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Toward a Total Synthesis of Pristinamycin II_B; A Chiron Approach to a C-9/C-16 Fragment

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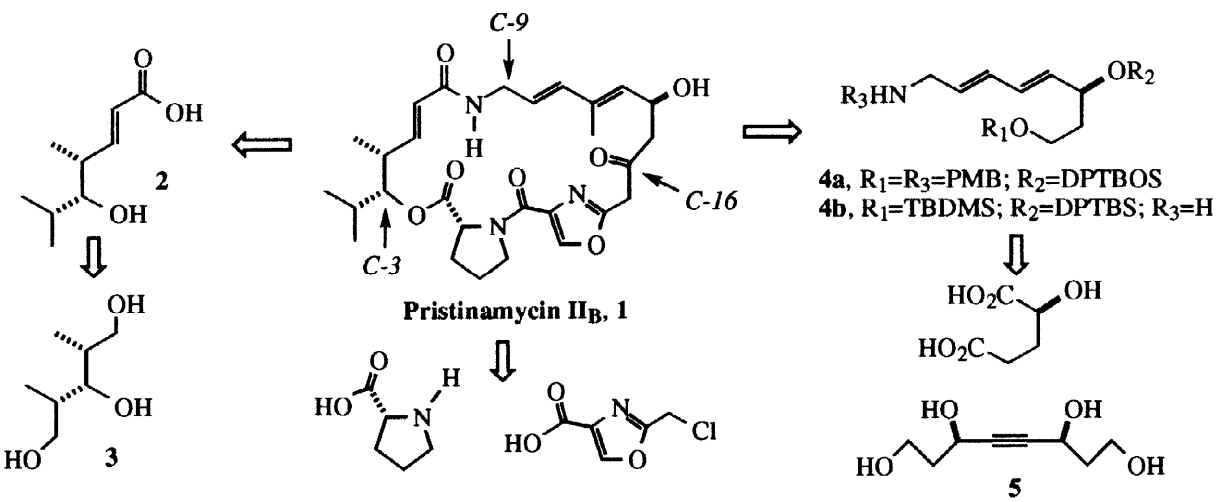
Abstract: *Copper(I)-catalysed addition of methyl Grignard reagent to the propagyl diol 8, which was efficiently prepared from S-malic acid, proceeds with a perfect E stereoselectivity, the diol thus obtained being then converted into the title fragment by known methodology.*

Due to their potent antibiotic activity against various bacterial pathogens, especially those strains which are resistant to usual antibacterial agents, the pristynamycins stand to be particularly useful therapeutic agents.[1]

Produced industrially at Rhône-Poulenc Rorer by culture of *Streptomyces pristinaespiralis*,[2] these naturally-occurring products are complex mixtures of, on the one hand, the pristinamycins II, also called streptogramins A, which are azamacrolactones, and on the other hand, the pristinamycins I, which are cyclopeptides. Whereas a synthesis of a pristynamycin I has been achieved not too long after its structure identification,[3] it was not until the past few months that a total synthesis of a pristinamycin II (*i.e.* pristinamycin II_B, **1**) was disclosed, ending a fifteen-years-long search for an efficient chemical access to these molecules.[4]



With the aim to prepare stereoselectively compound **1** by using the indicated strategy, we examined previously the preparation of the hydroxyacid **2**, which, as described in an earlier publication,[5a] was obtained by asymmetrisation of the *meso* triol **3**, followed by conventional functional-group transformations.

Next, we tried to derive the C-9/C-16 fragment **4** from the tetraol **5** by means of a related *meso* strategy but attempted desymmetrisation of this tetraol proved not really useful.[5b] Accordingly, a new approach based on the use of *S*-malic acid as starting material was explored. Results along this line are disclosed herein, the completion of the synthesis of pristynamycin II_B being described in the accompanying Letter.

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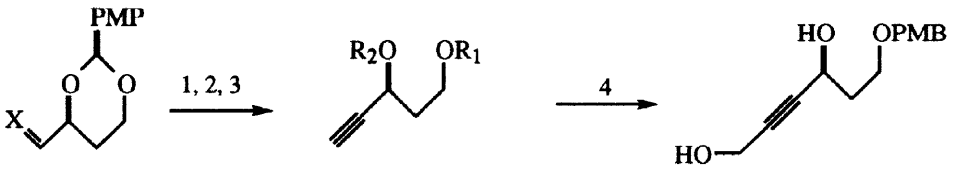
The crystalline acetal **6a**, which was formed almost quantitatively by condensing *p*-methoxybenzaldehyde with the triol issued from the full reduction of dimethyl (*S*)-malate,[6] was oxidised into the corresponding aldehyde **6b**. Due to the sensitivity of the acetal moiety in either **6a** or **6b**, the best conditions for performing this oxidation proved to be those described by Moffatt (DMSO-DCCI-TFA-pyridine), the work-up being restricted to a dilution of the crude oxidation mixture with CH_2Cl_2, filtration on Celite, and evaporation of solvents. The residue thus left was immediately reacted with the ylide (excess) generated by treatment of bromethyltriphenylphosphonium bromide with *t*-BuOK in THF to give, after usual work-up and chromatography on silica gel pretreated by $NaHCO_3$, the bromide **6c** as a 2/1 mixture of the *E* and the *Z* isomer, respectively, in good yield (81% overall, from **6a**). Treatment of bromide **6c** by excess LDA in THF furnished the acetylenic compound **7a** which was reacted with ethanedithiol (EDT) and a trace of PPTS to give the propargylic diol **7b** (87% overall, from **6c**).



6a, X=H, OH
6b, X=O
6c, X=CHBr

7a, R_1, R_2=(*p*-anisyl)-CH
7b, R_1= R_2=OH
7c, R_1= PMB; R_2=H
7d, R_1=R_2=PMB

8

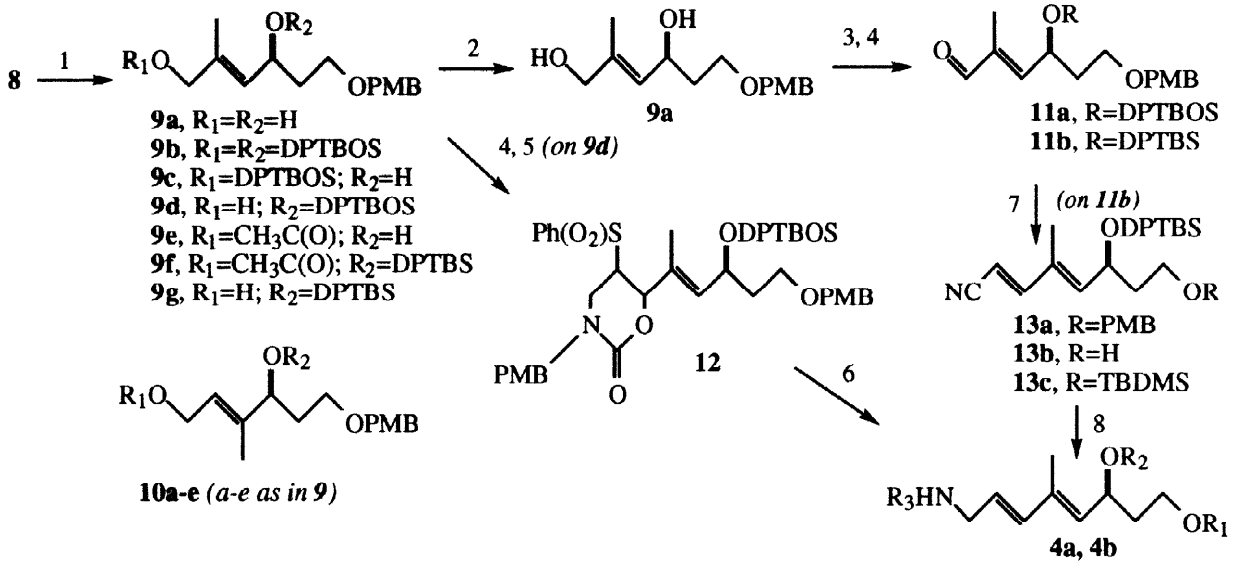
Reagents and conditions: 1- *i*) DCCI (3 eq.), DMSO (23.5 eq.), pyridine (1 eq.), CF_3CO_2H (0.5 eq.), toluene; r. t., overnight; *ii*) $BrCH_2PPh_3Br$ (2 eq.), *t*-BuOK (1.8 eq.), THF; -78 °C, 5 hours (81%, from **6a**); 2- *i*) LDA (2 eq.), THF; -78 °C, 0.5 hours (90%); *ii*) EDT (1 eq.), CH_2Cl_2; r. t., 2 hours (87%); 3- PMB trichloroacetimidate (1 eq.), PPTS (0.1 eq.), THF; r. t., 2 days (46%); 4- *i*) HMDS (0.5 eq.), TMSTf (0.05 eq.), THF; r. t., 2 hours, evaporation, then filtration on silica gel; *ii*) 1.55N BuLi (in hexane, 1.1 eq.), $(CH_2O)_n$ (1.3 eq.), THF; -78 °C to r.t., 7 hours; *iii*) HF.pyridine (1 eq.), THF (93% overall, from **7c**).

Attempted selective protection of the primary hydroxy group of this diol proved difficult. In the best conditions found so far, the diol **7b** was slowly added to a mixture of PMB trichloroacetimidate and PPTS to afford, after chromatography, the desired ether **7c** in moderate yield (48%), accompanied by unreacted **7b** (23%) and the bis-protected derivative **7d** (11%). By recycling the starting diol, the yield in **7c** could be increased to 61%. The ether **7c** was finally converted into the diol **8** (94%) by sequential O-silylation with HMDS, condensation with paraformaldehyde, and desilylation with HF.pyridine.

We faced now the problem of adding stereo and regioselectively a methyl group onto the acetylene moiety of **8** in order to generate the C-11/C-16 fragment **9a**. According to literature dealing with carbometallation of related diols,[7] this was first attempted by reacting **8** with excess methylmagnesium bromide in refluxing THF and/or ether with the hope that the addition of the methyl group would preferably proceed on the less hindered side of the acetylene moiety of **8**, so as to give, after hydrolysis, the diol **9a**. But, besides its sluggishness, condensation of diol **8** with MeMgBr in these conditions led to complex mixture in which allene compounds could be detected (NMR).[7c]

A quite better result was obtained by adding a reduced amount of copper iodide[8] to the cooled (ca 0-4 °C) slurry which formed by mixing the diol **8** with excess MeMgCl in THF. After two days at that temperature, the starting diol had almost disappeared and a new compound, which proved to be a 3/1 mixture (NMR) of, respectively, the desired diol **9a** with its regioisomer **10a** was isolated (89%). Attempt to fractionate that mixture by chromatography proved unfeasible. A convenient separation could be achieved however by treating the crude diol mixture with diphenyl-*t*-butoxysilyl chloride (DPTBOSCl). Whereas the major, desired, diol **9a** reacted immediately to give the corresponding bis O-DPTBOS compound **9b**, the minor isomer **10a** was only transformed into the monoprotected derivative **10c**, a small amount of the bis-ether **10b** being also formed however. Column chromatography of that mixture allowed us to isolate **9b**, mixed with a residual amount (ca 10%) of **10b**. Full

elimination of the unwanted regioisomer was obtained by reacting that 9/1 mixture of bis-protected derivatives with $Na_2S.9H_2O$,[9] which gave, after chromatography, the monodeprotected compound **10d** admixed with a small amount of compound **9d**, and then the pure diol **9a**. Interestingly, additional, useful, product could be obtained by treating the preceding **10d/9d** mixture with $BaMnO_4$. Flash-chromatography of the aldehydes thus formed gave a small amount of pure aldehyde **11a**.



Reagents and conditions: 1- *i*) 3 M MeMgCl (in THF; 4 eq.), CuI (0.05 eq.), THF; 0-4 °C, 2 days (84%); 2- *i*) DPTBOSCl (1.8 eq.), NEt_3 (1.8 eq.), DMAP (0.1 eq.), CH_2Cl_2; -78 °C to r. t., 7 hours ; *ii*) $Na_2S.9\ H_2O$ (1 eq.), EtOH; r. t., 4 days (41% overall, from **8**); 3- *i*) vinyl acetate (7 eq.), PFL (10 mg/mmol), THF; 0 °C, 1 day; *ii*) DPTBSCl (1.05 eq.), imidazole (2.6 eq.), DMF; r. t., overnight; *iii*) K_2CO_3 (1.3 eq.), MeOH; -15 °C, 5 hours (92% overall, from **9a**); 4- $BaMnO_4$ (8 eq.), CH_2Cl_2; r. t., overnight (quantitative); 5- according to ref. 10 (63%); 6- 5% NaHg, Na_2HPO_4 (3 eq.), MeOH; r.t., 4 hours; 7- $(i\text{-PrO})_2P(O)CH_2CN$ (3.1 eq.), *t*-BuOK (3 eq.), THF; -78 °C to r.t; 3.5 hours (98%); 8- AlH_3 (4 eq.), THF; 0 °C, 5 hours (96%).

We tried first to convert this aldehyde into the amino compound **4a** by using an aminosulfone-based methodology we had used previously for preparing allylic amines and, accordingly, **11a** was converted into the oxazinone **12** by means of the described protocol.[10] Sodium amalgam reduction of **12** gave indeed the amine **4a**, in moderate yield however (63%). Moreover, ^1H NMR revealed the presence (ca 10%) of side products, difficult to eliminate, and resulting either from partial hydrogenation of the butadienyl system or from hydrolysis of the DPTBOS protecting group. Owing to these difficulties, the procedure used by Schlessinger was preferred.

The diol **9a** was efficiently converted into the O-DPTBS derivative **9g** as follows. Enzymatic acetylation (PFL, vinyl acetate) of **9a** gave the monoacetate **9e** (100%). Subsequent treatment of **9e** by DPTBSCl afforded the compound **9f**, which, by hydrolysis in mild conditions (K_2CO_3, MeOH), furnished **9g** (91%, overall). Oxidation of **9g** by $BaMnO_4$ then delivered quantitatively the aldehyde **11b**, which was converted into nitrile **13a** by Wadsworth-Emmons methology. Removal of the PMB protecting-group was performed at this stage. Hence, treatment of **13a** by DDQ in a two-phase system (*i.e.* CH_2Cl_2-pH 7 phosphate buffer) resulted in the clean formation of the alcohol **13b**, which was silylated (TBDMSCl) to give **13c**. AlH_3 reduction of **13c** then afforded the amine **4b** in excellent yield. Both optical and spectral properties[11] of the amine thus obtained were in perfect accordance with published data, which, subsidiarily, confirms the assignment of the *S* configuration made to this product by Schlessinger.[4]

In conclusion, by starting from the readily available *S*-malic acid, an appreciable amount (ca 2 g) of a C-9/C-16 fragment of pristinamycin II_B has been stereoselectively obtained through a reasonable number of steps. Further elaboration of this synthon toward pristinamycin II_B is described in the accompanying Letter.

References and Notes

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11- Selected data: **7a**: m.p. 96 °C; C 71.48 (calc. 71.54), H 6.31 (calc. 6.46); $[\alpha]_D^{21}$ -26 (c=1, CH_2Cl_2); **7b**: $Bp_{0.6}$ 68 °C; ^1H NMR (MeOD): 1.77-1.99 (m, 2H), 2.8 (d, J=2.1 Hz, 1H), 3.62-3.8 (m, 2H), 4.46 (dt, J=8.9, 2.1 Hz, 1H); 4.87 (m, 2H); ^{13}C NMR (MeOD): 41.6, 59.3, 59.8, 73.8, 88.1; $[\alpha]_D^{21}$ -18 (c=1.2; MeOH); **8**: C 67.35 (calc. 67.18), H 7.34 (calc. 7.25); ^1H NMR: 1.87-2.06 (m, 2H), 2.25 (bs, 1H), 3.46 (bs, 1H), 3.61-3.85 (m, 5H, in which s at 3.8 (3H)), 4.25 (dd, J=6, 1.06 Hz, 2H), 4.46 (s, 2H), 4.55-4.7 (m, 1H), 6.84-7.27 (m, 4H); ^{13}C NMR: 37, 50.6, 55.4, 60.6, 66.9, 72.9, 83.4, 86, 113.7, 129.5, 130, 159.3; $[\alpha]_D^{21}$ -26 (c=1, CH_2Cl_2); **9a**: C 67.57 (calc. 67.6), H 8.51 (calc. 8.3); ^1H NMR: 1.38 (bs, 1H), 1.56-1.99 (m, 5H, in which d at 1.7 (J= 1.2 Hz, 3H)), 2.72 (bs, 1H), 3.49-3.73 (m, 2H), 3.8 (s, 3H), 4 (bs, 2H), 4.46 (s, 2H), 4.63 (dt, J=12.6, 4.4 Hz, 1H), 5.48 (dq, J=8.5, 1.4 Hz, 1H), 6.84-7.27 (m, 4H); ^{13}C NMR: 14, 37, 55.3, 66.9, 67.5, 67.9, 72.9, 113.9, 127.1, 129.5, 130.2, 137.3, 159.3; **11a**: ^1H NMR: 1.26 (s, 9H), 1.44 (s, 3H), 1.77-1.87 (m, 1H), 2.01-2.11 (m, 1H), 3.47-3.6 (m, 2H), 3.08 (s, 3H), 4.34 (s, 2H), 4.97-5.07 (m, 1H), 6.34 (dd, J=8.75, 0.98 Hz, 1H), 6.83-7.64 (m, 14H), 9.22 (s, 1H); ^{13}C NMR: 9.2, 32.1, 37.2, 55.4, 65.8, 67, 72.64, 74.1, 113.8, 127.7, 127.8, 129.2, 130.2, 130.5, 134.7, 135.1, 135.2, 137.4, 154.7, 159.2, 195.3; $[\alpha]_D^{21}$ +31 (c=2, CH_2Cl_2); **11b**: ^1H NMR: 1.06 (s, 9H), 1.26 (d, J=1.2 Hz, 3H), 1.71-1.86 (m, 1H), 1.92-2.08 (m, 1H), 3.4-3.59 (m, 2H), 3.81 (s, 3H), 4.32 (s, 2H), 4.8-4.9 (m, 1H), 6.27 (dd, J=8.6, 1.3 Hz, 1H), 6.83-7.66 (m, 14H), 9.15 (s, 1H); ^{13}C NMR: 9.1, 19.4, 27.1, 37.4, 55.4, 65.8, 67.7, 72.7, 113.8, 127.7, 127.8, 129.2, 130, 130.5, 133.5, 135.9, 137.2, 155, 159.2, 195.1; $[\alpha]_D^{21}$ +17 (c=1, CH_2Cl_2); **13a**: ^1H NMR: 1.06 (s, 9H), 1.21 (d, J=1.1 Hz, 3H), 1.71-1.84 (m, 1H), 1.91-2.04 (m, 1H), 3.37-3.61 (m, 2H), 3.82 (s, 3H), 4.32 (d, J=1.5 Hz, 2H), 4.65-4.78 (m, 1H), 5.08 (d, J=16 Hz, 1H), 5.72 (d, J=8.8 Hz, 1H), 6.79 (d, J=16.44 Hz, 1H), 6.84-7.69 (m, 14H); ^{13}C NMR: 11.5, 19.4, 27, 37.8, 55.4, 66, 67.7, 72.6, 95, 113.8, 118.6, 127.6, 127.7, 129.2, 129.8, 130.5, 131.4, 133.8, 134, 135.9, 144.2, 154.6, 159.2; $[\alpha]_D^{21}$ -46 (c=1.5, CH_2Cl_2); **13c**: $[\alpha]_D^{21}$ -80.2 (c=1, CH_2Cl_2); **4a**: ^1H NMR: 1.25-1.26 (s, 12H), 1.4 (s, 1H, N*H*), 1.95-2.38 (m, 2H), 3.27-3.54 (m, 4H), 3.77-3.8 (m, 8H), 4.31 (s, 2H), 5.59-5.78 (m, 1H), 6.07 (d, J=15.6 Hz, 1H), 6.82-7.63 (m, 18H); ^{13}C NMR: 12.7, 32, 51.2, 52.8, 55.4, 66.7, 67.4, 72.5, 73.8, 113.8, 113.9, 125.6, 127.5, 129.2, 129.5, 129.7, 130.8, 133.4, 134.1, 135.2, 135.6, 135.7, 158.7, 159.1; $[\alpha]_D^{21}$ -3 (c=2, CH_2Cl_2); **4b**: ^1H NMR: -0.03 (s, 3H), -0.02 (s, 3H), 0.83 (s, 9H), 1.04 (s, 9H), 1.27 (d, J=1.1 Hz, 3H), 1.36 (bs, 2H), 1.57-1.7 (m, 1H), 1.8-1.94 (m, 1H), 3.32 (dd, J=6.3, 1 Hz, 2H), 3.47-3.69 (m, 2H), 4.69 (q, J=6.3 Hz, 1H), 5.38 (d, J=9 Hz, 1H), 5.57 (dt, J=15.5, 6 Hz, 1H), 6 (d, J=15.5 Hz, 1H), 7.32-7.69 (m, 10H); ^{13}C NMR: -5.3, 12.6, 18.3, 19.4, 19.4, 26, 27.1, 41.6, 44.3, 59.6, 67.8, 127.4, 127.5, 127.9, 129.4, 129.5, 132.9, 134.4, 134.6, 136, 136.1; $[\alpha]_D^{21}$ -38 (c=1, CH_2Cl_2 (or $CHCl_3$)). Excepted when otherwise stated, the ^1H and ^{13}C NMR spectra described herein have been recorded at 200 and 50 MHz, respectively, on $CDCl_3$ solutions.