Acid-catalysed Benzylation and Allylation by Alkyl Trichloroacetimidates†

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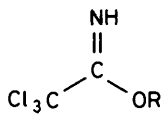
Benzyl and allyl trichloroacetimidate (**1**) and (**2**) are convenient reagents for the *O*-alkylation of hydroxy groups under mildly acidic conditions, which are compatible with imide, ester, and acetal protecting groups. The base-catalyzed addition of benzyl alcohol or allyl alcohol to trichloroacetonitrile provides a simple synthesis of these imidates, but published methods for the recovery of related molecules by distillation leads to variable amounts of a rearranged product, *N*-alkyl trichloroacetamide. A modified procedure, suitable for the large scale synthesis of (**1**) and (**2**) without the need for a distillation step, is reported. The introduction of benzyl and allyl ethers to a variety of carbohydrate derivatives illustrates the potential of these reagents.

Benzyl and allyl ethers play a central role as persistent protecting groups in strategies for oligosaccharide synthesis.[1,2] In order to prepare oligosaccharides derivatized for covalent coupling to proteins we have employed a methodology based upon the bifunctional molecule, ω-methoxycarbonyloctanol.[3] During elaboration of the oligosaccharide at the hydroxy group of this aglycone it is important to preserve the integrity of the ester function. Consequently conventional alkylations, which employ strongly basic conditions,[4] cannot be used to alkylate ω-methoxycarbonyloctyl glycosides. In order to permit benzylations of such derivatives, and, more generally, any ester-containing derivatives, we recently reported the use of benzyl trichloroacetimidate (**1**).[5] This reagent is readily prepared and effects benzylation under mildly acidic conditions, which are compatible with ester and acetal protecting groups.

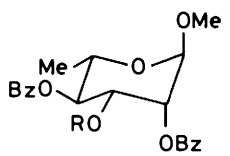


(**1**) R = CH_2Ph
(**2**) R = $CH_2CH{=}CH_2$

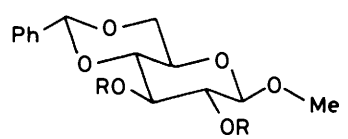
In this paper we report the preparation of allyl trichloroacetimidate (**2**) by a modified and improved procedure, also applicable to the synthesis of benzyl trichloroacetimidate (**1**). The effective *O*-allylation of a variety of monosaccharide derivatives is reported together with experimental details for similar benzylation reactions.[6]

Imidates (**1**) and (**2**) may be prepared by published procedures, by the sodium methoxide catalysed addition of benzyl or allyl alcohol to trichloroacetonitrile.[7] Following neutralization the product is isolated by vacuum distillation. Unfortunately this procedure in our hands resulted in variable amounts (up to 10%) of an *N*-alkyl or *N*-aryl amide, presumably caused by thermal rearrangement of the imidate. The presence of the amide was readily detected by i.r. spectroscopy, which was the most convenient method by which to monitor the purity of imidate product. Distillation of (**1**) and (**2**) is obviated by a modified synthesis which substitutes sodium hydride for sodium methoxide.[8] After reaction of the alcohol with the nitrile, pentane and methanol (1 equiv.) was added to precipitate the base and concentration of the filtered solution gave either (**1**) or (**2**) as a clear liquid, free of the contaminating amide.

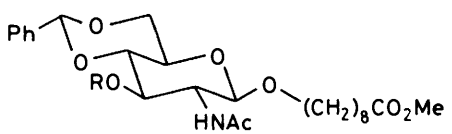
Alkyl and aryl imidates have been shown to rearrange to the corresponding *N*-alkyl or *N*-aryl amides most probably by an ionic mechanism rather than a concerted process.[9] This suggested that *O*-alkylation reactions using these imidates should be conducted in non-polar solvents. This was, in fact, the case and consequently the alkylation of relatively polar derivatives bearing more than two hydroxy groups, in the case of a hexopyranoside, was not a practical proposition due to insolubility of the starting material. Therefore the applications of benzyl trichloroacetimidate and allyl trichloroacetimidate as reported here, are limited to hexopyranosides with a maximum of two unsubstituted hydroxy groups.



(**3**) R = H
(**4**) R = CH_2Ph



(**5**) R = H
(**6**) R = OCH_2Ph



(**7**) R = H
(**8**) R = CH_2Ph

O-Alkylations of a series of monosaccharide derivatives (**3**), (**5**), (**7**), (**9**), (**11**), and (**14**) that possessed ester, amide, and acetal groups were conducted with benzyl trichloroacetimidate (**1**) and allyl trichloroacetimidate (**2**). In general the saccharide was dissolved in a minimum volume of carbon tetrachloride (or dichloromethane, if the starting material was sufficiently polar to preclude partial solubility in carbon tetrachloride). Cyclohexane and the alkylating reagent (2 mol per mol of hydroxy group) were added, followed by the catalyst, trifluoromethanesulphonic acid. After 18 h at 20 °C the reaction mixture was worked up and chromatographed if necessary to remove by-products.

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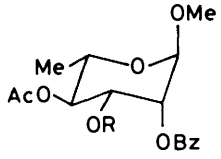
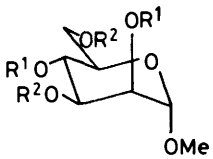
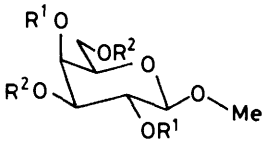
Benzylation of methyl 2,4-di-*O*-benzoyl-α-L-rhamnopyranoside (**3**) and methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**5**) by (**1**) gave the corresponding 3-*O*-benzyl ether (**4**) and the 2,3-di-*O*-benzyl ether (**6**) in good yield. ω-Methoxycarbonyloctyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (**7**) was benzylated by (**1**) (1.25 mol) to give (**8**) in 31% yield together with recovered starting alcohol (**7**) (61%). When a molar excess of (**1**) was employed, a component with a mobility faster than that of the benzyl ether (**8**) was observed. A non-aqueous work-up (p.t.l.c.) gave a component which was thought to be a sugar imidate. Under aqueous work-up conditions this product gave rise to amines or to regeneration of the starting material. This observation indicated that alkylation of acetamidodeoxy sugars by trichloroacetimidates is not a recommended procedure. Amino sugars can however be benzylated as their phthalimide derivatives.[5]



(**9**) R = H
(**10**) R = $OCH_2CH{=}CH_2$



(**11**) R^1 = H, R^2 = Bz
(**12**) R^1 = Allyl, R^2 = Bz
(**13**) R^1 = Allyl, R^2 = H



(**14**) R^1 = H, R^2 = Bz
(**15**) R^1 = Allyl, R^2 = Bz
(**16**) R^1 = Allyl, R^2 = H

Introduction of allyl ether groups was accomplished in a manner similar to benzylation. Allyl trichloroacetimidate (**2**) was treated with methyl 4-*O*-acetyl-2-*O*-benzoyl-α-L-rhamnopyranoside (**9**), and the 3,6 dibenzoate esters of methyl α-D-mannopyranoside (**11**) and methyl α-D-galactopyranoside (**14**) to give the mono-3-*O*-allyl ether (**10**) and the respective di-*O*-allyl ethers (**12**) and (**15**) in good yields. Transesterification provided the selectively protected monosaccharides, 2,4-di-*O*-allyl-mannopyranoside (**13**) and -galactopyranoside (**16**). It is of particular interest to consider the conversion of an α-D-mannopyranoside *via* a dibenzoate such as (**11**) into the partially alkylated mannopyranoside (**13**). This type of substitution pattern is exactly that required to synthesize the 3,6-branch points of glycan chains present in glycoproteins. Compared to the current strategies[10,11] used to achieve this objective the one described here possesses the same number of steps but only slightly higher yields, however, the imidate approach permits either allyl or benzyl groups to be introduced at O-2 and O-4, which is not the case for the published procedures.[11,12] In the latter methods, allyl groups must be introduced first and subsequently cleaved in the presence of benzyl ethers, thereby limiting the partially blocked mannopyranoside to one bearing 2,4-di-*O*-benzyl substituents.

Alkylation of isolated hydroxy groups by trichloroacetamidates is a useful and practical procedure, particularly for partially acetylated or benzoylated carbohydrate derivatives, a large, readily accessible and well characterised class of intermediates. A most effective application of this approach is the synthesis of 2,4-di-*O*-benzyl- or 2,4-di-*O*-allyl-α-D-mannopyranoside, suitable for use in the synthesis of the glycan chains of glycoproteins. A recent application of allylation by the imidate reagent has allowed us to elaborate a versatile rhamnose intermediate for the synthesis of rhamnose oligosaccharides containing glucose branch points.[13] Since the preparation of the alkylating reagents (**1**) and (**2**) has been simplified and the problems of intramolecular rearrangement[7] alleviated, it is thought that imidate alkylation will offer significant advantages in a variety of synthetic strategies, particularly where the compatibility with ester groups may be exploited.

Experimental

T.l.c. and preparative t.l.c. were performed with 0.25 mm and 2 mm Merck precoated silica gel 60 F-254 plates. Compounds were detected by quenching of u.v. fluorescence and by spraying with 5% sulphuric acid in ethanol and heating. Merck silica gel G60 (70—230 mesh) and redistilled solvents were used for column chromatography. Hexane refers to a mixture of hexanes supplied by Getty Refining and Marketing Co., Tulsa, Oklahoma and ether to diethyl ether. Solvents were purified and dried by standard procedures.[14] ^{13}C and ^1H N.m.r. spectra were recorded at 20 MHz and 79.9 MHz respectively. Chemical shifts, ^1H and ^{13}C, for solutions in deuteriochloroform and [$^2H_6$]benzene are expressed relative to internal $SiMe_4$. Assignment of ^{13}C resonances were made on the basis of published data.

Preparation of Benzyl Trichloroacetimidate (**1**) *and Allyl Trichloroacetimidate* (**2**).—Sodium hydride (0.5 g, 21 mmol) was suspended in anhydrous ether (20 cm^3) and a solution of either benzyl or allyl alcohol (210 mmol) in ether (30 cm^3) was added dropwise with stirring, under a nitrogen atmosphere. After 20 min the solids had dissolved and the solution was cooled to 0 °C with a salt–ice bath. Trichloroacetonitrile (20 cm^3, 200 mmol) was then added dropwise during 15 min and the reaction mixture was allowed to warm to 20 °C over 60 min. A small amount of brown precipitate formed during the addition of the nitrile but did not appear to influence the course or yield of the reaction. The reaction mixture was concentrated to a syrup and pentane (20 cm^3) containing anhydrous methanol (0.8 cm^3, 21 mmol) was added, followed by vigorous shaking, filtration and concentration of the filtrate and pentane washings[8] (2 × 20 cm^3). The resultant imidate was obtained as a clear liquid and was used without further manipulation. The imidates were stored at 5 °C as solutions in hexane for periods of up to 2 months.

Benzyl trichloroacetimidate (**1**) had $\nu_{max.}$ 3 380 (NH) and 1 670 cm^{-1} (C=N); δ($CDCl_3$) 5.45 (2 H, s, CH_2Ph), 7.47 (5 H, s, CH_2Ph) and 8.46 (1 H, s, NH); allyl trichloroacetimidate (**2**) had $\nu_{max.}$ 3 350 (NH) and 1 670 cm^{-1} (C=N); δ_H($CDCl_3$) 4.79 (2 H, ddd ~ dt, ^4J 1.4, 1.2, ^3J 5.2 Hz, CH_2CHCH_2), 5.28 (1 H, ddt, ^2J 2.0, $^3J_{cis}$ 10.0 ^4J, Hz, CH_2 CH=CH*H*), 5.41 (1 H, ddt, ^2J 2.0, $^3J_{trans}$ 17.1 Hz, $CH_2CH{=}CHH$), 6.04 (1 H, ddt, ^3J 5.2 Hz, $CH_2CH{=}CH_2$) 8.22 (1 H, br s, NH); δ_C ($CDCl_3$) 131.4 ($CH_2CH{=}CH_2$), 118.5 ($CH_2CH{=}CH_2$) 69.6 (OCH_2).

General Procedure for Benzylation or Allylation by Trichloroacetimidates (**1**) *and* (**2**).—The carbohydrate derivative was dissolved in a minimum volume of carbon tetrachloride or dichloromethane as required by the polarity of the starting material. Two volumes of cyclohexane and the trichloroacetimidate (**1**) and (**2**) (2 mol per mol of free hydroxy group) were added together with trifluoromethanesulphonic acid (50 μl per gram of starting hydroxy component). The reaction was left overnight at 20 °C and the precipitated trichloroacetamide was

filtered off. The filtrate was either neutralized by addition of pyridine or extracted with aqueous sodium hydrogen carbonate and water and then dried, (Na_2SO_4). The residue after concentration was usually purified by chromatography on silica gel to remove side products such as trichloroacetamide and *N*-allyl- or *N*-benzyl-trichloroacetamide.

Methyl 2,4-*Di*-O-*benzoyl*-3-O-*benzyl*-α-L-*rhamnopyranoside* (**4**).—Methyl 2,4-di-*O*-benzoyl-α-L-rhamnopyranoside[15] (3) (114 mg, 0.3 mmol) was dissolved in dichloromethane (1 cm^3) and cyclohexane (2 cm^3). Benzyl trichloroacetimidate (**1**) (150 mg, 0.59 mmol) was added to the solution with stirring, followed by 1 drop (*ca.* 0.05 cm^3) of trifluoromethanesulphonic acid. After 18 h at 20 °C, pyridine (1 cm^3) was added to the reaction mixture, which was then diluted with dichloromethane (10 cm^3) and extracted with water. The dried, organic phase was evaporated to a syrup that on dissolution in the hexane and ethyl acetate gave crystals of trichloroacetamide. Preparative t.l.c. of the mother liquors using hexane–ethyl acetate (3:1) as eluant, gave the title compound (**4**) (101 mg, 71%) as a syrup, $[\alpha]_D^{24}$ 79.5° (*c* 1.58 in dichloromethane) (Found: C, 69.6; H, 6.05. $C_{28}H_{28}O_7$ requires C, 70.55; H, 5.9); δ_H (79.9 MHz; C_6D_6), 1.38 (3 H, d, $J_{5,6}$ 6.2 Hz, 6-H_3), 3.05 (3 H, s, OMe), 4.01 (1 H, dq, $J_{4,5}$ 9.8 Hz, 5-H), 4.26 (1 H, dd, $J_{2,3}$ 3.4, $J_{3,4}$ 9.9 Hz 3-H), 4.37 (1 H, d, $J_{A,B}$ 12.4 Hz, PhCHH_B), 4.61 (1 H, d, PhCHH_A), 4.80 (1 H, d, $J_{1,2}$ 1.7 Hz, 1-H), 5.95 (1 H, dd, $J_{2,3}$ 3.4, $J_{3,4}$ 9.9 Hz, 3-H), 5.99 (1 H, br t, $J_{3,4}$ 9.9, $J_{4,5}$ 9.8 Hz, 4-H), 6.81—7.21 (11 H, m, ArH), 7.98—8.16 (2 H, m, ArH), 8.21—8.39 (2 H, m, ArH); δ_C (20 MHz; $CDCl_3$), 99.0 (1 C, C-1), 74.3 (1 C, C-3), 73.3 (1 C, C-4), 70.9 (1 C, OCH_2), 69.0 (1 C, C-2), 66.6 (1 C, C-5), 55.2 (1 C, OMe).

ω-*Methoxycarbonyloctyl* 2-*Acetamido*-3-O-*benzyl*-4,6-O-*benzylidene*-2-*deoxy*-β-D-*glucopyranoside* (**8**).—ω-Methoxycarbonyloctyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[3] (244 mg, 0.49 mmol) was dissolved in dichloromethane (13 cm^3) and cyclohexane (20 cm^3). The benzylation was performed with the imidate (**1**) (155 mg, 0.61 mmol) and trifluoromethanesulphonic acid (0.5 cm^3). The reaction was worked up in the usual manner and the products were separated on a column of silica gel (50 g) using chloroform–acetone (4:1) as eluant. The target compound (**8**) (90 mg, 31%) was obtained as a syrup, $[\alpha]_D^{20}$ 19.9° (*c* 0.1, in dichloromethane) (Found: C, 65.35; H, 7.7; N, 2.5. $C_{32}H_{43}NO_9$ requires C, 65.6; H, 7.4; N, 2.4%); δ_C (20 MHz; $CDCl_3$). 101.2 (1 C, Ph*C*HO_2), 100.4 (C-1), 82.9 (C-4), 76.4 (C-3), 74.5 (Ph*C*H_2O), 70.1 (C-5), 68.8 (C-6), 65.9 ($OCH_2(CH_2)_6$), 58.1 (C-2), 51.5 (OMe), 34.1 [$(CH_2)_6CH_2$-CO_2Me)], 29.5, 29.4, 29.0, 25.8, 24.9 [$(CH_2)_6$], 23.5 (*Me*CONH). Some unchanged starting material was also recovered (157 mg, 64%).

Methyl 4-O-*Acetyl*-3-O-*allyl*-2-O-*benzoyl*-α-L-*rhamnopyranoside* (**10**).—The rhamnoside (**9**)[16] (590 mg, 1.82 mmol) in carbon tetrachloride (5 cm^3), dichloromethane (10 cm^3), and cyclohexane (30 cm^3) was treated with allyl trichloroacetimidate (740 mg, 3.65 mmol) according to the general procedure described above. Chromatography of the crude product with hexane–ethyl acetate (3:1) as eluant afforded the product (**10**) contaminated with *N*-allyl trichloroacetamide (1g). A single product was indicated by t.l.c. and an analytical sample of (**10**) was prepared by preparative t.l.c., $[\alpha]_D^{24}$ 43.6° (*c* 0.36, in dichloromethane) (Found: C, 62.35; H, 6.7. $C_{19}H_{24}O_7$ requires C, 62.6; H, 6.65%; δ_H (79.9 MHz; C_6D_6), 1.36 (3 H, d, $J_{5,6}$ 6.3 Hz, 6-H_3), 1.78 (3 H, s, *Me*CO), 3.04 (3 H, s, OMe), 3.80—4.08 (4 H, m, 4-H, 5-H, CH_2=CHCH_2O), 4.77 (1 H, d, $J_{1,2}$ 1.8 Hz, 1-H), 4.94, 5.13 (2 H, m, $J_{A,B}$ 2.2 Hz, J_{AC} 17.2 Hz, $J_{B,C}$ 10.0 Hz, CH_2=CHCH_2O), 5.74 (1 H, m, CH_2=C*H*CH_2O), 5.85 (1 H, dd, $J_{2,3}$ 3.4, $J_{1,2}$ 1.8 Hz, 2-H), 6.77—7.35 (3 H, m, ArH), 8.18—8.33 (2 H, m, ArH); δ_C (20 MHz, $CDCl_3$), 98.7 (1 C, C-1), 74.5 (1 C, C-3), 72.8 (1 C, C-4), 70.5 (1 C, $OCH_2CH=CH_2$), 69.4 (1 C, C-2), 66.4 (1 C, C-5), 17.6 (1 C, C-6).

Methyl 2,4-*Di*-O-*allyl*-3,6-*di*-O-*benzoyl*-α-D-*mannopyranoside* (**12**).—Methyl 3,6-di-*O*-benzoyl-α-D-mannopyranoside (**11**)[17] (500 mg, 1.24 mmol) in dichloromethane (30 cm^3) and cyclohexane (60 cm^3) was treated with allyl trichloroacetimidate (**1**) (1.0 g, 4.9 mmol). Work-up and chromatography over silica-gel with hexane–ethyl acetate (3:1) as eluant afforded (**12**) (410 mg, 68.5%) as a homogeneous syrup, $[\alpha]_D^{24}$ 51.5° (*c* 0.22 in dichloromethane) (Found: C, 67.8; H, 6.6. $C_{27}H_{30}O_8$ requires C, 67.2; H, 6.3); δ_H (79.9 MHz; C_6D_6), 3.09 (3 H, s, OMe), 3.83 (2 H, dt, CH_2=CHCH_2O), 4.01—4.22 (4 H, m, 2-H, 5-H, CH_2=CHCH_2O), 4.33 (1 H, dd, $J_{4,5}$ 9.9, $J_{3,4}$ 8.8 Hz 4-H), 4.70 (1 H, d, $J_{1,2}$ 2.0, 1-H), 4.76 (br d, 6-H_2), 4.78—5.31 (4 H, m, 2x OCH_2CH=CH_2), 5.75 (2 H, m, 2x OCH_2C*H*=CH_2), 5.95 (1 H, dd, $J_{2,3}$ 3.3 $J_{3,4}$ 8.8, 3-H), 7.04—7.26 (6 H, m, ArH), 8.19—8.28 (4 H, m, ArH). The crude reaction mixture contained a slower moving component as judged by t.l.c. [presumably a monoallylated derivative of (**11**)], which was not further examined.

Methyl 2,4-*Di*-O-*allyl*-α-D-*mannopyranoside* (**13**).—De-*O*-benzoylation of (**12**) (124 mg, 0.26 mmol) in absolute methanol (5 cm^3) containing 0.1% sodium methoxide gave (**13**) (68 mg, 96%), after removal of sodium ions with ion exchange resin and filtration through silica gel to remove methyl benzoate. The product (**13**), a homogeneous syrup had $[\alpha]_D^{24}$ 38.2° (*c* 0.33 in dichloromethane) (Found: C, 56.75; H, 8.1. $C_{13}H_{22}O_6$ requires C, 56.9; H, 7.95); δ_H (79.9 MHz; C_6D_6), 3.1 (3 H, s, OMe), 3.64 (1 H, dd, $J_{2,3}$ 3.5, $J_{1,2}$ 1.7 Hz, 2-H), 3.51—3.90 (4 H, m, 4-H, 5-H, 6-H), 3.93 (2 H, br dt, CH_2=CHCH_2O), 4.16 (1 H), 4.17 (1 H, dd, $J_{3,4}$ *ca.* 8.7, $J_{2,3}$ 3.5 Hz, 3-H), 4.43 (1 H, m, CH_2=CHCH_2O), 4.66 (1 H, d, $J_{1,2}$ 1.7 Hz, 1-H), 4.94—5.02 (2 H, m, OCH_2CH=CH_2), 5.17 (1 H, m, OCH_2CH=CH_2), 5.25 (1 H, m, OCH_2CH=CH_2), 5.83 (1 H, m, OCH_2C*H*=CH_2), and 5.96 (1 H, m, OCH_2C*H*=CH_2).

Methyl 2,4-*Di*-O-*allyl*-3,6-*di*-O-*benzoyl*-β-D-*galactopyranoside* (**15**).—Methyl 3,6-di-*O*-benzoyl-β-D-galactopyranoside[17] (**14**) (210 mg, 525 μmol) in dichloromethane (50 cm^3) and cyclohexane (90 cm^3) was treated with (**1**) (425 mg, 2.1 mmol). After work-up, chromatography on silica gel using hexane–ethyl acetate (3:1) as the eluant afforded the product (**15**) (136 mg, 54%) as a homogeneous syrup; $[\alpha]_D^{24}$ −3.8° (*c* 0.21, in dichloromethane) (Found: C, 67.0; H, 6.50. $C_{27}H_{30}O_8$ requires C, 67.2; H, 6.25); δ_H (79.9 MHz; C_6D_6), 3.38 (3 H, s, OMe), 3.51 (1 H, br t, $J_{4,5}$ *ca.* 1.0, 5-H), 3.89—4.42 (7 H, m, 1-H, 2-H, 4-H, CH_2=CHCH_2O), 4.53 (1 H, dd, $J_{5,6}$ 5.9, $J_{6,6'}$ 10.3 Hz, 6-H), 4.70 (1 H, dd, $J_{5,6'}$ 5.9, $J_{6,6'}$ 10.3, 6'-H), 4.85—5.34 (4 H, m, OCH_2CH=CH_2), 5.42 (1 H, dd, $J_{2,3}$ 8.3, $J_{3,4}$ 3.1, 3-H), 7.04—7.53 (6 H, m, ArH), and 8.22—8.44 (4 H, m, ArH). The crude reaction mixture as judged by t.l.c. appeared to contain a monoallylated product, whilst none of the starting diol remained.

Methyl 2,4-*Di*-O-*allyl*-β-D-*galactopyranoside* (**16**).—Compound (**15**) (50 mg, 0.1 mmol) was de-*O*-benzoylated in absolute methanol (3 cm^3) in a similar fashion to that described for compound (**13**). After 18 h at 20 °C, the product was deionized and purified by preparative t.l.c. with hexane–ethyl acetate (2:1) as the eluant, to yield the title compound as a syrup (22 mg, 77%), $[\alpha]_D^{24}$ 6.1° (*c* 0.13, in dichloromethane) (Found: C, 56.7; H, 8.2. $C_{13}H_{22}O_6$ requires C, 56.9; H, 7.95; δ_H (79.9 MHz; C_6D_6), 3.15—4.70 (11 H, m, 1-H—6-H, CH_2=CHCH_2O), 3.44 (s, OMe), 4.91—5.46 (4 H, m, 2xCH_2=CH—CH_2O), and 5.68—6.18 (2 H, m, 2xCH_2=C*H*CH_2O).

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