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## Toward a Total Synthesis of an Aglycone of Spiramycin; Installation of the Hydroxy Groups at C-4 and C-5: a Model Study

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Abstract: The stereochemical course of the osmium-mediated bis-hydroxylation of the allylic derivative 6c, whose the structure is closely related to that of a C-1/C-7 fragment of the title aglycone, has been established unambiguously by X-ray analysis of a carboxylic acid derived from one of the two diastereomeric diols which formed. © 1998 Published by Elsevier Science Ltd. All rights reserved.

As we reported recently, due to the unstability of the aldehyde 1a, attempted preparation of the fragment 2 of the aglycone 3 of spiramycin by a Julia-Paris-Kociensky (JPK) condensation of 1a with the sulfone 4 proved unfeasible. This led us to prepare the related aldehydes 1b and 1c, which were expected to be more resistant than 1a to the basic conditions of such an olefination reaction.<sup>1</sup>



In order to define suitable conditions for executing the planned JPK coupling of the synthons 1b-c with the sulfone 4 and, in the sequel, to get a precise insight on the stereochemical course of the ensuing osmium-mediated bis-hydroxylation step required to implement the oxygenated functionality at the C-4 and the C-5 positions, it appeared more judicious to perform first a model study by using the sulfone 5a, which is easy to prepare<sup>2</sup> and whose substitution pattern is similar to that of the sulfone 4. The results of this study are presented herein.

Addition of the aldehyde 1b to a cooled (ca -78 °C) solution of the lithio derivative of the sulfone 5 in THF followed by an *in situ* acetylation with Ac<sub>2</sub>O/DMAP gave a mixture of acetoxysulfones, which, by treatment with sodium amalgam, afforded the expected JPK product 6a as a 3/1 mixture of *E* and *Z* isomers, respectively.



Reagents and conditions: 1- i) 2.3 M (in hexane) n-BuLi (1 eq.), THF (3 ml/mmol); -78 °C, 45 mn; ii) 0.3 M (in THF) 1b (or 1c) (1 eq.); -78 °C, 1 hour; iii) Ac<sub>2</sub>O (2.1 eq.), DMAP (0.1 eq.); room t., 30 mn; 2-6% HgNa (3x5 eq.), 1/1 MeOH/AcOEt (20 ml/mmol); -50 °C, 4-8 hours, then 1/1 sat. aqueous  $KH_2PO_4/AcOEt$  (excess); 0 °C, 15 mn and extraction.

0040-4039/98/\$19.00 © 1998 Published by Elsevier Science Ltd. All rights reserved. PII: S0040-4039(97)10760-2 The yield was low however (ca 30%), a result of the partial decomposition of the aldehyde 4b as evidenced by the detection (NMR) of 4-methoxybenzyl alcohol. Pre-treatment of the lithiated sulfone with BF3.Et2O or with (*i*-But)2AlOMe failed to improve the yield. A better result was obtained by using the aldehyde 1c, which was condensed with the sulfone 5 under the usual JPK-coupling conditions to give the unsaturated compound 6c in 75%. Interestingly, that JPK product was essentially the pure E isomer.

Having overcame the difficulties presented by the olefination step, we next examined the osmium tetroxidecatalysed bis-hydroxylation of 6c, our purpose being not only to find out optimal conditions with regards to the face-selectivity of this reaction, which, obviously, can deliver both diols S-7 (presently desired) and A-7, but also to design the analytical tools permitting to determine accurately the structure of these products.

Accordingly, compound 6c was submitted to classical syn-hydroxylation conditions (*i.e.* cat. OsO4-NMO) to give a mixture of two bis-hydroxy compounds ( $^{13}$ C NMR), which proved to be (*vide infra*) A-7 and S-7. Attempted fractionation of that crude product by chromatography was inefficient but, treatment of that diol mixture by methanol and PPTS afforded the four methyl-furanosides 8a, that, to our delight, proved to have well-differentiated Rf in TLC on silica gel and could, accordingly, be separated by flash-chromatography.<sup>3a</sup>



Subsequent NMR analysis, especially NOE experiments, permitted, as shown below, to characterise each isomer, their ratio being established simply by weighing the relevant fractions (Table).<sup>3b</sup>



Confirmation of that structure assignment was obtained by reacting separately  $\alpha$ -A-8a and  $\beta$ -S-8a with NaH and CH3I in DMF, then with 1,2-ethanedithiol and BF3.Et<sub>2</sub>O in chloroform. The 1,3-diols A-9a and S-9a that

formed, respectively, were reacted with 2-methoxy-propene and camphosulfonic acid to give the corresponding acetonide. The chemical shifts displayed in <sup>13</sup>C NMR by the geminated methyl groups and the quaternary carbon atom of the dioxopropane moiety of the single isomer which formed in both cases *-i.e.*  $\beta$ -A-9b, from  $\beta$ -A-8a and  $\beta$ -S-9b, from  $\beta$ -S-8a- are consonant with the indicated structure.<sup>4</sup> Finally, treatment of the mixed-acetals  $\alpha$ -A-8b and  $\beta$ -S-8b by DIBA-H, in order to remove the pivaloyl protecting group, followed by a two-step oxidation (Swern reagent, then KMnO4) afforded the acids  $\alpha$ -A-10 and  $\beta$ -S-10, respectively, the structure of the former being unambiguously established by X-ray analysis.<sup>5</sup>



The predominant formation of A-7 by bis-hydroxylation of 6c could be anticipated in view of the model suggested by Kishi<sup>6a</sup> for the OsO4-NMO oxydation of related allylic derivatives. Application of the more elaborated model of Sharpless<sup>6b</sup> to 6a showed that the use of the AD-mix- $\alpha$  reagent would favour in some extent the formation of the desired diol S-7 as observed effectively (Table). The more spectacular effect was recorded by using AD-mix- $\beta$  however, in which case the isomer A-7 was formed with a fairly good selectivity.

In conclusion, the aldehyde 1c proved to condense efficiently with the sulfone 5 to give the olefin 6c as the pure E isomer. The ensuing osmium-mediated bis-hydroxylation of 6c proceeded with an imperfect selectivity, giving an unseparable mixture of the two possible diastereometric diols S-7 and A-7. Fortunately, treatment of that mixture by methanol furnished the corresponding mixed-acetais 8a, which could be efficiently fractionated and accurately characterised by NMR. Finally, the possibility to convert the protected primary hydroxy group at C-1 of these acetals into a carboxylic acid functionality has been substantiated. Hence these results pave the way for a convenient conversion of the sulfone 4 into the acid 2, which is an essential part of our planned synthesis of the aglycone 3 of spiramycin. Results along this line will be reported in due course.

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## **References and Notes**

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2- The sulfone 5b (Schmittberger, T; Uguen, D. Tetrahedron Letters 1997, 38, 2837-2840) was reacted sequentially with TBAF in THF, TosCl in pyridine, KCN in DMSO, DIBA-H in CH<sub>2</sub>Cl<sub>2</sub>, and CH(OMe)<sub>3</sub>/CSA in MeOH to give 5a (33% overall Yield; Bpo 1 180 °C; <sup>13</sup>C NMR: 20.52, 25.51, 39.09, 52.64, 53.1, 62.3, 102.74, 127.97, 129.33, 133.62, 140.13; [a]D -7 (c=2.6). 3- a) Rf values (eluant: 95/5 hexane/AcOEt; 6 elutions): a-S-8a: 0.46; β-A-8a: 0.4; β-S-8a: 0.26; a-A-8a: 0.18; b) Whereas distinctive NOE correlations were observed for  $\alpha$ -S-8a, and  $\alpha$ -A-8a, that recorded for the isomer  $\beta$ -S-8a were not so conclusive. Selected data: 6c: C 64.34 (calc. 64.27), H 7.33 (calc. 7.19); <sup>1</sup>H NMR: -0.05 (s, 3H), -0.04 (s, 3H), 0.8 (s, 9H), 0.93 (d, J=6.6 Hz, 3H), 1.12 (s, 9H), 1.45-1.8 (m, 4H), 2.15-2.3 (m, 1H), 3.2 (s, 3H), 3.22 (s, 3H), 4.03 (t, J=6.3 Hz, 2H), 4.05-4.15 (m, 1H), 4.28 (t, J=5.7 Hz, 1H), 5.3-5.4 (m, 2H); <sup>13</sup>C NMR: 4.9, -4.1, 18.2, 20.7, 25.9, 27.3, 32.6, 37.5, 38.67, 39.29, 52.42, 52.62, 61.1, 70.47, 103, 131.9, 136, 178.3; [α]<sub>D</sub> -2 (c=2.3); S-7: <sup>13</sup>C NMR: -4.51, -4.22, 14.08, 18.07, 25.91, 27.28, 32.04, 32.95, 36,64, 38,79, 52,64, 52,94, 60.89, 70.07, 72,35, 73,73, 103,19, 178,42; A-7: <sup>13</sup>C NMR: -4.68, -4.53, 17.08, 18.04, 25.88, 27.25, 32, 32.24, 35.53, 38.75, 52.74, 60.88, 71.76, 72.41, 73.93, 103.33, 178.52; α-S-8a: m.p. 47 °C; <sup>1</sup>H NMR: 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.12 (d, J=6.7 Hz, 3H), 1.19 (s, 9H), 1.68 (ddd, J=13.3, 9.3, 3.9 Hz, 1H), 1.75-1.86 (m, 1H), 1.92-2.02 (m, 1H), 2.28-2.36 (m, 1H), 2.37-2.46 (m, 1H), 3.29 (d, J=10.3 Hz, 1H, OH), 3.43 (s, 3H), 3.49 (ddd, J=10.3, 5.1, 1.5 Hz, 1H), 3.82-3.88 (m, 1H), 4.02-4.09 (m, 1H), 4.24-4.3 (m, 1H), 4.33 (dd, J=7.5, 1.5 Hz, 1H), 5.02 (dd, J=6.1, 3.9 Hz, 1H); [α]<sub>D</sub> +10 (c=0.5); β-A-8a: <sup>1</sup>H NMR: 0.08 (s, 6H), 0.88 (s, 9H), 1.04 (d, J=6.6 Hz), 1.19 (s, 9H), 1.6 (ddd, J=12.8, 11, 5.1 Hz, 1H), 1.95-2.05 (m, 2H), 2.09 (dd, J=12.8, 7.3Hz, 1H), 2.35-2.5 (m, 1H), 2.71 (d, J=8.6 Hz, 1H, OH), 3.27 (t, J=8.2 Hz, 1H), 3.34 (s, 3H), 3.75 (dt, J=8, 4.9 Hz, 1H), 3.91 (d, J=8 Hz, 1H), 4.15-4.3 (m, 2H), 4.91 (d, J=4.9 Hz, 1H);  $[\alpha]_D$  +18 (c=1);  $\beta$ -S-8a: <sup>1</sup>H NMR: 0.09 (s, 6H), 0.89 (s, 9H), 1.05 (d, J=7 Hz, 3H), 1.19 (s, 9H), 1.7-1.85 (m, 1H), 1.9-2.05 (m, 1H), 2.39 (d, J=8.3 Hz, 1H, OH), 2.45-2.55 (m, 1H), 3.34 (s, 3H), 3.35-3.45 (m, 1H), 3.5-3.6 (m, 1H), 3.74 (dd, J=8.7, 1.4 Hz, 1H), 4.05-4.35 (m, 1H), 5.04  $(dd, J=5.1, 1.8 Hz, 1H); [\alpha]_D + 65 (c=1); \alpha-A-8a: <sup>1</sup>H NMR: 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.04 (d, J=6.8 Hz, 3H), 0.98 (s, 9H), 1.04 (d, J=6.8 Hz, 3H), 0.98 (s, 9H), 1.04 (d, J=6.8 Hz, 3H), 0.98 (s, 9H), 0.98 (s$ 1.18 (s, 9H), 1.48 (ddd, J=13.4, 8.1, 7.8 Hz, 1H), 1.95-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.24 (d, J=8.6 Hz, 1H, OH)), 2.34 (ddd, J=13.4, 8.1, 7.8 Hz, 1H), 1.95-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.24 (dd, J=8.6 Hz, 1H, OH)), 2.34 (ddd, J=13.4, 8.1, 7.8 Hz, 1H), 1.95-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.24 (dd, J=8.6 Hz, 1H, OH)), 2.34 (ddd, J=13.4, 8.1, 7.8 Hz, 1H), 1.95-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.24 (dd, J=8.6 Hz, 1H), 0.14 (ddd, J=13.4, 8.1, 7.8 Hz, 1H), 1.95-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.24 (dd, J=8.6 Hz, 1H), 0.14 (ddd, J=13.4, 8.1, 7.8 Hz, 1H), 1.95-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.24 (dd, J=8.6 Hz, 1H), 0.14 (ddd, J=13.4, 8.1, 7.8 Hz, 1H), 1.95-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.24 (dd, J=8.6 Hz, 1H), 0.14 (ddd, J=13.4, 8.1, 7.8 Hz, 1H), 1.95-2.05 (m, 2H), 2.1-2.2 (m, 1H), 2.24 (dd, J=8.6 Hz, 1H), 0.14 (ddd, J=13.4, 8.1, 7.8 Hz), 0.14 (ddd, J=13.4, 7.8 Hz), 0.14 (dddd, J=13.4, 7.8 Hz), 0.14 J=13.4, 5.8, 5.6 Hz, 1H), 3.33 (s, 3H), 3.37 (t, J=7.4 Hz, 1H), 3.74 (dd, J=8.7, 1.4 Hz, 1H), 3.78-3.83 (m, 1H), 4.1-4.18 (m, 1H), 4.24-4.31 (m, 1H), 5 (dd, J=5.8, 3.1 Hz, 1H); [a]D -60 (c=1); S-9b: <sup>13</sup>C NMR: 14.91, 18.92, 27.31, 29.72, 31.14, 34.11, 38.36, 38.55, 38.82, 42.16, 51.57, 60.96, 61.36, 69.64, 74.99, 76.65, 98.91, 178.54; A-9b: <sup>13</sup>C NMR: 15.76, 23.7, 24.74, 27.3, 32.21, 34.79, 38.25, 38.83, 43.22, 52.2, 58.7, 60.97, 70.06, 75.32, 82.46, 100.97, 178.58; a-A-10: m. p. 75-76 °C; C 56.2 (calc. 56.32), H 9.25 (calc. 9.45);  $[\alpha]_D$  -65 (c=1). <sup>1</sup>H and <sup>13</sup>C NMR spectra: 400 and 50 MHz, respectively, CDCl<sub>3</sub>;  $[\alpha]_D$ : 21 °C, CH2Cl2.

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5- Crystal data for  $\alpha$ -A-10 : C<sub>17</sub>H<sub>34</sub>O<sub>6</sub>Si, M.W. = 362.5, orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, a = 6.844(2), b = 11.593(3), c = 26.107(7) Å, U = 2071.6 Å<sup>3</sup>, Z = 4, dcalc = 1.162 gcm<sup>-3</sup>,  $\mu$  (MoK $\alpha$ ) = 1.333 mm<sup>-1</sup>. Data were collected at room temperature using graphite monochromated MoK $\alpha$  radiation ( $\lambda$  = 0.7107 Å) on a Nonius-CAD4-F diffractometer and a crystal of dimensions 0.38\*0.32\*0.32 mm<sup>3</sup>. 2466 reflections were collected (2° <  $\theta$  < 26°). 1597 were unique with I>3 $\sigma$ (I). Absorption corrections from the psi scans of 4 reflections were applied. The structure was solved using direct methods and refined against IFI (full matrix,  $\sigma^2$ (F<sup>2</sup>) =  $\sigma^2_{\text{counts}}$  + 0.0064 F<sup>4</sup>). Hydrogen atoms were introduced as fixed contributors (C-H = 0.95 Å, B(H)=1.3\*Beqv of attached C). The absolute configuration was determined by refining Flack's parameter. Final results : R(F) = 0.040, Rw(F) = 0.059, GOF = 1.181, largest residues in final difference map = +0.20/-0.16 eÅ<sup>-3</sup>. For all computations the Nonius OpenMolen Package (Fair, C.K. in MolEN. An Interactive Intelligent System for Crystal Structure Analysis. Enraf-Nonius, Delft, The Netherlands, 1990) on a DEC Alpha 3600S computer was used.

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