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SYNTHESIS OF INTERMEDIATES FOR STEREOSPECIFIC SYNTHESIS OF α- AND ß-C-NUCLEOSIDES: RING CONTRACTION OF PROTECTED 2-O-TRIFLUOROMETHANESULPHONATES OF GALACTO- AND ALTRO-PYRANOSIDES

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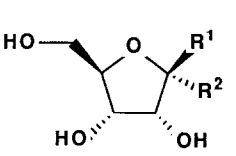
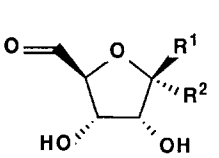
The reactions of sodium azide with methyl 6-O-(tert-butyldiphenyl)silyl-3,4-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-galactopyranosides and with methyl 6-O-(tert-butyldiphenyl)silyl-3,4-O-isopropylidene-2-O-trifluoromethanesulphonyl-α-D-altropyranoside give, respectively, intermediates suitable for the stereospecific synthesis of α- and ß-C-nucleosides.

There are a number of naturally occurring C-nucleosides with interesting biological activity.[1] Also, synthetic C-nucleoside isosteres of adenosine[2] and oxanosine[3] have potential anti-viral properties. Suitably protected forms of the aldehydes (1) and (2) have been used in the synthesis of such compounds;[4] moreover chiral equivalents of the dialdehydes (3) and (4), which would allow sequential development of side chain by Wittig olefinations, would be useful in approaches to the synthesis of the efrotomycin-aurodox family of antibiotics.[5] This paper reports the synthesis of the alkoxyazides (5) [a protected equivalent of (1) and (3)] and (6) [a protected equivalent of (2) and (4)] by an efficient ring contraction of protected 2-O-trifluoromethanesulphonyl esters of galacto- and altro-pyranosides.



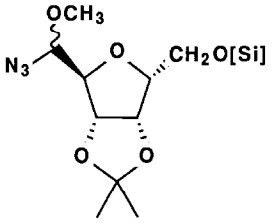
(1) R^1=H; R^2=CHO

(2) R^1=CHO; R^2=H

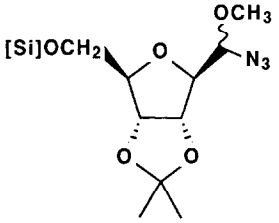


(3) R^1=H; R^2=CHO

(4) R^1=CHO; R^2=H



(5)

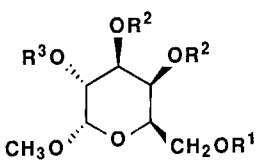


(6)

[Si] = $^tBuPh_2Si$

Treatment of methyl α-D-galactopyranoside (7) with tert-butylchlorodiphenylsilane in the presence of imidazole caused selective protection of the primary hydroxyl group to form (8)[6] [79% yield] which with acetone - dimethoxypropane in the presence of camphor sulphonic acid gave (9) [90% yield]. Esterification of the remaining free hydroxyl group in (9) with trifluoromethanesulphonic anhydride and pyridine in dichloromethane gave the triflate (10) [88% yield]. When the triflate (10) was treated with sodium azide in dimethylformamide at 40° for 15 h, the alkoxyazides (5)[7] were produced in 81% yield in a ratio of 2:1 [52% yield from (7)]; no other azides could be

isolated from the reaction mixture. By a similar sequence of reactions, methyl ß-D-galactopyranoside (11) was converted to the protected ß-alcohol (12) [60% overall yield]. Reaction of (12) with trifluoromethane sulphonic anhydride, followed by sodium azide also gave the epimeric azides (5) in a yield of 91% and a ratio of 1:2.5; again no other organic azides could be isolated from the reaction mixture. When the alkoxyazides (5) were hydrogenated in ethanol-water in the presence of 5% palladium on carbon, the protected 2,5-anhydro-D-talose (14), isolated by flash chromatography, was formed in 91% yield. Reduction of the aldehyde (14) with sodium borohydride gave (15) [59% yield]; the silyl group was removed from (15) by treatment with tetrabutyl ammonium fluoride in tetrahydrofuran to give 2,5-anhydro-3,4-O-isopropylidene-D-talitol (16),[8] $[\alpha]_D^{20}$ -7.4° (c, 1.8 in EtOH) [lit.[9] $[\alpha]_D^{20}$ -9.3° (c, 0.37 in EtOH)], in 93% yield. Acetylation of (16) with acetic anhydride in pyridine gave the diacetate (17) with an identical ^{13}C NMR spectrum to that previously reported.[10] α-Alkoxyazides have been used as intermediates in the reductive amination of aldehydes and ketones to primary amines;[11] thus reduction of (5) with lithium aluminum hydride in tetrahydrofuran gave the amine (18), $[\alpha]_D^{20}$ -5.2° (c, 1.8 in $CHCl_3$), which on treatment with acetic anhydride in pyridine gave the acetamide (19), $[\alpha]_D^{20}$ $+13.7^{\circ}$ (c, 1.6 in $CHCl_3$), in 60% overall yield.

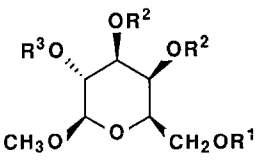


(7) R^1=R^2=R^3=H

(8) R^1=[Si]; R^2=R^3=H

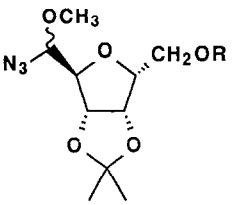
(9) R^1=[Si]; R^2=Me_2C; R^3=H

(10) R^1=[Si]; R^2=Me_2C; R^3=CF_3SO_2



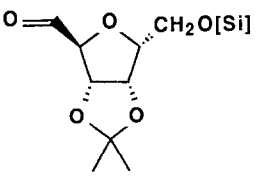
(11) R^1=R^2=R^3=H

(12) R^1=[Si]; R^2=Me_2C; R^3=H



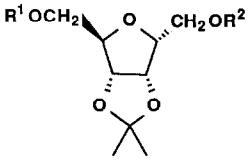
(5) R=[Si]

(13) R=H



(14)

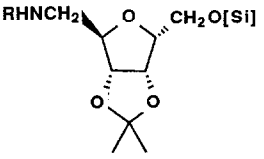
The potential of the alkoxyazides (5) as intermediates in synthesis was demonstrated by Wittig extensions of aldehydes derived from C-1 and C-6 of galactose. Thus, the aldehyde (14) in which the aldehyde carbon was C-1 of galactose gave the Z-olefin (20)[12] with acetylmethylene triphenylphosphorane, $Ph_3PCHCOMe$, in dichloromethane (67% yield). Removal of the silyl protecting group in (5) by fluoride ion formed (13) in 95% yield and a Swern oxidation of (13) using dimethylsulphoxide - oxalyl chloride at $-78^{\circ}C$, followed by triethylamine gave an aldehyde derived from C-6 of galactose; the aldehyde so generated was treated in situ with acetylmethylene triphenylphosphorane to give a mixture of the Z- (21) and E- (22) isomers in a ratio of 1:4 and in an overall yield of 68% from (13). Thus suitable manipulation of (5) should allow the stereospecific synthesis of α-C-nucleosides.



(15) R^1=H; R^2=[Si]

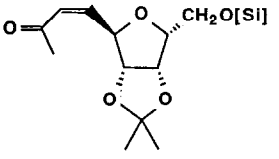
(16) R^1=R^2=H

(17) R^1=R^2=MeCO

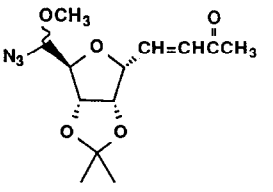


(18) R=H

(19) R=MeCO



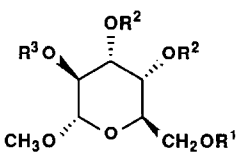
(20)



(21) Z isomer

(22) E isomer

The alkoxyazides (6) were prepared from the readily available[13] methyl α-D-altropyranoside (23). By procedures similar to those used for the galactopyranoside series, the altropyranoside (23) was first selectively silylated to give (24) and then converted to the acetonide (25) [67% yield from (23)]. The free hydroxyl group in (25) was esterified with trifluoromethanesulphonic anhydride, and the resulting triflate (26) was treated with sodium azide to give the alkoxyazides (6)[14] in 89% yield [61% overall yield from (23)]. No other azide was isolated from this reaction mixture. Hydrogenation of the alkoxyazides (6) in ethanol-water in the presence of 5% palladium on charcoal gave the protected 2,5-anhydro-D-allose (27) in 89% yield. Reduction of the aldehyde (27) with sodium borohydride gave (28), $[\alpha]_D^{20}$ +8.4° (c, 1.9 in CH_2Cl_2), [61% yield from (6)]; the silyl group was removed from (28) by treatment with tetrabutyl ammonium fluoride in tetrahydrofuran to give 2,5-anhydro-3,4-O-isopropylidene-allitol (29), $[\alpha]_D^{20}$ 0° (c, 1.12 in CH_2Cl_2) [lit.[9] $[\alpha]_D^{20}$ 0°], in 89% yield. The ^{13}C NMR spectrum of (29)[15] shows 6 magnetically different types of carbon in contrast to the 9 magnetically different types of carbon in the ^{13}C NMR spectrum of the talitol (16). The structure of the alkoxyazides (6) was further confirmed by lithium aluminum hydride reduction of (6) to the primary amine (30) $[\alpha]_D^{20}$ +4.5° (c, 1.1 in $CHCl_3$); reaction of (30) with acetic anhydride in pyridine gave the acetamide (31), $[\alpha]_D^{20}$ +2° (c, 0.74 in $CHCl_3$), in 63% overall yield from (6).

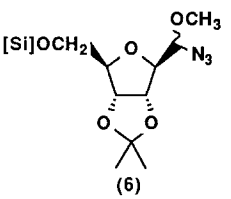


(23) R^1=R^2=R^3=H

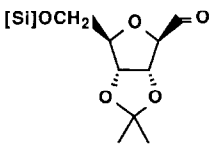
(24) R^1=[Si]; R^2=R^3=H

(25) R^1=[Si]; R^2=Me_2C; R^3=H

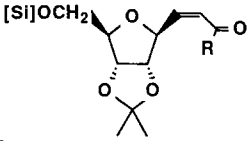
(26) R^1=[Si]; R^2=Me_2C; R^3=CF_3SO_2



(6)

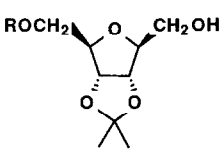


(27)



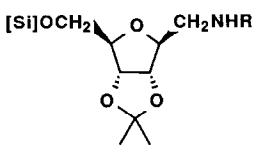
(32) R=CH_3

(33) R=OCH_3



(28) R=[Si]

(29) R=H



(30) R=H

(31) R=MeCO

The possible value of the alkoxyazides (6) as intermediates for the stereospecific synthesis of ß-C-nucleosides was demonstrated by Wittig olefinations of the aldehyde (27), prepared by hydrogenation of (6). Thus a solution of (27) in dichloromethane with acetylmethylene triphenylphosphorane gave the unsaturated ketone (32),[16] $[\alpha]_D^{20}$ -8.2° (c, 1.3 in $CHCl_3$), in 61% yield from (6); treatment of (27) with carbomethoxymethylene triphenylphosphorane formed the unsaturated ester (33),[17] $[\alpha]_D^{20}$ -12.6° (c, 1.0 in $CHCl_3$), in 61% yield (from 6).

The efficient ring contractions in the reactions of sodium azide in dimethylformamide with the highly hindered 2-O-trifluoromethanesulphonates of the altropyranoside (25) and the galactopyranosides (9) and (12) are in marked contrast to the high yield direct displacement by azide of the less hindered 2-O-trifluoromethanesulphonates of glucopyranosides[18] and glucofuranosides.[19] Although there are many examples of ring contractions of 4-O-sulphonates of hexopyranosides,[20] ring contractions of 2-O-sulphonates of hexopyranosides are rare. There are similarities between the ring contractions reported in this paper and those arising from the reactions of 2-aminoglycosides with nitrous acid.[21] We are currently investigating the potential of the alkoxyazides (5) and (6) in the synthesis of α- and ß-C-nucleosides.

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5. A. J. Kempe, K. E. Wilson, O. D. Hensens, R. L. Monaghan, S. B. Zimmerman and E. L. Delaney, J. Antibiotics, 1986, 39, 1361.
6. All new compounds in this paper have satisfactory spectral data; correct CHN microanalyses have been obtained for compounds (5), (6), (12), (13) [both separate epimers], (16), (19), (20), (22), (25), (29), (31), (32) and (33).
7. The two alkoxyazides (5) are readily separated by flash chromatography. The reactions discussed in the paper were performed on the separated epimers of (5) and also on the mixture of epimers.
8. ^{13}C NMR spectrum of talitol (16) δ ($CDCl_3$): 24.70 (q), 26.18 (q), 61.64 (t), 62.15 (t), 80.83 (d), 81.50 (d), 82.55 (d), 84.37 (d) and 113.07 (s).
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12. Coupling constant between the olefinic protons at δ 6.34 and 6.35 is 6 Hz.
13. N. K. Richtmeyer, Methods in Carbohydr. Chem., 1962, 1, 107.
14. The two alkoxyazides (6), formed in a ration of 3:1 are readily separated by flash chromatography. The reactions discussed in the paper were performed on the separated epimers of (6) and also on the mixture of epimers.
15. ^{13}C NMR spectrum of allitol (29) δ ($CDCl_3$): 25.45 (q), 27.45 (q), 63.15 (t), 81.60 (d), 85.14 (d), and 113.81 (s).
16. Coupling constant between the olefinic protons at δ 6.37 and 6.83 is 6.1Hz.
17. Coupling constant between the olefinic protons at δ 6.17 and 7.04 is 5.7Hz.
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