomethoxylation of Dimethyl [1-Phenyl-2(*E*)-butenyl]malonate (4). Decarbomethoxylation of **4** (71.6 mg, 0.273 mmol, $[\alpha]^{20}_D$ +12° (*c* 1.0, chloroform), 30% ee), in a similar manner to that of **3**, gave 31.4 mg (56%) of methyl [1-phenyl-2-(*E*)-butenyl]acetate (**7**). $[\alpha]^{20}_D$ +1.1° (*c* 0.9, chloroform). ^{1}H NMR δ 1.64 (d, *J* = 5 Hz, 3 H), 2.58 (d, *J* = 8 Hz, 2 H), 3.54 (s, 3 H), 3.60–3.92 (m, 1 H), 5.12–5.80 (m, 2 H), 7.00–7.52 (m, 5 H).

Hydrogenation of Methyl [1-Phenyl-2(*E*)-butenyl]acetate (7). A solution of 31.4 mg (0.154 mmol) of **7** ($[\alpha]^{20}_D$ +1.1° (*c* 0.9, chloroform)) in 1.5 mL of benzene and 7 mg of Pd/C (10% Pd) were placed in a stainless micro autoclave, and magnetically stirred with hydrogen at 130 atm for 21 h. The reaction mixture was passed through a short silica gel column and evaporated to give 31.1 mg (98%) of methyl 3-phenylhexanoate (**8**). ($[\alpha]^{24}_D$ −3.8° (*c* 0.9, chloroform); lit.[7] (*S*)-**8**, $[\alpha]^{24}_D$ +13.4° (neat)).

Decarbomethoxylation and Deacetylation of Methyl [1-((*E*)-Styryl)ethyl]acetoacetate (14). A solution of 398 mg (1.62 mmol) of **14** ($[\alpha]^{20}_D$ −69.1° (*c* 0.95, chloroform)) and 40 mg (0.75 mmol) of sodium methoxide in 10 mL of methanol was refluxed for 22 h. Water was added and the mixture was extracted with ether. The ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. Preparative TLC on silica gel (hexane/ethyl acetate = 5/1) gave 94 mg (29%) of methyl [1-((*E*)-styryl)ethyl]acetate (**5**) ($[\alpha]^{20}_D$ −49.0° (*c* 0.99, CCl_4), 35 mg (12%) of [1-((*E*)-styryl)-ethyl]acetone (**15**) ($[\alpha]^{20}_D$ −57.3° (*c* 0.78, CCl_4)), and 145 mg (36%) of recovered **14**. The ester **5** obtained here is 79% ee *R* according to its maximum specific rotation $[\alpha]^{20}_D$ +62.2° (CCl_4) *R*-(−), and therefore the maximum specific rotation of the ketone **15** is calculated to be $[\alpha]^{20}_D$ 72.5° (CCl_4) *R*-(−) since **15** should have the same configuration and enantiomeric purity as **5**. **15**: ^{1}H NMR δ 1.10 (d, *J* = 7 Hz, 3 H), 2.04 (s, 3 H), 2.41 (m, 2 H), 2.83 (septet, *J* = 7 Hz, 1 H), 5.96 (dd, *J* = 7 and 15 Hz, 1 H), 6.28 (d, *J* = 15 Hz, 1 H), 6.94–7.36 (m, 5 H). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.07; H, 8.67.

Deacetylation of [1-((*E*)-Styryl)ethyl]acetylacetone (13). A solution of 332 mg (1.44 mmol) of **13** ($[\alpha]^{20}_D$ −101° (*c* 1.0, chloroform)) and 35 mg (0.65 mmol) of sodium methoxide in 10 mL of methanol was refluxed for 16 h. Water was added and the mixture was extracted with ether. The ether extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. Preparative TLC on silica gel (hexane/ethyl acetate = 5/1) gave 218 mg (80%) of [1-((*E*)-styryl)ethyl]acetone (**15**) ($[\alpha]^{20}_D$ −55.3° (*c* 0.97, CCl_4), 76% ee *R*). The maximum specific rotation of the acetylacetone **13** is calculated to be $[\alpha]^{20}_D$ 132° (chloroform), *S*-(−).

Oxidative Addition of the Allyl Acetate (*R*)-(*Z*)-2 to Palladium(0). To a mixture of 63 mg (0.11 mmol) of dichloro[bis(diphenylphosphino)ethane]palladium(II) and 29 mg (0.11 mmol) of triphenylphosphine in 3 mL of ether was added at room temperature 0.44 mL (0.22 mmol) of diisobutylaluminum hydride (0.5 M) in hexane. After the mixture was stirred for 20 min, 101 mg (0.53 mmol) of (*R*)-(*Z*)-**2** ($[\alpha]^{20}_D$ −35.4° (CCl_4), 67% ee) was added at 0 °C. The mixture was stirred at 0 °C for 21 h, and 15.4 mg (0.14 mmol) of sodium tetrafluoroborate was added. After 1 h, the mixture was hydrolyzed with 10 mL of water and extracted 3 times with chloroform. The chloroform extracts were washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. Preparative TLC on silica gel (hexane/ethyl acetate = 1/4; R_f 0.1–0.2) of the residue gave 31 mg (39%) of the cationic π-allylpalladium complex (1*R*,2*S*,3*S*)-**12**[4] ($[\alpha]^{20}_D$ +32.6° (*c* 1.1, chloroform), 27% ee).

Acknowledgment. We thank Emeritus Professor Makoto Kumada for encouragement and the Ministry of Education, Japan, for Grant-in-Aid for Scientific Research (No. 59550591) for partial financial support of this work.

Registry No. (*S*)-(*E*)-**1**, 88154-75-0; (*R*)-(*Z*)-**1**, 100017-26-3; (*S*)-(*E*)-**1** (alcohol), 81176-43-4; (*R*)-(*Z*)-**1** (alcohol), 92075-80-4; (*S*)-(*E*)-**2**, 100017-27-4; (*R*)-(*Z*)-**2**, 100017-28-5; (*S*)-(*E*)-**2** (alcohol), 92075-81-5; (*R*)-(*Z*)-**2** (alcohol), 100017-30-9; (*R*)-(*Z*)-**2** (1-triethoxysilyl deriv), 99903-35-2; (*S*)-**3**, 88057-04-9; (*R*)-**4**, 100017-29-6; (*R*)-**5**, 99903-36-3; (*R*)-**6**, 22644-27-5; (*S*)-**7**, 99903-37-4; (*R*)-**8**, 99903-38-5; (1*R*,2*S*,3*S*)-**12**, 88083-20-9; (*S*)-**13**, 99903-32-9; (*S*,*R*)-**14**, 99903-33-0; (*S*,*S*)-**14**, 99903-34-1; (*R*)-**15**, 100017-31-0; (*R*)-**16**, 79767-68-3; $NaCH(COMe)_2$, 15435-71-9; $NaCH(CO_2Me)COMe$, 50321-58-9; PhZnBr, 38111-44-3; $NaCH(CO_2Me)_2$, 18424-76-5; $Pd(PPh_3)_4$, 14221-01-3; PhCH=CHCOMe, 122-57-6; (*S*)-(*Z*)-$MeCH(SiMe_3)CH$=CHPh, 88133-09-9; (*R*)-(*E*)-MeCH=CHCH-$(SiMe_3)$Ph, 82570-93-2; H_2C=CHCH=CHPh, 30733-89-2; (*R*)-$HO_2CCH(Me)CH_2CO_2H$, 3641-51-8; bis(μ-chloro)bis(π-allyl)dipalladium, 12012-95-2; bis(diphenylphosphino)ethane, 1663-45-2; 1,1′-bis(diphenylphosphino)ferrocene, 12150-46-8; 4-(*N*,*N*-dimethylamino)pyridine, 1122-58-3; dichloro[bis(diphenylphosphino)ethane]palladium(II), 19978-61-1.

Studies in Sugar Chemistry. 2.[1] A Simple Method for O-Deacylation of Polyacylated Sugars

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Total solvolytic O-deacylation of polyacylated sugars is readily accomplished upon stirring for 15 min–6 h a solution of a sugar in methanol in the presence of a catalytic amount of cyanide. The reaction proceeds in high yields, under neutral conditions, at room temperature. The overall rate of the reaction, readily followed by observing the changes in the ^{1}H 300-MHz NMR spectra, is greatly influenced by the substituent at the anomeric position in the order of 1-OH > 1-OAc ≫ 1-OR.

Synthetic studies in sugar chemistry most frequently require the introduction of O-protective groups and their subsequent removal. Successful deprotection constitutes a critical step in the synthesis of desired products.[2] The selective removal of protecting groups in carbohydrates has been reviewed.[3]

A facile, room-temperature, rapid, under neutral conditions, virtually quantitative method for cyanide-catalyzed removal of acetate (and benzoate) groups at all positions

(1) Fischer, B.; Nudelman, A.; Ruse, M.; Herzig, J.; Gottlieb, H. E.; Keinan E. *J. Org. Chem.* **1984**, *49*, 4988.
(2) Keglevich, D. *Adv. Carbohydr. Chem. Biochem.* **1979**, *36*, 57.
(3) Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 13 and references cited therein.

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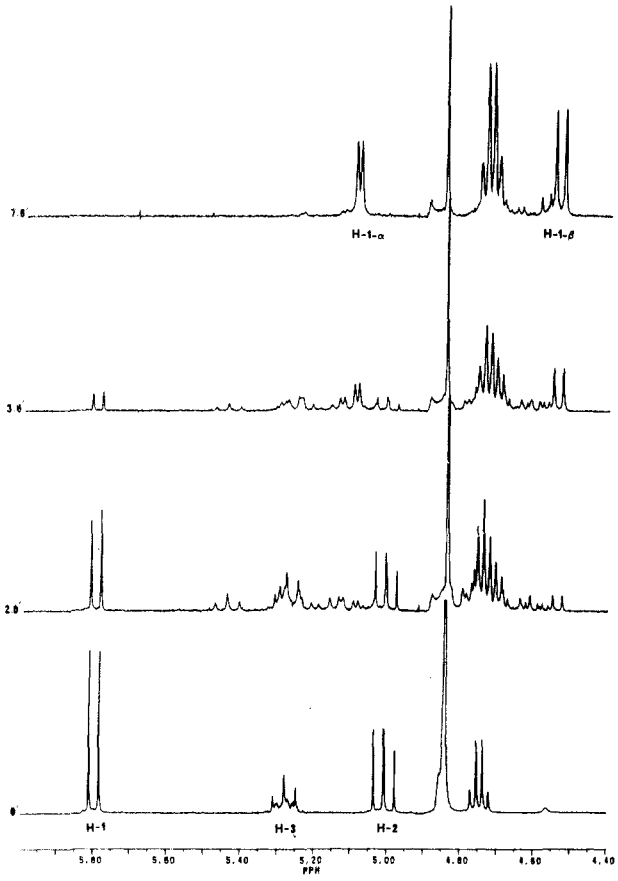


Figure 1. Cyanide-catalyzed methanolysis of 12-β to 11-α + 11-β as a function of time.

in a variety of sugar derivatives is here described.[4,5] The general procedure for O-deacylation, involves the addition of a catalytic amount of an alkali (or polymeric) cyanide (0.3–0.5 mol) to a methanolic molar solution or suspension of the appropriate polyacylated sugar. The reactions proceed at room temperature (8 min up to 6 h) resulting invariably in clear solutions of the deacylated products. The removal of the potassium cyanide may be carried out readily and quantitatively by various methods (see Experimental Section). Evaporation of the solvent and crystallization or chromatography of the residue give essentially quantitative yields of the desired deprotected products, uncontaminated with cyanide. The course of the reactions can easily be followed by thin-layer chromatography or by proton NMR spectroscopy in deuterated methanol.

The overall reaction must proceed through a multistep sequence of deacylation steps. A priori, it is plausible that a large number of partially deacylated intermediates should be obtained, which eventually will give a single, totally O-deprotected product. This is indeed the situation in some cases; however, frequently the reaction rates are

(4) Several earlier uses of cyanide-catalyzed esterifications have been described: (a) Birch, A. J.; Corrie, J. E. T.; Macdonald, P. L.; Rao, G. S. *J. Chem. Soc.*, Perkin *Trans. 1* **1972**, 1186. (b) Mori, K.; Tominaga, M.; Matsui, M. *Synthesis* **1973**, 790. (c) Imamura, K.; Sugabe, Y.; Nabekawa, S.; Kozu, S. Japan Kokai 72 50091; *Chem. Abstr.* **1973**, *78*, 110565*f*. (d) Tominaga, M.; Matsui, M.; Mori, K.; Takigawa, T. Japan Kokai 75 52013; *Chem. Abstr.* **1975**, *83*, 205778*v*. (e) Mori, K.; Sasaki, M. *Tetrahedron Lett.* **1979**, 1329. (f) Hanessian, S.; Pougny, J. R.; Boessenkool, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 6164.

(5) After this paper had been submitted for publication, an article dealing with deacetylation of galactosides in the presence of a large molar excess of cyanide was reported. Here, it is shown that efficient deacylation can be readily accomplished in the presence of catalytic amounts of cyanide. Schuerch, C.; El-Shenawy, H. A. *J. Carbohydr. Chem.* **1985**, 215.

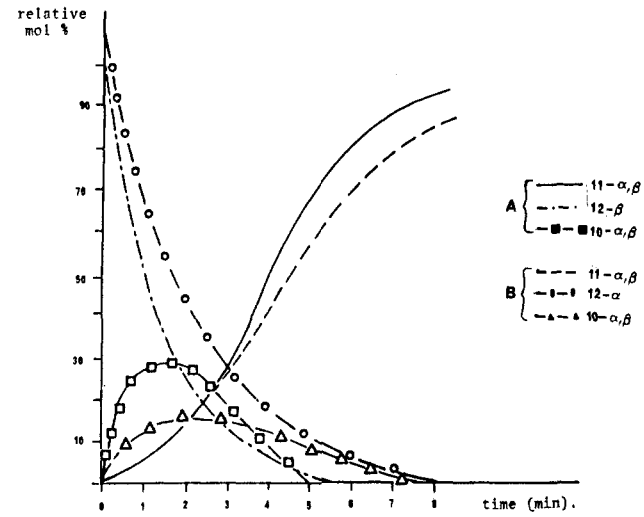
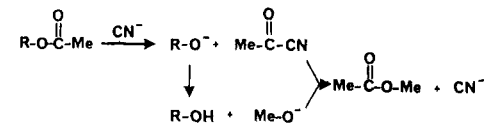
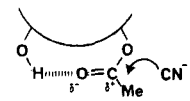


Figure 2. Time-dependent changes in composition of reaction mixtures of cyanide-catalyzed methanolysis of 12-α and 12-β.

Scheme I



Scheme II



such that only a few main intermediates are formed preferentially. At 300 MHz, many individual peaks can be recognized, and the progress of the reaction can be followed by sequential acquisition of spectra. Thus, semiquantitative kinetic data are obtained which provide some insight into the chemistry of the reactions. A typical NMR kinetic run is shown in Figure 1 and the corresponding time-dependent changes in reaction mixture composition are shown in Figure 2.

Results and Discussion

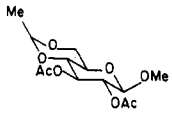
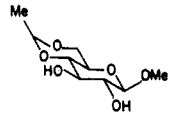
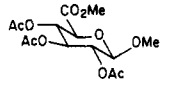
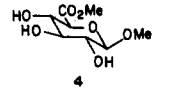
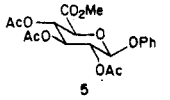
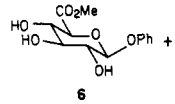
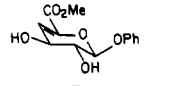
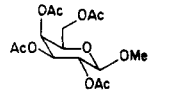
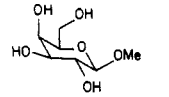
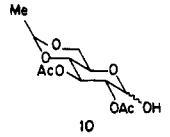
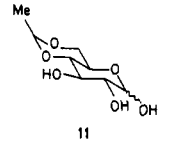
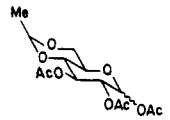
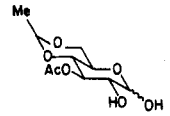
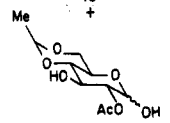
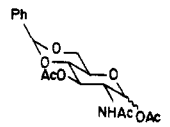
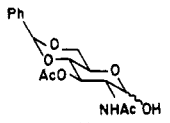
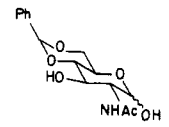
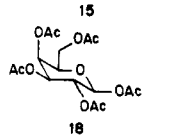
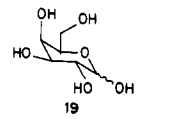
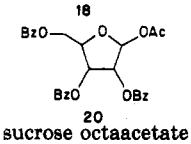
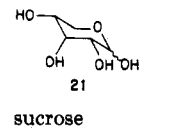
In Table I are listed the sugars examined and the respective products and detected intermediates obtained in the deacylation process. From the NMR spectra it is evident that the O-deacylation is quantitative in all compounds examined.

The mechanistic course of the deacylation process involves an overall transesterification which is believed to proceed via a nucleophilic displacement of an acyl group by cyanide, giving a reactive acyl cyanide which further undergoes rapid methanolysis, whereby the cyanide catalyst is regenerated[4a] (Scheme I).

The acylated carbohydrates studied possess a variety of *O*-acyl groups whose reactivity depends on their position and configuration. In general, it is observed that the overall rate of reaction is greatly influenced by the substituent at the anomeric position in the order of 1–OH > 1–OAc ≫ 1–OR. The course of the reactions was followed qualitatively by thin-layer chromatography, and a more quantitative rate was obtained following changes in the 300-MHz proton NMR spectra of the reaction mixtures in deuteromethanol.

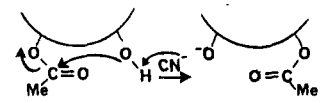
The simplest cases encountered are with compounds that lack anomeric and primary *O*-acyl groups. In these cases (**1**, **3**, **5**, **8**, and **10**), the deacylation was nonselective, and partially deacetylated intermediates were not detected.

Table I. Starting Sugars, Detected Intermediates, and Products

starting sugar	intermediates	products
 1		 2
 3		 4
 5		 6
		 7
 8		 9
 10		 11
 12	 13 +  14	11
 15	 16	 17
 18		 19
 20		 21
sucrose octaacetate		sucrose

The overall reaction took between 3–5 h with an average $t_{1/2}$ (half-life of starting material) of ca. 40 min. It appears that the speed of the removal of the first acetyl group is rate determining. Once this has taken place, the presence of a free OH group catalyzes the deacetylation of a neighboring acetate. This catalytic effect may involve a hydrogen-bonding interaction between the free OH group and the adjacent OAc group, whereby the electrophilicity of the acetyl group is increased, facilitating the nucleophilic attack by cyanide[6] (Scheme II). In compound **10**-α where there is no need for initial anomeric deacetylation the reaction is practically complete in 8 min (no trace of starting material is detectable after 4 min); however, in this case dihydroxy intermediates **11** and **12** were detectable, implying a difference in catalytic effect by the presence of the anomeric OH.

Scheme III



An unexpected side product (up to ca. 10% yield) was detected in the course of the reaction of **5**. The appearance of a vinylic absorption in the proton NMR spectrum [(CD_3OD) δ 7.28 (m, 2 H, Ar), 7.15 (m, 2 H, Ar), 7.00 (m, 1 H, Ar), 6.13 (dd, 3.7, 0.6, H-4), 5.57 (dd, 5.7, 0.7, H-1), 4.21 (ddd, 5.0, 3.7, 0.6, H-3), 3.91 (ddd, 5.7, 0.7, H-2)] indicated the formation of glucal **7** derived from dehydration of **6**, due to the acidity of the hydrogen α to the carboxy group. The expected transesterification in **3** and **5** of $COOCH_3$ to $COOCD_3$ is clearly evident from the NMR spectra of **4** and **7**.

A more complicated and interesting situation develops once an anomeric acetate is present (**12**, **15**, **18**, and **20**). Invariably, as expected, the anomeric acetyl is initially removed. No great difference in reactivity (Figure 2) was detected in the individual epimeric 1-*O*-acetates of compounds **12**-α or **12**-β. However, the same anomeric mixture of final products was obtained, since the rate of anomerization of the 1-OH group is rapid under the reaction conditions. It was further shown that an authentic sample of 4,6-*O*-ethylidene-α-D-glucose (**11**-α) underwent cyanide-catalyzed anomerization in methanol. In **15**, where the starting material was a mixture of α and β-anomeric acetates (in an α/β ratio of ca. 3:2), the rate of disappearance of the α isomer was so fast that none remained while some of the β-starting material could still be detected. The furanose-1-*O*-acetate group (**20**) seemed to react faster than the corresponding pyranose-1-*O*-acetate (**12**, **15**). After 3 min (minimum time for NMR sample preparation) none of the starting ester could be detected in the former case, whereas in the latter some of the starting material was still observed. In contradistinction to **1**, **3**, **5**, **8**, and **10**, partially deacetylated intermediates of **12**-α and **12**-β (**13**, **14**) were detected and their NMR spectra could be partially assigned. Here, the rate of removal of the anomeric acetate was very fast but comparable to that of the subsequent deacetylations, whereas in **1**, **3**, **5**, **8**, and **10** the rate of the first deacetylation was much slower than the following ones, which explains why in these cases partially deacetylated intermediates were not detected.

The sequential deacetylation steps of **1** may be explained as indicated in Scheme II, whereby hydrogen-bonded polarized acyl groups are readily attacked by cyanide ions or alternatively by a rapid sequence of steps involving initial anomeric deacetylation followed by *O*-acetyl migration from position 2,[7] again giving a highly reactive 1-*O*-acetyl intermediate[8] (Scheme III). Although the phenomenon of *O*-acyl transfer in sugars is well established,[7] the examples discussed involve mainly O-1 to O-6 transfer and sometimes migration from adjacent positions other than the anomeric one. Our results, however, seem

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to indicate and O-2 to O-1 migration process which has not been reported previously. The rate of removal of the benzoate groups in sugar **20** is very rapid and similar to that of the nonanomeric acetates in **1** and **2**.

Further substantiation for the participation of a neighboring OH group in the solvolysis of an adjacent OAc group (either by polarization of the OAc or by *O*-acyl migration), is seen in the reaction of **15**, where the isolated 3-*O*-acetate group reacts ca. 10 times slower than the 2- and 3-*O*-acetate groups of compounds **12**-α and **12**-β. The reaction is selective to ester groups leaving the acetamido function intact.

The NMR kinetic data of galactose derivatives **8** and **18** indicate that (a) the anomeric acetate of **18** reacts initially (b) the $t_{1/2}$ of **18** is less than 1 min, which prevents the detection of partially deacetylated intermediates, and (c) compound **8**, in spite of the fact that it has an anomeric OMe group, undergoes deacetylation ($t_{1/2}$ ca. 7 min) much faster than compounds **1**, **3**, **5**, and **10**, probably due to the presence of primary acetate.

Experimental Section

General Remarks. Proton NMR spectra were recorded on a Bruker AM-300 spectrometer in deuteromethanol/Me_4Si, on a ca. 0.05-mol scale. All reactions were carried out under anhydrous conditions in flame-dried glass apparatus under nitrogen, in absolute methanol. The KCN (analytical grade Merck 4967) was dried under high vacuum for several hours. The starting sugars for which no reference is given are commerically available (Aldrich, Fluka). Polymer-bound cyanide used was Fluka 28490. Mixed ion-exchange resin Duolite MB-5113 was obtained from BDH. Progress of reactions was monitored by thin-layer chromatography (TLC) on aluminum sheets precoated with silica gel (Merck, Art. 5554), and eluted with chloroform/methanol mixtures; the developing agent was 1% sulfuric acid in methanol, followed by heat.

General Procedure for Deacylation. To a stirred solution of KCN (0.5 mmol) in methanol was added in one portion a polyacylated sugar (1 mmol). The resulting mixture (solution or suspension) was stirred at room temperature until complete conversion to the polyhydroxy product took place, as indicated by TLC. The following illustrates alternative procedures used to purify the products.

Procedure A. To a stirred solution of KCN (45 mg, 0.7 mmol) in methanol (12 mL) was added β-galactose pentaacetate (**18**) (500 mg, 1.3 mmol), and the mixture was stirred for 20 min. The resulting clear solution was filtered through silica gel (Merck 7734), and the eluent was evaporated to dryness, affording a mixture of **19**-α and **19**-β (206 mg, 88% yield) as a white solid.

Procedure B. To a stirred mixture of polymer-supported cyanide (470 mg, 1.5 mmol of cyanide) in methanol (15 mL) was added β-4,6-*O*-ethylidene-1,2,3-tri-*O*-acetylglucose[9] (**12**-β) (500 mg, 1.5 mmol), and the mixture was stirred for 4 h. The polymer was filtered off and the filtrate evaporated to dryness, to give a mixture of **11**-α and **11**-β (284 mg, 92% yield), as a white solid.

Procedure C. 4,6-*O*-Ethylidene-2,3-di-*O*-acetyl-β-methoxyglucose (**1**)[9] (304 mg, 1 mmol) was added to a solution of KCN (42 mg, 0.65 mmol) in methanol (10 mL), an the mixture was stirred for 6 h. Evaporation of the solvent, followed by flash chromatography of the residue (silica gel, Merck 9385; eluted with 95:5 chloroform–methanol) gave **2** (210 mg, 95% yield).

Procedure D. To a stirred solution of KCN (200 mg, 3.1 mmol) in methanol (50 mL) was added sucrose octaacetate (6.3 g, 9.3 mmol), and the solution was stirred for 0.5 h. A precipitate formed, which was filtered, washed with methanol, and dried to give a solid (2.39 g, 75% yield), mp 185–193 °C (undepressed by admixture with an authentic sample of sucrose).

Procedure E. In addition to procedures A–D, the removal of the potassium cyanide catalyst could be carried out by adding at the end of the reaction an equilmolar amount of mixed ion-exchange resin. After stirring the mixture for several minutes, the resin was filtered off and evaporation of the filtrate provided KCN-free products.

Registry No. **1**, 100021-29-2; **2**, 27994-35-0; **3**, 34213-34-8; **4**, 18486-38-9; **5**, 4630-61-9; **6**, 55811-42-2; **7**, 100021-30-5; **8**, 5019-23-8; **9**, 1824-94-8; **10**, 100021-31-6; **11**, 13403-24-2; β-**12**, 27994-30-5; α-**12**, 29810-01-3; **13**, 100021-32-7; **14**, 100021-33-8; β-**15**, 73038-55-8; α-**15**, 100021-35-0; **16**, 100021-34-9; **17**, 22536-08-9; **18**, 4163-60-4; **19**, 59-23-4; **20**, 100101-51-7; **21**, 50-69-1; KCN, 151-50-8; sucrose octaacetate, 126-14-7; sucrose, 57-50-1.

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Notes

Studies in Ranitidine Chemistry: An Unusual O→N Methyl Migration

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Ranitidine (IV), an H_2-receptor antagonist, has been recently introduced in ulcer therapy as a powerful inhibitor of gastric acid secretion.[1] Its synthesis is described in serveral patents.[2–5] Some of the published procedures[2–3] involve the intermediacy of III, prepared by the reaction of I with II (Scheme I). Compound III has been reported to be isolated either as an oil[6] or as its oxalate salt.[7] We have recently been able to synthesize III as the free base and isolate it as a crystalline solid.

In the course of this work we became aware of the instability of III in methanolic solutions where it is completely transformed to another product upon standing at room temperature. This product, a very polar compound, was isolated and fully characterized. Spectral and analytical results confirmed its structure to be that of 1-oxo-1-[(2-(((((5-trimethylammonio)methyl)-2-furanyl)-methyl)thio)ethyl)amino]-2-nitroethene (V), indicating

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