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

Raymond Baker* and Margaret A. Brimble

Department of Chemistry, The University, Southampton SO9 5NH, U.K.

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,[2] polyether antibiotics,[3] and the potent antiparasitic agents, the milbemycins and avermectins.[4] Amongst the many methods for constructing the spiroacetal skeleton are those which incorporate as the key step a hetero Diels–Alder reaction,[5] a nitrile oxide cyclization approach,[6] a cation–olefin cyclization,[7] an organoselenium-mediated cyclization,[8] an intramolecular Michael addition to an α,β-unsaturated sulphoxide,[9] a Horner–Wittig coupling of cyclic ethers with aldehydes or lactols,[10] a nucleophilic opening of an oxirane by an organocuprate,[11] and, more commonly, the addition of carbanions to δ-valerolactones followed by cyclization of the resultant lactols.[1,12]

The polyether antibiotics salinomycin (**1**),[13] narasin (**2**),[14] norboritomycin,[15] and CP44,661[16] 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[1,5—12] 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.

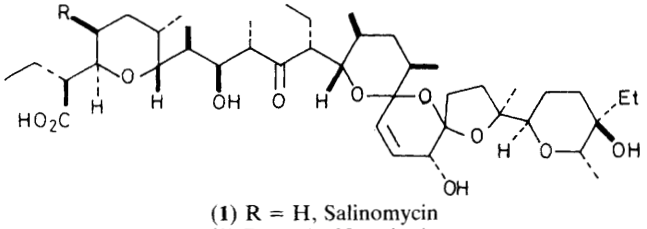
Initial work focussed on the cyclisation of keto-epoxide

(**10**). The starting point for the synthesis was the mercury(II) trifluoroacetate-catalysed transetherification 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.*[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**)[17] in 80% yield after distillation. Addition of aldehyde (**4**) to the organo-zinc reagent (2 equiv.) prepared from propargyl bromide and an excess of activated zinc powder[18] afforded the acetylenic alcohol (**5**)† in 77% yield which was subsequently protected as its trimethylsilyl ether (91%). Generation of the lithium acetylide with n-butyl-lithium 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. ($CDCl_3$) δ 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, $-CH_2C{\equiv}C$), 2.81–2.98 (1H, br. d, *J* 2 Hz, exchangeable on deuteriation, OH), 3.40 (3H, s, OMe), 3.62—3.91 (3H, m, $-CHOH$ and $-OCH_2$), and 4.68—4.80 (2H, m, $-C{=}CH_2$); i.r. $\nu_{max.}$ ($CHCl_3$) 3600—3200, 3080, 2260, 1640, 1030, and 900 cm^{-1}].

After reprotection as its trimethylsilyl ether, alcohol (**7**) was treated with *m*-chloroperbenzoic 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% Pd–C in pentane for 1 h) followed by cleavage of the trimethylsilyl group ($Bu^n_4N^+F^-$) afforded alcohol (**9**) in 90% yield. Subsequent Swern oxidation[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. ($CDCl_3$) δ 1.31 (3H, s, Me), 1.40—2.01 (12H, br. m, 6 × CH_2), 2.21—2.60 (6H, m, 2 × CH_2CO and CH_2 epoxide), 3.19 (3H, s, OMe), and 3.63 (2H, m, $-OCH_2$); $\nu_{max.}$ (thin film) 2940, 1710, 1100, 1060, and 1040 cm^{-1}].

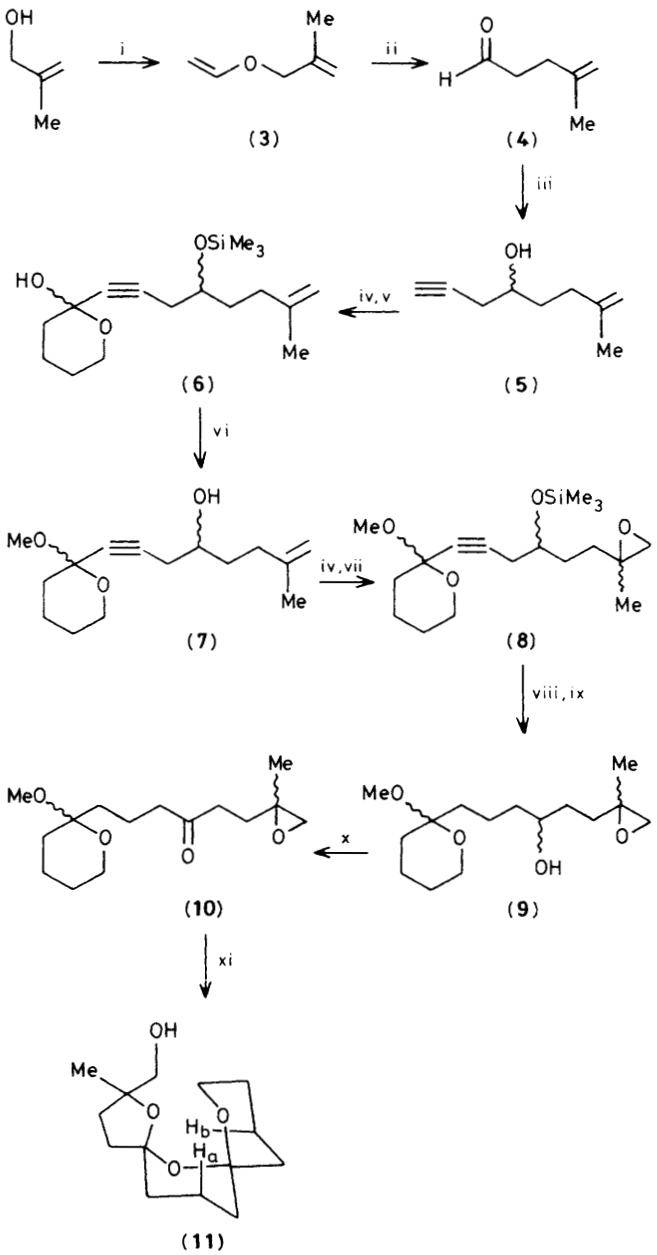
Treatment of keto-epoxide (**10**) (70 mg, 0.26 mmol) with a catalytic amount of camphorsulphonic acid (CSA) in dichloromethane gave the primary alcohol (**11**) (42 mg, 0.16 mmol) in 63% yield after purification by 'flash' chromatography;[20] [(**11**), colourless oil, b.p. 120 °C at 0.5 mmHg (Kugelrohr); ^{1}H n.m.r. (360 MHz, $CDCl_3$) δ 1.18 (3H, s, Me), 1.41—1.98 (14H, br., $-CH_2$), 2.51—2.62 (2H, m, H_a and H_b), 3.38 (1H, t, *J* 11.1 Hz, $-CHOH$), 3.59 (1H, d, *J* 11.1 Hz, $-CHOH$), 3.62—3.83 (3H, m, $-OCH_2-$ and OH); $\nu_{max.}$ (CCl_4) 3470, 1090, 1070, and 1050 cm^{-1}]. The single major product isolated can be explained by the preference for the desired spiroacetal to adopt the conformation in which the ring oxygens are axial to the adjacent ring thus gaining stability from the anomeric effect.[21] The signal at δ 2.51—2.62 results from the characteristic deshielding of these protons (H_a and H_b) owing to the 1,3-diaxial interaction with the oxygen of the adjacent ring. The observation of only one methyl resonance at δ 1.18 in the ^{1}H n.m.r. spectrum together with 14 carbon resonances in the ^{13}C n.m.r. spectrum confirmed that the product was in fact a single diastereoisomer.

Whilst the intramolecular cyclization of keto-epoxide (**10**) proved to be a facile process the results obtained from the analogous unsaturated keto-epoxide (**12**) [available from partial hydrogenation of (**8**)] with a range of protic and Lewis acids were less encouraging, none of the required product being isolated. An alternative strategy was developed involving an initial cyclization to form a spiroacetal derivative which was subsequently converted into a bis-spiroacetal utilizing an oxy-radical generated by photolysis (Scheme 2).

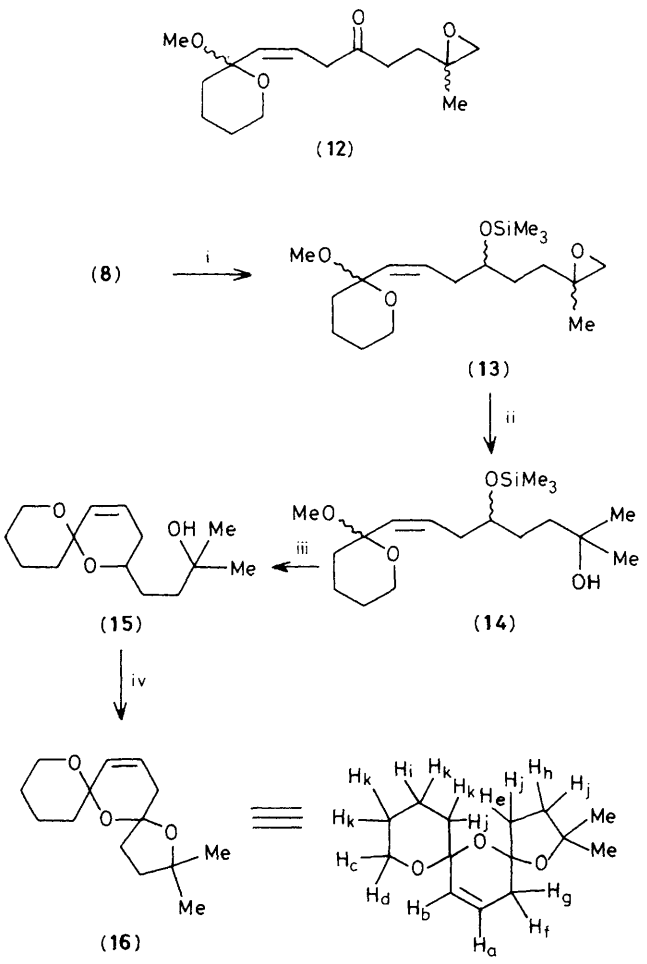


(**1**) R = H, Salinomycin
(**2**) R = Me, Narasin A

† All compounds gave satisfactory spectral and analytical data.



Scheme 1. *Reagents*: i, $EtOCH{=}CH_2$, $Hg(O_2CCF_3)_2$, 58%; ii, 120 °C, 24 h, 80%; iii, $HC{\equiv}CCH_2Br$, Zn, tetrahydrofuran (THF), 0 °C, 77%; iv, Me_3SiCl, Et_3N, THF, 91%; v, Bu^nLi, THF, δ-valerolactone, −78 °C; vi, MeOH, Amberlite IR 118, 84% overall; vii, m-CPBA, CH_2Cl_2, NaOAc, 76%; viii, 10% Pd on charcoal, pentane, H_2, 95%; ix, $Bu^n_4N^+F^-$, THF, 95%; x, TFAA, DMSO, Et_3N, CH_2Cl_2, −60 °C, 72%; xi, CSA, CH_2Cl_2, room temperature, 63%.



Scheme 2. *Reagents*: i, H_2, 5% Pd on $CaCO_3$–$Pb(OAc)_2$, 95%; ii, $LiAlH_4$, Et_2O, 89%; iii, CSA, CH_2Cl_2, room temperature, 93%; iv, $PhI(OAc)_2$, I_2, cyclohexane, *hν*, 53%.

Hydrogenation of acetylene (**8**) over 5% Pd on calcium carbonate poisoned with lead acetate afforded *Z*-ene-epoxide (**13**) in 95% yield. Reaction of (**13**) with $LiAlH_4$ (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 93% yield; [(**15**) colourless oil; ^{1}H n.m.r. (360 MHz, $CDCl_3$) δ 1.24 (6H, s, 2 × Me), 1.49—2.14 (12H, br. m, 6 × $-CH_2$), 3.58—3.69 (1H, m, CHO), 3.80—3.91 (2H, m, $-OCH_2$), 5.58—5.62 (1H, m, HC=C), and 5.86—5.92 (1H, m, C=C*H*–CH_2); $\nu_{max.}$ 3640—3260, 3040, 1660, and 1010 cm^{-1}]. The ^{13}C n.m.r. spectrum showing only 14 carbon resonances indicated that the product was diastereoisomerically pure. Finally, irradiation of a solution of spiroacetal (**15**) (30 mg, 0.13 mmol), iodobenzene diacetate (1 equiv.), and iodine (0.5 equiv.) in cyclohexane at room temperature for 24 h[22] yielded the novel bis-spiroacetal (**16**) (16 mg, 0.07 mmol), in 53% yield {colourless oil, b.p. 106 °C at 0.3 mmHg (Kugelrohr); ^{1}H n.m.r. (360 MHz, $CDCl_3$) δ 1.24 (3H, s, Me), 1.48 (3H, s, Me), 1.49—1.64 (4H, m, H_k), 1.72—1.83 (3H, m, H_j), 1.86—1.99 (1H, m, H_i), 2.04—2.12 (1H, m, H_h), 2.16 [1H, ddd, *J*(f,g) 16.9, *J*(a,g) 5.8, *J*(b,g) 1.2 Hz, H_g], 2.45 [1H, ddd, *J*(f,g) 16.9, *J*(a,f) 2.6, *J*(b,f) 2.6 Hz, H_f], 2.59—2.70 (1H, m, H_e), 3.67 (1H, m, H_d) 4.02 [1H, ddd, *J*(c,d) 11.3, *J*(c,k) 11.3 *J*(c,k) 3.0 Hz, H_c], 5.59 [1H, ddd, *J*(a,b) 10, *J*(b,g) 11.3, *J*(b,f) 2.6 Hz, H_b], and 5.86 [1H, ddd, *J*(a,b) 10, *J*(a,g) 5.8, *J*(a,f) 2.6 Hz, H_a]; $\nu_{max.}$ (CCl_4), 3040 and 1050 cm^{-1}}. The ^{1}H n.m.r. data, including the 2-dimensional n.m.r. spectrum of (**16**) are fully consistent with the assigned structure. In an analogous fashion to the precursor (**15**), the ^{13}C n.m.r. spectrum of (**16**) showed only 14 carbon resonances, thereby establishing that the product was diastereoisomerically pure.‡

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