Pergamon

Tetrahedron Letters, Vol. 38, No. 25, pp. 4411-4414, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00945-3

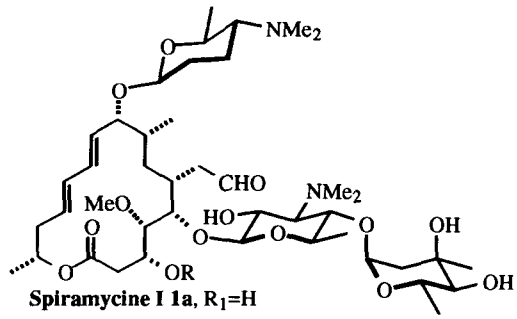
Toward a Total Synthesis of an Aglycone of Spiramycine; Two Complementary Accesses to a C-5/C-9 Fragment

G. Oddon and D. Uguen*

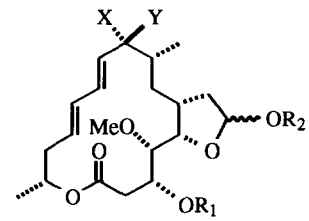
Laboratoire de Synthèse Organique, associé au CNRS
Ecole Européenne de Chimie, Polymères et Matériaux, Université Louis Pasteur
1, rue Blaise Pascal; 67008 Strasbourg (France)

Abstract: *Both homochiral acetates **4d** and **5f**, which were obtained by lipase-catalysed acetylation of either the tetraol **4a** or the diol **5e**, respectively, have been converted stereoconvergently into a C-5/C-9 fragment of the title antibiotic.* © 1997 Published by Elsevier Science Ltd.

Spiramycines **1a** and **1b** are two naturally-occurring macrolides produced by culture of the genus *Spiromyces ambofabiens*. First isolated and characterised at Rhône-Poulenc,[1] these 16-membered lactones display potent antibiotic activity against gram-positive bacteria and are currently used in chemotherapy. Although no total synthesis of these spiramycines has been achieved to date, four syntheses of the corresponding aglycone **2a** (*i.e.* leuconolide) and/or of its oxidation product at C-9 **2b** (*i.e.* carbonolide) have been reported.[2]

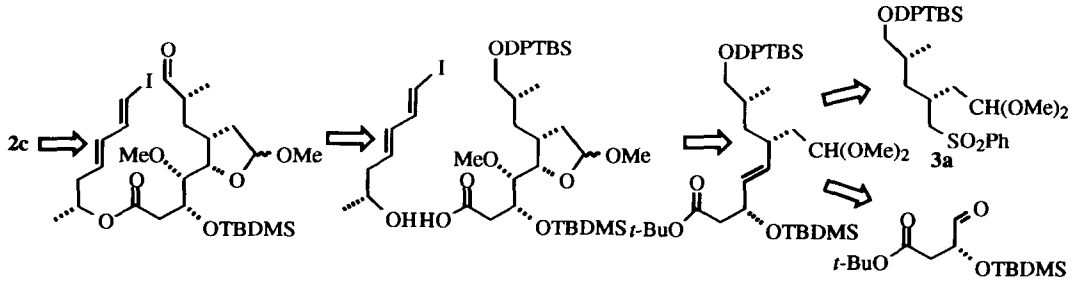


Spiramycine I 1a, R_1=H
Spiramycine II 1b, R_1=C(O)CH_3



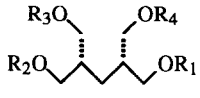
Leuconolide A_3 2a, R_1=C(O)CH_3; R_2=H; X=OH; Y=H
Carbonolide B 2b, R_1=C(O)CH_3; R_2=H; X=Y=O
2c; R_1=TBDMS; R_2=Me; X=OH; Y=H

To prepare modified spiramycines, in which the osidic residues would be substituted by thiosugar analogues, and to evaluate the antibiotic properties of these surrogates, we embarked on a synthesis of the aglycone **2c**, hoping that the selected protecting groups would make possible later a regioselective addition of the macrolide core of **2c** to these sugar mimes.

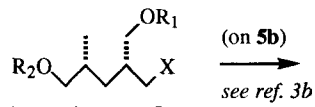


The strategy retained is highly convergent, and differs significantly from that used in previous approaches. As shown, a Kishi-Nozaki coupling reaction was favoured to achieve, at a late stage of the synthesis, the crucial ring-closure step. The ensuing disconnection led to the indicated plan, which necessitated first to prepare, then to assemble by a Julia-Paris-Kocienski reaction the sulfone **3a** and an aldehyde accessible from (*R*)-malic acid.[2d] Both *syn* bis-hydroxylation of the Δ^4 carbon-carbon double bond and oxidation of the hydroxyl at C-9 in the resulting fragment would deliver an acid, the esterification of which by a dienyl iodide would provide a suitable candidate for the final cyclisation step. We described herein how the key sulfone **3a** was obtained by two complementary pathways.

First approach: Previously, we had showed that the lipase-catalysed acetylation of the double-meso tetraol **4a** and a subsequent silylation afforded the C_{2v}-shaped bis-acetate **4b**.[3a] Controlled hydrolysis of this diacetate gave the monoacetate **4c**, which could be transformed selectively, via the sulfide **5a**, into the chlorosulfone **3b** by treatment of the corresponding silyloxy sulfoxide **5b** with SO_2Cl_2.[3b]

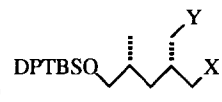


4a, R_1-R_4=H
4b, R_1=R_3=C(O)CH_3, R_2=R_4=DPTBS
4c, R_1=H, R_3=C(O)CH_3, R_2=R_4=DPTBS
4d, R_1=R_3=H; R_2=R_4=DPTBS



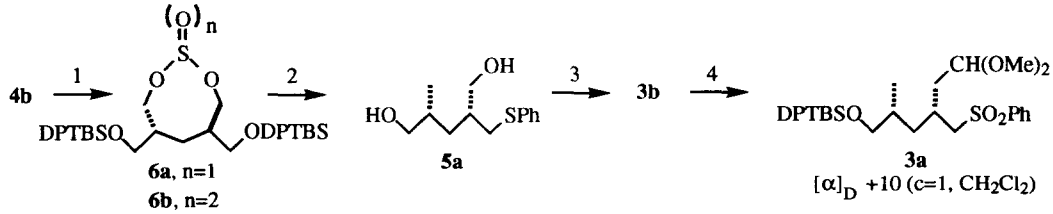
(on **5b**)
see ref. 3b

5a, X=SPh; R_1=R_2=H
5b, X=S(O)Ph; R_1=R_2=TES
5c, X=OH; R_1=R_2=DPTBS
5d, X=OTosyl; R_1=R_2=DPTBS
5e, X=OH; R_1=H; R_2=DPTBS
5f, X=OAc; R_1=H; R_2=DPTBS



3a, X=SO_2Ph; Y=$CH(OMe)_2$
3b, X=SO_2Ph; Y=Cl
3c, X=SO_2Ph; Y=CN
3d, X=SO_2Ph; Y=CHO
3e, X=OAc; Y=CN
3f, X=OH; Y=CN

A major drawback of this approach was the low yield of the mono-hydrolysis step, leading to **4c**. A significant improvement was obtained by converting first the diacetate **4b** into the diol **4d**. Treatment of **4d** by $SOCl_2$ under high-dilution conditions resulted in the formation of the sulfite **6a**, which, by oxidation, furnished the sulfate **6b**.[4] Taking advantage of the known lower reactivity of monoalkyl sulfates, as compared to the corresponding dialkyl sulfates, **6b** was reacted with Super-Hydride® in THF to give, after hydrolysis, the alcool **5c**. Tosylation of **5c**, followed by successive treatment of the resulting tosylate **5d** with PhSLi and TBAF, gave the sulfide **5a**, which was then converted into the sulfone **3b** via the bis-O-TES sulfoxide **5b** as previously described.[3b]



6a, n=1
6b, n=2

5a

3a
$[\alpha]_D$ +10 (c=1, CH_2Cl_2)

Reagents and conditions: 1- *i*) K_2CO_3 (2 eq.), MeOH; -15 °C, 72 hours; *ii*) $SOCl_2$ (1.1 eq.), NEt_3 (2 eq.), CCl_4 (290 ml/mmol); r.t., 36 hours; *iii*) $RuCl_3.3\ H_2O$ (0.01 eq.), $NaIO_4$ (2 eq.), 2/2/3 $CCl_4/CH_3CN/H_2O$ (5.5 ml/mmol); r.t., 12 hours; 2- *i*) $LiHBEt_3$ (1 eq.), THF (15 ml/mmol); r.t., 1 hour, then 1/1 0.1N H_2SO_4/ether (100ml/mmol); r.t., 4 days (67%); *ii*) TosCl (1 eq.), pyridine (5 eq.), DMAP (0.2 eq.); 0 °C, 11 days; *iii*) PhSLi (2 eq.), DMF (2 ml/mmol); r.t., 2 hours; *iv*) TBAF (1N, in THF; 2.2 eq); r.t., 2 hours (79% overall, from **6b**); 3- according to ref. 3b; 4- *i*) DPTBSCl (1.1 eq.), NEt_3 (1.2 eq.), DMAP (0.2 eq.), CH_2Cl_2 (2.5 ml/mmol); r.t., 3 hours; *ii*) KCN (1.1 eq.), NaI (0.05 eq.), DMSO (2 ml/mmol); 50°C, 12 hours; *iii*) 1N (in hexane) DIBA-H (1 eq.), CH_2Cl_2 (-78 °C, 45 min, then pH 2 tartrate buffer; *iv*) $HC(OMe)_3$ (1 eq.), 1/3 MeOH/CH_2Cl_2 (5 ml/mmol), Amberlyst 15 (1 g/mmol); r.t., 4 hours (73% overall, from **3b**).

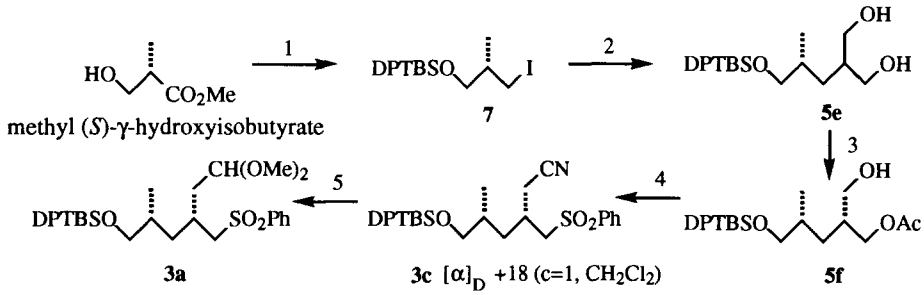
The transformation of the chlorosulfone **3b** into the target acetal **3a** was obvious: sequential treatment of **3b** by DPTBSCl and KCN in DMSO afforded the nitrile **3c**, which, by DIBAH reduction, followed by acetalisation of the resulting aldehyde **3d** with methanol, furnished the sulfone **3a**. This C-5/C-9 fragment of spiramycine was thus

obtained in 20 steps by starting from diethyl malonate and formaldehyde,[3a] with an overall yield of 4.6% (average yield for each step: 86%).[5]

Second approach: The sulfone **3a** could thus be obtained on a 5 g scale. However, the necessary recourse to high-dilution conditions in the **4b-6a** conversion and to the expensive PFL in the acetylation of the tetraol **4a** precluded the use of this scheme to prepare larger amounts of this sulfone. Accordingly, another way, starting from the reasonably-prized methyl ester of (*S*)-γ–hydroxyisobutyric acid, was explored.

This ester was converted into the iodide **7** by using described methodology.[6] Treatment of the sodio derivative of diethyl malonate in a toluene/DMF mixture[7] followed by LAH reduction of the resulting alkylation product gave the diol **5e** in good yield (78% overall from **7**).

Enzyme-catalysed acetylation of **5e** by vinyl acetate was subsequently experimented by using various enzymes. PFL gave good results, the pure monoacetate **5f** being formed in excellent yield (97%). Interestingly, the less expensive lipase from pig pancreas (PPL) proved to be as efficient as PFL, inducing the formation of the acetate **5f** in 93% yield and with a comparable enantiomeric purity (e.e.=96%).[8]



Reagents and conditions: 1- According to ref.; 2- *i*) diethyl malonate (1.6 eq.), NaH (1.5 eq.), 4/1 toluene/DMF; 80 °C, 5 hours; *ii*) LAH (2 eq.), THF; 0 °C, 4 hours (78% overall); 3- PPL (0.2 g/mmol), vinyl acetate (15 eq.), THF; r.t., 2 weeks (93%); 4- TosCl (1 eq.), pyridine (5 eq.), DMAP (0.2 eq.); 0 °C, 24 hours; *ii*) NaCN (1.8 eq.), DMSO; 90 °C, 4 hours; *iii*) K_2CO_3 (1 eq.), MeOH; 0 °C, 3 hours; *iv*) I_2 (1 eq.), PPh_3 (1 eq.), imidazole (1 eq.), 1/3 acetonitrile/ether; 0 °C, 3 hours; *v*) $PhSO_2Na$ (1.1 eq.), DMF; r.t., 24 hours (68% overall); 5- as above.

The monoacetate **5f** was then reacted with tosyl chloride and NaCN in DMSO to give the nitrile **3e**. Mild hydrolysis of **3e** and sequential treatment of the resulting alcohol **3f** with I_2/PPh_3 and sodium benzenesulfinate in DMF delivered the sulfone **3c**, identical (NMR, $[\alpha]_D$) with the product obtained previously from the diacetate **4b**. Given the C_{2v} symmetry of the diacetate **4b** and the *S* absolute configuration of the starting hydroxyisobutyric ester, this result confirmed both our previous assignment of the *R,R* configuration of the enzyme-catalysed acetylation product of the tetraol **4a** and the pro-*R* selectivity of the lipase from pig pancreas. Finally, reduction of **3c** by DIBAH and subsequent treatment with methanol as above gave the sulfone **3a** in a fairly good yield (18% overall, from methyl hydroxyisobutyrate) and with optical properties very close to those observed precedently.

In conclusion, two enantioselective preparations of an important synthon of our planned synthesis of an aglycone of spiramycine have been accomplished. The former approach offered the opportunity to develop a few interesting synthetic concepts such as, for instance, the enzyme-catalysed acetylation of a double-meso-shaped tetraol and the formation of a eight-membered cyclic sulfate to monoreact selectively with a 1,5-pentanediol with C_{2v} symmetry. The latter approach proved to be more expeditive (13 steps overall; average yield for each step: 84%), allowing to obtain conveniently the sulfone **3a** on a 15-20 g scale. Elaboration of **3a**, leading to the target aglycone of spiramycine will be reported in due course.

Acknowledgements: Thanks are due to Rhône-Poulenc Rorer and the CNRS for a grant (to G. O.).

References and Notes

1- Paul, R.; Tchelicheff, S. *Bull. Soc. Chim. France* **1965**, 650-656, and references therein.

2- a) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 2837-2840; b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1224-1226; c) Nakajima, N.; Uoto, K.; Yonemitsu, O.; Hata, T. *Chem. Pharm. Bull.* **1991**, *39*, 64-74; Keck, G. E.; Palani, S. F.; Hardy, F. M. *J. Org. Chem.* **1994**, *59*, 3113-3122.

3- a) Breuilles, P.; Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1993**, *34*, 4205-4208; b) Oddon, G.; Uguen, D. preceding letter.

4- A solution of triethylamine (1.74 ml, 2 eq.) in anhydrous CCl_4 (1500 ml) was placed in a 4l three-neck flask, equipped with an efficient mechanical stirrer and with two dropping funnels linked to an argon line and containing, respectively, a solution of the diol **4d** (4g, 6.2 mmol) in CCl_4 (300ml) and a solution of $SOCl_2$ (0.5 ml, 1.1 eq.) in CCl_4 (300 ml). These two solutions were added slowly (9 ml/h) and synchronously to the vigorously-stirred solution of triethylamine, at room temperature. After 36 hours, the addition was over and the solvents were evaporated. The residue was taken up in CH_2Cl_2 (100 ml) and the resulting pale-yellow solution was filtered on a short column of silica gel. Evaporation of the solvents left the sulfite **6a** as a colourless oil (4.32g; anal.: C 68.15 (calc. 68.18), H 7.34 (calc. 7.42); ^{13}C NMR: 19.41, 27.09, 28.49, 37.32, 37.69, 62.11, 64.49, 64.96, 65.23, 128, 130.01, 130.04, 133.35, 135.71, 135.74; $[\alpha]_D$ -22 (c=2, CH_2Cl_2)). The oxidation of **6a** into the sulfate **6b** was performed by using a protocol described by Sharpless (Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538-7539).

5- Selected data: *i*) **3a**: ^1H NMR: 0.72 (d, J= 6.4 Hz, 3H), 1.03 (s, 9H), 1.1-1.3 (m, 1H), 1.4-1.68 (m, 3H), 1.87-2.15 (m, 2H), 3.06 (ddd (AB part of an ABX system), J_{AB}=14.5 Hz, J_{AX}=3.9 Hz, J_{BX}=7 Hz ($\Delta\nu$=27.1 Hz), 2H), 3.26 (s, 3H), 3.27 (s, 3H), 3.38 (d, J=5.9 Hz, 2H), 4.38 (t, J= 5.6 Hz, 1H), 7.32-7.7 (m, 13H), 7.75-7.85 (m, 2H); ^{13}C NMR: 16.57, 19.34, 26.96, 27.65, 33.21, 37, 38.07, 52.36, 53.19, 59.95, 68.91, 102.75, 127.72, 128.1, 129.28, 129.7, 133.58, 133.87, 135.65, 139.85; $[\alpha]_D$ +10 (c=1, CH_2Cl_2); *ii*) **3c**: m.p. 85°C; anal.: C 69.45 (calc. 69.32), H 6.96 (calc. 7.18); ^1H NMR: 0.78 (d, J= 6.4 Hz, 3H), 1.03 (s, 9H), 1.25-1.4 (m, 1H), 1.45- 1.74 (m, 2H), 2.45-2.55 (m, 1H), 2.73 (ddd (AB part of an ABX system), J_{AB}=16.9 Hz, J_{AX}=4 Hz, J_{BX}=5.7 Hz ($\Delta\nu$=41 Hz), 2H), 3.04 (d, J=6.2 Hz, 2H), 3.35-3.5 (m, 2H), 7.3-7.5 (m, 6H), 7.55-7.7 (m, 7H), 7.85-7.95 (m, 2H); ^{13}C NMR: 16.64, 19.27, 22.6, 26.97, 28.16, 32.82, 38, 58.22, 68.63, 117.5, 127.82, 127.92, 129.63, 129.85, 133.51, 134.17, 135.62, 135.68, 139.35; $[\alpha]_D$ +21 (c=1, CH_2Cl_2); *iii*) **3f**: 0.96 (d, J=6.6 Hz, 3H), 1.09 (s, 9H), 1.1-1.31 (m, 1H), 1.49-1.77 (m, 2H), 1.94 (m, 1H+OH), 2.43 (d, J=5.9 Hz, 2H), 3.43-3.53 (m, 3H), 3.67 (dd, J=10.9 and 4 Hz, 1H), 7.35-7.45 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR: 17.3, 19.37, 19.82, 27.02, 33.04, 34.2, 35.33, 63.74, 68.82, 118.91, 127.81, 129.82, 133.76, 135.72; $[\alpha]_D$ +10 (c=1, CH_2Cl_2); *iv*) **5c**: anal.: C 74.83 (calc. 74.95), H 8.21 (calc. 8.39); ^1H NMR: 0.86 (d, J=6.6 Hz, 3H), 1.03-1.05 (m, 9H), 1.3-1.5 (m, 2H), 1.55-1.64 (m, 1H), 1.75-1.9 (m, 1H), 2.61 (t, J=4.7 Hz, 1H (OH)), 3.4 (d, J=5.7 Hz, 2H), 3.57-3.8 (m, 4H), 7.3-7.45 (m, 12H), 7.6-7.7 (m, 8H); ^{13}C NMR: 17.57, 19.47, 19.59, 27,23, 31,57, 33,48, 40,11, 65,67, 65,59, 69,16, 127,94, 128,09, 129,88, 130,11, 133,45, 134,13, 135,88; $[\alpha]_D$ +2 (c=2, CH_2Cl_2); *v*) **5f**: 0.91 (d, J= 6.7 Hz, 3H), 1.06 (s, 9H), 1-1.14 (m, 1H), 1.41-1.55 (m, 1H), 1.7-1.91 (m, 2H), 2.05 (s, 3H), 3.47 (d, J=6 Hz, 4H), 4.1 (ddd (AB part of an ABX system), J_{AB}=11.2 Hz, J_{AX}=6.3 Hz, J_{BX}=7 Hz ($\Delta\nu$=36.6 Hz), 2H), 7.35-7.45 (m, 6H), 7.6-7.7 (m, 4H); ^{13}C NMR: 17.08, 19.37, 20.99, 26.97, 31.47, 33.09, 37.97, 63.46, 64.4, 68.98, 127.72, 129.68, 133.91, 135.7, 171.76; $[\alpha]_D$ +14 (c=2, CH_2Cl_2); *vi*) **6b**: anal.: C 66.44 (calc. 66.63), H 7.34 (calc. 7.17); ^1H NMR: 1 (s, 18H), 1.15-1.45 (m, 2H), 2.25-2.4 (m, 2H), 3.4-3.6 (m, 4H), 4.44 (ddd (AB part of an ABX system), J_{AB}=11.7 Hz, J_{AX}=7.6 Hz, J_{BX}=4 Hz ($\Delta\nu$=53.6 Hz), 4H), 7.3-7.3 (m, 8H); ^{13}C NMR: 19.36, 27.03, 28.83, 37.29, 64.34, 74.85, 128.05, 130.11, 133.13, 135.67; $[\alpha]_D$ -28 (c=3, CH_2Cl_2). All ^1H and ^{13}C NMR spectra described herein have been recorded at 200 and 50 MHz, respectively, on $CDCl_3$ solutions. $[\alpha]_D$ values have been measured at 21°C.

6- Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1995**, *36*, 7445-7448.

7- Eliel, E. L.; Wilken, P. H.; Fang, F. T. *J. Org. Chem.* **1957**, *22*, 231-234.

8- As determined by HPLC, by using a Pirkle column (isopropanol/hexane).

(*Received in France* 24 *April* 1997; *accepted* 9 *May* 1997)