Synthesis of functionalised derivatives of pentaerythritol

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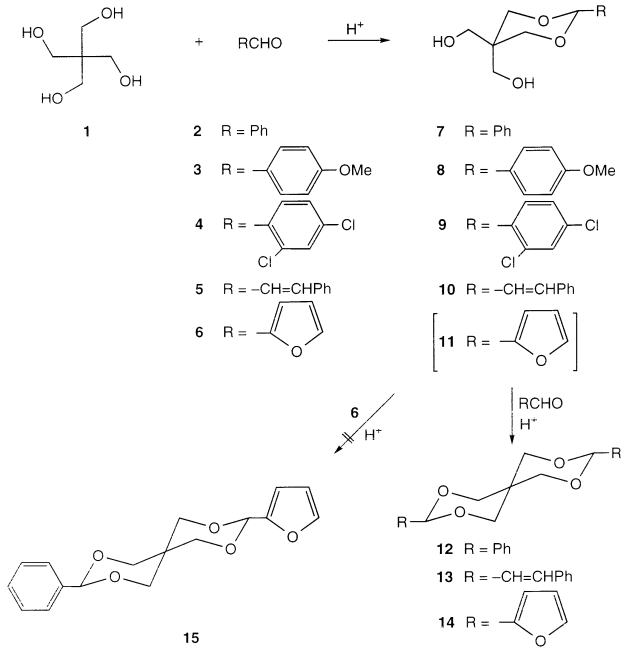
The synthesis of functionalised derivatives of pentaerythritol has been attempted by the reaction of **1** with different aldehydes and nucleophilic reagents; the activity of various derivatives against hepatitis B virus has been studied.

Keywords: pentaerythritol, acyclic nucleosides, hepatitis B virus

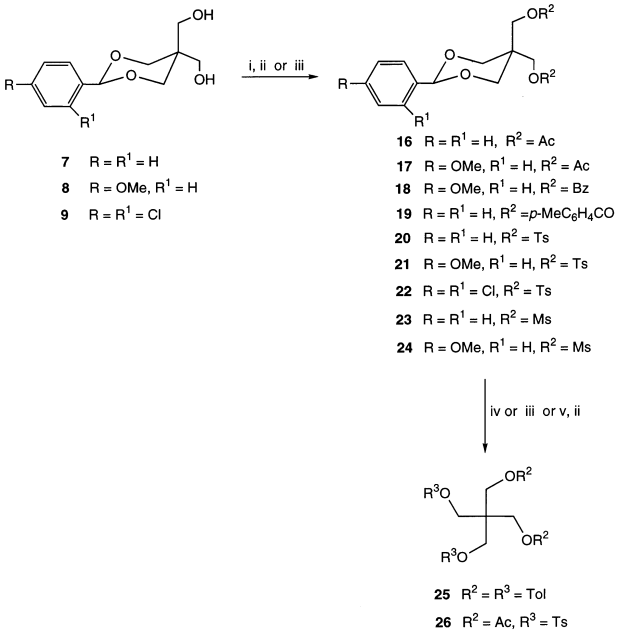
Acyclic nucleosides[1–3] with their chemotherapeutic value[4–22] as well as denderimers[23–29] are important classes of compounds. Synthesis of precursors that could lead to such classes are of considerable importance. The structural features of pentaerythritol make it suitable for functionalisation and consequently further branching can be possible. Thus, introducing a good leaving group that could be displaced by a heterocyclic ring and the capability of the respective acetals for further chemical modification attracted our attention to the investigation of the functionalisation of pentaerythritol.



Scheme 1

Reaction of pentaerythritol **(1)** with benzaldehyde **(2)** gave the mono **7** and dibenzylidene **12** derivatives[30] Scheme 1. Similarly, reaction of **1** with cinnamaldehyde gave **10** and **13**. However, reaction of **1** with *p*-anisaldehyde **(3)** or 2,4-dichlorobenzaldehyde **(4)** afforded the monoarylidene derivatives **8** or **9**, respectively as the only isolated products. This can be due to their high insolubilities which led to their crystallisation out from reaction mixture prior to further reaction with the corresponding aldehyde to give the respective diarylidene derivatives. The ^{1}H NMR of the monoarylidene derivatives showed the acetal proton in the range δ 5.09–5.59 ppm and the two methylene groups on position-5 at different locations agreeing with their axial and equatorial natures. The two equatorial 4-H and 6-H appeared at different chemical shifts from those in the axial positions. The ^{1}H NMR spectrum of the dicinnamylidene derivative **13** showed a doublet at δ 6.66 ppm corresponding to the two acetal protons, which are equivalent and are coupled with the styryl proton. Treatment of **1** with furfuraldehyde **(6)** gave only the diacetal derivative **14**. Attempts to prepare the monoacetal derivative by controlling the reaction conditions were unsuccessful.

In order to prepare the mixed acetal derivatives of **1**, reaction of **7** with furfural gave a product which was identified as **12** and not the expected derivative **15**. The isolation of **12** may be attributed to the partial hydrolysis of **7** by the action of acid, present in the reaction medium, to give benzaldehyde whose reaction with **7** was faster than the respective reaction with furfuraldehyde.



i = Ac_2O / Py, ii = BzCl / Py, iii = TolCl = *p*-MeC_6H_4COCl / Py, iv = HBr / AcOH, v = AcOH / H_2O

Scheme 2

Treatment of **7** and **8** with acetic anhydride in pyridine gave the corresponding acetylated products **16** and **17**, respectively (Scheme 2). Their IR spectra showed the absence of a band corrresponding to the OH group of their precursors and the appearance of the C=O acetyl group at 1725 and 1734 cm^{-1}, respectively. The ^{1}H NMR of **16** showed a singlet for the two acetyl groups.

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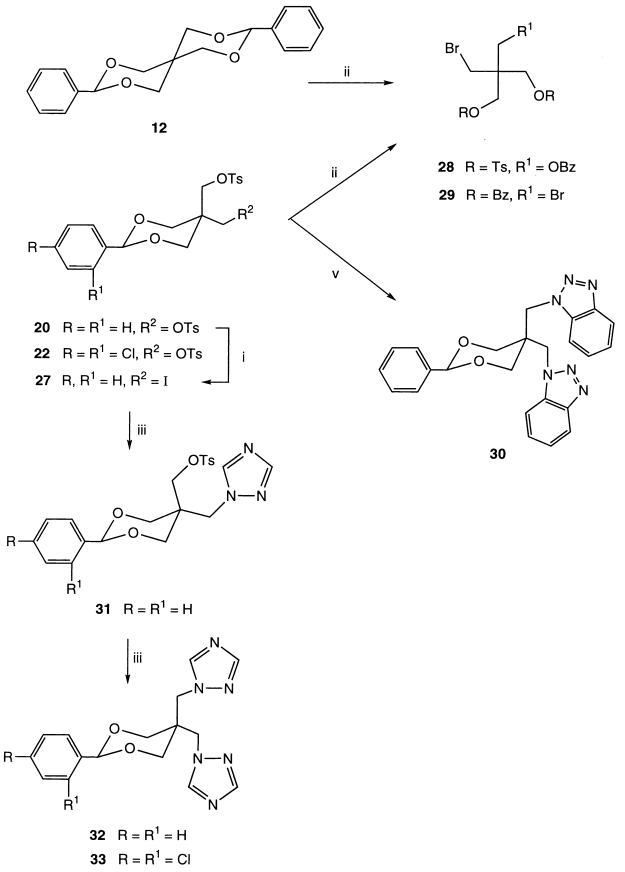
Dedicated to Prof. Dr. Joachim Theim on the occasion of his 60th birthday

Benzoylation of **8** gave the corresponding benzoylated product **18** the IR spectrum of which showed the C=O of the benzoyl group at 1705 cm^{-1}. Toluoylation of **7** gave **19**. Treatment of pentaerythritol with toluoyl chloride gave **25**, the IR spectrum of which showed a band at 1719 cm^{-1} due to the C=O of the toluoyl group.



Scheme 3

Reaction of **7–9** with tosylchloride in pyridine gave the corresponding di-*O*-tosylated products **20–22**, respectively. Their ^{1}H NMR spectra confirmed the presence of two tosyl groups. Treatment of **7** and **8** with mesyl chloride in pyridine gave the corresponding di-*O*-mesyl derivatives **23** and **24**, respectively. Nucleophilic displacement of one of the tosyloxy groups in **20** occurred selectively at the equatorial position by the iodide ion to give **27,** where ethylmethyl ketone was found to be a better solvent for the reaction than acetone[33]. Treatment of dibenzylidene **12** with *N*-bromosuccinimide (NBS) produced **29**, the IR spectrum of which showed a band at 1722 cm^{-1} which was not present in the spectrum of its precursor **12**, and indicated the presence of the C=O of the benzoyl group (Scheme 3). Its ^{1}H NMR spectrum showed two singlets at δ 4.49 and 3.66 ppm corresponding to the two CH_2–OBz and the two CH_2–Br, respectively. Similarly reaction of **20** with *N*-bromosuccinimide gave **29** the IR spectrum of which showed a band at 1715 cm^{-1} corresponding to the C=O of the benzoyl groups and its ^{1}H NMR spectrum showed the absence of the acetal proton.

The ditosyloxy compounds **20** and **22** were found to be good candidates for nucleophilic displacement with 1,2,4-triazole and benzotriazole. Thus, reaction of **20** with the sodium salt of 1,2,4-triazole in DMF produced the monosubstituted product **31** as white crystals in 48% yield when the mixture was heated under reflux for 2 h, whereas when the reflux was increased up to 24 hrs, the disubstituted product **32** was obtained. Similarly, reaction of **22** with 1,2,4-triazole and **20** with benzotriazole gave the disubstituted products **33** and **32**, respectively. The structure of **31** was confirmed by studying its ^{1}H NMR spectrum which showed two singlets at δ 8.12 and 7.99 ppm corresponding to the two CH of the triazole ring. The singlets which apppeared at δ 5.34 and 2.43 ppm were due to the acetal proton and the CH_3 of the tosyl group, respectively. The ^{1}H NMR spectrum of compound **32** showed the absence of two tosyloxy groups, and the presence of two singlets at δ 8.61 and 8.21 ppm corresponding to the two CH- of the two triazole rings. The other two CH- of the triazole rings appeared as two singlets at δ 7.99 and 8.03 ppm. The 2-H proton appeared as a singlet at δ 5.51 ppm. The assignment of structure **31** for the product of displacement of one of the tosyloxy groups was based on the preferential displacement of the equatorially oriented tosyloxy group in **20**.

Compounds **8, 13, 17, 18, 22, 23** and **28** were tested for their activity against Hepatitis B Virus (HBV) in HepG2 2.2.15 cells. The concentrations for the tested compounds were 10 M. Compound **22** showed promising activity and **23** was less active. Both showed low cytotoxicity (Table 1). However, the rest of the tested compounds were inactive against Hepatitis B Virus (HBV).

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