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DETERMINATION OF THE STEREOCHEMISTRY OF 2,2-DIMETHYL-1,6,8-TRIOXADISPIRO(4.1.5.3)PENTADEC-13-ENE FORMED BY TWO SEQUENTIAL CYCLIZATION REACTIONS USING HIGH FIELD ^{1}H N.M.R. SPECTROSCOPY

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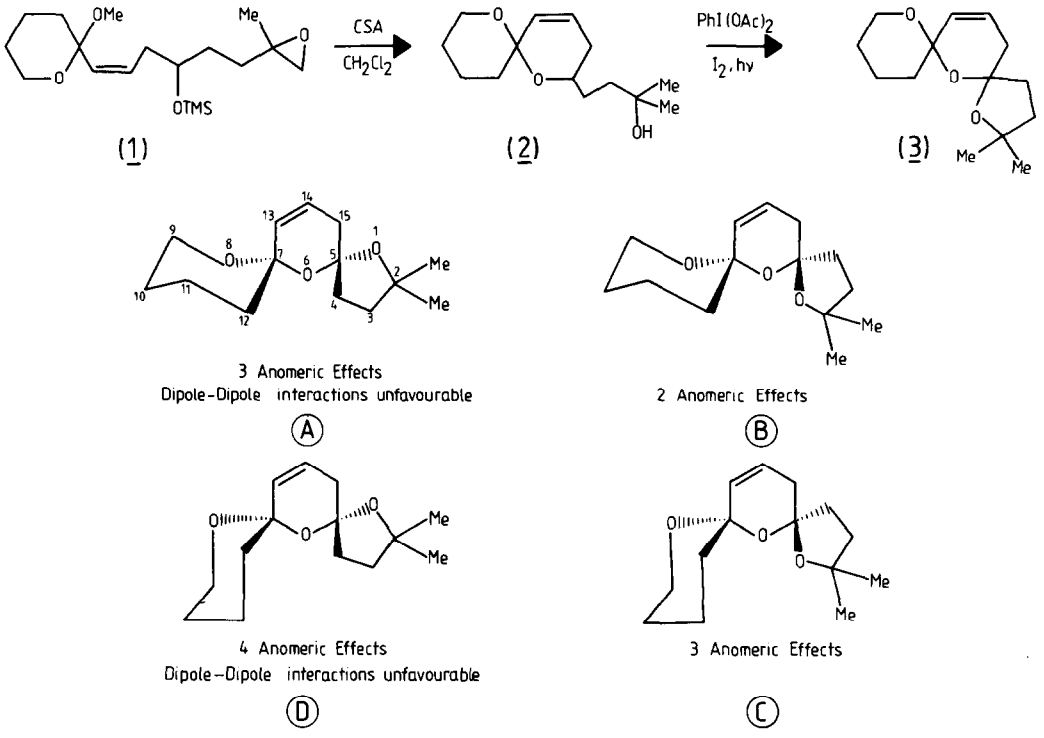
SUMMARY: The stereochemistry of 2,2-Dimethyl-1,6,8-trioxadispiropentadec-13-ene, formed by two cyclization steps, has been determined by ^{1}H n.m.r. spectroscopy utilizing COSY and NOE difference experiments.

The occurrence of a spiroacetal moiety as the prime functional group in a host of natural products, particularly insect pheromones[1], polyether antibiotics[2], and the potent antiparasitic agents, the milbemycins and avermectins[3], has prompted development of a range of methods to construct the spiroacetal skeleton[4]. The polyether antibiotics salinomycin[5], narasin, norboritomycin and CP44,661 all incorporate the 1,6,8-trioxadispiro(4.1.5.3) pentadec-13-ene ring system as a main structural feature. In an earlier communication[6] we reported the preparation of the novel unsaturated bis-spiroacetal (3) in 53% yield via the diastereoselective Barton-type reaction of substituted hydroxy spiroacetal (2). In this communication we wish to disclose the full details of the stereochemistry of this bis-spiroacetal (3) together with the assignment of the ^{1}H n.m.r. spectrum.

The two possible stereoisomers (A and B) formed from the sequential cyclization reactions are depicted below with their respective conformational isomers (D and C). Based on the number of anomeric effects[7], B could be predicted to be less thermodynamically stable than the other three. The unfavourable dipole-dipole interaction due to the two syn carbon-oxygen bonds existing in A and D would also render them thermodynamically less favourable. Thus, considering anomeric effects in conjunction with dipole-dipole interactions C is predicted to be the thermodynamic product.

The stereochemistry at C-7, established in the first of the two steps, could be predicted to follow that already reported in a similar cyclization by Hanessian et al[8] and also from our own studies[9]. Formation of A or B could therefore be discounted. The second cyclization would establish the relative configuration at C-5 with consequent formation of either C or D. We have now determined by the use of ^{1}H n.m.r. spectroscopy with the aid of two dimensional COSY, and NOE difference experiments, that the diastereomer isolated was, in fact, C. This is consistent with the observation that the analogous bis-spiroacetal moiety in the natural product, deoxysalinomycin, has been shown by X-ray analysis to have the same relative configuration at the spiro centres[10].

The ^{1}H n.m.r. data were obtained at 360MHz using a Bruker AM-360 spectrometer (Table). The resonance at 4.02 appeared as a double double doublet with two large coupling constants $J_{9ax,9eq}$ 11.3Hz, $J_{9ax,10ax}$ 11.3Hz



and one smaller coupling constant, $J_{9ax,10eq}$ 3.3Hz, thereby assigning this signal to the axial proton attached to C-9. The remainder of the ^1H n.m.r. spectrum was interpreted with the aid of the two-dimensional COSY experiment. In the COSY spectrum the signals at δ5.59 and δ5.86 assigned to the vinylic protons were coupled only to the one proton multiplets which resonated at δ2.16 and δ2.45. Hence these latter two double double doublets were assigned to the allylic protons attached to C-15. The coupling constants observed (Table) are of similar magnitude to the analogous coupling constants observed in deoxysalinomycin[11]. Similarly, the methylene protons attached to C-9 which were assigned to the multiplets at δ3.67 and δ4.02 were only coupled to the four proton multiplet at δ1.49-1.64. Thus, two of the four protons resonating at δ1.49-1.64 were assigned to the methylene protons attached to C-10. The residual resonances, namely, three multiplets at δ1.86-1.99, δ2.04-2.12 and δ2.59-2.70 each integrating for one proton, the multiplet at δ1.72-1.83 integrating for three protons, and two protons of the four proton multiplet at δ1.49-1.64, remained to be assigned to the eight methylene protons attached to carbons 3, 4, 11 and 12.

The COSY spectrum showed that the protons appearing as multiplets at δ2.59-2.70 and δ2.04-2.12 were not only coupled to each other but also to the protons resonating as a multiplet at δ1.72-1.83. The proton giving rise to the multiplet at δ1.86-1.99, however, was coupled to the protons which

Table

Assignment of ^{1}H n.m.r. spectrum[a] for bis-spiroacetal (3)

δ(ppm)	Assignment	Coupling Constants (J.Hz)
1.24	Me(s)	
1.48	Me(s)	
1.49-1.64	10_{ax},10_{eq},11_{eq}[b],12′[b](m)	
1.72-1.83	3′,4′,12^{b}(m)	
1.86-1.99	11_{ax}(m)	
2.04-2.12	3(m)	
2.16	15′(allylic, ddd)	$J_{15,15'}$16.9,$J_{13,15'}$1.2,$J_{14,15'}$5.8
2.45	15(allylic, ddd)	$J_{15,15'}$16.9,$J_{13,15}$=$J_{14,15}$2.6
2.59-2.70	4(m)	
3.67	9_{eq}(-OCH_2, m)	
4.02	9_{ax}(-OCH_2,ddd)	$J_{9ax,10eq}$3.3,$J_{9ax,9eq}$=$J_{9ax,10ax}$11.3
5.59	13(vinylic, ddd)	$J_{13,14,10}$,$J_{13,15}$2.6,$J_{13,15'}$1.2
5.86	14(vinylic, ddd)	$J_{13,14,10}$,$J_{14,15}$2.6,$J_{14,15'}$5.8

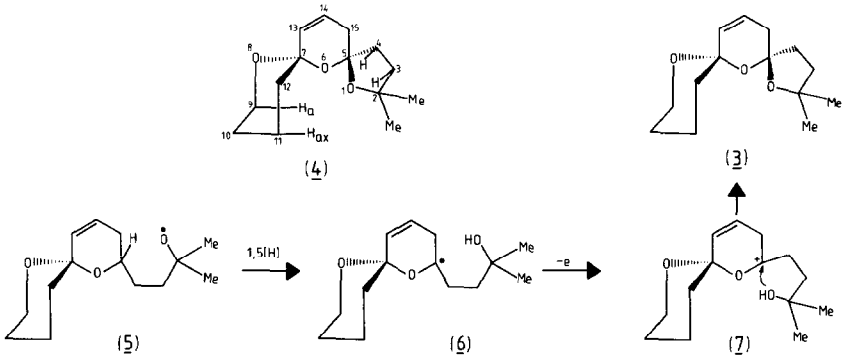
[a] Obtained at 360MHz.

[b] These proton assignments may be interchanged.

gave rise to the multiplets at δ1.72-1.83 and δ1.49-1.64. Double resonance experiments indicated that the protons occurring as multiplets at δ2.04-2.12 and δ2.59-2.70 were, in fact, vicinal to each other. Thus, the absence of any coupling between the methylene protons attached to C-10 resonating at δ1.49-1.64 and the protons occurring as multiplets at δ2.04-2.12 and δ2.59-2.70 precluded the possibility of assigning these latter multiplets to the protons attached to C-11 or C-12.

The above observations suggested the assignment of the multiplets at δ2.04-2.12 and δ2.59-2.70 to two vicinal methylene protons in the five-membered ring and the multiplet at δ1.86-1.99 to the axial proton attached to C-11. The observation of an NOE effect between the protons resonating at δ1.86-1.99 and δ4.02 was consistent with those protons bearing a 1,3-diaxial relationship to each other. The characteristic deshielding of the axial proton at C-11 relative to the geminal equatorial proton and the vicinal protons at C-10 and C-12 which appear at δ1.49-1.83 is attributed to the 1,3-diaxial interaction with the oxygen of the adjacent ring (4). The observation of an NOE effect between the proton resonating at δ2.04-2.12 and the methyl group giving rise to the singlet at δ1.48 was consistent with the assignment of this signal to a methylene proton attached to C-3 and the signal at δ2.59-2.70 to a methylene proton attached to C-4. The remaining two methylene protons of the five-membered ring were assigned to the multiplet at δ1.72-1.83 using the information from the COSY experiment as described above.

Finally, the most striking feature observed from NOE difference spectra was an NOE effect between the axial proton at C-9 resonating at δ4.02 and the methylene protons attached to C-4 and C-3 resonating at δ2.59-2.70 and δ2.04-2.12 respectively. This observed NOE effect is fully consistent with the assignment of structure C to bis-spiroacetal (3) in that this diastereomer may readily adopt a conformation in which the axial proton at C-9 and the methylene protons at C-4 and C-3 are in close proximity (4).



The stereochemistry observed at C-7, established in the initial cyclization of hydroxy-spiroacetal (2), is therefore fully consistent with the results obtained by Hanessian et al in their synthesis of the spiroacetal unit of avermectin B_{1a}[10]. The stereochemistry at C-5, however, is established in the final free radical substitution reaction. Thus, the oxy-radical (5), generated by photolysis, undergoes 1,5-hydrogen transfer to give the stabilised radical (6); this is subsequently oxidized to cation (7) which is trapped by the hydroxyl substituent from the least hindered β-face thus avoiding the unfavourable 1,3-dipole interactions.

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