Pergamon

Tetrahedron Letters 39 (1998) 3149–3152

TETRAHEDRON
LETTERS

Total Synthesis of Pristinamycin II$_B$

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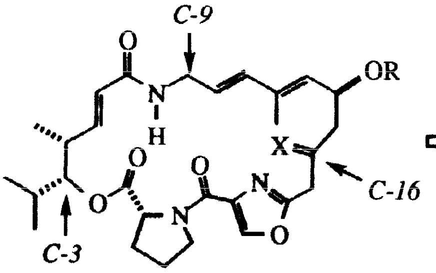
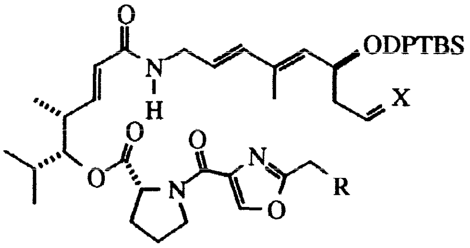
Received 23 February 1998; accepted 27 February 1998

***Abstract:** An intramolecular Takai reaction of the iodoaldehyde **4a** proceeded with a moderate efficiency to give the macrocyclic hydroxy compound **1b**, identified to an authentic sample.*

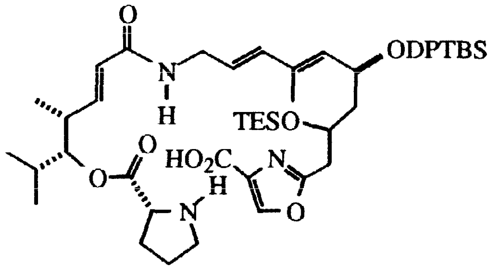
Recently, the first synthesis of pristinamycin II$_B$ **1a**, a potent antibiotic of the streptogramin family, was disclosed by Schlessinger.[1] The strategy used consisted in the elaboration of the amine **2** into the aminoacid **3**, whose cyclisation by an intramolecular amidation reaction, followed by selective hydrolysis of the O-TES group, afforded the hydroxy compound **1b**. Dess-Martin oxidation of **1b** then provided the O-DPTBS derivative of pristinamycin II$_B$ **1c**.



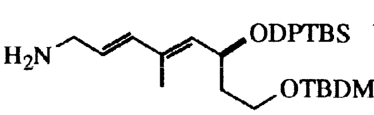
1a, R=H; X=O
1b, R=DPTBS; X=H, OH
1c, R=DPTBS; X=O



4a, R=I; X=O
4b, R=Cl; X=H, OTBDMS
4c, R=Cl; X=H, OH
4d, R=I; X=H, OH



3 *(Schlessinger intermediate)*



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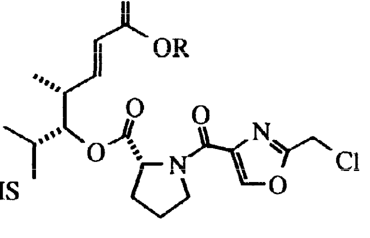

5a, R=H
5b, R=Me

Given that report, the preparation of the amine **2** we described in the preceding letter could be considered in itself as a formal synthesis of **1**. However, we considered that an approach based on the cyclisation of the iodoaldehyde **4a** into the hydroxy compound **1b** by a chromium(II)-mediated Barbier reaction could provide an useful alternative, since the scheme we favoured for preparing the seco derivative **4a**, which involves, as indicated, the coupling of the amine **2** with the acid **5a**, appeared to some extent more convergent than that, leading to **3**, realised by Schlessinger. We disclose in this Letter how that planned synthesis of **1b** was rendered effective.

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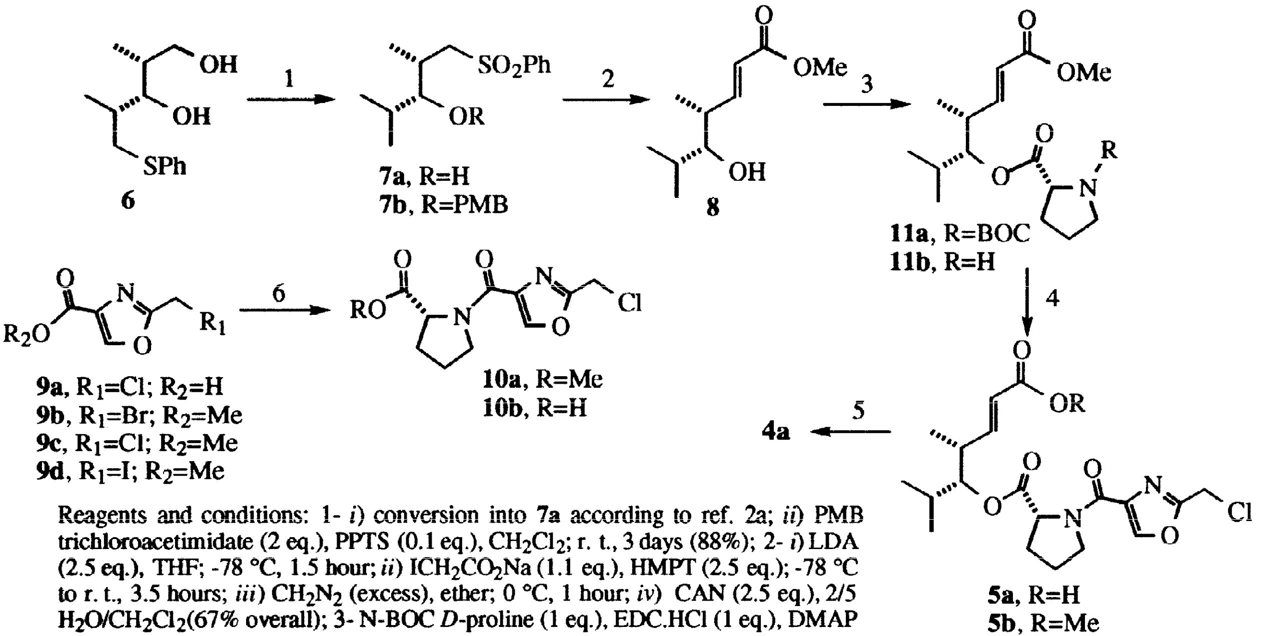
PII: S0040-4039(98)00499-7

First, the sulfide **6**, which originated from enzyme asymmetrisation of the corresponding triol,[2] was converted into the sulfone **7a** as described earlier.[2a] Protection of the hydroxy group of **7a** as a O-PMB derivative and condensation of the lithio derivative of the resulting sulfone **7b** with sodium iodoacetate, followed by sequential esterification by diazomethane and removal of the PMB group with CAN afforded the ester **8** in an overall yield (67%, from **7b**) higher than that registered previously by using directly **7a**.[2a]



Reagents and conditions: 1- *i*) conversion into **7a** according to ref. 2a; *ii*) PMB trichloroacetimidate (2 eq.), PPTS (0.1 eq.), CH_2Cl_2; r. t., 3 days (88%); 2- *i*) LDA (2.5 eq.), THF; -78 °C, 1.5 hour; *ii*) ICH_2CO_2Na (1.1 eq.), HMPT (2.5 eq.); -78 °C to r. t., 3.5 hours; *iii*) CH_2N_2 (excess), ether; 0 °C, 1 hour; *iv*) CAN (2.5 eq.), 2/5 H_2O/CH_2Cl_2(67% overall); 3- N-BOC *D*-proline (1 eq.), EDC.HCl (1 eq.), DMAP (2 eq.), CH_2Cl_2; r. t., 5 hours (94%); *ii*) CF_3CO_2H; 0 °C, 30 min (96%); 4- *i*) **9a** (1.3 eq.), EDC.HCl (1.3 eq.), HOBT (1.3 eq.), NEt_3 (1.3 eq.), 25/1 1,2-$C_2H_4Cl_2/H_2O$ (2 ml/mmol); r. t., 5 hours (74%); *ii*) 1M LiOH (2 eq.), 9/1 THF/H_2O (4 ml/mmol); r. t., 6 hours (quant.); 5- *i*) **2** (1 eq.), same conditions as for the **11b-5b** conversion (77%); *ii*) 3/1/1 AcOH/H_2O/THF (15 ml/mmol; r. t., 7 hours (66%); *iii*) NaI (1.1 eq.), acetone; r. t., 6 hours (100%); *iv*) IBX (2 eq.), DMSO; r. t., 6 hours (97%); 6- methyl *D*-prolinate (1.1 eq.), EDC.HCl (1 eq.), NEt_3 (1 eq.), CH_2Cl_2; r. t., 6 hours (80%).

The properties of the ester **8** thus prepared matched perfectly that of the compound we had been previously obtained from **7a** and to which the 4*R*, 5*R* configuration had been assigned.[2a] Confirmation of that assignment was secured by hydrolysing crude, natural, pristinamycin II in an acidic medium (hot 1N HCl),[3] which furnished, after chromatography on silica gel (hexane/ether) and treatment by diazomethane, a hydroxy ester displaying spectral and optical properties consistent with those registered for synthetic **8** (synthetic material: $[\alpha]_D$ + 25.3, c=2 (CH_2Cl_2); from natural source: $[\alpha]_D$ + 26, c=2 (CH_2Cl_2)).

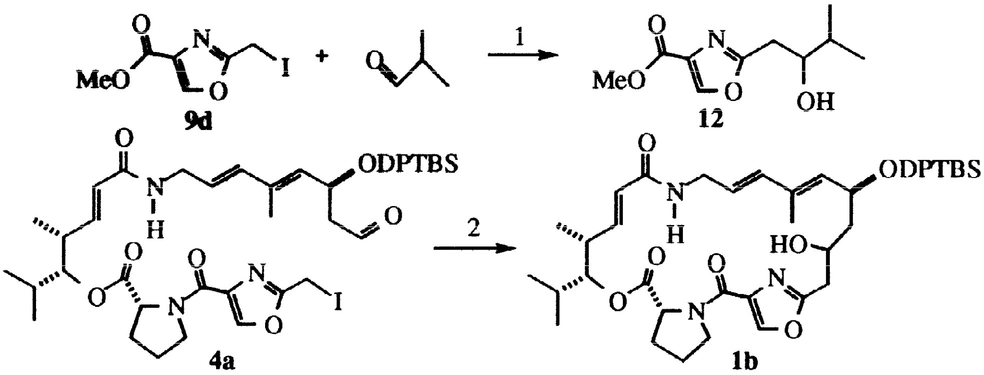
Conversion of the ester **8** into the acid **5a** was next examined. The more expeditious approach appeared to couple methyl *D*-prolinate with the acid **9a** to form the ester **10a**. Conversion of **10a** into the corresponding acid **10b**, followed by coupling of **10b** with **8** and subsequent hydrolysis would have then provided **5a**.

Obtention of the chloroacid **9a** was secured by treating the bromo ester **9b**[4a] with excess LiCl in DMF to furnish the chlorooxazol derivative **9c** (98%). Hydrolysis of **9c** in mild conditions (LiOH, THF) afforded the crystalline acid **9a** (97%).[4b] Coupling of **9a** with methyl *D*-prolinate was realised by using a carbodiimide methodology but attempted hydrolysis of the resulting ester **10a** (80%) with LiOH, in order to get **10b**, proved difficult, proceeding in low yield and with substantial hydrolysis of the peptide bond. That unexpected difficulty forced us to modify slightly our initial scheme. Hence, the ester **8** was reacted with the N-BOC derivative of *D*-proline by using EDC.HCl and DMAP to give the ester **11a** (94%). Treatment of **11a** by trifluoroacetic then gave the free amine **11b** (96%).

Noteworthy, whereas **11b** exhibited NMR data consonant with the indicated structures, both ^{1}H and ^{13}C NMR spectra of compound **11a** were complex, the result of the occurrence of two rotamers (1/1 ratio); which was evidenced later by performing NMR experiments at various temperature on a more advanced derivative (**4a**, *vide infra*). Coupling of the aminoester **11b** with the chloroacid **9a** was executed by using EDC in two-phase conditions,[5] the ester **5b** (77%) thus obtained being then hydrolysed (LiOH, THF/H_2O) to give quantitatively the acid **5a**. Ensuing coupling of **5a** with the amine **2** in the same conditions as for the **8b**-**11a** conversion proceeded well, giving the seco derivative **4b** as an almost colourless foam after chromatography on $NaHCO_3$-washed silica gel (hexane/ether) and in a satisfactory 77% yield.

As observed with **11a**, though the compound **4b** thus obtained displayed satisfactory elemental analysis, splitting of numerous signals was perceptible in its NMR spectra, their coalescence being observed when the temperature of the NMR sample reached 80 °C. Subsequent removal of the TBDMS protecting group by stirring **4b** in a AcOH/H_2O/THF mixture for a few hours, followed by treatment of the chloro alcohol **4c** thus obtained with sodium iodide in acetone then provided the corresponding iodo derivative **4d**, which was immediately, and quantitatively, oxidised into the iodoaldehyde **4a** by using the IBX reagent.[6]

In order to define the conditions permitting to convert this iodide into the target macrocyclic derivative **1**, the iodoester **9d**, which formed by treating the bromo compound **9b** with sodium iodide in acetone, was reacted with *i*-butyraldehyde in the conditions of the Takai coupling reaction. After a few experiments, it appeared that the chromous species which formed by *in situ* reduction of anhydrous $CrCl_3$ with LAH, in THF, gave the best result, the expected coupling product **12** being thus obtained in fair yield (51%), after chromatography.[7]



Reagents and conditions: 1- $CrCl_3$ (15 eq.), LAH (7.5 eq.), THF; 0 °C to r. t., 1 hour, then slow addition of **9d** and *i*-butyraldehyde (1 eq.); r.t., 2 hours (51%); 2- see ref. 8 (23%)

The conditions thus delineated were applied to the iodide **4a**. Slow addition with a syringe of a THF solution of **4a** to large excess of the same reducing species resulted, after two days, in the formation, besides an unidentified de-iodinated product, of a new, more polar (TLC), product which proved to be, after purification by thick-layer chromatography (9/1 CH_2Cl_2/MeOH), the hydroxy compound **1b** (23%), which was identified (^{1}H, ^{13}C NMR; T.L.C.) to an authentic sample.[9]

In conclusion, an asymmetric synthesis of O-DPTBS pristinamycin II_B has been secured by combining chiron and enzyme methodologies. The moderate efficiency of the Cr(II)-mediated macrocyclisation step, leading to **1b**, could result from restricted rotation of the peptide bond located between the oxazol and the proline residues: inspection of models suggests that only one of the two possible rotamers should efficiently cyclized in these conditions. Nevertheless, the strategy we used for preparing and assembling the selected subunits appears easily adaptable for synthesizing numerous pristinamycin II analogues, which is essential to establish SAR relationships. Results along this line will be reported in due course.

References and Notes

1- Schlessinger, R. H.; Li, Y.-J. *J. Am. Chem. Soc.* **1996**, *118*, 3301-3302. Two syntheses of madumycin, a strongly-related antibiotic, have been also disclosed recently: *i*) Tavares, F.; Lawson, J. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 3303-3304; *ii*) Ghosh, A. K.; Liu, W. *J. Org. Chem.* **1997**, *62*, 7908-7909.

2- a) Adjé, N.; Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1992**, *33*, 2151-2154; b) Domon, L.; Vogeleisen, F.; Uguen, D. *Tetrahedron Lett.* **1996**, *37*, 2773-2776.

3- Thanks are due to Rhône-Poulenc Rorer for a gift of that crude antibiotic mixture.

4- a) Nagao, Y.; Yamada, S.; Fujita, E. *Tetrahedron Lett.* **1983**, *24*, 2291-2294; b) Selected data: **9a**: m. p. 166-170 °C (dec.); ^{1}H NMR: 4.7 (s, 2H), 8.35 (s, 1H); ^{13}C NMR: 35.14, 133.3; 146.2; 160.4; 164.7; **9c**: m. p. 72-74 °C (ether); ^{1}H NMR: 3.82 (s, 3H), 4.56 (s, 2H), 8.19 (s, 1H); ^{13}C NMR: 35.34, 52.31, 133.76, 145.11, 159.9, 161.1; **9d**: m. p. 66 °C (hexane/ether); C 27.03 (calc. 27.23), H 2.42 (calc. 2.3), N 5.08 (calc. 5.2); ^{1}H NMR: 3.92 (s, 3H), 4.4 (s, 2H), 8.23 (s, 1H).

5- Nozaki, S.; Muramatsu, I. *Bull. Chem. Soc. Jpn* **1982**, *55*, 2165-2168.

6- Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272-7276, and references therein.

7- Related coupling reaction of the ethyl ester of the corresponding bromoacid with aldehydes by using zinc has been previously reported: Gangloff, A. R.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1992**, *57*, 4797-4799.

8- Protocol for the macrocyclisation step: LAH (0.286 g; 7.5 mmol) was added at once to a well-deaerated (three freeze and thaw cycles), cooled (ca 0 °C), deep-purple suspension of $CrCl_3$ (2.535 g; 16 mmol) in THF. The resulting grey suspension was then stirred at room temperature for 30 min., after that a deaerated solution of the iodoaldehyde **4a** (143 mg; 013 mmol) in THF (20 ml) was added slowly, in 12 hours (Noteworthy, any vessel was protected from light throughout), the stirring being then continued for two days. The resulting suspension was added slowly, with cooling (ice/methanol), to a well-stirred mixture of 0.5 M sodium serinate (100 ml) and ethyl acetate (100 ml), the final pH being 6. After 30 min stirring, the mixture was filtered on Celite, previously washed with water until neutral. The organic layer was separated and the aqueous one was further extracted with ethyl acetate (2x20 ml). The pooled organic phases were washed with brine (3x10 ml), dried (Na_2SO_4), and evaporated *in vacuo*, at room t.. The residual orange foam (143 mg) was taken up in CH_2Cl_2 (20 ml) and the resulting solution was further freed of chrome species by washing with 0.5 M sodium serinate (5 ml) and brine (2x5 ml), then dried. The pasty residue (0.141 g) left by evaporation of the solvents displayed two spots in TLC on silica gel with Rf of, respectively, 0.31 and 0.46 (9/1 $CHCl_3$/MeOH). Ensuing column chromatography on $NaHCO_3$-washed silica gel ($CHCl_3$/MeOH) permitted to isolate the more polar product (28.3 mg; 23%), which proved to be identical (NMR) with an authentical sample (Thanks are due to Dr. Eric Bacqué (Rhône-Poulenc Rorer) for a gift of compound **1b**). Furthermore, compound **1b** could be transformed into **1c** as described (Schlessinger, *loc. cit.*)

9- Selected data: **11b**: ^{1}H NMR: 0.85-0.91 (m, 6H), 1.04 (d, J=6.7 Hz, 3H), 1.42-1.95 (m, 4H), 2.09-2.23 (m, 2H), 2.58-2.73 (m, 1H), 2.84-2.96 (m, 1H), 3.02-3.14 (m, 1H), 3.72-3.79 (m, 4H, in which s (3H; OCH_3) at 3.72), 4.82 (dd, J=6.7, 5.6 Hz, 1H), 5.85 (dd, J=15.7, 1.3 Hz, 1H), 6.84 (dd, J=15.7, 8 Hz, 1H); ^{13}C: 14.4, 16.81, 19.49, 25.4, 29.9, 30.5, 38.4, 46.9, 51.5, 59.9, 79.9, 121.2, 150, 166.6, 175.1; $[\alpha]_D$ + 31, c=2; **5b** (two rotamers): 0.82-1 (m, 9H), 1.68-2.27 (m, 5H), 2.52-2.66 (m, 1H), 3.61-3.81 (m, 4H, in which s at 3.65; O-CH_3), 4-4.07 (m, 1H), 4.47 and 4.56 (two s, 2H), 4.6-4.78 and 5.48-5.53 (two m, 2H), 5.74 and 5.79 (two dd, J= 15.75, 1.02 Hz, 1H), 6.72 and 6.76 (two t, J=15.8, 1H), 8.19 and 8.22 (two s, 1H); $[\alpha]_D$ + 66, c=1; **4c** (two rotamers): C 65.84 (calc. 65.69), H 7.25 (calc. 7.26), N 4.99 (calc. 5.22); ^{13}C NMR: 12.54, 14.18 (14.47), 17.39 (17.68), 19.31, 19.49, 19.69, 21.53 (25.41), 27.06, 28.9 (31.7), 29.96 (30.04), 35.55 (35.64), 37.82 (38.25), 40.15, 41.55, 47.32 (48.91), 59.75 (59.82), 60.43 (60.54), 69.22 (69.28), 80.94 (81.33), 123.91 (124.18), 124.45 (124.64), 127.53 (127.74), 129.69 (129.83), 132.56 (132.67), 133.78 (133.83), 134.45 (134.66), 135.92 (136), 136.28 (136.55), 137.54 (137.74), 144.81 (144.87), 145.21 (145.3), 158.44 (158.52), 159.87, 165.32 (166.05), 171.82 (172.13); $[\alpha]_D$ - 39, c=1; **12**: C 56.21 (calc. 56.33), H 7.27 (calc. 7.09), N 6.26 (calc. 6.56); ^{13}C: 17.58, 18.53, 32.98, 33.44, 52.17, 73.77, 133.1, 143.94, 161.55, 164.49. ^{1}H and ^{13}C NMR at 200 and 50 MHz, respectively, in $CDCl_3$ (The chemical shifts in brackets refer to the second rotamer). $[\alpha]_D$ values at 21 °C, in CH_2Cl_2.