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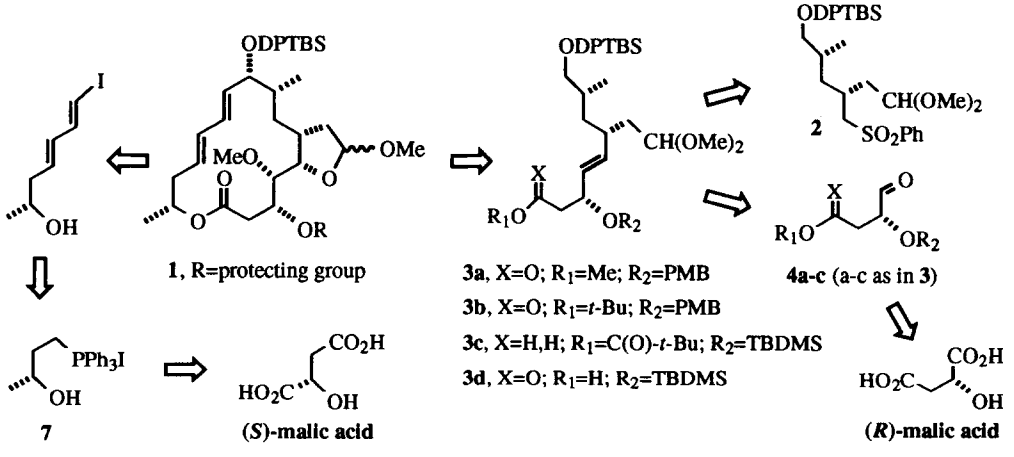
Toward a Total Synthesis of an Aglycone of Spiramycin; A Chiron Approach to the C-1/C-4 and the C-13/C-15 Fragments

P. Breuilles, 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: *Acetalisation of p-anisaldehyde by either (R) or (S)-butanetriol has been shown to occur selectively and quantitatively by using Noyori's protocol. The crystalline dioxane derivatives* ***R-6a*** *and* ***S-6a*** *which formed, respectively, in these conditions have been converted efficiently into the title fragments of spiramycin.* © 1997 Elsevier Science Ltd.

Recently, as part of a projected synthesis of the aglycon **1** of spiramycin, we described a convenient preparation of the sulfone **2**.[1] Pursuing our plan, we attempted next to synthesize the C-1/C-9 fragment **3a** by performing a Julia-Paris-Kocienski (JPK) condensation of the sulfone **2** with the known aldehyde **4a**.[2] However, presumably due to the sensitivity of both **4a** and the expected JPK product **3a** to the basic conditions of this reaction, that resulted exclusively in the formation of decomposition products. Accordingly, the use of the aldehydes **4b-c** was considered. On the one hand, the *t*-butyl ester functionality of **4b** should be more resistant to bases than the corresponding methyl ester group in **4a**, on the other hand, should the decomposition of **4a** (res. **3a**) result from a possible β-elimination of an alcoxide anion, the pivalate **4c** (res. **3c**) would remain unaffected in basic conditions, the compound **3c** being potentially transformable however, *e.g.* by DIBA-H reduction and subsequent oxidation, into the acid **3d**.

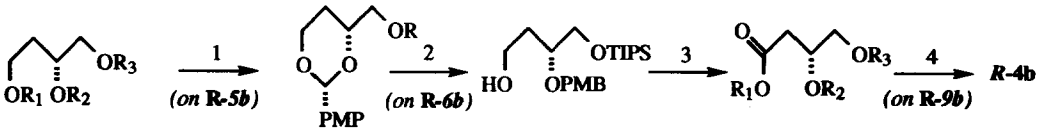


Whereas the preparation of the aldehyde **4a** could be accomplished without major difficulty by selective reduction of the O-PMB derivative of the dimethyl ester of (*R*)-malic acid,[2] access to the synthons **4b** and **4c** by a related scheme appeared not so straightforward and an alternative pathway, based on the selective protection of the triol ***R*-5a**, which can be obtained easily by reduction of (*R*)-malic acid,[3] was experimented.

The acetalisation of *p*-anisaldehyde by butanetriol **5a** has been reported as giving mainly the corresponding dioxane derivative **6a**[4] and it could be hoped that, by using the *R* enantiomer ***R*-5a**, the acetal ***R*-6a** would form and could be transformed into the target synthons **4b** and **4c** by a sequence of protection/deprotection/oxidation steps. Though it appeared necessary to set out a new protocol for executing the acetalisation of *p*-anisaldehyde by **5a**, we are pleased to report herein that this strategy proved to be very efficient, allowing to prepare not only the target synthons **4b** and **4c** but also, by starting from (*S*)-malic acid, the fragment **7** of spiramycin.

Attempted APTS-catalysed condensation of the dimethyl acetal of *p*-anisaldehyde with ***R*-5a** in refluxing toluene and with continuous removal of the formed water by means of 4 Å molecular sieves as described[4a] resulted in the formation of a brown mixture from which the pure acetal ***R*-6a** was isolated in low yield (27%). Other conditions were tried but, in the best case, by using CSA as a catalyst and CH_2Cl_2 as solvent, the yield did not exceeded 60%.[5] A major improvement resulted from the use of Noyori's acetalisation conditions.[6]

Thus, addition of a reduced amount of TMS triflate to a CH_2Cl_2 solution of *p*-anisaldehyde and of the tris-O-TMS derivative ***R*-5b**, at -78°C and under strictly anhydrous conditions,[7] followed by treatment, after a few hours, of the crude reaction mixture with sodium hydroxide in methanol at the same temperature, resulted in the isolation of the crystalline, pure (elemental analysis, NMR), acetal ***R*-6a** in an almost quantitative yield. This compound was indeed sensitive to acidic conditions, isomerising partially to the corresponding dioxolane derivative ***R*-8** during attempted filtration on silica gel.

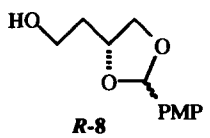


***R*-5a**, R_1=R_2=R_3=H
***R*-5b**, R_1=R_2=R_3=TMS
***R*-5c**, R_1=H; R_2=PMB; R_3=TIPS
***R*-5d**, R_1=R_2=H; R_3=Bn
***R*-5e**, R_1=Piv; R_2=H; R_3=Bn
***R*-5f**, R_1=Piv; R_2=TBDMS; R_3=Bn
***R*-5g**, R_1=Piv; R_2=TBDMS; R_3=H

***R*-6a**, R=H
***R*-6b**, R=TIPS
***R*-6c**, R=Bn

***R*-5c**

***R*-9a**, R_1=H; R_2=PMB; R_3=TIPS
***R*-9b**, R_1=*t*-Bu; R_2=PMB; R_3=TIPS
***R*-9c**, R_1=*t*-Bu; R_2=PMB; R_3=H



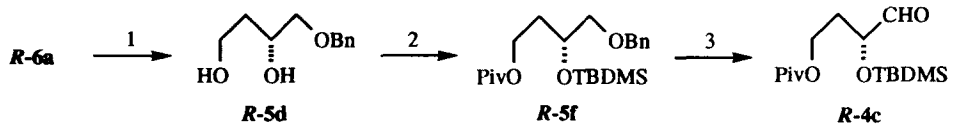
***R*-8**

Reagents and conditions: 1- *i*) *p*-anisaldehyde (1 eq.), TMSTf (0.2 eq.), CH_2Cl_2 (4 ml/mmol); -78°C, 5 hours (quant.); *ii*) TIPSTf (1.1 eq.), NEt_3 (3 eq.), CH_2Cl_2 (6 ml/mmol); r. t., 5 hours (98%); 2- 1M DIBA-H (in hexane; 1.7 eq.), CH_2Cl_2 (7 ml/mmol); 0.5 hour (94%); 3- *i*) DMSO (1.5 eq.), $(COCl)_2$ (2 eq.), DIPEA (8 eq.), CH_2Cl_2 (5 ml/mmol); -78 °C, 1 hour, then r. t. (80%); *ii*) $NaClO_2$ (1.4 eq.), 0.5 M aqueous KH_2PO_4 (1 ml/mmol), CH_3CN (3 ml/mmol), 30% H_2O_2 (1.05 eq.); 10 °C, 2 hours (75%); *iii*) *t*-butyl trichloroacetimidate (2 eq.), 1/3 CH_2Cl_2/cyclohexane (5 ml/mmol), $BF_3.Et_2O$ (20 µl/mmol); 0 °, 1 hour (78%); 4- *i*) TBAF.3 H_2O (1.1 eq.), THF; r. t., 1 hour (90%); *ii*) DMSO (1.5 eq.), $(COCl)_2$ (1.5 eq.), DIPEA (4 eq.), CH_2Cl_2 (5 ml/mmol); -78 °C, 1 hour, then -78 °C to - 20°C (94%).

Treatment of the acetal ***R*-6a** by TIPS triflate and triethylamine, followed by cleavage with DIBA-H of the acetal functionality in the resulting silyl derivative ***R*-6b** afforded the alcohol ***R*-5c** in high yield (92%, from ***R*-5b**).[8] Sequential oxidation of ***R*-5c** by Swern reagent and sodium chlorite furnished the acid ***R*-9a** which was converted to the corresponding *t*-butyl ester ***R*-9b** (78%, from ***R*-5c**) by means of the trichloroacetimidate methodology. Finally, desilylation of ***R*-9b** by treatment with TBAF and Swern oxidation of the resulting alcohol ***R*-9c** provided the aldehyde ***R*-4b** in a satisfactory 36% overall yield (from ***R*-5b**).

Obtention of the pivalate ***R*-4c** was secured by reacting first the acetal ***R*-6a** with NaH and benzyl bromide to form the benzyl ether ***R*-6c**, which, by subsequent treatment with ethanedithiol and CSA gave the diol ***R*-5d** (86%, from ***R*-5b**). Selective esterification of the primary hydroxy group of ***R*-5d** was performed very efficiently by

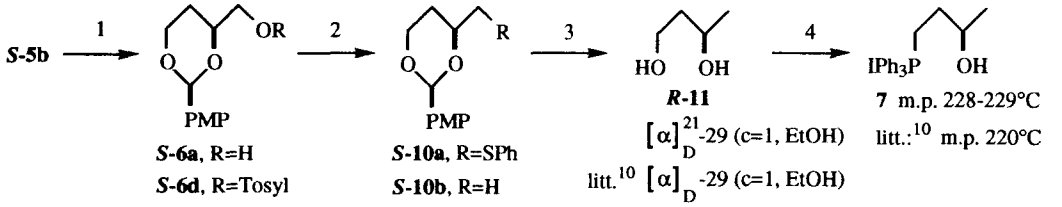
reacting sequentially ***R*-5d** with Bu_2SnO in methanol and pivaloyl chloride. The resulting pivalate ***R*-5e** (99%) was silylated (TBDMSCl, imidazole) to form ***R*-5f** which was hydrogenated (H_2, Pd/C), the alcohol ***R*-5g**, thus released, being finally oxidized into the aldehyde ***R*-4c** by using Swern reagent.



Reagents and conditions: 1- *i*) NaH (1.05 eq.), BnBr (1.05 eq.), THF; r.t., 5 hours; *ii*) $(CH_2SH)_2$ (1 eq.), CSA (0.05 eq.), CH_2Cl_2; r.t., 12 hours (86%); 2- *i*) Bu_2SnO (1 eq.), MeOH (9 ml/mmol); reflux, 2 hours, then evaporation and azeotropy with toluene (quant.); *ii*) pivaloyl chloride (1.1 eq.), NEt_3 (0.05 eq.), toluene; 0 °C to r.t., 2 hours (99%); *iii*) TBDMSCl (1.1 eq.), imidazole (3 eq.), DMF; r.t., 24 hours (quant.); 3- *i*) H_2 (1 bar), 10% Pd/C (5%, by weight), AcOEt; r.t., 5 hours (88%); *ii*) DMSO (1.5 eq.), $(COCl)_2$ (1.5 eq.), DIPEA (4 eq.), CH_2Cl_2; -78 °C to -20 °C, 2 hours (94%).

By this procedure, the target synthon ***R*-4c** could be prepared on a 10g-scale and in a fairly good overall yield (52%, from ***R*-5b**; average yield by step: 94%).[9]

An obvious way to obtain the required C-13/C-15 fragment **7** was to prepare likewise the enantiomeric acetal ***S*-6a** from (*S*)-malic acid and to perform an hydrogenolysis of the free hydroxy group of this acetal.



Reagents and conditions: 1- *i*) same conditions as for the ***R*-5b**-***S*-6a** conversion; *ii*) tosyl chloride (1.3 eq.), TEBA-Cl (0.1 eq.), 30% aqueous NaOH (2 ml/mmol), CH_2Cl_2 (2 ml/mmol); r.t., 18 hours (93%); 2- *i*) PhSLi (1.3 eq.), DMF (2.5 ml/mmol); r.t. 3 hours; *ii*) Ni-Raney (excess), 96% EtOH; r.t., 12 hours; 3- same conditions as for the ***R*-6c**-***R*-5d** conversion (71%, from ***S*-6d**); 4- according to ref. 10.

This was done easily by treating ***S*-6a** with tosyl chloride in aqueous sodium hydroxide to obtain ***S*-6d**, which was reacted immediately with lithium thiophenoxide. Desulfuration of the resulting sulfide ***S*-10a** by Raney nickel afforded the acetal ***S*-10b**. Final conversion of this acetal to the phosphonium salt **7** was ensured by treatment of ***S*-10b** with ethanedithiol to liberate the known diol ***R*-11**, which was then transformed into **7** as described.[10]

In conclusion, a very efficient process for protecting selectively the triol **5a** by acetalisation of *p*-anisaldehyde has been contrived. The reliability of this new protocol has been firmly established: the preparation of the acetals ***R*-6a** and ***S*-6a** has been executed several times by undergraduate students on a scale as large as 30g without any trouble. This procedure should, accordingly, be useful to a wide range of synthetic chemists.

The recourse to a full-reduction product (*i.e.* the triol **5a**) of malic acid to prepare the synthon ***R*-4b** could surprised. Obviously, that lengthens in some extent the procedure since it is necessary, at a latter stage, to perform an oxidation to generate back the carboxylic functionality of ***R*-4b**. It has to be realised however that each step of the present process proceeds in high yield, without any significant experimental difficulties, and that the overall yield thus recorded competes favourably with that registered by using more classical, prevalent, methods of selective protection of malic acid. Moreover, the synthetic flexibility of the acetal **6a** has been illustrated by the preparation of various key elements of our projected synthesis of the aglycone **1**. Further elaboration of these synthons toward this target will be disclosed in due course.[11]

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

References and Notes

1- Oddon, G.; Uguen, D. *Tetrahedron Lett.* **1997**, *38*, 4411-4414.

2- Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113-3122.

3- a) Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1983**, *48*, 4427-4430; b) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067-4086. (*R*)-malic could be conveniently prepared from (*R,R*)-tartaric acid on a 100 g-scale by using a published procedure (Gao, Y; Zepp, C. M. *Tetrahedron Lett.* **1991**, *32*, 3155-3158).

4- a) Herradon, B.; Cueto, S.; Morcuende, A.; Valverde, S. *Tetrahedron: Asymmetry* **1993**, *4*, 845-864; b) Tsuri, T.; Kamata, S. *Tetrahedron Lett.* **1985**, *26*, 5195-5198.

5- The crude product was a 7/1/1 mixture of ***R*-6a** with the two diastereomeric dioxolanes ***R*-8**, as determined, in ^{1}H NMR, by integration of singlets at 5.5, 5.76 and 5.9 ppm, respectively, corresponding to the acetalic proton of each isomeric acetal.

6- Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357-1358.

7- **Cautionary note**: It is essential to use perfectly dried and freshly-distilled reagents. Furthermore, sample withdrawal with syringe during the condensation should be avoided in order to prevent any contamination of the reaction mixture with moisture, which is detrimental. *Protocol for the acetalisation process*: A solution of the silyl derivative ***R*-5b** (31 mmol) and of *p*-anisaldehyde (31 mmol) in anhydrous (distilled from CaH_2, then from P_4O_{10}) CH_2Cl_2 (120 ml) was prepared in a flame-dried flask, under argon. This solution was gently stirred while cooled to -78 °C, after that freshly-distilled TMSTf (1.12 ml, 0.2 eq.) was added with a syringe. After 5 hours of stirring at -78 °C, the mixture, while kept at that temperature (any rise of the temperature during both the acetalisation and the work-up process induced the formation of the isomeric acetal ***R*-8**), was transferred slowly, via cannula, to a cooled (ca 0 °C), well-stirred, 4% solution of NaOH in MeOH (50 ml). The resulting mixture was stirred at 0 °C for 1 hour, then poured into a stirred mixture of brine (150 ml), ether (250 ml), and ice (100g). The organic layer was separated and the aqueous one was further extracted with ether (3x250 ml). The pooled organic phases were dried on K_2CO_3 and evaporated to leave an oil (6.89 g) which crystallised on standing in the freezer. A recrystallisation from ether (96% yield, in two crops) gave an analytically-pure product (m.p. 70 °C; anal.: C 64.34 (calc. 64.27), H 7.33 (calc. 7.19); ^{1}H NMR: 1.4-1.5 (m, 1H), 1.91 (ddd, J=12.5, 5.2, 5.1 Hz, 1H), 2.1 (t, J=6.5 Hz, 1H, O*H*), 3.65-3.75 (m, 2H), 3.8 (s, 3H), 3.9-4.1 (m, 2H), 4.25-4.35 (m, 1H), 5.5 (s, 1H), 6.89 (d, J=8.7 Hz, 2H), 7.42 (d, J=8.7 Hz, 2H); ^{13}C NMR: 27, 55.4, 65.6, 66.7, 77.7, 101.2, 113.7, 127.6, 131.1, 160.1; $[\alpha]_D$ -12 (c=3, CH_2Cl_2). The acetal ***S*-6a**, which was prepared similarly by starting from ***S*-5b**, displayed the following optical properties: $[\alpha]_D$ +14 (c=3, CH_2Cl_2). Attempted similar acetalisation of benzaldehyde proved not so satisfactory: the reaction did not proceed before the temperature rose -20 °C and, in these conditions, a mixture of dioxane and dioxolane derivatives was formed.

8- Compare with: Oikawa, H.; Matsuda, I.; Ichihara, A.; Kohmoto, K. *Tetrahedron Lett.* **1994**, *35*, 1223-1226. The TIPS group of ***R*-5c** prevents probably the complexation of DIBA-H by the two vicinal oxygen atoms, what explains the observed high regioselectivity of that reductive ring-opening step.

9- Selected data: ***R*-5c**: ^{1}H NMR: 0.95-1.1 (m, 21H), 1.7-1.9 (m, 2H), 2.54 (t, J=5.6 Hz, 1H, O*H*), 3.65-3.95 (m, 3H), 3.8 (s, 3H), 4.6 (dd, J_{AB}=11.3 Hz ($\Delta\nu$= 29.4 Hz), 2H), 6.87 (d, J=8.5 Hz, 2H), 7.27 (d, J=8.5 Hz, 2H); ^{13}C NMR: 12, 18.1, 34.5, 55.4, 60.6, 66, 72.6, 79, 114, 129.6, 130.4, 159.4; $[\alpha]_D$ +27 (c=2, CH_2Cl_2); ***R*-4b**: ^{1}H NMR: 1.45 (s, 9H), 2.66 (ddd (AB part of an ABX system), J_{AB}=15 Hz, J_{AX}=4.5 Hz, J_{BX}=3.1 Hz, $\Delta\nu$=15 Hz, 2H), 3.8 (s, 3H), 4.12 (t, J=5.8 Hz, 1H), 4.62 (s, 2H), 6.88 (d, J=8.6 Hz, 2H), 7.28 (d, J=8.6 Hz, 2H), 9.69 (s, 1H); ***R*-4c**: anal.: C 59.82 (calc. 59.56), H 9.75 (calc. 10.01); ^{1}H NMR: 0.08 (s, 3H), 0.1 (s, 3H), 0.92 (s, 9H), 1.18 (s, 9H), 1.9-2.05 (m, 2H), 4.05-4.3 (m, 3H), 9.94 (d, J=1.3 Hz, 1H); ^{13}C NMR: -5, -4.6, 18.2, 25.8, 27.2, 29.8, 38.8, 59.6, 74.5, 178.3, 203.6; $[\alpha]_D$ +23 (c=1, CH_2Cl_2). All the ^{1}H and ^{13}C NMR spectra reported herein have been recorded at 200 and 50 MHz, respectively, on $CDCl_3$ solutions. The $[\alpha]_D$ values have been measured at 21 °C.

10- Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755-760.

11- The results presented herein are taken in parts from the thesis dissertation of G. Oddon (Université Louis Pasteur, Strasbourg, 1996).

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