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Total Synthesis of an Aglycone of Spiramycin

G. Oddon and D. Uguen*

Laboratoire de Synthèse Organique, associé au CNRS Ecole Européenne de Chimie, Polymères et Matériaux, Université Louis Pasteur 1, rue Blaise Pascal; 67008 Strasbourg (France)

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Abstract: The iodoaldehyde β -8f has been converted efficiently into the title aglycone by means of the Kishi-Nozaki-Takai coupling reaction. © 1998 Published by Elsevier Science Ltd. All rights reserved.

In order to prepare the aglycone 1 of spiramycin, we considered the compounds 2, 3 and 4 as possible synthetic precursors of this 16-membered macrolide and, accordingly, a stereo-controlled access to these building blocks was gained by means of chiron and enzyme methodologies, as detailed in previous communications.¹ After having verified, by using model substrates, that crucial steps of the indicated plan would be feasible, ^{1c} we next attempted to bring together these synthons in order to get the target aglycone.



Though it appeared necessary, at an advanced stage of the synthesis, to modify the silyl groups favoured initially for protecting the oxygen atoms at the C-3 and C-9 positions, we are pleased to report herein that the above strategy proved to be efficient.

The Julia-Paris-Kocienski (JPK) condensation of the aldehyde **3a** with sulfone **2** in conditions defined earlier¹c proceeded well, giving the olefin **5** in a fairly good yield (69%) and with a perfect *E* stereoselectivity, as judged by NMR. Bis-hydroxylation of **5** was then performed by using either AD-mix- $\alpha^{(B)}$ or the OsO4-NMO system.

In both instances, the crude reaction product was composed of the diols S-6 and A-6 (NMR) and was immediately reacted with methanol and PPTS to afford a mixture of the mixed-acetals α -9a, β -9a, α -10a and β -10a, which were efficiently separated by chromatography and characterised by NMR.² As observed precedently in a related case, ¹C the all-*syn* product (*i.e.* S-6, in the present case) was indeed slightly favoured by using the former reagent. The latter was preferred however, the isolated yield in acetals 9a being better in these conditions (44%).



Reagents and conditions: 1- *i*) 1.55 M (in hexane) n-BuLi (1 eq.), THF (10 ml/mmol); -78 °C, 45 mn; *ii*) 3a (1 eq.); -78 °C, 1 hour; *iii*) Ac₂O (2.1 eq.), DMAP (0.1 eq.); r.t., 4 hours; 2- 6% HgNa (3x5 eq.), 1/1 MeOH/AcOEt (20 ml/mmol); -50 °C, 6 hours (69% overall, from 2); 3- OsO₄ (0.08 eq.), NMO (2 eq.), 9/1 acetone/water (5 ml/mmol); r.t., 2 hours, or AD-mix- α (1.4 g/nmol), CH₃SO₂NH₂ (1.5 eq.), K₂OsO₄.2H₂O (0.001 eq.), (DHQ)₂-PHAL (0.06 eq.), 1/1 *t*-BuOH/H₂O (10 ml/mmol); r.t., 2 weeks; 4- PPTS (0.2 eq.), 1/1 MeOH/CH₂Cl₂ (14 ml/mmol); r.t., 2 days; 5- NaH (1.2 eq.), 1/1 MeI/DMF (3.3 ml/mmol); r.t., overnight (81%).

The ensuing methylation of the C-5 hydroxy group in the compound β -9a was not straightforward, the use of the more prevalent methylation conditions leading invariably to a mixture of β -9b with the isomeric ether 11.³ This side trans-silylation reaction was minimised however by performing that methylation with NaH in DMF and methyl iodide, used both as reagent and as cosolvent, the small amount (ca 7%) of ether 11 still formed being separated easily by chromatography from the desired methoxy compound β -9b (81%).



Reagents and conditions: 1- *i*) 1M (in hexane) DIBA-H (2.5 eq.), CH_2Cl_2 ; -78 °C, 0.5 hour, then pH 5-6 tartaric buffer (96%); *ii*) (COCl)₂ (1.5 eq.), DMSO (2 eq.), Hünig base (4 eq.), CH_2Cl_2 ; -78 °C to -20°C, 2 hours (76%); *iii*) 3/2/1 0.4 M aqueous KMnO₄/1.3 M KH₂PO₄/t-BuOH (30 ml/mmol); 0°C, 15 mn, then NaHSO₃ (100%); 2- *i*) NEt₃ (1.3 eq.), 2,4,6-trichlorobenzoyl chloride (1.2 eq.), THF; r.t., 1 hour, then filtration; *ii*) DMAP (6 eq.), 4 (1.05 eq.), toluene; r.t., 3 hours (92%); 3- TBAF.H₂O (1 eq.), pyridine.HF (1 eq.), THF; r.t., 2 hours (94%).

Conversion of β -9b into the acid β -7a (73% overall) and ensuing condensation of β -7a with the alcohol 4 to give the ester β -8a (92%) were then performed by using protocols previously designed.^{1d} Somewhat unexpectedly, attempted selective hydrolysis of the O-DPTBS group at C-9 in β -8a, in order to form β -8b, proved unfeasible, the only detectable product being the diol β -8c whatever the used reagent (*e.g.* TBAF, alone or buffered with HF.pyridine) was. It is worth noting that any mono-deprotected compound failed to be detected. After numerous unsuccessful trials, implementation of the TIPS protection of the C-3 oxygen atom was decided.

This was first tried by preparing the O-TIPS derivative 3b but attempted JPK condensation of this aldehyde with sulfone 2 proved unfeasible, probably as a result of the large size of the OTIPS group. Accordingly, the planned exchange of protection was realised at a more advanced stage by treating the pivalate β -9b with TBAF.H₂O to form the diol β -9c (96%), which, by sequential treatment with TBDMSCl and TIPSTf as above afforded the compound β -9d in good overall yield (89%, from β -9b). Conversion of β -9d into the acid β -7b (84%) was then realised by means of the sequence used precedently. Ensuing esterification of 4 by β -7b (61% yield), followed by treatment of the resulting ester β -8d with AcOH/THF/H₂O delivered the alcohol β -8e (67%). Finally, oxidation of β -8e by SO3.pyridine and DMSO furnished the iodoaldehyde β -8f in good yield (89%).



Reagents and conditions: 1- *i*) TBAF.3 H₂O (4 eq.), THF; r.t., 7 hours (96%); *ii*) TBDMSCl (1 eq.), NEt₃ (1.2 eq.), CH₂Cl₂; 1 day (98%); *iii*) TIPSTf (1.2 eq.), 2,6-lutidine (1 eq.), CH₂Cl₂; 0 °C, 5 hours (95%); *iv*) same conditions as for the β -9b-7a conversion (84%, overall); 2- *i*) same conditions as for the **7a-8a** conversion (61%); *ii*) 3/1/1 AcOH/THF/H₂O (13 ml/mmol); r.t., 2 days (67%); *iii*) SO₃.pyridine (4 eq.), NEt₃ (8 eq.), DMSO (large excess), CH₂Cl₂; 0 °C to r.t., 1 hour (89%); 3- *i*) CrCl₂ (100 eq.), NiCl₂ (1 eq.), DMSO; r.t., 5 hours (76%); *ii*) DDQ (1.2 eq.), CH₂Cl₂; r.t., 12 hours (40%).

The final problem we had to solve was to convert the iodoaldehyde β -8f into the aglycone β -1a. In a first experiment, a solution of β -8f in DMSO was added slowly to a slurry of excess (ca 4 eq.) CrCl₂ and NiCl₂ (Cr(II)/Ni(II)=100/1) in the same solvent, the final concentration being approximately 0.01 M. Unfortunately, almost no reaction took place after two days at room temperature, obviously a result of the high dilution of both the substrate and the reducing agent. Indeed, by using a very large excess (ca 100 eq.) of reducing species, the other conditions being unchanged, the hydroxy compound β -1a was formed in good yield (76%) as a 9/1 mixture of two diastereomers (NMR). In order to facilitate the characterisation of the product, that mixture was reacted with DDQ to give a ketone (40%), whose the structure was firmly established as being β -1b by NMR (¹H, ¹³C, COSY, TOCSY, NOESY, ¹H/¹³C correlation, HMBC), mass, IR and UV spectroscopies.⁴

In conclusion, the scheme we used for synthesizing the aglycone 1 suffers from the lack of stereoselectivity of the step by which the olefin 5 was converted into the bis-hydroxy compound S-6 and, to a lesser extent, from the sensitivity of dienyl iodides 4 and 8d-f to light, which forced us to protect carefully from daylight all the vessels we used at any stage of the 4-8f conversion. A few rewarding points emerge however. Besides being highly convergent, the synthesis of β -1b presented herein⁵ appears relatively short, the longer sequence comprising 36 steps (average yield by step: 82%). Moreover, the strategy retained permitted to control efficiently the configuration at the C-3, C-4, C-5, C-6, C-8 and C-15 chiral centers.

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References and Notes

1- a) Oddon, G.; Uguen, D. Tetrahedron Lett. **1997**, 38, 4411-4414; b) Breuilles, P.; Oddon, G.; Uguen, D. Tetrahedron Lett. **1997**, 38, 6607-6610; c) Oddon, G.; Uguen, D. Tetrahedron Lett. **1998**, 39, 1153-1156. The results presented herein are taken from the thesis dissertation of Gilles Oddon (Strasbourg, 1996).

2- The A-6/S-6 ratio (table) was determined by HPLC (C-18 column; 1/9 isopropanol/hexane). Column chromatography of the crude methanolysis product of the S-6/A-6 mixture was performed efficiently on silica gel (Rf values (eluant: 9/1 hexane/AcOEt; 2 elutions): α -9a: 0.56; β -10a: 0.54; β -9a: 0.42; α -10a: 0.19). Structure assignment to each individual mixed-acetal was performed unambiguously by NMR, *i.a.* NOE experiments (see ref. 1c).

3- The 9a/11 ratio reached 2/1 by using KH and CH₃I (1 eq. each) in THF.

4- Selected data: 5: ¹H NMR (200 MHz): 0.03 (s, 3H), 0.05 (s, 3H), 0.86-0.92 (m, 12H), 1.04 (s, 9H), 1.2 (s, 9H), 1.32-1.85 (m, 7H), 2.15-2.38 (m, 1H), 3.28 (s, 3H), 3.29 (s, 3H), 3.43 (d, J=6 Hz, 2H), 4.08-4.3 (m, 3H), 4.34 (dd, J=7.6, 4.1 Hz, 1H), 5.24 (dd, J=15.5, 9 Hz, 1H), 5.46 (dd, J=15.5, 6.7 Hz, 1H), 7.45-7.55 (m, 6H), 7.6-7.7 (m, 4H); ¹³C NMR: -4.83, -4.13, 16.09, 18.24, 19.41, 25.92, 26.95, 27.34, 32.07, 33.31, 37.85, 38.89, 38.98, 52.72, 52.8, 61.22, 69.51, 70.3, 103, 127.64, 129.56, 133.99, 134.1, 134.13, 135.69, 178.44; $[\alpha]_D^{21}$ +5 (c=1, CH₂Cl₂); β -9a: ¹H NMR (400 MHz): 0.08 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.05 (s, 9H), 0.97 (d, J=6.5 Hz, 3H), 1.19 (s, 9H), 1.22-1.4 (m, 1H), 1.62-1.95 (m, 6H), 2.32 (d, J=7.5 Hz, 1H; OH); 2.5-2.6 (m, 1H), 3.32 (s, 3H), 3.42-3.56 (m, 3H), 3.85-3.91 (m, 1H), 4.03-4.1 (m, 1H), 4.2-4.26 (m, 1H), 4.14 (d, J=8.2 Hz, 1H), 4.9 (d, J=4.5 Hz, 1H), 7.35-7.45 (m, 6H), 7.6-7.7 (m, 4H); ¹³C NMR (50 MHz): -4.49, -4.38, 18.13, 19.38, 25.96, 26.99, 27.32, 32.57, 33.29, 34.82, 36.95, 38.8, 39.24, 54.81, 61.06, 68.43, 70.87, 72.03, 78.7, 104.94, 127.69, 129.63, 133.95, 135.72, 178.52; $[\alpha]_{D}$ +50 (c=0.7, CH₂Cl₂); α -9a: ¹H NMR (200 MHz): 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.05 (s, 9H), 0.98 (d, J=6.2 Hz, 3H), 1.2 (s, 9H), 1.33-2.5 (m, 8H), 3.38-3.57 (m, 6H), 3.77-3.9 (m, 1H), 3.98-4.37 (m, 2H), 4.36 (d, J=7.7 Hz, 1H), 4.99 (t, J=5.3 Hz, 1H), 7.35-7.45 (m, 6H), 7.6-7.7 (m, 4H); ¹³C NMR (50 MHz): -4.84, -3.9, 18, 18.17, 19.38, 25.99, 26.98, 27.34, 31.82, 33.07, 34.62, 38.8, 39.01, 39.15, 56.29, 61.58, 68.38, 71.54, 72.06, 79.91, 106.61, 127.7, 129.66, 133.89, 135.7, 178.53; $[\alpha]_D + 7$ (c=1, CH₂Cl₂); β -7b: ¹H NMR (200 MHz): 0.02 (s, 6H), 0.88 (s, 9H), 0.91 (d, J=6.5 Hz, 3H), 1-1.1 (m, 21H), 1.11-1.2 (m, 2H), 1.5-1.92 (m, 3H), 2.52-2.77 (m, 2H), 3 (dd, J=14, 8 Hz, 1H), 3.3-3.5 (m, 9H), 4.54 (d, J=8.2 Hz, 1H), 4.5-4.6 (m, 1H), 5.05 (d, J=4.2 Hz, 1H); ¹³C NMR (50 MHz): -5.38, 12.54, 18.03, 18.2, 18.4, 26.01, 29.76, 33.51. 34.41, 37.02, 39.23, 54.92, 57.03, 66.75, 67.61, 77.34, 81.15, 105.02, 175.51; $[\alpha]_D$ +53 (c=0.6, CH₂Cl₂); β -8f; ¹H NMR (200 MHz): 1-1.1 (m, 21H), 1.18 (d, J=7,1 Hz, 3H), 1.21 (d, J=6.3 Hz, 3H), 1.3-1.9 (2m, 4H), 2.22-2.6 (m, 5H), 2.95 (dd, J=16.7, 3.8 Hz, 1H), 3.25 (d, J=4.6 Hz, 1H), 3.34 (s, 3H), 3.39 (s, 3H), 4.48 (dd, J=7.9 Hz, 1H), 4.67-4.76 (m, 1H), 4.9-5.04 (m, 2H), 5.66 (dt, J=14.8, 7.3 Hz, 1H), 6.01 (dd, J=15.1, 10.5 Hz, 1H), 6.21 (d, J=14.3 Hz, 1H), 6.97 (dd, J=14.4, 10.5 Hz, 1H), 9.62 (d, J=2 Hz, 1H); 1³C NMR (50 Mhz): 12.6, 14.63, 18.25, 19.58, 31.22, 37.37, 38.64, 38.86, 38.99, 45.28, 54.8, 57.19, 66.79, 69.78, 76.74, 77.29, 81.01, 104.58, 130.55, 132.98, 145.11, 172.58, 204.3; β -1b: ¹H NMR (600 MHz): 1-1.1 (m, 21H), 1.2 (d, J=6.5 Hz, 3H), 1.3 (d, J=6.5 Hz, 3H), 1.3-1.4 (m, 1H), 1.78-1.85 (m, 1H), 1.88-1.95 (m, 2H), 2.1-2.16 (m, 1H), 2.2-2.28 (m, 1H), 2.42 (dd, J=18, 6.5 Hz, 1H), 2.43-2.5 (m, 1H), 2.7 (dd, J=18, 3.5 Hz, 1H), 2.6-2.68 (m, 1H), 2.93 (t, J=4 Hz, 1H), 3.31 (s, 3H), 3.43 (s, 3H), 3.97 (dd, J=6.5, 4 Hz, 1H), 4.4-4.46 (m, 1H), 4.98 (dd, J=5.5, 2 Hz, 1H), 5.1-5.16 (m, 1H), 6.05 (ddd, J=16, 9.5, 5 Hz, 1H), 6.15 (dd, J= 16, 11 Hz, 1H), 6.25 (d, J=15 Hz, 1H), 7 (dd, J=15, 11 Hz, 1H); 13 C NMR (150 MHz): 12.3, 17.2, 19.8, 21.1, 35.2, 39.5, 40.5, 41.5, 44, 46, 55.3, 59.9, 69.5, 70, 81.1, 83.9, 104.8, 127.5, 131.8, 140.1, 143, 171.3, 204.9; Mass (NH3): m/z: 553 (MH⁺), 570 (M+NH4⁺), 575 (M+Na⁺); 591 (M+K⁺); 157 (TIPS); UV: λ_{max}=278nm (MeOH); IR (CHCl₃): 2929, 2867, 2833, 1734, 1690, 1675 cm⁻¹. ¹H and ¹³C NMR spectra: on CDCl₃ solutions; [α]_D values: 21 °C.

5- For previous syntheses of related aglycones, see: i) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. Tetrahedron Lett. 1980, 21, 2837-2840; ii) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. J. Am. Chem. Soc. 1981, 103, 1224-1226; iii) Nakajima, N.; Uoto, K.; Yonemitsu, O.; Hata, T. Chem. Pharm. Bull. 1991, 39, 64-74; iv) Keck, G. E.; Palani, S. F.; Hardy, F. M. J. Org. Chem. 1994, 59, 3113-3122.