The Allyl Ether as a Protecting Group in Carbohydrate Chemistry. Part 11.[1] The 3-Methylbut-2-enyl (' Prenyl ') Group

By **Roy Gigg**, Laboratory of Lipid and General Chemistry, National Institute for Medical Research, Mill Hill, London NW7 1AA

The ' prenyl ' group in allyl 3,4,6-tri-*O*-benzyl-2-*O*-(3-methylbut-2-enyl)-α-D-galactopyranoside was stable to the action of chlorotris(triphenylphosphine)rhodium(I) during 24 h, whilst the allyl group was isomerised within 1 h. Previous work has shown that the but-2-enyl group is completely isomerised within 24 h by the rhodium catalyst. Thus an allyl group can be removed without affecting a ' prenyl ' group in the same molecule. The ' prenyl ' group is cleaved at about the same rate as a but-2-enyl group by potassium t-butoxide in dimethyl sulphoxide. The isomerisation of the allyl group by the rhodium catalyst gives a mixture of *cis*- and *trans*-prop-1-enyl ethers.

We have reviewed [2] the use of the allyl, prop-1-enyl, but-2-enyl, 2-methylallyl, and 1-methylallyl ethers for the protection of hydroxy-groups in carbohydrate chemistry. The but-2-enyl ether is cleaved by the action of potassium t-butoxide in dimethyl sulphoxide, whereas the other allyl ethers are isomerised to the corresponding enol-ethers and this difference in behaviour has been exploited in synthetic work.[1-3] The but-2-enyl ethers exist as a mixture of *trans*- and *cis*-isomers in a ratio of *ca.* 95 : 5 and although this is not a problem when the but-2-enyl group is used as a ' temporary ' protecting group, a symmetrical group giving a single isomer might be preferable for the isolation of crystalline intermediates.

We have therefore investigated the use of the 3-methylbut-2-enyl (' prenyl ') ethers, which are readily prepared from 1-bromo-3-methylbut-2-ene (Lancaster Synthesis Ltd.) and sodium hydride in *NN*-dimethylformamide. We find that the ' prenyl ' group is cleaved at about the same rate as the but-2-enyl group by potassium t-butoxide in dimethyl sulphoxide. Thus the ' prenyl ' group has no advantage over the but-2-enyl group if it is required to preserve an allyl group when removing a but-2-enyl group in the same molecule, as described previously [4] for a synthesis of allyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside.

Golborn and Scheinmann [5] have shown that whereas allyl and *trans*-but-2-enyl ethers were isomerised to the enol-ethers by dichlorobis(benzonitrile)palladium(II), 2-methylallyl, *cis*-but-2-enyl, and ' prenyl ' ethers were not isomerised. Recently, Baudry *et al.*[6] also showed that a cationic iridium complex readily isomerised allyl and *trans*-but-2-enyl ethers to the corresponding *trans*-enol-ethers, whereas 1-methylallyl, *cis*-but-2-enyl, and ' prenyl ' ethers were not affected by the catalyst. We have shown previously [7] that the but-2-enyl group was isomerized more slowly than the allyl group by chlorotris(triphenylphosphine)rhodium(I), and we have now investigated the effect of the rhodium catalyst on the ' prenyl ' group in some carbohydrate derivatives.

RESULTS AND DISCUSSION

Allyl 6-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (1) [8] was converted into the 2-*O*-(3-methylbut-2-enyl) ether (2) which on acidic hydrolysis gave the diol (3). Benzylation of compound (3) gave allyl 3,4,6-tri-*O*-benzyl-2-*O*-(3-methylbut-2-enyl)-α-D-galactopyranoside (4). When compound (4) was treated with chlorotris(triphenylphosphine)rhodium(I) under the conditions described previously,[7] t.l.c. showed conversion of the starting material into a new product during 1 h and no further change during 24 h. Acidic hydrolysis of the product (to remove the prop-1-enyl group) gave a product with a similar mobility to 2-*O*-allyl-3,4,6-tri-*O*-benzyl-D-galactopyranoside on t.l.c., which on reduction with sodium borohydride and subsequent treatment with potassium t-butoxide in dimethyl sulphoxide (to remove the ' prenyl ' group) gave crystalline 3,4,6-tri-*O*-benzyl-D-galactitol, identical with the material prepared previously.[8]

The ' prenyl ' group is therefore stable to the action of the rhodium catalyst during 24 h, thus allowing the removal of an allyl group in the same molecule. Under the same conditions the but-2-enyl group is isomerised in 24 h by the rhodium catalyst.[7]

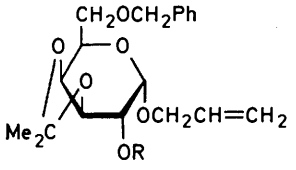
The isomerisation of an allyl ether by potassium t-butoxide in dimethyl sulphoxide gives [9] *ca.* 99% of the *cis*-prop-1-enyl ether but isomerisations with various complex metal derivatives give [5,6] mixtures of *cis*- and *trans*-prop-1-enyl ethers or pure *trans*-prop-1-enyl ethers.

Although the rhodium catalyst has been used extensively [7,10] for the isomerisation of allyl groups in the carbohydrate field, there is no recorded information on the composition of the prop-1-enyl ethers obtained. This is not generally important since the prop-1-enyl group is usually hydrolysed directly, but it could be an important consideration if crystalline intermediates were required.

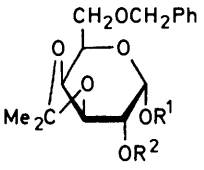
The galactose derivative (4) was treated with the rhodium complex, and when t.l.c. showed that the isomerisation was complete the product was treated with potassium t-butoxide in dimethyl sulphoxide to remove the ' prenyl ' group. It has been shown previously [9b] that potassium t-butoxide does not cause the isomerisation of a *trans*-prop-1-enyl ether to a *cis*-prop-1-enyl ether. A crystalline product was isolated from the total product and this was shown by ^{1}H n.m.r. spectroscopy to be the *trans*-prop-1-enyl ether (8). When compound

(4) was treated directly with potassium t-butoxide in dimethyl sulphoxide the ' prenyl ' group was cleaved and the allyl group was isomerised to give the *cis*-prop-1-enyl ether (7) which was obtained as a syrup. The ^{1}H n.m.r. spectra of *cis*- and *trans*-prop-1-enyl ethers have been studied previously [5,6] and these show characteristic coupling constants for the vinyl proton adjacent to the oxygen atom of *cis*- and *trans*-prop-1-enyl ethers.

The *cis*- and *trans*-prop-1-enyl ethers (5) and (6) were not resolved by t.l.c. but when the derivative (2) was treated with the rhodium catalyst, conversion into two less polar products (10) and (11) (*ca.* 3 : 2 by t.l.c.) was observed in 1 h. The *cis*-prop-1-enyl ether (10) was also prepared by a different route for comparison; the action of potassium t-butoxide on compound (1) gave the *cis*-prop-1-enyl glycoside (9) and this was alkylated with 1-bromo-3-methylbut-2-ene to give the *cis*-prop-1-enyl glycoside (10) which co-chromatographed with the faster of the two products obtained by the action of the rhodium catalyst on compound (2).

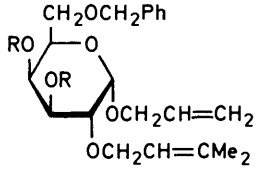


(1) R = H
(2) R = $CH_2CH{=}CMe_2$

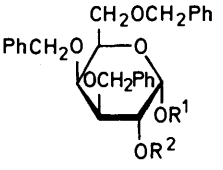


(9) R^1 = *cis* − CH=CHMe ; R^2 = H
(10) R^1 = *cis* − CH=CHMe ; R^2 = $CH_2CH{=}CMe_2$
(11) R^1 = *trans* − CH=CHMe ; R^2 = $CH_2CH{=}CMe_2$

sodium hydride was destroyed by the addition of methanol and the product (7.9 g) was isolated in the usual way and chromatographed on basic alumina to remove traces of impurities. After elution of by-products with ether–light petroleum (1 : 2) the pure product (2) (6.7 g) was eluted with ether–light petroleum (1 : 1). Compound (2) (6.3 g) was taken up in methanol (90 ml) and 1N hydrochloric acid (10 ml) and the solution was heated under reflux for 20 min, after which time t.l.c. (as above) showed complete conversion of compound (2) into the diol (3) (R_F 0). An excess of sodium hydrogencarbonate was added and the solvents were evaporated off. The product (5.5 g) was extracted from the residue with chloroform and benzylated with benzyl bromide and sodium hydride in *NN*-dimethylformamide and the crude product (4) (R_F 0.85, t.l.c. as above) was isolated in the usual way and chromatographed on basic alumina. After elution of by-products with ether–light petroleum (1 : 4), elution with ether–light petroleum (1 : 1) gave the *benzyl ether* (4) (7 g), $[\alpha]_D$ +42.5° (*c* 1.0 in $CHCl_3$) (Found: C, 75.5; H, 7.6. $C_{35}H_{42}O_6$ requires C, 75.2; H, 7.6%).



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



(5) R^1 = *cis* − CH=CHMe ; R^2 = $CH_2CH{=}CMe_2$
(6) R^1 = *trans* − CH=CHMe ; R^2 = $CH_2CH{=}CMe_2$
(7) R^1 = *cis* − CH=CHMe ; R^2 = H
(8) R^1 = *trans* − CH=CHMe ; R^2 = H

EXPERIMENTAL

Solvents were evaporated off under reduced pressure. The light petroleum used had b.p. 40—60 °C. T.l.c. was carried out on microscope slides coated with silica gel G. Optical rotations were measured at 22—24 °C with a Bendix automatic polarimeter.

Allyl 3,4,6-Tri-O-benzyl-2-O-(3-methylbut-2-enyl)-α-D-galactopyranoside (4).—Allyl 6-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (1) [8] (6.4 g), sodium hydride (3 g), and 1-bromo-3-methylbut-2-ene (6 g) (Lancaster Synthesis Ltd.) were stirred in dry *NN*-dimethylformamide at 20 °C for 2 h, after which time t.l.c. [ether–light petroleum (1 : 2)] showed complete conversion of the alcohol (1) (R_F 0.2) into the ' prenyl ' ether (2) (R_F 0.7). The excess of

Action of Chlorotris(triphenylphosphine)rhodium(I) on Compound (4).—A mixture of compound (4) (350 mg), diazabicyclo[2.2.2]octane (35 mg) and chlorotris(triphenylphosphine)rhodium(I) (35 mg) in ethanol (7 ml), benzene (3 ml), and water (1 ml) was heated under reflux. After 1 h t.l.c. [ether–light petroleum (1 : 2)] showed complete conversion of compound (4) (R_F 0.85) into a new product (R_F 0.9). After 24 h the t.l.c. pattern was similar with only traces of other products visible. The solvents were evaporated off and toluene was evaporated from the residue to remove traces of polar solvents. The crude product was chromatographed on basic alumina and elution with ether–light petroleum (1 : 1) gave the product (300 mg) free from the base and rhodium derivatives. The product was taken up in 1N-hydrochloric acid–acetone (1 : 9) (10 ml) and the solution was heated under reflux for 15 min after which time

t.l.c. [ether–light petroleum (2 : 1)] showed complete conversion of the starting material (R_F 1) into a new product (R_F 0.5) and only traces of other products. The product (250 mg), which co-chromatographed with 2-*O*-allyl-3,4,6-tri-*O*-benzyl-D-galactopyranose prepared previously,[11] was reduced with sodium borohydride in ethanol to give 3,4,6-tri-*O*-benzyl-2-*O*-(3-methylbut-2-enyl)-D-galactitol (R_F 0.4, t.l.c. as above). The galactitol derivative was treated with potassium t-butoxide in dimethyl sulphoxide, in the usual way, to remove the 'prenyl' group and the product was crystallised from ether–light petroleum to give 3,4,6-tri-*O*-benzyl-D-galactitol (50 mg), m.p. and mixed m.p. (with material prepared previously [8]) 98—99 °C.

trans-*Prop*-1-*enyl* 3,4,6-*Tri*-O-*benzyl*-α-D-*galactopyranoside* (8).—Allyl 3,4,6-tri-*O*-benzyl-2-*O*-(3-methylbut-2-enyl)-α-D-galactopyranoside (4) (1.5 g), diazabicyclo[2.2.2]octane (100 mg), and chlorotris(triphenylphosphine)rhodium(I) (100 mg) in ethanol (21 ml), benzene (9 ml), and water (3 ml) were heated under reflux for 1 h, after which time t.l.c. showed complete conversion of compound (4) into the prop-1-enyl glycoside (see above). The crude product was chromatographed on basic alumina as described above, to remove the base and rhodium derivatives, to give the purified product (1.4 g). This product (1.3 g) was treated with potassium t-butoxide (2 g) in dry dimethyl sulphoxide (25 ml) at 50 °C for 2 h after which time t.l.c. [ether–light petroleum (1 : 2)] showed complete conversion of the 'prenyl' derivative (R_F 0.9) into the alcohol (R_F 0.25). The product was isolated in the usual way and crystallised from ether–light petroleum to give the trans-*prop*-1-*enyl glycoside* (8) (100 mg), m.p. 95—98 °C; $[\alpha]_D$ +86.6° (*c* 1.0 in $CHCl_3$); τ 3.86 (*J* 12.3 Hz) for the vinyl proton of the prop-1-enyl group adjacent to the oxygen atom (Found: C, 73.9; H, 7.0. $C_{30}H_{34}O_6$ requires C, 73.4; H, 7.0%). The mother-liquors contained both *cis*- (7) and *trans*- (8) isomers of the prop-1-enyl glycoside.

cis-*Prop*-1-*enyl* 3,4,6-*Tri*-O-*benzyl*-α-D-*galactopyranoside* (7).—Allyl-3,4,6-tri-*O*-benzyl-2-*O*-(3-methylbut-2-enyl)-α-D-galactopyranoside (4) (950 mg) and potassium t-butoxide (2 g) in dry dimethyl sulphoxide (25 ml) were kept at 50 °C. T.l.c. [ether–light petroleum (1 : 1)] showed rapid conversion of the 'prenyl' ether (4) (R_F 0.95) into the corresponding alcohol (R_F 0.5) and after 2 h this was converted entirely into the *cis*-prop-1-enyl glycoside (7) (R_F 0.6). The product was isolated in the usual way and chromatographed on basic alumina. Elution with ether removed traces of impurities and elution with ether–methanol (49 : 1) gave the *product* (7) (650 mg) as a syrup; $[\alpha]_D$ +57.3° (*c* 1.0 in $CHCl_3$); τ 3.95 (*J* 6.2 Hz) for the vinyl proton of the prop-1-enyl group adjacent to the oxygen atom (Found: C, 73.6; H, 6.9. $C_{30}H_{34}O_6$ requires C, 73.4; H, 7.0%).

Action of Chlorotris(triphenylphosphine)rhodium(I) *on Allyl* 6-O-*Benzyl*-3,4-O-*isopropylidene*-2-O-(3-*methylbut*-2-*enyl*)-α-D-*galactopyranoside* (2).—The allyl glycoside (2) (180 mg), diazabicyclo[2.2.2]octane (10 mg) and the rhodium catalyst (10 mg) in ethanol (7 ml), benzene (3 ml), and water (1 ml) were heated under reflux for 1 h. T.l.c. [ether–light petroleum (1 : 2)] then showed complete conversion of compound (2) into two new products (R_F 0.75 and 0.8), in a ratio of *ca.* 3 : 2, respectively, presumed to be the *cis*-isomer (10) and the *trans*-isomer (11) respectively. The *cis*-isomer (10) was also prepared as follows. Allyl 6-*O*-benzyl-2,3-*O*-isopropylidene-α-D-galactopyranoside (1) [8] was treated with potassium t-butoxide in dimethyl sulphoxide at 50 °C for 1 h after which time t.l.c. [ether–light petroleum (3 : 2)] showed complete conversion of the allyl glycoside (1) (R_F 0.5) into the *cis*-prop-1-enyl glycoside (9) (R_F 0.6). The product was isolated in the usual way and alkylated with 1-bromo-3-methylbut-2-ene and sodium hydride in *NN*-dimethylformamide at 20 °C. After 2 h, t.l.c. [ether–light petroleum (1 : 2)] showed complete conversion of the alcohol (9) (R_F 0.3) into the 'prenyl' ether (10) (R_F 0.8) which co-chromatographed with the less polar of the two isomers (10) and (11), prepared as described above using the rhodium catalyst.

We thank Dr. J. Feeney and Mrs. J. Cayley for the n.m.r. spectra and Mr. R. Conant for technical assistance.

[9/877 *Received*, 8*th June*, 1979]

REFERENCES

[1] Part 10, R. Gigg, *J.C.S. Perkin I*, 1979, 712.
[2] R. Gigg, *A.C.S. Symposium Series*, No. 39, 1977, p. 253; No. 77, 1978, p. 44.
[3] P. A. Gent, R. Gigg, and A. A. E. Penglis, *J.C.S. Perkin I*, 1976, 1395.
[4] P. A. Gent and R. Gigg, *Carbohydrate Res.*, 1976, **49**, 325.
[5] P. Golborn and F. Scheinmann, *J.C.S. Perkin I*, 1973, 2870.
[6] D. Baudry, M. Ephritikhine, and H. Felkin, *J.C.S. Chem. Comm.*, 1978, 694.
[7] P. A. Gent and R. Gigg, *J.C.S. Chem. Comm.*, 1974, 277.
[8] J. Gigg and R. Gigg, *J. Chem. Soc.* (*C*), 1966, 82.
[9] (*a*) C. C. Price and W. H. Snyder, *J. Amer. Chem. Soc.*, 1961, **83**, 1773; (*b*) T. J. Prosser, *ibid.*, p. 1701.
[10] M. A. E. Shaban, V. N. Reinhold, and R. W. Jeanloz, *Carbohydrate Res.*, 1977, **59**, 213; C. D. Warren and R. W. Jeanloz, *ibid.*, 1977, **53**, 67; E. Walker-Nasir and R. W. Jeanloz, *ibid.*, 1979, **68**, 343; C. Augé and A. Veyrières, *ibid.*, 1977, **54**, 45; J. C. Jacquinet and P. Sinaÿ, *J.C.S. Perkin I*, 1979, 314, 319.
[11] P. A. Gent and R. Gigg, *J.C.S. Perkin I*, 1975, 361.