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# Preparation of 14,36-didehydro pristinamycins IIs

Baptiste Ronan,* Eric Bacqué, Jean-Claude Barrière and Serge Sablé

*Centre de Recherche de Vitry-Alfortville, Aventis Pharma S.A., 13 Quai Jules Guesde BP 14, 94403 Vitry sur Seine Cedex, France*

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

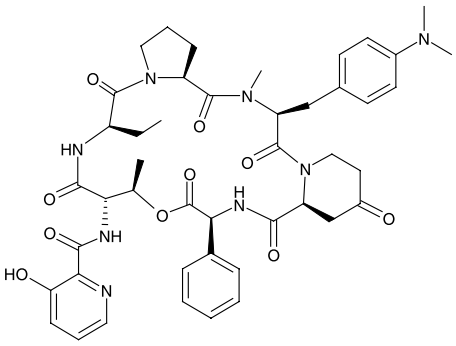
**Abstract**—The first successful preparation of 14,36-didehydro pristinamycins $II_A$ and $II_B$ is reported via different strategies. 

## 1. Introduction

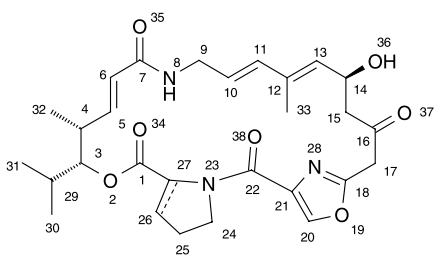
Pristinamycin is a naturally occurring antibiotic of the streptogramin class. This family of antibiotics is characterized by the original association of two types of chemically unrelated molecules, pristinamycins I (PI) and pristinamycins II (PII), which act synergistically on the ribosome of bacteria, thereby inhibiting protein synthesis.[1–4] Whereas Pristinamycins I such as $PI_A$ (**1**) are cyclic depsipeptides, Pristinamycins II, as typified by the most abundant pristinamycins II $PII_A$ (**2a**) and $PII_B$ (**2b**), are peptidic macrolactones (Scheme 1).

In the 1980s, we initiated a program of semisynthesis aimed at discovering water-soluble antibacterial pristinamycins. These endeavors culminated with the development of Synercid®, the first injectable streptogramin, which was approved in the US in 1999 for the treatment of severe Gram-positive infections in hospital.[5–7] In our continuing efforts to identify the next generation streptogramins, we envisioned that the 14,36-didehydro PIIs **3** could be very attractive precursors amenable to a large variety of semisynthetic modifications. Prior to our involvement in the field of PII semi synthesis, it had been reported[8] that oxidation of the C-14 hydroxyl of **2a** could be accomplished by DDQ in $CH_2Cl_2$ at room temperature to afford 14,36-didehydro $PII_A$ **3a** (Scheme 2) in 33% isolated yield, a new $PII_A$ devoid of any antibacterial activity alone or in association with **1**.

Hereafter, we report that this DDQ oxidation yields an unexpected compound rather than **3a** and the successful outcome of a subsequent study aimed at discovering efficient syntheses of the 14,36-didehydro PIIs **3**. We will



**Pristinamycin $I_A$ (1)**



**Pristinamycin $II_A$ (2a)** : Δ-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; β-hydroxy ketones; allylic alcohols; ketones; 1,3-diketones; diols, enoxysilanes; oxidation; reduction; DDQ; DMP; Diels–Alder reaction; acyl iminium.

* Corresponding author. Tel.: +33-1-5893-8072; fax: +33-1-5893-80-14; e-mail: baptiste.ronan@aventis.com

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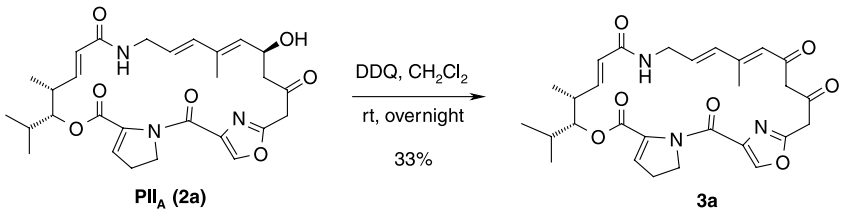



**Scheme 2.** DDQ oxidation of $PII_A$ (**2a**) according to Ref. 8.

also describe our unsuccessful attempts to extend the new DDQ induced reaction to other PIIs.

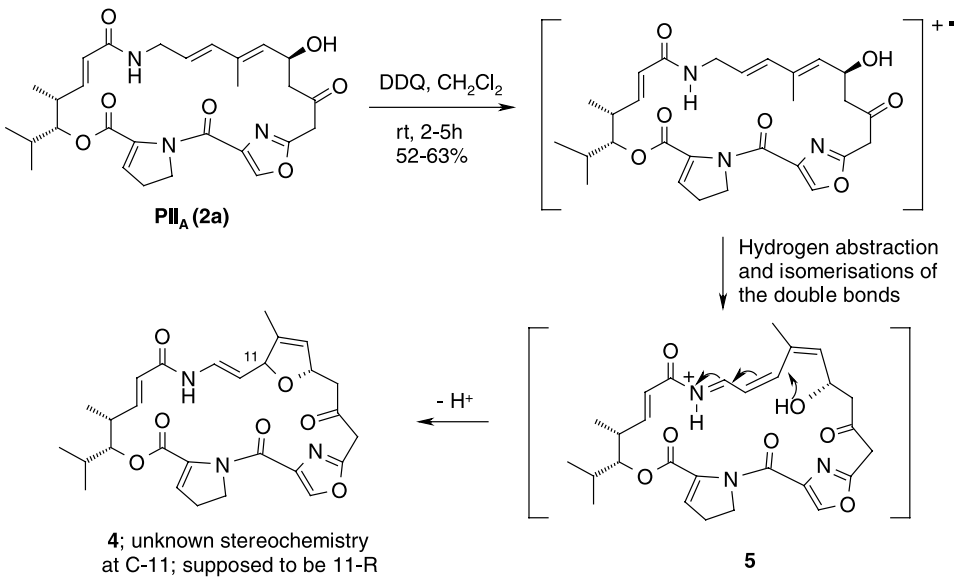
## 2. Results and discussion

With the initial objective of preparing a few grams of **3a** in view of a subsequent semi synthesis program, we tried to reproduce the described synthesis[8] of this derivative. Much to our surprise, the only isolated product in this reaction was not **3a** but, according to an in-depth analysis of the spectroscopic data mainly based on two-dimensional $^1H,^1H$ and $^1H,^{13}C$ correlation NMR spectra, dihydrofuran **4** in 52% isolated yield (Scheme 3), as a single isomer (stereochemical assignment for the new chiral center at C-11 could not be determined by NMR but was tentatively supposed to be 11-R according to molecular modeling).

Compounds **3a** and **4** exhibited the same molecular formula $C_{28}H_{33}N_3O_7$. The initial structure elucidation reported in the litterature[8] for compound **3a** relied upon limited MS (*m/e* 523), $^{13}C$ NMR (*C*HOH signal shift from 65.7 ppm to *C*=O signal at 113.8 ppm) and UV ($\lambda_{max}$ 165 nm) data. As confirmed by our complementary spectroscopic investigations (see Section 3), these data were not sufficient to unambiguously attribute the correct structure. Therefore, we assumed that 14,36-didehydro $PII_A$ **3a** had never been synthesized. Formation of **4** was rationalized as the result of an original intramolecular interception by 36-O of a putative vinylogous acyl iminium **5** generated by an initial oxidation of $PII_A$ (**2a**) by DDQ (see Scheme 3). To the best of our knowledge, oxidation of an allylic *N*-acyl amine by DDQ or by other oxidants into an acyl iminium has never been reported.

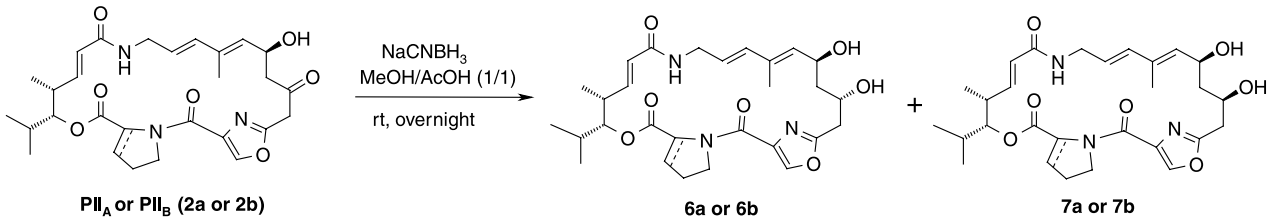
With this unexpected result in hand, we next decided to extend this new DDQ oxidation to **2b** and to the diols **6** and **7** (series $PII_A$ and $PII_B$). As a prerequisite to this study, we required a reliable method of preparation of these diols. In our hands, the known $NaBH_4$ reduction[8] of **2a** into the corresponding *anti* and *syn* diols **6a** and **7a**, in a 45/55 ratio, afforded an inseparable mixture of the two expected diols along with the two corresponding known anti and *syn* diols[4] **6b** and **7b**, resulting from the reduction of Δ-26,27 ($PII_A$ diols/$PII_B$ diols: 90/10). Upon screening of other reductive reagents, we found that the reduction proceeded selectively at the carbonyl group with $NaCNBH_3$ in MeOH/AcOH (1/1 to 5/1 in volumes) at room temperature. Under these conditions, **6a** and **7a** were obtained cleanly in high yield by flash chromatography on silica gel (see Table 1). Likewise, similar conditions also afforded both **6b** and **7b** in good yields (see also Table 1). During this study, we observed that the ratios **7/6** ranged from 1 to 2 depending on the reaction scale up. This observation was ascribed to a higher susceptibility toward acidic conditions of the *anti* isomer: scale up results in prolonged contact with acetic acid during reaction and work-up hence entailing increased degradation of the *anti* isomer.

Having secured a reliable synthesis of the PIIs diols **6** and **7**, we next examined the reaction of **2b** and of these diols **6** and **7** with DDQ under the conditions used for **2a**. Whereas all




**Scheme 3.** Revisited DDQ oxidation of $PII_A$ (**2a**) via the vinylogous acyl iminium **5**.

**Table 1**. $NaCNBH_3$ reduction of **2a** and **2b** into the corresponding diols **6** and **7**




**PII$_A$ or PII$_B$ (2a or 2b)** **6a or 6b** **7a or 7b**

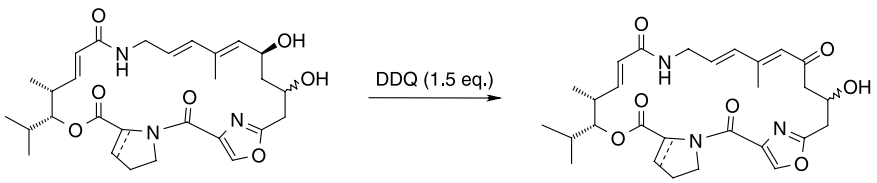
| PII | Scale (g) | **6**; yield (%) | **7**; yield (%) | **7/6** |
|---|---|---|---|---|
| $PII_A$ **2a** | 20 | **6a**; 34–40 | **7a**; 35–38 | 1 |
| $PII_A$ **2a** | 1000 | **6a**; 33 | **7a**; 45 | 1.4 |
| $PII_B$ **2b** | 40 | **6b**; 27 | **7b**; 29 | 1.1 |
| $PII_B$ **2b** | 100 | **6b**; 28 | **7b**; 40 | 1.4 |
| $PII_B$ **2b** | 500 | **6b**; 27 | **7b**; 55 | 2 |

the diols underwent the classical allylic oxidation of the 14-hydroxy to afford ketones **8a–d**, no reaction was observed starting from **2b**. In the diol series, we observed that the *anti* isomers systematically gave higher yields of the corresponding ketones **8** than the *syn* isomers and that the reactions in the $PII_B$ series were always more efficient than in the $PII_A$ series, as the result of an increased stability, under the reaction conditions, of these 14-oxo PIIs in the $PII_B$ series (Table 2).

We assumed that these differences of behavior among the PIIs upon DDQ oxidation stemed from subtle stereo-electronic and conformational factors. All known XR and model structures of PIIs[4] show that the C-14 hydrogen lies in the plan of the diene moiety whereas DDQ oxidations of allylic alcohols are known to require an angle close to 90° to be successful.[9] This remark suggests that DDQ oxidation of the C-14 hydroxy should not proceed whatever the PII and therefore, that the original alternative oxidation of the allylic *N*-acyl amine observed for **2a** should be the rule. To account for the differences of reactivity of **2a** and the diols, we suppose that the presence or the absence of the ketone at C-16 of the PII is key, either due to its unfavorable impact on the formation of an intermediary C-14 carbocation and/or its role upon the flexibility of this part of the molecule which, in turn, influences the competition between the two possible oxidative paths. Regarding the different behaviours of **2a** and **2b**, this discrepancy could be the consequence of the different conformations within the 7,8-amide region that result in the existence or the absence of a hydrogen bond between O-38 and NH-8 (present in **2a** but absent in **2b**).

At this stage, we returned to our initial problem: find an effective method leading to **3a** and **3b**, starting from **2a,b** or alternatively from **8a–d**. Various oxidation methodologies[10] were examined but without any success. PDC, $CrO_3$.pyridine, $Ac_2O$–DMSO, DCC–NaOAc, oxalyl chloride–DMSO–$Et_3N$, TFA–DMSO–$Et_3N$, $SO_3$.pyridine and $(Bu_3Sn)_2O$ gave either starting material, a complex mixture or dehydration. Finally, we turned our attention toward the Dess–Martin Periodinane reagent[11] (DMP; either commercial[12] or prepared according to the Ireland modification[11b]). This reagent has indeed been reported to be one of the mildest oxidants for the selective oxidation of primary and secondary alcohols into aldehydes and ketones. When DMP oxidations were carried out on **6** and **7**, whatever the series only complex mixtures were obtained. On the other hand, much to our delight, we observed that **2a** was submitted to DMP oxidation conditions in $CH_2Cl_2$ around 0°C to give **3a** as the diketone form in 17 to 43% isolated yield, depending on the temperature and the quantities of DMP used (see Table 3). As previously

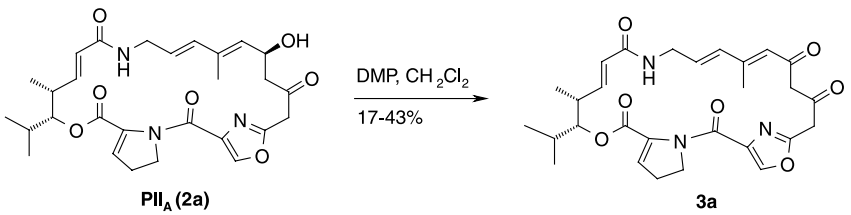
**Table 2**. Allylic DDQ oxidation of **6** and **7**




**6a or 6b**
**7a or 7b** **8a-d**

| Diols **6** or **7** | Solvent | Temperature (°C) | Time (h) | Products **8** | Yield (%) |
|---|---|---|---|---|---|
| **6a** | $CH_2Cl_2$ | rt | 27 | **8a** | 31 |
| **7a** | $CH_2Cl_2$ | 0 | 27 | **8b** | 17 |
| **6b** | $CH_2Cl_2$ | rt | 30 | **8c** | 68 |
| **6b** | $CH_2Cl_2$/1,4-dioxane=1/2 | rt | 4 | **8c** | 69 |
| **7b** | $CH_2Cl_2$ | rt | 5 | **8d** | 19 |
| **7b** | $CH_2Cl_2$ | 0 | 5 | **8d** | 42 |
| **7b** | $CH_2Cl_2$/1,4-dioxane=1/2 | −5 | 2 | **8d** | 50 |

**Table 3**. Oxidation of $PII_A$ **2a** with DMP



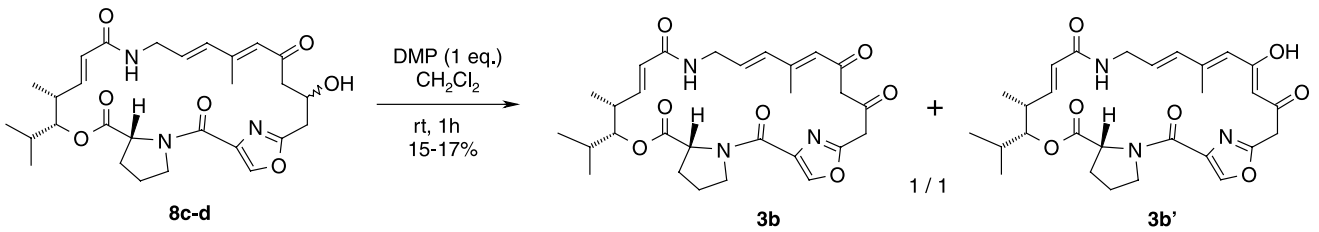

| Scale (g) | DMP (equiv.) | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 0.1 | 2 | rt | 0.25 | 43 |
| 0.5 | 1.5 | 5 | 3 | 17 |
| 5 | 1.5 | −10 | 4.5 | 34 |

reported for the DDQ oxidation of **2b** compared to the DDQ oxidation of **2a**, no reaction was observed starting from $PII_B$ **2b** in the presence of DMP.

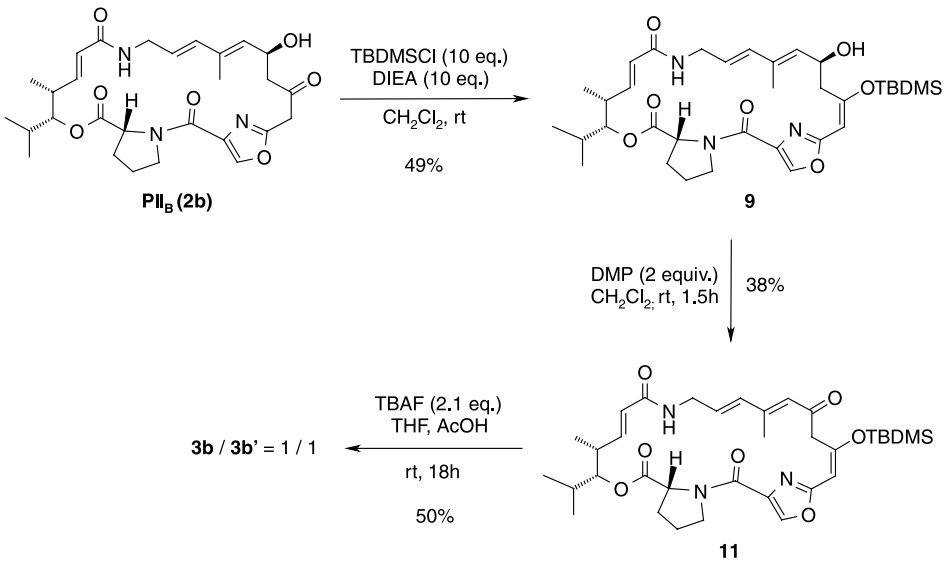
We next discovered that exposure of **8c–d** to DMP in $CH_2Cl_2$ at room temperature led to **3b** in modest yields (15–17%), which was isolated as a 1/1 mixture of the diketo form **3b** and of the enol form **3b′** (Scheme 4).

In a last approach and based on our previous successes, we investigated the reactivity of silyl enol ethers **9** toward DMP (Scheme 5) and **10** toward DDQ (Scheme 6).[13] Silyl enol ethers **9** and **10** were synthesized by treatment of **2a** or **2b** with *t*-butyl dimethylsilyl chloride (TBDMSCl) and diisopropylethyl amine (DIEA) in dichloromethane at room temperature. When **9** was submitted to DMP oxidation, ketone **11** was obtained in 38% isolated yield. Desilylation of **11** was performed with TBAF in THF in the presence of acetic acid at room temperature to produce **3b**, which was isolated, as a 1/1 mixture of the diketo **3b** form and the enol form **3b′** in 50% yield. These results were supported by 2D NMR experiments. The long range $^1H/^{13}C$ 2D experiments showed correlations between hydrogens at position 13, 15 and 17 with two carbons at 194 and 198 ppm for the diketo form, and at 180 and 193 ppm for the enol form.

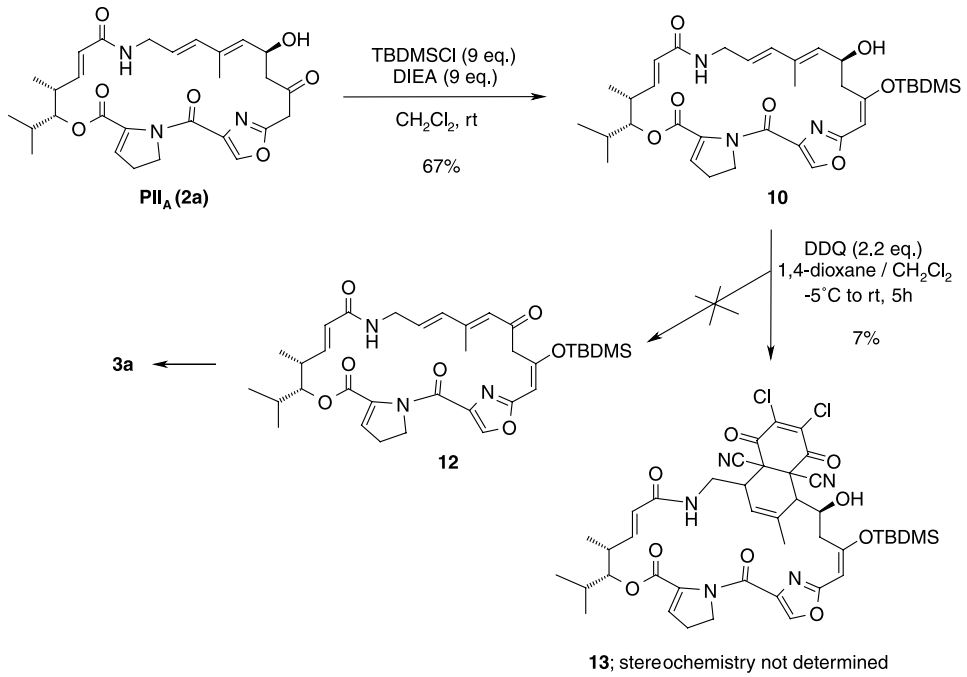
On the other hand, reaction of **10** with DDQ in 1,4-dioxane and $CH_2Cl_2$ did not afford a trace of the oxidation product **12** but rather a complex mixture from which we could only isolated the unexpected Diels–Alder adduct[14,15] **13** in a very poor isolated yield (7%) as a single isomer (stereochemical assignment for the new chiral centers not




**Scheme 4.** DMP oxidation of **8c–d**.




**Scheme 5.** Preparation of **3b** via DMP oxidation of **9**.




**Scheme 6.** Attempted preparation of **3a** via DDQ oxidation of **10**.

determined; see Scheme 6). The structure of this product (**13**) was supported by the NMR measurements. The assignments of signals in the $^{1}H$ and $^{13}C$ spectra was performed by recording two-dimensional $^{1}H$, $^{1}H$ and $^{13}C$, $^{1}H$ correlation spectra. Here again, subtle differences between the two allylic moieties are thought to be responsible for this discrepancy of behavior of **9** and **10**.

In summary, 14,36-didehydro pristinamycin $II_A$ **3a** and 14,36-didehydro pristinamycin $II_B$ **3b/3b′** have been prepared using DMP starting from either $PII_A$ (**2a**) or β-hydroxy ketones **8c–d** or silyl enol ether **9**. During this work, we have discovered a new DDQ triggered oxidative process of the allylic *N*-acyl amine of $PII_A$ that was shown not to be applicable to closely related substrates. Antibacterial activities of **3a** and **3b**, as well as those of the other PIIs described in this paper, will be reported elsewhere. Likewise, our current efforts to modify by semisynthesis these various PIIs in order to identify the PII component of the next generation streptogramin will be published later.

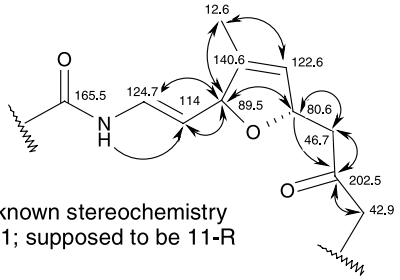
## 3. Experimental

### 3.1. General

Reagents and solvents were purchased from Prolabo or Janssen Chemica 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 ($\delta$) 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 NERMAG R10-10 spectrometer for electronic impact (EI; 70 eV), a FINNIGAN TSQ46 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. Preparation of 4 via DDQ oxidation of $PII_A$ (2a).** To a solution of 0.526 g (1 mmol) of **2a** in dichloromethane (20 mL) cooled to −10°C was added under argon, 0.25 g (1.1 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. The reaction mixture was stirred between −10 and 0°C for 1 h, then at room temperature for 1 h. The resulting reaction mixture was directly chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (92/4/4 v/v/v)] to afford 0.331 g (0.63 mmol) (63%) of **4**, as a beige solid (mp=120°C (dec.)); $[\alpha]_D^{20}$=+13.3±0.5 (*c* 0.5, EtOH); 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, 63.98; H, 6.69; N, 8.08; O, 21.29; M.W.=523, DCI: *m/z*=541 $[M+NH_4]^+$, *m/z*=524 $[M+H]^+$; IR ($CH_2Cl_2$) 3296, 2975, 1728, 1659, 1626, 1518, 1420, 1184, 1115, 956 and 890 $cm^{-1}$; $^{1}H$ NMR (600 MHz, $CDCl_3$, $\delta$ in ppm): 0.95 (d, *J*=7 Hz, 3H), 0.98 (d, *J*=7 Hz, 3H), 1.13 (d, *J*=7 Hz,

3H), 1.61 (s, 3H), from 1.95 to 2.10 (m, 1H), from 2.65 to 2.80 (m, 2H), 2.68 (dd, $J$=12.5, 5 Hz, 1H), 2.87 (dd, $J$=12.5, 5.5 Hz, 1H), 2.98 (m, 1H), 3.87 (d, $J$=16.5 Hz, 1H), 4.15 (m, 1H), 4.27 (d, $J$=16.5 Hz, 1H), 4.35 (m, 1H), 4.95 (broad d, $J$=9.5 Hz, 1H), 5.03 (dd, $J$=10, 1.5 Hz, 1H), 5.08 (broad s, 1H), 5.43 (s, 1H), 5.75 (dd, $J$=14.5, 9.5 Hz, 1H), 6.06 (t, $J$=3.5 Hz, 1H), 6.14 (d, $J$=16 Hz, 1H), 6.70 (dd, $J$=16, 7.5 Hz, 1H), 7.02 (dd, $J$=14.5, 10 Hz, 1H), 8.00 (s, 1H), 9.38 (d, $J$=10 Hz, 1H), $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$ in ppm) 12.6, 13.3, 19.3, 19.7, 30.6 (×2), 37.9, 42.9, 46.7, 49.5, 80.6, 82.5, 89.5, 114.0, 120.3, 122.6, 124.7, 125.9, 135.3, 137.5, 140.6, 142.0, 144.7, 159.2, 159.9, 161.3, 165.5, 202.5; main $^{1}$H,$^{13}$C long range correlations:




**3.1.2. (16*S*)-16-Hydroxy pristinamycin II$_A$ (6a) and (16*R*)-16-hydroxy pristinamycin II$_A$ (7a).** To a solution of 2.1 g (4 mmol) of **2a** in methanol (30 mL) and acetic acid (30 mL) was added under argon at room temperature, 0.58 g (8.4 mmol) of sodium cyanoborohydride. After stirring at room temperature for 21 h, the reaction mixture was concentrated under vacuum and then neutralized with a saturated aqueous sodium bicarbonate solution (150 mL). The resulting mixture was extracted with dichloromethane (3×150 mL). The organic layers were combined, washed with water (200 mL) and then dried over magnesium sulfate, filtered and concentrated under vacuum to afford 2.2 g of a residue. It was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (84/8/8 v/v/v)] to afford 0.709 g (1.34 mmol) (34%) of **6a**, as a white solid (mp=131°C (dec.)) and 0.73 g (1.38 mmol) (35%) of **7a**, as a white solid (mp=140°C (dec.)).

*Compound* **6a**. $^{1}$H NMR (400 MHz, $CDCl_3$, $\delta$ in ppm): 0.98 (d, $J$=7 Hz, 3H), 1.00 (d, $J$=7 Hz, 3H), 1.13 (d, $J$=7 Hz, 3H), 1.66 (s, 3H), from 1.90 to 2.10 (m, 3H), from 2.60 to 2.85 (m, 4H), 2.87 (dd, $J$=16, 11 Hz, 1H), 3.09 (dd, $J$=16, 3.5 Hz, 1H), 3.37 (ddd, $J$=16, 10, 3.5 Hz, 1H), 3.65 (very broad s, 1H), from 4.05 to 4.30 (m, 2H), from 4.35 to 4.55 (m, 2H), from 4.85 to 4.95 (m, 1H), 4.92 (dd, $J$=10, 2.5 Hz, 1H), 5.55 (m, 1H), 5.59 (broad d, $J$=9 Hz, 1H), 5.90 (dd, $J$=16, 1.5 Hz, 1H), from 6.00 to 6.10 (m, 2H), from 6.45 to 6.55 (m, 1H), 6.53 (dd, $J$=16, 6 Hz, 1H), 8.06 (s, 1H); M.W.=527, DCI: $m/z$=545 $[M+NH_4]^+$, $m/z$=528 $[M+H]^+$, $m/z$=510$[M+H]^+-H_2O$; IR ($CH_2Cl_2$) 3344, 2975, 1730, 1672, 1622, 1519, 1412, 1182, 1067, 969 and 887 cm$^{-1}$; $[\alpha]_D^{20}$=−42.5 ±1.1 ($c$ 0.5, EtOH); elemental analysis calculated for $C_{28}H_{37}N_3O_7$: C, 63.74; H, 7.07; N, 7.96; O, 21.23; found: C, 63.76; H, 7.08; N, 7.83; O, 21.19.

*Compound* **7a**. $^{1}$H NMR (400 MHz, $CDCl_3$, $\delta$ in ppm): 0.99 (m, 6H), 1.12 (d, $J$=7 Hz, 3H), 1.73 (s, 3H), from 1.80 to 2.10 (m, 3H), 2.21 (very broad s, 1H), from 2.60 to 2.85 (m, 3H), 2.91 (dd, $J$=15, 9 Hz, 1H), 2.94 (very broad s, 1H), 3.02 (dd, $J$=15, 5 Hz, 1H), from 3.85 to 4.10 (m, 3H), from 4.10 to 4.35 (m, 2H), 4.66 (m, 1H), 4.93 (dd, $J$=10, 2.5 Hz, 1H), 5.07 (broad d, $J$=9 Hz, 1H), 5.62 (ddd, $J$=16, 6, 5 Hz, 1H), 5.95 (dd, $J$=16, 1.5 Hz, 1H), 5.97 (d, $J$=16 Hz, 1H), 6.15 (t, $J$=3 Hz, 1H), 6.60 (dd, $J$=16, 7 Hz, 1H), 6.98 (broad t, $J$=6 Hz, 1H), 7.94 (s, 1H); M.W.=527, DCI: $m/z$=545 $[M+NH_4]^+$, $m/z$=528 $[M+H]^+$, $m/z$=510$[M+H]^+-H_2O$; IR ($CH_2Cl_2$) 3361, 2975, 1730, 1672, 1620, 1535, 1421, 1182, 971 and 888 cm$^{-1}$; $[\alpha]_D^{20}$=−94.8±1.7 ($c$ 0.5, EtOH); elemental analysis calculated for $C_{28}H_{37}N_3O_7$: C, 63.74; H, 7.07; N, 7.96; O, 21.23; found: C, 63.75; H, 7.25; N, 7.90; O, 21.27.

**3.1.3. (16*S*)-16-Hydroxy pristinamycin II$_B$ (6b) and (16*R*)-16-hydroxy pristinamycin II$_B$ (7b).** To a solution of 40 g (76 mmol) of **2b** in methanol (400 mL) and acetic acid (400 mL) was added under argon at room temperature, 10.5 g (152 mmol) of sodium cyanoborohydride. After stirring at room temperature for 4 h, the reaction mixture was concentrated under vacuum and then neutralized with a 10% aqueous sodium bicarbonate solution (500 mL). The resulting mixture was extracted with dichloromethane (2×700 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under vacuum to afford 49 g of a residue, which was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (90/5/5 v/v/v)] to afford 10.9 g (20.6 mmol) (27%) of **6b**, as a white solid (mp=131°C (dec.)) and 11.8 g (22.3 mmol) (29%) of **7b**, as a white solid (mp=140°C (dec.)).

*Compound* **6b**. $^{1}$H NMR (400 MHz, $CDCl_3$, $\delta$ in ppm): 0.95 (d, $J$=7 Hz, 3H), 1.01 (d, $J$=7 Hz, 3H), 1.06 (d, $J$=7 Hz, 3H), from 1.65 to 2.00 (m, 5H), 1.74 (s, 3H), 2.12 (m, 1H), 2.24 (broad d, $J$=14 Hz, 1H), from 2.65 to 2.80 (m, 2H), 2.89 (dd, $J$=16, 10 Hz, 1H), 3.06 (dd, $J$=16, 3 Hz, 1H), 3.36 (ddd, $J$=14.5, 10, 4 Hz, 1H), 3.81 (t, $J$=6.5 Hz, 2H), 4.07 (broad s, 1H), from 4.35 to 4.55 (m, 2H), 4.70 (m, 2H), 5.00 (m, 1H), from 5.60 to 5.80 (m, 2H), 5.75 (dd, $J$=16, 1.5 Hz, 1H), 6.03 (broad dd, $J$=9, 4 Hz, 1H), 6.20 (d, $J$=16 Hz, 1H), 6.46 (dd, $J$=16, 4.5 Hz, 1H), 8.12 (s, 1H); M.W.=529, DCI: $m/z$=547 $[M+NH_4]^+$, $m/z$=530 $[M+H]^+$, $m/z$=512 $[M+NH_4]^+-H_2O$; IR ($CH_2Cl_2$) 3412, 2978, 1734, 1673, 1625, 1516, 1434, 1186, 1066 and 969 cm$^{-1}$; $[\alpha]_D^{20}$=−17.6±0.8 ($c$ 0.5, EtOH); elemental analysis calculated for $C_{28}H_{39}N_3O_7$: C, 63.50; H, 7.42; N, 7.93; O, 21.15; found: C, 63.48; H, 7.64; N, 8.21; O, 20.70.

*Compound* **7b**. $^{1}$H NMR (400 MHz, $CDCl_3$, $\delta$ in ppm): 0.96 (d, $J$=7 Hz, 3H), 1.00 (d, $J$=7 Hz, 3H), 1.11 (d, $J$=7 Hz, 3H), from 1.65 to 2.00 (m, 6H), 1.81 (s, 3H), from 2.00 to 2.20 (m, 2H), 2.76 (m, 1H), 2.84 (dd, $J$=16.5, 6 Hz, 1H), 3.01 (dd, $J$=16.5, 6.5 Hz, 1H), 3.06 (d, $J$=4 Hz, 1H), 3.45 (ddd, $J$=15.5, 10, 4 Hz, 1H), from 3.80 to 4.10 (m, 2H), 4.29 (m, 1H), 4.48 (ddd, $J$=15.5, 8, 4 Hz, 1H), 4.79 (dd, $J$=10, 2 Hz, 1H), 4.84 (dd, $J$=9, 3 Hz, 1H), 4.88 (m, 1H), 5.43 (d, $J$=9 Hz, 1H), 5.66 (ddd, $J$=16, 10, 4 Hz, 1H), 5.85 (dd, $J$=16, 1.5 Hz, 1H), 5.95 (broad dd, $J$=9, 4 Hz, 1H), 6.19 (d, $J$=16 Hz, 1H), 6.53 (dd, $J$=16, 4.5 Hz, 1H), 8.15 (s, 1H); M.W.=529, DCI: $m/z$=547 $[M+NH_4]^+$, $m/z$=530 $[M+H]^+$, $m/z$=512 $[M+NH_4]^+-H_2O$; IR ($CH_2Cl_2$) 3440, 2977, 1736, 1674, 1626, 1514, 1431, 1186, 1108 and 962 cm$^{-1}$; $[\alpha]_D^{20}$=−40.9±1.1 ($c$ 0.5, EtOH); elemental

analysis calculated for $C_{28}H_{39}N_3O_7$: C, 63.99; H, 6.71; N, 7.99; O, 21.31; found: C, 63.51; H, 7.36; N, 8.26; O, 21.16.

**3.1.4. (16*S*)-14,36-Didehydro-16-hydroxy pristinamycin $II_A$ (8a).** To a solution of 2 g (3.8 mmol) of **6a** in dichloromethane (20 mL) was added under argon at room temperature 1.3 g (5.7 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. After stirring at room temperature for 24 h, the reaction mixture was concentrated under vacuum. The resulting material (3.4 g) was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (90/5/5 v/v/v)] to afford 0.621 g (1.18 mmol) (31%) of **8a**, as a yellow solid (mp=125°C (dec.)); M.W.=525, *m/z*=543 $[M+NH_4]^+$, *m/z*=526 $[M+H]^+$, *m/z*=508 $[M+H]^+-H_2O$; $^1H$ NMR (400 MHz, $CDCl_3$, $\delta$ in ppm): 1.01 (m, 6H), 1.15 (d, *J*=7 Hz, 3H), 2.03 (m, 1H), 2.20 (s, 3H), 2.50 (dd, *J*=15, 5 Hz, 1H), from 2.60 to 2.75 (m, 4H), 3.04 (dd, *J*=15, 10 Hz, 1H), 3.21 (dd, *J*=15, 5 Hz, 1H), 3.74 (d, *J*=8.5 Hz, 1H), 3.35 (broad dt, *J*=17, 5 Hz, 1H), from 4.10 to 4.45 (m, 4H), 4.91 (dd, *J*=10, 2 Hz, 1H), 5.92 (dd, *J*=16, 1.5 Hz, 1H), 6.04 (broad s, 1H), 6.10 (broad d, *J*=16 Hz, 1H), 6.17 (t, *J*=3 Hz, 1H), 6.24 (dt, *J*=16, 5 Hz, 1H), 6.36 (m, 1H), 6.64 (dd, *J*=16, 5.5 Hz, 1H), 8.06 (s, 1H); IR ($CH_2Cl_2$) 3440, 3373, 2975, 1730, 1674, 1646, 1622, 1585, 1528, 1414, 1184 and 888 $cm^{-1}$; 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, 63.66; H, 7.04; N, 7.84; O, 21.06.

**3.1.5. (16*R*)-14,36-Didehydro-16-hydroxy pristinamycin $II_A$ (8b).** To a solution of 10 g (18.95 mmol) of **7a** in dichloromethane (200 mL) was added under argon at room temperature 4.3 g (18.95 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. After stirring at room temperature for 5 h, the reaction mixture was concentrated under vacuum. The resulting material was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (90/5/5 v/v/v)] to afford 1.24 g (2.36 mmol) (12%) of **8b** as a beige solid (mp=130°C (dec.)); $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$ in ppm): 1.00 (m, 6H), 1.14 (d, *J*=7 Hz, 3H), 2.02 (m, 1H), 2.18 (s, 3H), from 2.60 to 2.90 (m, 5H), 3.01 (dd, *J*=15.5, 8 Hz, 1H), 3.20 (dd, *J*=15.5, 3 Hz, 1H), 3.38 (broad d, *J*=6.5 Hz, 1H), 3.90 (broad dt, *J*=17, 5 Hz, 1H), from 4.15 to 4.35 (m, 3H), 4.51 (m, 1H), 4.91 (dd, *J*=10, 2 Hz, 1H), 5.93 (dd, *J*=16, 1.5 Hz, 1H), 6.02 (broad s, 1H), 6.09 (broad d, *J*=16 Hz, 1H), 6.15 (t, *J*=3 Hz, 1H), 6.21 (dt, *J*=16, 5 Hz, 1H), 6.40 (m, 1H), 6.67 (dd, *J*=16, 6 Hz, 1H), 8.05 (s, 1H); M.W.=525, DCI: *m/z*=543 $[M+NH_4]^+$, *m/z*=526 $[M+H]^+$, *m/z*=508$[M+H]^+-H_2O$; IR ($CH_2Cl_2$) 3442; 3383; 2975; 1730; 1674; 1621; 1583; 1527; 1414; 1181 and 887 $cm^{-1}$; 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, 63,54; H, 6.38; N, 8.02; O, 21.73.

**3.1.6. (16*S*)-14,36-Didehydro-16-hydroxy pristinamycin $II_B$ (8c).** To a solution of 8.8 g (16.6 mmol) of **6b** in dichloromethane (160 mL) was added under argon at room temperature 4.9 g (21.58 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. After stirring at room temperature for 30 h, the reaction mixture was concentrated under vacuum. The resulting brown residue (15 g) was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (90/5/5 v/v/v)] to afford 5.98 g (11.3 mmol) (68%) of **8c** as a yellow solid (mp=130°C (dec.)); $^1H$ NMR (400 MHz, $CDCl_3$, $\delta$ in ppm): 0.97 (d, *J*=7 Hz, 3H), 1.05 (d, *J*=7 Hz, 3H), 1.12 (d, *J*=7 Hz, 3H), from 1.70 to 2.05 (m, 4 H), 2.18 (m, 1H), 2.25 (s, 3H), 2.44 (dd, *J*=16, 5 Hz, 1H), 2.79 (m, 2H), 3.12 (dd, *J*=14.5, 10 Hz, 1H), 3.23 (dd, *J*=14.5, 5 Hz, 1H), 3.69 (very broad dt, *J*=17, 4 Hz, 1H), 3.89 (m, 1H), 4.07 (m, 1H), 4.15 (d, *J*=9 Hz, 1H), 4.24 (m, 1H), 4.55 (ddd, *J*=17–8, 4.5 Hz, 1H), 4.72 (dd, *J*=9, 3.5 Hz, 1H), 4.79 (dd, *J*=10.5, 1.5 Hz, 1H), 5.85 (dd, *J*=16, 1.5 Hz, 1H), 5.96 (m, 1H), 6.11 (s, 1H), 6.18 (d, *J*=16 Hz, 1H), 6.29 (dt, *J*=16, 4.5 Hz, 1H), 6.49 (dd, *J*=16, 5.5 Hz, 1H), 8.18 (s, 1H); M.W.=527, DCI: *m/z*=545 $[M+NH_4]^+$, *m/z*=528 $[M+H]^+$, *m/z*=510 $[M+H]^+-H_2O$; IR (KBr) 2971, 1744, 1671, 1629, 1585, 1434, 1183, 1111 and 987 $cm^{-1}$; $[\alpha]_D^{20}=+90.7\pm1.8$ (*c* 0.5, EtOH); elemental analysis calculated for $C_{28}H_{37}N_3O_7$: C, 63.74; H, 7.07; N, 7.96; O, 21.23; found: C, 63.70; H, 6.91; N, 7.97; O, 21.24.

**3.1.7. (16*R*)-14,36-Didehydro-16-hydroxy pristinamycin $II_B$ (8d).** To a solution of 10.62 g (20.1 mmol) of **7b** in dichloromethane (200 mL) was added under argon at 0°C 5 g (22.1 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. After stirring at room temperature for 5 h, the reaction mixture was concentrated under vacuum. The resulting brown residue (17 g) was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (90/5/5 v/v/v)] to afford 4.47 g (8.47 mmol) (42%) of **8d** as a beige solid (mp=130°C (dec.)); $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$ in ppm): 0.97 (d, *J*=7 Hz, 3H), 1.02 (d, *J*=7 Hz, 3H), 1.10 (d, *J*=7 Hz, 3H), from 1.70 to 2.30 (m, 5 H), 2.24 (s, 3H), 2.60 (dd, *J*=16, 7 Hz, 1H), 2.77 (m, 1H), 2.84 (dd, *J*=16, 5.5 Hz, 1H), 2.96 (dd, *J*=16, 7.5 Hz, 1H), 3.18 (dd, *J*=16, 3.5 Hz, 1H), 3.35 (d, *J*=4 Hz, 1H), 3.72 (broad dt, *J*=18, 4.5 Hz, 1H), 3.87 (m, 1H), 4.06 (m, 1H), from 4.35 to 4.60 (m, 2H), 4.74 (dd, *J*=9, 4 Hz, 1H), 4.79 (dd, *J*=10.5, 2.5 Hz, 1H), 5.84 (dd, *J*=16, 2 Hz, 1H), 6.01 (dd, *J*=8, 4.5 Hz, 1H), 6.15 (s, 1H), 6.17 (d, *J*=16 Hz, 1H), 6.23 (dt, *J*=16, 4.5 Hz, 1H), 6.49 (dd, *J*=16, 5 Hz, 1H), 8.17 (s, 1H); M.W.=527, DCI: *m/z*=545 $[M+NH_4]^+$, *m/z*=528 $[M+H]^+$, *m/z*=510 $[M+H]^+-H_2O$; IR (KBr) 3307, 2967, 1740, 1668, 1626, 1579, 1428, 1186 and 972 $cm^{-1}$; $[\alpha]_D^{20}=-13.5\pm0.5$ (*c* 0.5, EtOH); elemental analysis calculated for $C_{28}H_{37}N_3O_7$: C, 63.74; H, 7.07; N, 7.96; O, 21.23; found: C, 63.74; H, 7.09; N, 7.93; O, 21.22.

**3.1.8. 14,36-Didehydro pristinamycin $II_A$ (3a).** To a solution of 4.5 g (8.6 mmol) of **2a** in dichloromethane (90 mL) was added dropwise over 15 min under argon at −15°C a solution of 5.45 g (12.8 mmol) of DMP in dichloromethane (55 mL). After stirring at −15°C for 5 h, the reaction mixture was successively washed with a 10% aqueous sodium thiosulfate solution (50 mL), brine (50 mL) and then dried over magnesium sulfate, filtered and concentrated under vacuum. The resulting brown residue (4.9 g) was chromatographed on silica gel [$CH_2Cl_2$/-MeOH/$CH_3CN$ (93/3.5/3.5 v/v/v)] to afford 1.52 g (2.9 mmol) (34%) of **3a** as a yellow solid (mp=130°C (dec.)); M.W.= 523, DCI: *m/z*=541 $[M+NH_4]^+$, *m/z*=524 $[M+H]^+$; $^1H$ NMR (600 MHz, $CDCl_3$, $\delta$ in ppm): 0.99 (m, 6H), 1.02 (d, *J*=7 Hz, 3H), 2.04 (m, 1H), 2.18 (s, 3H), from 2.65 to 2.90 (m, 3H), 3.62 (d, *J*=14.5 Hz, 1H), 3.78 (d, *J*=14.5 Hz, 1H), 3.89 (d, *J*=16 Hz, 1H), 3.93 (d, *J*=16 Hz, 1H), 4.12 (m, 2H), 4.29 (m, 2H), 4.92 (d, *J*=10 Hz, 1H),

5.56 (s, 1H), 6.02 (d, $J$=16 Hz, 1H), 6.06 (d, $J$=16 Hz, 1H), 6.15 (t, $J$=3 Hz, 1H), 6.26 (dt, $J$=16, 5.5 Hz, 1H), 6.63 (dd, $J$=16, 7.5 Hz, 1H), 6.96 (m, 1H), 7.96 (s, 1H); IR ($CH_2Cl_2$) 3375, 2975, 1730, 1674, 1623, 1580, 1528, 1414 and 969 $cm^{-1}$.

**3.1.9. 14,36-Didehydro pristinamycin $II_B$ (3b) and 14,15-didehydro pristinamycin $II_B$ (3b′) via DMP oxidation of 8c.** To a solution of 5 g (11.8 mmol) of DMP in dichloromethane (35 mL) was added dropwise over 5 min under argon at −15°C a solution of 3.11 g (5.9 mmol) of **8c** in dichloromethane (35 mL). After stirring at −15°C for 0.5 h, the reaction mixture was diluted with ethylacetate (350 mL) and washed with a 10% aqueous sodium thiosulfate solution (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to afford 2.45 g of a brown residue. This material was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (92/4/4 v/v/v)] to afford 0.45 g (0.86 mmol) (15%) of a mixture of **3b** and **3b′** (1/1); $^1H$ NMR (400 MHz, $CDCl_3$, $\delta$ in ppm): from 0.90 to 1.20 (m, 9H), from 1.75 to 2.30 (m, 5H), 2.22 (s: 3H), from 2.65 to 2.85 (m: 1H), from 3.55 to 3.80 (m: 1H), 3.61 and 3.72 (2d, $J$=15 Hz: 1H in totality), 3.83–3.85 and 3.90 (respectively s–d, $J$=16 Hz and m: 2.5H in totality), 4.02 and 4.05 (respectively d, $J$=16 Hz and m: 1.5H in totality), 4.25 (m: 0.5H), 4.50 (m: 0.5H), 4.65 (dd, $J$=8.5, 3 Hz, 0.5H), 4.73 (broad d, $J$=10 Hz, 0.5H), 4.80 (broad d, $J$=10 Hz, 0.5H), 5.86 (dd, $J$=8.5, 3 Hz, 0.5H), from 5.65 to 5.75 (m, 0.5H), 5.67 (s, 0.5H), from 5.80 to 5.95 (m, 1.5H), from 5.95 to 6.05 (m, 1H), 6.09 (d, $J$=16 Hz, 0.5H), from 6.15 to 6.40 (m, 1.5H), 6.52 (dd, $J$=16, 5.5 Hz, 0.5H), 6.66 (dd, $J$=16, 6.5 Hz, 0.5H), 8.12 (s, 0.5H), 8.20 (s, 0.5H); M.W.=525, DCI: $m/z$=543 $[M+NH_4]^+$, $m/z$=526 $[M+H]^+$; IR ($CH_2Cl_2$) 3370, 2975, 1735, 1675, 1625, 1578, 1425, 1185 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, 63.74; H, 7.14; N, 7.86; O, 20.98.

**3.1.10. 37-*O*-*tert*-Butyldimethylsilyl-16,17-didehydro pristinamycin $II_B$ (9).** To a solution of 10 g (0.02 mol) of **2b** in dichloromethane (400 mL) was successively added under argon at room temperature 35 mL (0.2 mol) of diisopropylethylamine and 30 g (0.2 mol) of *tert*-butyldimethylsilyl chloride. After stirring at room temperature for 3 h, the reaction mixture was washed with water (3×500 mL). The organic layer was then dried over magnesium sulfate, filtered and concentrated under vacuum to afford 14 g of a brown oil. This material was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (94/3/3 v/v/v)] to afford 6.28 g (9.81 mmol) (49%) of **9** as a white solid (mp=130°C (dec.)); $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$ in ppm): 0.32 (s, 6H), 0.93 (d, $J$=7 Hz, 3H), from 0.95 to 1.05 (m, 12H), 1.09 (d, $J$=7 Hz, 3H), from 1.65 to 2.25 (m, 5H), 1.73 (s, 3H), 2.74 (m, 1H), 2.88 (d, $J$=6.5 Hz, 1H), 2.92 (dd, $J$=14, 4.5 Hz, 1H), 3.30 (dd, $J$=14, 7 Hz, 1H), 3.46 (ddd, $J$=15, 8.5, 4 Hz, 1H), 3.72 (m, 1H), 4.01 (m, 1H), 4.36 (ddd, $J$=15, 9, 5 Hz, 1H), from 4.70 to 4.85 (m, 1H), 4.74 (dd, $J$=10.5, 2 Hz, 1H), 4.82 (dd, $J$=9, 3 Hz, 1H), 5.65 (broad d, $J$=9.5 Hz, 1H), 5.68 (s, 1H), 5.73 (m, 1H), 5.79 (dd, $J$=16, 2 Hz, 1H), 6.03 (m, 1H), 6.14 (d, $J$=16 Hz, 1H), 6.51 (dd, $J$=16, 5 Hz, 1H), 8.05 (s, 1H); M.W.=641, DCI: $m/z$=659 $[M+NH4]^+$, $m/z$=642 $[M+H]^+$, $m/z$=528 $[642+H-TBDMS]^+$; IR ($CH_2Cl_2$) 3443, 2959, 1739, 1675, 1625, 1515, 1428, 1185 and 981 $cm^{-1}$.

**3.1.11. 37-*O*-*tert*-Butyldimethylsilyl-14,36-didehydro-16,17-didehydro pristinamycin $II_B$ (11).** To a solution of 0.425 g (1 mmol) of DMP in dichloromethane (7.5 mL) was added dropwise over a period of 5 min under argon at 0°C a solution of 0.32 g (0.5 mol) of **9** in dichloromethane (7.5 mL). After stirring at 0°C for 1.5 h, the reaction mixture was diluted with ethylacetate (50 mL) and washed with a saturated aqueous sodium bicarbonate solution (2×20 mL). The resulting organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to afford 0.28 g of an orange residue. This material was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (92/4/4 v/v/v)] to afford 0.12 g (0.188 mmol) (38%) of **11** as a yellow solid (mp=130°C (dec.)); M.W.=640, DCI: $m/z$=657 $[M+NH_4]^+$, $m/z$=640 $[M+H]^+$.

**3.1.12. 14,36-Didehydro pristinamycin $II_B$ (3b) and 14,15-didehydro pristinamycin $II_B$ (3b′) via desilylation of 11.** To a solution of 0.12 g (0.19 mmol) of **11** in tetrahydrofuran (4 mL) was successively added under argon at room temperature 0.02 mL (0.4 mmol) of acetic acid and 0.04 mL (0.044 mmol) of a 0.1 M tetrahydrofuran solution of tetrabutylammonium fluoride. After stirring at room temperature for 20 h, the reaction mixture was diluted with ethylacetate (20 mL) and washed with a saturated aqueous sodium bicarbonate solution (5 mL). The resulting organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to afford an orange solid residue. This material was chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (92/4/4 v/v/v)] to afford 0.05 g (0.095 mmol) (15%) of a mixture of **3b** and **3b′** (1/1); see Section 3.1.9 for characterization.

**3.1.13. 37-*O*-*tert*-Butyldimethylsilyl-16,17-didehydro pristinamycin $II_A$ (10).** To a solution of 2.63 g (5 mmol) of **2a** in dichloromethane (100 mL) was successively added under argon at room temperature 8 mL (45 mmol) of diisopropylethylamine and 6.8 g (45 mmol) of *tert*-butyldimethylsilyl chloride. After stirring at room temperature for 20 h, the reaction mixture was washed with water (3×100 mL). The resulting organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was then chromatographed on silica gel [$CH_2Cl_2$/MeOH/$CH_3CN$ (92/4/4 v/v/v)] to afford 2.15 g (3.36 mmol) (67%) of **10** as a white solid (mp=125°C (dec.)); $^1H$ NMR (250 MHz, $CDCl_3$, $\delta$ in ppm): 0.30 (s, 6H), from 0.90 to 1.05 (m, 15H), 1.12 (d, $J$=7 Hz, 3H), 1.67 (s, 3H), 2.03 (m, 1H), 2.13 (d, $J$=5 Hz, 1H), from 2.60 to 2.85 (m, 3H), 2.85 (dd, $J$=12.5, 3 Hz, 1H), 3.35 (dd, $J$=12.5, 9 Hz, 1H), 3.78 (dt, $J$=17.5, 6 Hz, 1H), from 4.00 to 4.40 (m, 3H), 4.72 (m, 1H), 4.82 (dd, $J$=10, 2 Hz, 1H), 5.20 (broad d, $J$=9.5 Hz, 1H), 5.49 (ddd, $J$=16, 7, 4 Hz, 1H), 5.58 (s, 1H), 5.80 (d, $J$=16 Hz, 1H), 5.93 (broad d, $J$=16 Hz, 1H), 6.00 (t, $J$=3 Hz, 1H), 6.71 (dd, $J$=16, 8 Hz, 1H), 6.87 (broad t, $J$=5.5 Hz, 1H), 7.85 (s, 1H); M.W.=639, DCI: $m/z$=657 $[M+NH_4]^+$, $m/z$=640 $[M+H]^+$, $m/z$=622 $[M+H-H_2O]^+$, $m/z$=526 $[640+H-TBDMS]^+$; IR ($CH_2Cl_2$) 3380, 1730, 1675, 1640, 1620, 1425, 1165, 1000 and 975 $cm^{-1}$.

**3.1.14. Diels–Alder adduct 13.** To a solution of 0.2 g (0.313 mmol) of **10** in dichloromethane (1.5 mL) and dioxan (3 mL) was added under argon at −5°C 0.156 g (0.688 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. After stirring between −5°C and room temperature for 4 h, the reaction mixture was filtered and concentrated under vacuum to afford 0.414 g of a brown residue. This material was chromatographed on silica gel [$CH_2Cl_2$/-MeOH/$CH_3CN$ (92/4/4 v/v/v)] to afford 0.02 g (0.023 mmol) (7%) of **13** as a yellow solid (mp=130°C (dec.)); $^1$H NMR (500 MHz, $CDCl_3$, $\delta$ in ppm): 0.25 (s, 3H), 0.27 (s, 3H), 0.90 (s,9H), from 0.95 to 1.05 (m, 6H), 1.16 (d, $J$=7 Hz, 3H), 1.95 (s, 3H), 1.98 (broad d, $J$=12.5 Hz, 1H), 2.04 (m, 1H), 2.51 (d, $J$=2.5 Hz, 1H), from 2.60 to 2.80 (m, 2H), 2.96 (m, 1H), 3.09 (dt, $J$=12.5, 6 Hz, 1H), 3.55 (broad d, $J$=12.5 Hz, 1H), 3.98 (d, $J$=11 Hz, 1H), 4.11 (m, 1H), 4.24 (m, 1H), 4.37 (m, 1H), 4.58 (t, $J$=13 Hz, 1H), 4.85 (broad d, $J$=10 Hz, 1H), 5.53 (s, 1H), 5.91 (d, $J$=16.5 Hz, 1H), 6.10 (broad s, 1H), 6.26 (broad s, 1H), 6.47 (dd, $J$=16.5, 10 Hz, 1H), 7.84 (s, 1H), 7.97 (broad t, $J$=6 Hz, 1H); M.W.=637, DCI: $m/z$=638 $[M+H]^+$; IR ($CH_2Cl_2$) 3386, 2959, 1731, 1709, 1652, 1627, 1529, 1222 and 843 $cm^{-1}$.

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## References

1. Mancy, D.; Ninet, L.; Preud'homme, J. (Rhône Poulenc S.A.) Fr. Patent Appl. 1,301,857, June 27, 1961; *Chem. Abstr*. **1963**, *58*, 3859.
2. Preud'homme, J.; Belloc, A.; Charpentié, Y.; Tarridec, P. *C. R. Acad. Sci. Paris* **1965**, *260*, 1309–1312.
3. Preud'homme, J.; Tarridec, P.; Belloc, A. *Bull. Soc. Chim. Fr.* **1968**, 585–591.
4. Paris, J. M.; Barrière, J. C.; Smith, C.; Bost, P. E. The Chemistry of Pristinamycins. In *Recent Progress in the Chemical synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1991; pp 183–248.
5. Barrière, J. C.; Bouanchaud, D. H.; Paris, J. M.; Rolin, O.; Harris, N. V.; Smith, C. *J. Antimicrob. Chemother.* **1992**, *30*(suppl.A), 1–8.
6. Barrière, J. C.; Paris, J. M. *Drugs Future* **1993**, *18*(9), 833–845.
7. Barrière, J. C.; Bouanchaud, D.; Desnottes, J. F.; Paris, J. M. *Exp. Opin. Invest. Drugs* **1994**, *3*(2), 115–131.
8. Le Goffic, F.; Capmau, M. L.; Abbé, J.; Charles, L.; Montastier, J. *Eur. J. Med. Chem. Chim. Ther.* **1981**, *16*(1), 69–72.
9. Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparation*; VCH: Weinheim, 1989; pp 604–615.
10. Haines, A. H. *Methods for the Oxydation of Organic Compounds*; Academic/Harcourt Brace Jovanovitch: London; Vol. 2, pp 142–144.
11. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156–4158. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (c) VanderRoest, J. M.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 5841–5842. (d) Stickley, S. H.; Martin, J. C. *Tetrahedron Lett.* **1995**, *36*, 9117–9120.
12. Dess–Martin Periodinane can be now purchased from Lancaster.
13. The 'crossover' experiments, reaction of **9** with DDQ and **10** with DMP, have not been done.
14. Diels–Alder reactions of DDQ across the dienic moiety of other PIIs have been already observed: Ronan, B.; Bacque, E.; Barrière, J. C. Unpublished results.
15. For precedents of DDQ behaving as a dienophile in DA reactions, see: (a) Kuroda, S.; Oda, M.; Zuo, S.; Kanayama, K.; Shah, Shaheen I. M.; Furuta, S.; Miyatake, R.; Kyogoku, M. *Tetrahedron Lett.* **2001**, *42*(36), 6345–6348. (b) Wallace Debra, J.; Gibb Andrew, D.; Cottrell Ian, F.; Kennedy Derek, J.; Brands Karel, M. J.; Dolling Ulf, H. *Synthesis* **2001**, 1784–1789. (c) Kasuhiro, C.; Takaaki, A.; Masahiro, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2939–2942. (d) Takehiro, S.; Hoshie, H.; Hoshisuke, T. *Chem. Pharm. Bull.* **1990**, *38*(12), 3283–3295. (e) Nishida, S.; Murakami, M.; Oda, H.; Tsuji, T.; Mizuno, T.; Matsubara, M.; Kikai, N. *J. Org. Chem.* **1989**, *54*(16), 3859–3868. (f) Murakami, M.; Tsuji, T.; Oda, H.; Nishida, S. *Chem. Lett.* **1987**, 863–866. (g) Rieger, R.; Breitmaier, E. *Synthesis* **1990**, 697–701.