The Chemistry of Spiroacetals. Approaches to the Novel 1,6,8-Trioxa-dispiro[4.1.5.3]pentadecane Ring System

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The synthesis of saturated bis-spiroacetal (11) from an intramolecular catalysed cyclization of a keto-epoxide together with the preparation of unsaturated bis-spiroacetal (16) via a Barton-type reaction of substituted hydroxy spiroacetal (15) highlight a means of constructing the above-named ring system.

Interest in spiroacetals has been increasing because of their occurrence as prime functional groups in a wide range of natural products, particularly insect pheromones, polyether antibiotics, and the potent antiparasitic agents, the milbemycins and avermectins. Amongst the many methods for constructing the spiroacetal skeleton are those which incorporate as the key step a hetero Diels–Alder reaction, a nitrile oxide cyclization approach, a cation-olefin cyclization, an organoselenium-mediated cyclization, an intramolecular Michael addition to an α,β-unsaturated sulfoxide, a Horner-Wittig coupling of cyclic ethers with aldehydes or lactols, a nucleophilic opening of an oxirane by an organocuprate, and, more commonly, the addition of carbanions to δ-valerolactones followed by cyclization of the resultant lactols.

The polyether antibiotics salinomycin (1), narasin (2), norboritomycin, and CP44,661 all incorporate as the main structural feature the 1,6,8-trioxadispiro[4.1.5.3]pentadecane ring system. This novel ring system presents an interesting synthetic target in that the existing methodology for the construction of the analogous 1,7-dioxaspiro[5.5]undecane ring system is not directly applicable. In this communication, we report our studies leading to the formation of a saturated (Scheme 1) and unsaturated (Scheme 2) bis-spiroacetal derivative.

Initial work focused on the cyclisation of keto-epoxide...
vinyl ether trifluoroacetate proved to be more expedient than the alcohol with ethyl vinyl ether which provided the required allyl y-6-unsaturated aldehyde (4) in 80% yield after distillation. Addition of allyl ether (4) to the organo-zinc reagent (2 equiv.) prepared from propargyl bromide and an excess of activated zinc powder afforded the acetylenic alcohol (10). The starting point for the synthesis was the mercury(II) trifluoroacetate-catalysed transethification of methyl allyl alcohol with ethyl vinyl ether which provided the required allyl vinyl ether (3) in 58% yield after distillation. Mercury(II) trifluoroacetate proved to be more expedient than the mercury(II) acetate catalysed reaction reported by Vig et al.\(^\text{17}\) Claisen rearrangement of the resulting allyl vinyl ether (3) at 120°C for 24 h in a sealed tube yielded the required γ,δ-unsaturated aldehyde (4) in 77% yield which was subsequently protected as its trimethylsilyl ether (5) in 91% yield. Generation of the lithium acetylide with n-butyllithium at -78°C for 1.5 h followed by reaction with δ-valerolactone yielded the hemiacetal (6). The hemiacetal was stirred overnight with Amberlite IR 118 in methanol to effect cleavage of the trimethylsilyl group giving the methoxy acetal (7) in 84% yield; [colourless oil; \(^1\)H n.m.r. (CDCl\(_3\)) \(\delta\) 1.43–1.98 (8H, m, 4 × CH\(_2\)), 1.76 (3H, s, Me), 2.01–2.29 [2H, m, –CH\(_2\)(Me)C═C], 2.38–2.61 (2H, m, –CH\(_2\)C═C), 2.81–2.98 (1H, br. d, J 2 Hz, exchangeable on deuteration, OH), 3.40 (3H, s, OMe), 3.62–3.91 (3H, m, –OCH\(_2\) and OH); \(\nu\)\(_{\text{max}}\) (CHCl\(_3\)) 3600–3200, 3080, 2260, 1640, 1030, and 900 cm\(^{-1}\)].

After reprotection as its trimethylsilyl ether, alcohol (7) was treated with \(m\)-chloroperoxybenzoic acid (\(m\)-CPBA) at room temperature for 48 h to give a mixture of epoxides (8) which were not separated. Hydrogenation of the acetylenic group (10% Ru/C in pentane for 1 h) followed by cleavage of the trimethylsilyl group (Bu\(_3\)N\(+\)F\(-\)) afforded alcohol (9) in 90% yield. Subsequent Swern oxidation\(^\text{19}\) with dimethyl sulphoxide (DMSO) activated with trifluoroacetic anhydride (TFAA) afforded the desired keto-epoxide (10) in 72% yield; [colourless oil; \(^1\)H n.m.r. (CDCl\(_3\)) \(\delta\) 1.40–2.61 (12H, br. m, 6 × CH\(_2\)C\(_2\) and CH\(_2\) epoxide), 3.19 (3H, s, OMe), and 3.63 (2H, m, –0CH\(_2\)); \(\nu\)\(_{\text{max}}\) (thin film) 2940, 1710, 1100, 1060, and 1040 cm\(^{-1}\)]. The single major product isolated was a bis-spiroacetal derivative which was subsequently converted into a bis-spiroacetal utilizing an oxy-radical generated by photolysis (Scheme 2).

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Hydrogenation of acetylene (8) over 5% Pd on cadmium carbonate poisoned with lead acetate afforded Z-ene-epoxide (13) in 95% yield. Reaction of (13) with LiAlH₄ (0.5 equiv.) yielded the tertiary alcohol (14) in 89% yield. Cyclization of alcohol (14) to spiroacetal (15) was achieved with a catalytic amount of CSA in dichloromethane in 95% yield. Reaction of (15), iodobenzene (16 mg, 0.07 mmol), in 53% yield (colourless oil, b.p. 22°C), yielded the novel bis-spiroacetal (16) in 89% yield. The 13C n.m.r. spectrum of (16) showed 14 carbon resonances indicated that the product was diastereoisomerically pure.

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References


‡ Full details on the stereochemistry of (16) will be presented in a subsequent paper.