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17-Diazo pristinamycin II_B preparation and synthetic applications

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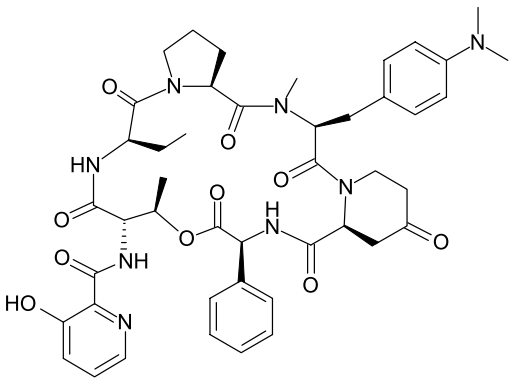
This article is dedicated to the memory of our colleague Jean-Claude Barrière

Abstract—We report hereafter the preparation of 17-diazo pristinamycin II_B and its synthetic applications based on the generation of the corresponding carbene/carbenoid. In particular, we describe rhodium-catalyzed insertion reactions and the Wolff rearrangement of this α-diazo-ketone.

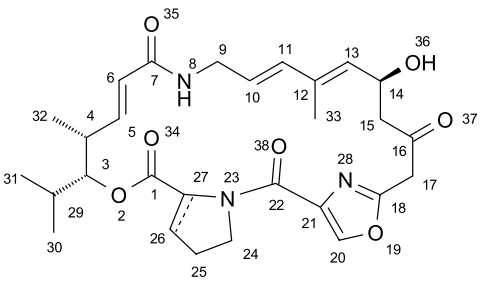
1. Introduction

Pristinamycin is a naturally occurring antibiotic of the streptogramin class. This family of antibiotics is characterized by the original association of two types of chemically unrelated molecules, pristinamycins I (PI) and pristinamycins II (PII), which act synergistically on the ribosome of bacteria, thereby inhibiting protein synthesis.[1–4] Whereas pristinamycins I such as PI_A (**1**) are cyclic depsipeptides, pristinamycins II, as typified by PII_A (**2a**) and PII_B (**2b**) (the most abundant pristinamycins II), are peptidic macrolactones (Scheme 1). Semi-synthesis on pristinamycins II is a particularly challenging task. Because of its very sensitive array of functions (a β-hydroxy ketone, an allylic alcohol, a lactone, the strongly acidic 17-CH_2s and, for some PIIs, a Michaël-acceptor dehydroproline), natural pristinamycins II are stable in a very narrow range of pH spanning from 4 to 6. This fragility makes the discovery of efficient semi-synthetic transformations very tricky and generally results, even in the most successful cases, in modest yields of chromatographed compounds.

In the 1980s, we initiated a program of semi-synthesis aimed at discovering water-soluble antibacterial pristinamycins. These endeavours culminated with the development of Synercid®, the first injectable streptogramin, which



Pristinamycin I_A (1)



Pristinamycin II_A (2a) : -26,27
Pristinamycin II_B (2b) : 27-R

Scheme 1. Structures of pristinamycins I_A (**1**), II_A (**2a**) and II_B (**2b**).

Keywords: Antibiotics; Pristinamycins II; α-Diazo-ketone; Carbene; Insertion; Wolff rearrangement, rhodium acetate; Ring contraction; Dihydro-furan-3-one, lactone; Diol.
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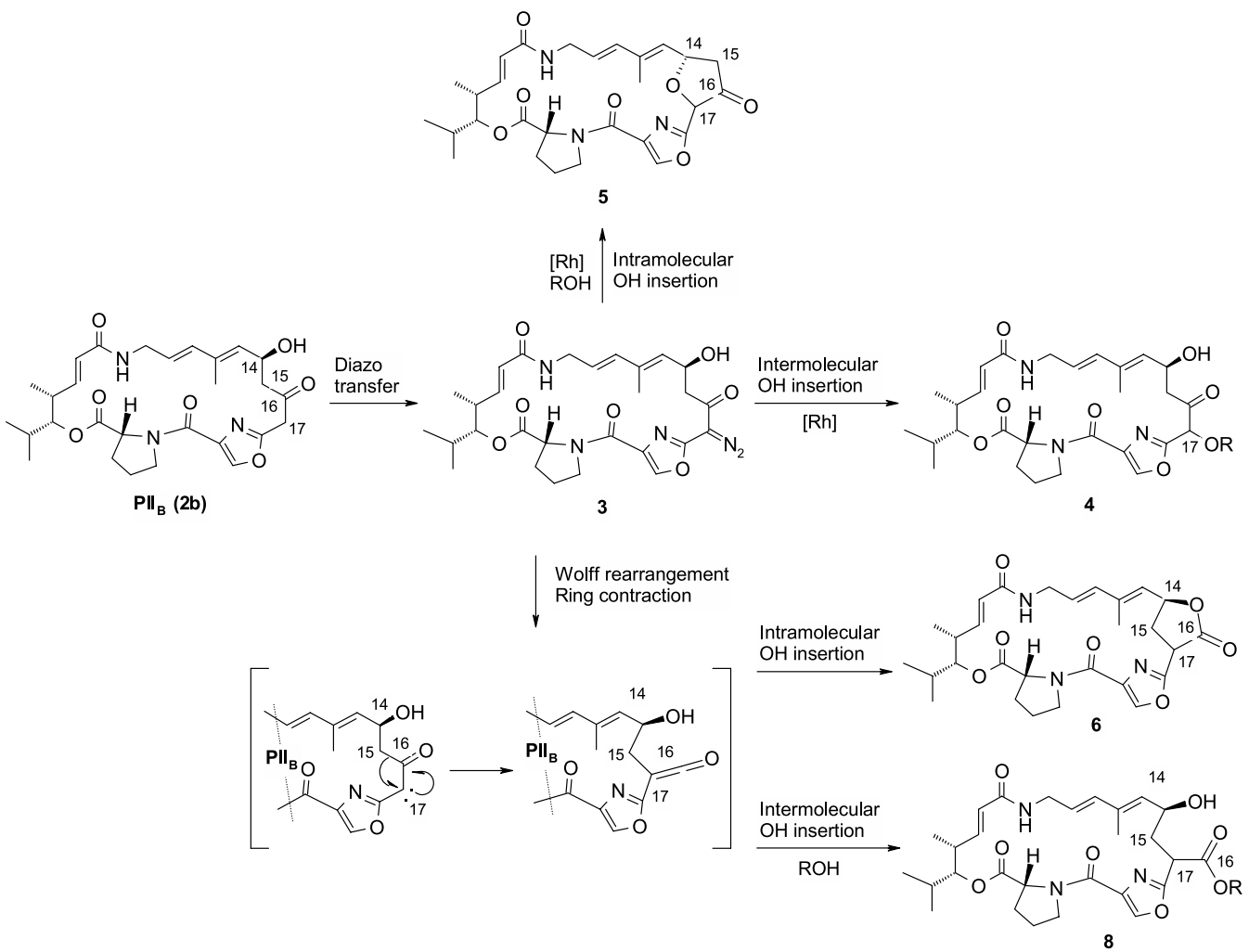
was approved in the US in 1999 for the treatment of severe Gram-positive infections in hospital.[5–7] In our continuing efforts[8] to identify the next generation streptogramin, we realized that position C-17 of PII_B was a very attractive position amenable to a large variety of semi-synthetic modifications owing to the strongly acidic nature of the hydrogens born by C-17. In particular, we envisioned that 17-diazo pristinamycin II_B **3**, a diazo-ketone that would be stabilized by the 16-carbonyle and the oxazole ring, would provide a convenient access to a variety of original PII_B derivatives (Scheme 2). Indeed, α-diazo carbonyl compounds are versatile intermediates, now widely used in organic synthesis[9] as a result of their easy, efficient transformation into the corresponding carbenes/carbenoids upon thermal conditions or upon catalysis by transition metals such as Rhodium II. These carbenes/carbenoids give rise to a variety of reactions such as Wolff rearrangement[10] or insertions into O–H bonds.[9a]

We report hereafter the results of a program aimed at preparing 17-diazo pristinamycin II_B **3** and studying its reactivity. In particular, we will describe the preparation of two 17-OR PII_Bs **4** (R=methyl or acetyl), of dihydro-furan-3-one **5** and of the ring contraction product **6**, compounds not easily accessible by other routes.

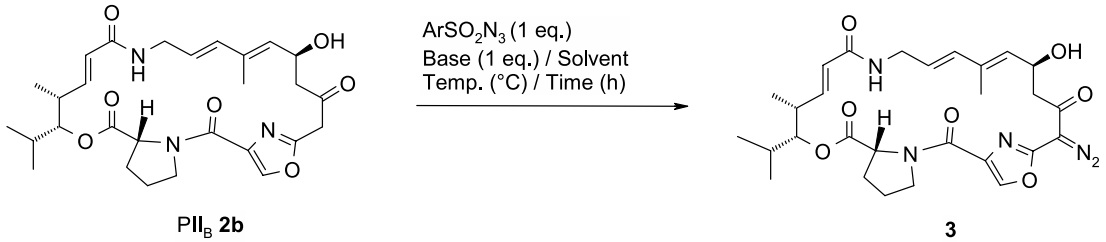
2. Results and discussion

We first concentrated on the development of an efficient, scalable and safe synthesis of diazo-ketone **3**. Due to the strongly acidic 17-CH_2s (estimated pK_a in DMSO=2), we thought that a simple diazo transfer reaction, under mild basic conditions, was likely to be successful. Starting from **2b** (pristinamycin II_B), we screened two safe, commercially available arylsulfonyl azides (trisyl azide: 2,4,6-triisopropylphenylsulfonyl azide **7a** and *p*-acetamidobenzenesulfonyl azide **7b**) as the diazo-transferring reagent, in the presence of various bases (entries 1–5, Table 1). We found that triethylamine (TEA), in ethanol, at room temperature was the best choice for the base, leading to **3** in 44–45% yield (entries 4 and 5, Table 1) when sulfonyl azide **7a** was used and whatever the reaction scale from 0.5 to 5 g. Furthermore, under similar conditions (TEA, EtOH, rt), **3** could be obtained in better yield using **7b**[9d] (71%, entry 6, Table 1) rather than **7a**. Safety studies[11] showed that the stability of 17-diazo PII_B **3** was relatively good in solution with only a soft decomposition being observed, whereas a very energetic decomposition was noted above 80 °C, in the solid state. Based on these data, we were able to routinely achieve safe, large-scale preparations of **3**. For instance, starting from 50 g of **2b** (entry 7, Table 1), we were able to



Scheme 2. Synthetic applications of 17-diazo pristinamycin II_B **3**.

Table 1. Preparation of 17-diazo PII_B **3** from PII_B **2b**



PII_B **2b** **3**

Entry	$ArSO_2N_3$ **7**	Scale (g of **2b**)	Base	Solvent	Temperature (°C)	Time (h)	Yield (%) **3**
1	**7a**	0.528	NaHMDS	THF	−60 to 0	4	Degradation
2	**7a**	0.528	Cs_2CO_3	THF	rt	6.5	30
3	**7a**	0.528	DBU	THF/CH_2Cl_2	rt	1.5	15
4	**7a**	0.528	TEA	EtOH	rt	2	44
5	**7a**	5.75	TEA	EtOH	rt	6.5	45
6	**7b**	10	TEA	EtOH	rt	5	71
7	**7b**	52.8	TEA	EtOH	rt	2	55

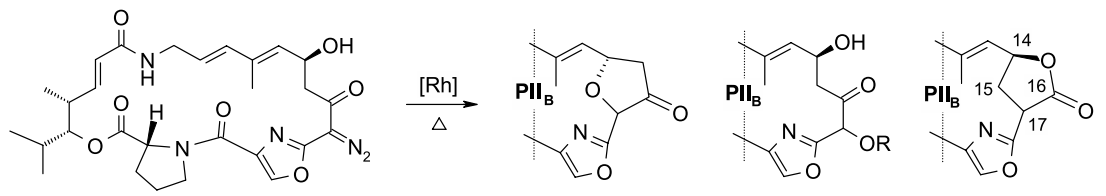
isolate **3**, without event, in 55% yield and with a NMR purity of 100%, following purification by a simple flash-chromatography on silica gel.

With a reliable synthesis of **3** in hand, we were ready to investigate the decomposition of this diazo ketone either in the presence of a transition metal-catalyst or thermally triggered. Decomposition of **3** catalyzed by rhodium(II) acetate dimer (quality 99.99%+), in a mixture of dichloromethane and toluene warmed at 47 °C, exclusively led to the intramolecular insertion of the intermediary carbenoid into the 14-OH bond to afford furanone **5** in a modest 39% isolated yield (entry 1, Table 2). Compound **5** was obtained as a single diastereomer. Though we were not able to secure by NMR the stereochemistry at C-17, molecular modelling suggested a 17-*R* configuration as the only low-energy possibility.

In the presence of rhodium(II) acetate dimer (quality brown) and in the same mixture of solvents, Wolff rearrangement which afforded fused lactone **6**, turned out to be competitive with the insertion reaction. However, whatever the conditions, less than 10% of **6** was generated (entries 2–4, Table 2) in these reactions. Here again, spectroscopic data indicated for **6** a single diastereomer for which molecular modelling also suggested a 17-*R* configuration.

In these reactions, the quantity of **5** isolated was dependent on the temperature and the length of the reaction. A few hours at 50 °C led to a poor yield of **5** (entry 2, Table 2), whereas a longer period at 68 °C did not afford a trace of **5** (entry 4, Table 2). The best conditions that maximized the formation of **5** (51% isolated yield) were found to be 24 h at 50 °C (entry 3, Table 2).

Table 2. Transition metal-catalyzed or thermal decomposition of 17-diazo PII_B **3**



3 **5** **4** **6**

Entry	Catalyst (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%) **4/5/6**
1	$[(Rh(OAc)_2]_2$ (0.1)[a]	CH_2Cl_2/Tol	47	3	0/39/0
2	$[(Rh(OAc)_2]_2$ (0.2)[b]	CH_2Cl_2/Tol	20/50	4/4	0/14/< 10
3	$[(Rh(OAc)_2]_2$ (0.2)[b]	CH_2Cl_2/Tol	20/50	2/24	0/51/< 10
4	$[(Rh(OAc)_2]_2$ (0.2)[b]	CH_2Cl_2/Tol	68	33	0/0/< 10
5	$[(Rh(OAc)_2]_2$ (0.1)[a]	MeOH	45	2.5	33 (R=Me)/0/0
6	$[(Rh(OAc)_2]_2$ (0.1)[a]	MeOH	20	2	58 (R=Me)/0/0
7	$[(Rh(OAc)_2]_2$ (0.05)[a]	AcOH	20	3	14 (R=Ac)/0/0
8	$Cu(acac)_2$ (0.025)	CH_2Cl_2	21/50	18/24	0/0/10
9	Cu_2O (0.15)	CH_2Cl_2	21/50	24/24	0/0/15
10	Cu_2O (0.27)	CH_2Cl_2	62	23	0/0/24
11	—	CH_2Cl_2/Tol	61	23	0/0/23
12	—	MeOH	58	30	35 (R=Me)/0/0

[a] Rhodium (II) acetate dimer, 99.99%+.
[b] Rhodium (II) acetate dimer, brown.

Decomposition of **3** in the presence a catalytic amount of rhodium(II) acetate dimer (quality 99.99%+), in methanol or acetic acid, at room temperature, surprisingly led only to **4a** (R=Me) or **4b** (R=Ac), in poor to modest yields (entry 5–7, Table 2), without a trace of **5**. Intermolecular insertions of the carbenoid were clearly more efficient than intramolecular insertion into the 14-OH bond. Compounds **4a** and **4b** were shown by NMR to consist of a mixture of two epimers at C-17 in a ratio 75:25. Configuration of the major isomers could not be secured by NMR techniques.

As anticipated,[9a,11] use of copper (I) or (II) as the catalyst (entries 8–10, Table 2) or even simple thermal conditions (entry 11, Table 2) only afforded Wolff rearrangement product **6**, albeit in modest isolated yields. When the reaction was run in methanol, interception of the intermediary ketene by methanol to give **8** (Scheme 2) was not observed (entry 13, Table 2). Instead, compound **4a** was isolated with a lower yield (35%) compared to that of the reactions run with the rhodium catalyst (entry 6, Table 2).

It should be noted that compound **6** was the first pristinamycin II with a carbon less in the ring and was shown to be devoid of any antibacterial activity. We supposed that this lack of activity could be due to the absence within this molecule of the characteristic features of the natural pristinamycins II, namely a free 14-hydroxy and a carbonyl or a hydroxy at position 16, that are known to be important for biological activity.[4] In order to make a sound evaluation of the influence of ring contraction upon antibacterial activity, we therefore decided to reduce the lactone present in **6**. This reaction would unmask the 14-OH and generate a hydroxymethyl group structurally close to the natural pristinamycin II_B diols. Sodium borohydride reduction of **6** in THF at room temperature smoothly provided the original ring-contracted diol **9** in 64% isolated yield (Scheme 3). However, this compound was still biologically inactive, which suggested that the integrity of the pristinamycin backbone is important for the antibacterial activity of pristinamycins II.

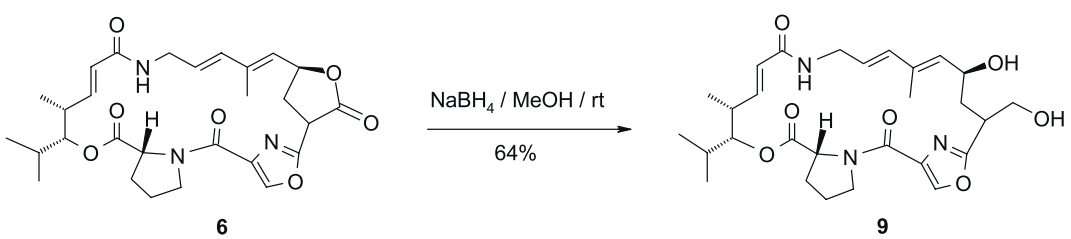
In summary, we have reported an efficient preparation of 17-diazo pristinamycin PII_B **3** and described its synthetic applications through generation of the corresponding carbene/carbenoid. This intermediate has been shown to undergo, in generally moderate yields, either intermolecular or intermolecular insertions into O–H bonds and Wolff rearrangement. This latter reaction afforded the first ring-contracted pristinamycin II. All the compounds reported in this work were inactive. Subsequent efforts aimed at identifying the PII component of the next generation streptogramin by semi-synthetic transformations of the natural pristinamycins II will be reported later.

3. Experimental

3.1. General

Reagents and solvents were purchased from Acrôs, Aldrich, Prolabo or SDS and used as supplied unless otherwise noted. Melting points were recorded on a Köfler apparatus and were not corrected. Optical rotations at 20 °C were taken on a Perkin–Elmer 341 polarimeter. ^{1}H NMR spectra were recorded on Bruker AC 250 (250 MHz) or AM 400 (400 MHz) spectrometers. Chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane. The atoms of pristinamycin II_A are numbered according to Scheme 1. Infrared spectra (IR) were determined with a Perkin–Elmer Model 938G or 580B. Mass spectra (MS) were recorded on a FINNIGAN TSQ47 or SSQ7000 for desorption/chemical ionisation (DCI; ammonia as the reactant gas) and a VG AUTOSPEC for liquid secondary ion mass spectrometry (LSIMS; 35 keV). Elemental analysis has been done for carbon, hydrogen, nitrogen and oxygen using a Fisons EA1108 microanalyser. Water content was calculated using Karl Fisher technique. Crude products were purified by flash column chromatography on silica gel (0.04–0.063 mm; Merck). For thin layer chromatography (TLC), 250 mm E. Merck silica gel 60 F_{254} plates were used. Evaporations of PII derivatives were carried out below 35 °C. Combustion data will not be systematically provided hereafter as this analysis is rarely correct for PII derivatives owing to the capacity of these compounds to sequester water and other solvents. Melting points of PII derivatives (measured on a Kofler bank) are not generally sharp. The compounds stick on the bank over several degrees. The figures indicated below for the melting points generally correspond to the temperature when sticking begins.

3.1.1. 17-Diazo pristinamycin II_B (3). To a solution of 10 g (19 mmol) of **2b** in ethanol (200 mL) was added under argon at room temperature, 2.7 mL (19 mmol) of triethylamine and a solution of 2.7 g (19 mmol) of *p*-acetamidobenzenesulfonyl azide in ethanol (100 mL). After stirring at room temperature for 5 h, the reaction mixture was diluted with dichloromethane (750 mL), washed with an aqueous solution saturated with sodium chloride (3×500 mL), dried over magnesium sulfate, filtered and concentrated under vacuum to provide a residue which was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (92:4:4, v/v/v)] to afford 7.4 g (13.4 mmol) (71%) of **3**, as a yellow solid; safety studies:[10] energetic decomposition started at 80 °C at



6 9

Scheme 3. Preparation of **9** via reduction of **6**.

the solid state; $[\alpha]_D^{20}=+76.2\pm1.2$ (*c* 0.5, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 0.94 (d, *J*=7 Hz, 3H), 0.96 (d, *J*=7 Hz, 3H), 1.09 (d, *J*=7 Hz, 3H), 1.71 (s, 3H), from 1.80 to 2.15 (m, 6H), 2.73 (m, 1H), 3.00 (dd, *J*=17, 10 Hz, 1H), 3.49 (dd, *J*=17, 2.5 Hz, 1H), 3.58 (ddd, *J*=15–9, 5 Hz, 1H), 3.72 (m, 1H), 4.05 (m, 1H), 4.22 (ddd, *J*=15–8, 5 Hz, 1H), 4.81 (broad d, *J*=10 Hz, 1H), 4.85 (dd, *J*=9, 2 Hz, 1H), 5.01 (m, 1H), 5.56 (broad d, *J*=8.5 Hz, 1H), 5.63 (ddd, *J*=16–9, 5 Hz, 1H), 5.77 (broad d, *J*=16 Hz, 1H), 5.97 (dd, *J*=8, 5 Hz, 1H), 6.19 (d, *J*=16 Hz, 1H), 6.59 (dd, *J*=16, 5 Hz, 1H), 8.16 (s, 1H). MW=553, LSIMS: *m/z*=554 [MH^+], *m/z*=536 [MH^+-H_2O], *m/z*=526 [MH^+-N_2]; IR (KBr) 3444, 3173, 2977, 2117, 1742, 1676, 1629, 1585, 1511, 1425, 1373, 1206, 1184, 1100 and 967 cm^{-1}. Elemental analysis calculated for $C_{28}H_{35}N_5O_7$: C, 60.75; H, 6.37; N, 12.65; O, 20.23. Found: C, 60.76; H, 6.31; N, 12.78; O, 19.98.

3.1.2. 17-Methoxy pristinamycin II_B (4a). To a suspension of 11 mg (0.0242 mmol) of rhodium(II) acetate dimer (quality 99.99%+) in methanol (200 mL) was added under argon at room temperature, a solution of 134 mg (0.242 mmol) of **3** in methanol (10 mL). After stirring at room temperature for 4 h, the reaction mixture was concentrated under vacuum to provide a residue which was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (92:4:4, v/v/v)] to afford 78 mg (0.14 mmol) (58%) of **4a** as a mixture of two diastereomers in a 75:25 ratio (stereochemical assignment for the new chiral center at C-17 could not be determined), as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm) we observed a mixture of two diastereomers in ratio 75:25: from 0.85 to 1.10 (m, 9H), 1.72 and 1.74 (2s, 3H in totality), from 1.80 to 2.10 (m, 4H), from 2.10 to 2.30 (m, 1H), from 2.60 to 2.80 (m, 1H), 2.71–2.87–3.23 and 3.26 (4 dd, respectively *J*=17.5, 7; 16, 4.5; 17.5, 8; 16, 6.5 Hz, 2H in totality), 3.15 (broad band, 1H), from 3.25 to 3.45 (m, 1H), 3.44 and 3.56 (2s, 3H in totality), 3.69 (m, 1H), 3.95 and 4.09 (2 m, 1H in totality), from 4.40 to 4.55 (m, 1H), from 4.60 to 4.80 (m, 2H), 4.78 and 4.80 (2s, 1H in totality), 4.85 and 5.00 (2 m, 1H in totality), 5.27 and 5.45 (2 broad d, *J*=9 Hz, 1H in totality), from 5.65 to 5.85 (m, 2H), 6.07 (broad d, *J*=16 Hz, 1H), from 6.40 to 6.50 (m, 1H), from 6.55 to 6.70 (m, 1H), 8.05 and 8.13 (2s, 1H in totality). MW=557, IC: *m/z*=558 [MH^+], *m/z*=540 [MH^+-H_2O], *m/z*=526 [MH^+−MeOH]; IR (KBr) 3596, 3440, 3170, 2977, 1734, 1673, 1625, 1517, 1434, 1187, 1113 and 969 cm^{-1}. Elemental analysis calculated for $C_{29}H_{39}N_3O_8$: C, 62.46; H, 7.05; N, 7.54; O, 22.95. Found: C, 62.49; H, 7.30; N, 7.61; O, 22.92.

3.1.3. 17-Acetoxy pristinamycin II_B (4b). To a solution of 3.3 g (6 mmol) of **3** in glacial acetic acid (60 mL) was added under argon at room temperature, 133 mg (0.3 mmol) of rhodium(II) acetate dimer (quality 99.99%+). After stirring at room temperature for 3 h, the reaction mixture was concentrated under vacuum to provide a residue which was diluted with dichloromethane (100 mL), washed with a saturated aqueous sodium bicarbonate solution (3×100 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The resulting residue was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (92:4:4, v/v/v)] to afford 473 mg (0.81 mmol) (14%) of **4b** as a mixture of two diastereoisomers in a 75:25 ratio (stereochemical assignment for the new chiral center at C-17 could not be determined) as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm) we observed a mixture of two diastereomers in ratio 75:25: from 0.85 to 1.10 (m, 9H), 1.73 and 1.76 (2s, 3H in totality), from 1.80 to 2.10 (m, 5H); from 2.10 to 2.35 (m, 1H); 2.22 and 2.29 (2s, 3H in totality); 2.74 (m, 1H), from 2.85 to 3.20 (m, 2H), from 3.30 to 3.50 (m, 1H), from 3.60 to 3.85 (m, 1H), 3.89 and 4.08 (2m, 1H in totality), 4.47 (ddd, *J*=16–8, 5 Hz, 1H), from 4.60 to 4.70 (m, 1H), 4.73 and 4.78 (2 dd, *J*=10, 2 Hz, 1H in totality), 4.91 and 5.02 (2 m, 1H in totality), 5.18 and 5.53 (2 broad d, *J*=9 Hz, 1H in totality), from 5.70 to 5.90 (m, 2H), 6.07 and 6.11 (2 broad d, *J*=16 Hz, 1H in totality), 6.09 (s, 1H), 6.30 and 6.86 (2m, 1H in totality), 6.47 (dd, *J*=16, 5 Hz, 1H), 8.06 and 8.19 (2s, 1H in totality). MW=585, IC: *m/z*=586 [MH^+], *m/z*=568 [MH^+-H_2O], *m/z*=526 [MH^+−AcOH], *m/z*=508 [*m/z*=526−H_2O]; IR (KBr) 3594, 3440, 3340, 3170, 2977, 1739, 1673, 1626, 1517, 1434, 1220, 1186, 1045 and 969 cm^{-1}. Elemental analysis calculated for $C_{30}H_{39}N_3O_9$: C, 61.53; H, 6.71; N, 7.17; O, 24.59. Found: C, 61.14; H, 6.96; N, 7.05; O, 24.95.

3.1.4. (14*S*)-Dehydro-furan-3-one pristinamycin II_B (5). To a suspension of 88 mg (0.2 mmol) of rhodium(II) acetate dimer (quality 99.99%+) in dichloromethane (20 mL) and toluene (10 mL) was added under argon at 47 °C, a solution of 1.1 g (2 mmol) of **3** in dichloromethane (20 mL) and toluene (10 mL). After stirring at 47 °C for 3 h, the reaction mixture was filtered over Celite®. The resulting filtrate was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (96:2:2 and 92:4:4, v/v/v)] to afford 409 mg (0.78 mmol) (39%) of **5** as a single diastereomer (stereochemical assignment for the new chiral center at C-17 could not be determined) as a pale yellow solid; $[\alpha]_D^{20}=+116.2\pm1.6$ (*c* 0.5, CH_2Cl_2) (putative stereochemistry at C-17: R); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 0.96 (d, *J*=6.5 Hz, 3H), 0.99 (d, *J*=6.5 Hz, 3H), 1.11 (d, *J*=6.5 Hz, 3H), from 1.75 to 2.05 (m, 4H), 1.82 (s, 3H), 2.18 (mt, 1H), 2.66 (dd, *J*=18, 3 Hz, 1H), 2.77 (m, 1H), 3.07 (dd, *J*=18, 9 Hz, 1H), 3.63 (very broad d, *J*=17 Hz, 1H), 3.93 (m, 1H), 4.11 (m, 1H), 4.42 (broad dt, *J*=17, 4.5 Hz, 1H), 4.77 (dd, *J*=10, 1.5 Hz, 1H), 4.83 (dd, *J*=9, 4 Hz, 1H), 5.04 (s, 1H), 5.51 (td, *J*=9, 2 Hz, 1H), from 5.70 to 5.85 (m, 2H), 5.85 (dd, *J*=16, 1.5 Hz, 1H), 6.01 (d, *J*=16 Hz, 1H), 6.06 (mt, 1H), 6.53 (dd, *J*=16, 5 Hz, 1H), 8.17 (s, 1H). MW=525, IC: *m/z*=526 [MH^+]; IR (KBr) 3431, 2976, 1767, 1737, 1674, 1629; 1515, 1428, 1186, 1110 and 967 cm^{-1}. Elemental analysis calculated for $C_{28}H_{35}N_3O_7$: C, 63.99; H, 6.71; N, 7.99; O, 21.31. Found: C, 63.77; H, 6.91; N, 7.92; O, 21.12.

3.1.5. Ring-contracted lactone pristinamycin II_B (6). A solution of 138 mg (0.25 mmol) of **3** in dichloromethane (5 mL) and toluene (10 mL) was stirred under argon at 61 °C for 23 h. The reaction mixture was concentrated under vacuum to provide a residue which was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (92:4:4, v/v/v)] to afford 30 mg (0.057 mmol) (23%) of **6** as a single diastereomer (stereochemical assignment for the new chiral center at C-17 could not be determined) as a yellow solid; $[\alpha]_D^{20}=-64\pm1.2$ (*c* 0.5, CH_2Cl_2) (putative stereochemistry at C-17: R); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 0.96 (d, *J*=6.5 Hz, 3H), 1.01 (d, *J*=6.5 Hz, 3H), 1.11 (d, *J*=6.5 Hz, 3H), from 1.70 to 2.05 (m, 4H), 1.84 (s, 3H), 2.18 (m, 1H),

2.78 (m, 1H), 2.94 (dd, J=15, 1.5 Hz, 1H), 3,01 (dd, J=15, 8 Hz, 1H), 3.50 (broad dd, J=17, 5 Hz, 1H), 3.95 (m, 1H), 4.03 (dd, J=9, 3 Hz, 1H), 4.15 (m, 1H), 4.61 (ddd, J=17–8, 3 Hz, 1H), from 4.75 to 4.85 (m, 2H), 5.90 (broad t, J=8 Hz, 1H), from 5.80 to 5.90 (m, 1H), 5.83 (dd, J=16, 1.5 Hz, 1H), 5.88 (d, J=8 Hz, 1H), 5.99 (broad d, J=8 Hz, 1H), 6.10 (d, J=16 Hz, 1H), 6.55 (dd, J=16, 5 Hz, 1H), 8.28 (s, 1H). MW=525, IC: m/z=543 [MNH_4^+], m/z=526 [MH^+], m/z=482 [MH^+-CO_2]; IR (KBr) 3436, 3172, 2978, 1779, 1736, 1675, 1629, 1580, 1515, 1430, 1186 and 977 cm^{-1}. Elemental analysis calculated for $C_{28}H_{35}N_3O_7$: C, 63.99; H, 6.71; N, 7.99; O, 21.31. Found: C, 63.99; H, 5.60; N, 7.98; O, 21.30.

3.1.6. Ring-contracted diol pristinamycin II_B (9). To a solution of 630 mg (1.2 mmol) of **6** in methanol (30 mL) was added under argon at 40 °C, 63 mg (1.68 mmol) of sodium borohydride. After stirring at room temperature for 1 h, the reaction mixture was diluted with dichloromethane (100 mL), washed with a saturated aqueous sodium bicarbonate solution (3×100 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The resulting residue was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (80:10:10, v/v/v)] to afford 405 mg (0.77 mmol) (64%) of **9** as a mixture of a single diastereoisomer (stereochemical assignment for the new chiral center at C-17 could not be determined) as a white solid; $[\alpha]_D^{20}=-253.4\pm3.2$ (c 0.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, δ in ppm): 0.93 (d, J=6.5 Hz, 3H), 0.98 (d, J=6.5 Hz, 3H), 1.01 (d, J=6.5 Hz, 3H), 1.75 (s, 3H), from 1.85 to 2.20 (m, 6H), from 2.20 to 2.35 (m, 2H), 2,53 (broad t, J=6 Hz, 1H), 2.73 (m, 1H), 3,10 (m, 1H), 3.23 (ddd, J=14–10, 3 Hz, 1H), 3.45 (m, 1H), from 3.85 to 4.05 (m, 3H), 4.47 (ddd, J=14–9, 5 Hz, 1H), from 4.55 to 4.70 (m, 1H), 4.61 (dd, J=9, 3 Hz, 1H), 4.73 (dd, J=10, 2 Hz, 1H), 4,85 (d, J=9 Hz, 1H), 5.68 (ddd, J=16–10, 5 Hz, 1H), 5.78 (broad d, J=16 Hz, 1H), 5.85 (d, J=16 Hz, 1H), 6.45 (dd, J=16, 5 Hz, 1H), 7.52 (broad dd, J=9, 3 Hz, 1H), 7.62 (s, 1H). MW=529, IC: m/z=530 [MH^+]; IR (KBr) 3597, 3339, 2977, 1732, 1671, 1622, 1544, 1443 and 967 cm^{-1}. Elemental analysis calculated for $C_{28}H_{39}N_3O_2$: C, 63.50; H, 7.42; N, 7.93; O, 21.15. Found: C, 63.12; H, 7.09; N, 7.75; O, 20.90.

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