Application of a Lanthanide Shift-reagent for Conformational and Configurational Assignment in the Carbohydrate Field

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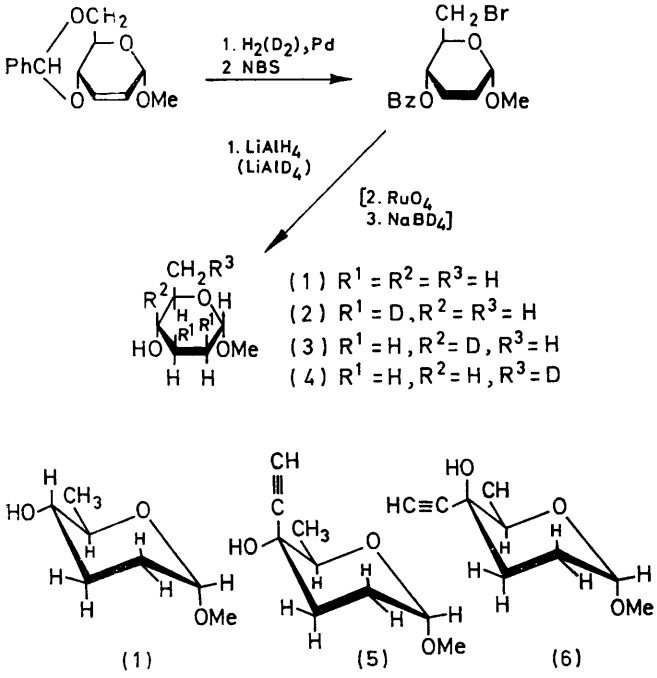
Summary The paramagnetic shift-reagent, tris-(2,2,6,6-tetramethylheptanedionato)europium(III), was used to resolve the n.m.r. spectrum of methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (methyl α-amicetoside, **1**); the extreme spectral dispersion thus effected permitted determination of the conformation of (**1**) in solution and the configuration of a 2,3-dideuterio-derivative (**2**), and allowed the differentiation of a pair of 4-*C*-ethynyl derivatives (**5** and **6**) obtained from (**1**).

THE lanthanide shift-reagent tris-(2,2,6,6-tetramethylheptanedionato)europium(III) [Eu(dpm)$_3$] introduced by Hinckley[1] is useful for the interpretation of complex ^{1}H n.m.r. spectra.[2] Work in this laboratory on the mass-spectral fragmentation of the methyl glycoside of amicetose (a component deoxy-sugar of the antibiotic amicetin) has made available this glycoside, methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside[3] (**1**), having specific deuterium labelling at C-2 and C-3 (**2**), at C-4 (**3**), and at C-6 (**4**).



Also prepared, by ethynylation of the 4-ketone obtained by oxidation of (**1**), was a pair of 4-epimeric *C*-ethynyl derivatives. By conventional n.m.r. spectroscopy at 60 or 100 MHz only gross spectral assignments for these derivatives were possible; the very small differences in chemical shift between certain protons exhibiting strong vicinal or geminal couplings led to second-order effects that precluded detailed assignments interpretable in terms of stereochemistry and conformation. Thus the stereochemistry of the isotopic labelling in (**2**), obtained by reduction of an alkene precursor with deuterium, was not established, nor were the ethynyl derivatives (**5**) and (**6**) individually differentiated. The determination of configuration at tertiary hydroxy-groups, as encountered in branched-chain sugars of the type (**5**) and (**6**) and the similar problem of assigning anomeric configuration in ketoses, is difficult, since n.m.r. spectral techniques based on proton–proton spin-couplings are not applicable. The present report illustrates the use of the shift-reagent Eu(dpm)$_3$ in the elucidation of stereochemical detail; with a 60 MHz n.m.r. spectrometer it was possible to establish the position of deuterium labelling in (**2**), to differentiate the branched-chain derivatives (**5**) and (**6**), and to assign the favoured conformations in solution for each of the derivatives.

The upper spectrum in the Figure is the 60 MHz n.m.r. spectrum of the glycoside (**1**) in carbon tetrachloride; the gross assignments shown are the only ones readily made. Studies at higher field-strengths and with different solvents did not give much additional information. However, when a 0·4 molar equivalent of Eu(dpm)$_3$ was added to the solution, the 60 MHz spectrum recorded in the lower part of the Figure was observed. The reagent evidently complexes with O-4 and, by a proximity effect, causes displacement of the 4-H signal to extremely low field; similar displacements of progressively smaller magnitude are observed for the signals of 5-H, 3*a*-H, 3*e*-H, and 6-H. The remaining signals, those of 1-H, 2*a*-H, 2*e*-H, and the methoxy-group, are shifted somewhat downfield, but are not significantly dispersed. The first-order approximation can be used to determine spin couplings between 3*a*-H, 3*e*-H, 4-H, and 5-H, and these values are consistent with the expected *C*1(D) conformation for (**1**), having 4-H axial ($J_{4,5}$ 9, $J_{3a,4}$ 11 Hz). The signal assigned to 4-H was absent in the spectrum of the 4-deuteriated derivative (**3**), and the signal assignments made for 3*a*-H, 3*e*-H, and 5-H were confirmed by observing the expected changes in

signal multiplicities, use of the 6-deuteriated derivative (**4**) gave additional confirmation of the 5-H assignment

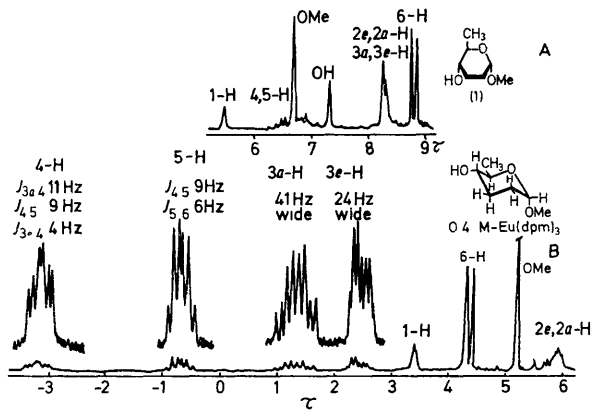


FIGURE *The 60 MHz spectra of* (**1**) *in* CCl_4, A, *alone*, B, *with* 0·4M-Eu(dpm)$_3$

In the spectrum of the dideuteriated derivative (**2**), the higher-field 3-H signal (3*e*-H) was absent, and the 3*a*-H signal decreased in width from 41 to *ca* 17 Hz (by the magnitude of the 3*e*,3*a*-H geminal and 2*a*,3*a*-H vicinal proton–proton couplings), and the 2*e*,2*a*-H multiplet decreased in intensity by one proton Assuming that the catalytic reduction step used in preparing (**2**) proceeds by *cis*-addition, it is evident that reduction of the alkene precursor by deuterium takes place stereospecifically from the "top" side of the molecule Compound (**2**) can thus be formulated as methyl 2,3,6-trideoxy-2,3-dideuterio-α-D-mannopyranoside

One of the two C-4 epimeric acetylenic derivatives, m p 103°, $[\alpha]_D$ +177° ($CHCl_3$), gave an n m r spectrum in carbon tetrachloride containing 0·4M-Eu(dpm)$_3$ that was almost identical with that observed for the glycoside (**1**) except that no signal corresponding to 4-H was observed, and the signal multiplicities for 3*a*-H, 3*e*-H, and 5-H reflected the absence of 4-H, accordingly, structure (**5**), having O-4 disposed as in (**1**), was assigned to this isomer In contrast, the other ethynyl derivative, a syrup having $[\alpha]_D$ +132° ($CHCl_3$), showed an altogether different spectrum in carbon tetrachloride containing 0·4M-Eu(dpm)$_3$, the relative order of signal shifts (when compared with the spectrum in carbon tetrachloride alone) was 6-H ≈ 3*e*-H > 5-H > 3*a*-H, and the structure (**6**) can thus be assigned to this isomer These assignments agree with those made by converting (**5**) and (**6**) into their alditols, treating the latter with phenyl azide, and applying a rule[4] relating optical rotation with chirality of the tertiary centre in the resultant 2,3,6-trideoxy-4-(1-phenyltriazol-4-yl)hexitols

(**1**) has the *C*1(D) conformation before Eu(dpm)$_3$ is added to the solution However, for systems where a mobile conformational equilibrium might be expected,[5] care should be exercised to ensure that the possible contribution of the complexing agent in influencing the conformation is recognized

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