ORGANIC LETTERS

1999
Vol. 1, No. 7
1129−1132

Synthesis and Structure of Tolyporphin A *O,O*-Diacetate

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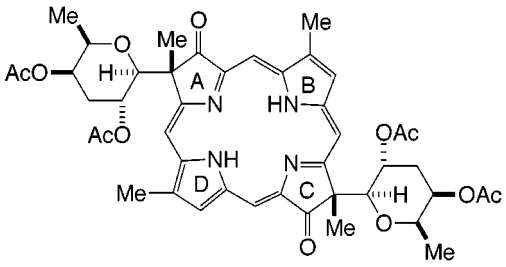
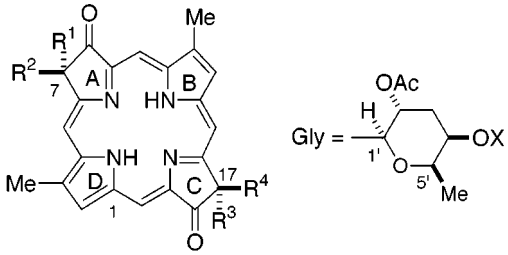
Received August 18, 1999

ABSTRACT



The revised structure of tolyporphin A *O,O*-diacetate (2b) was synthesized by assembling fragments 4, 5, and 12. The synthetic substance was found to be identical to the *O,O*-diacetate derived from natural tolyporphin A in every respect, thus establishing the relative and absolute configurations of this natural product.

In 1992, Moore and co-workers reported the isolation of tolyporphin A from the lipophilic extract of the cyanophyte microalga *Tolypothrix nodosa*. This structurally unique porphyrin was found to reverse multidrug resistance (MDR)[1] in a vinblastine-resistant population of human ovarian adenocarcinoma cells.[2a] Subsequently, 10 additional tolyporphins (B−K) were isolated and were found to possess varying degrees of anti-MDR activity.[2b−d] On the basis of extensive spectroscopic studies, the structure of tolyporphin A, the representative member of the tolyporphin class of natural products, was concluded to be **1a**.[2a] We previously described a total synthesis of the proposed structure of (+)-tolyporphin A *O,O*-diacetate (**1b**) but found that the synthetic material was not identical to the *O,O*-diacetate derived from natural (+)-tolyporphin A.[3]



1a : $R^1 = R^3 = Me$; $R^2 = R^4 = Gly$; X = H
1b : $R^1 = R^3 = Me$; $R^2 = R^4 = Gly$; X = Ac

2a : $R^2 = R^4 = Me$; $R^1 = R^3 = Gly$; X = H
2b : $R^2 = R^4 = Me$; $R^1 = R^3 = Gly$; X = Ac

Subsequently, we carried out extensive spectroscopic studies on both the synthetic material and the *O,O*-diacetate derived from natural tolyporphin A and proposed the revised structure **2a** for tolyporphin A.[4] In this Letter, we report a total synthesis of the *O,O*-diacetate **2b** of the revised structure of tolyporphin A, unambiguously establishing the relative and absolute configurations of this natural product.[5]

(1) For recent reviews on MDR, see: (a) Pastan, I.; Gottesman, M. M. *Annu. Rev. Biochem.* **1993**, *62*, 385. (b) Simon, S. M.; Schindler, M. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3497.

(2) (a) Prinsep, M. R.; Caplan, F. R.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 385. (b) Prinsep, M. R.; Patterson, G. M. L.; Larsen, L. K.; Smith, C. D. *Tetrahedron* **1995**, *51*, 10523. (c) Prinsep, M. R.; Patterson, G. M. L.; Larsen, L. K.; Smith, C. D. *J. Nat. Prod.* **1998**, *61*, 1133. (d) Morliere, P.; Maziere, J.-C.; Santus, R.; Smith, C. D.; Prinsep, M. R.; Stobbe, C. C.; Fenning, M. C.; Golberg, J. L.; Chapman, J. D. *Cancer Res.* **1998**, *58*, 3571.

(3) Minehan, T. G.; Kishi, Y. *Angew. Chem. Int. Ed.* **1999**, *38*, 923.

(4) Minehan, T. G.; Cook-Blumberg, L.; Kishi, Y.; Prinsep, M. R.; Moore, R. E. *Angew. Chem. Int. Ed.* **1999**, *38*, 926.

10.1021/ol9902374 CCC: $18.00
Published on Web 09/09/1999

Structurally, tolyporphin A consists of an unsymmetrical dioxobacteriochlorin core with quaternary centers at C.7 and C.17 containing β-linked *C*-glycosides. We were interested in assembling the tolyporphin skeleton from monocyclic precursors (Figure 1). A tactical advantage of this approach

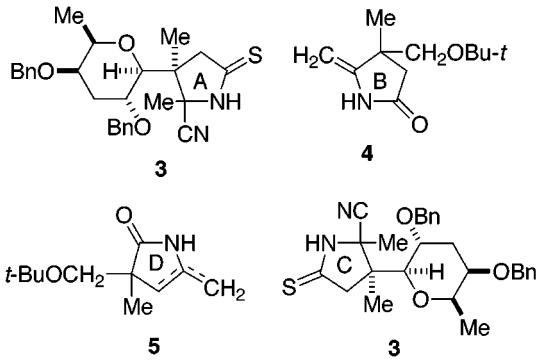
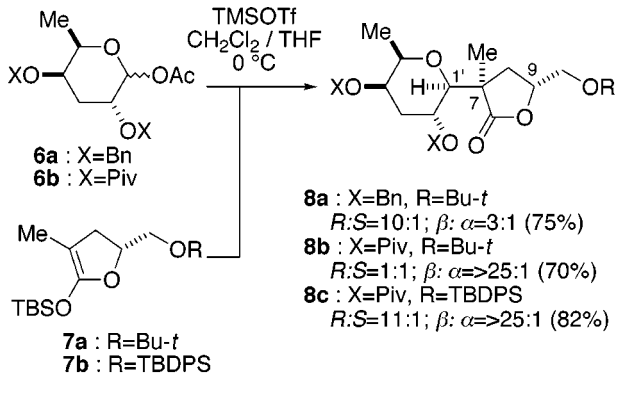


Figure 1.

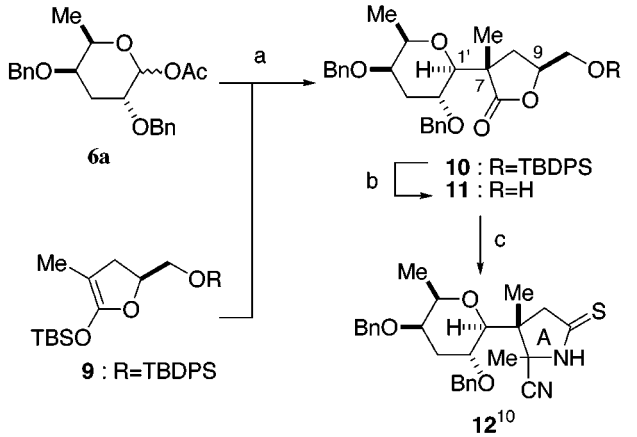
is that the ring-C precursor is identical to the ring-A precursor. The feasibility of this approach was first demonstrated by the synthesis of a model of the tolyporphin A chromophore[6] and was then extended to the synthesis of the proposed structure of (+)-tolyporphin A *O,O*-diacetate (**1b**).[3] To investigate the proposed revised structure of tolyporphin A, we planned to synthesize the *O,O*-diacetate **2b** in an analogous fashion to the synthesis of **1b**. This strategy would therefore require ring-A (and the ring-C) precursor **12**, the C.7 stereoisomer of the previously used ring-A fragment **3**. Previously, **3** was prepared via the *C*-glycosidation of 3,6-dideoxy-D-galactopyranose (Scheme 1),[3,7] a process in which

Scheme 1



two new stereogenic centers were selectively introduced. Related to this process, several previous observations should be noted: (1) β-*C*-glycosides can be obtained by Lewis-acid-promoted addition of sterically hindered silyl ketene acetals to carbohydrate 1-*O*-acetates and (2) an additional C.9 stereogenic center in the nucleophile can influence the facial selectivity of the *C*-glycosidation, thereby installing the desired quaternary stereogenic center in a highly controlled manner. Although optimal stereoselectivity and chemical yield were obtained for the case of **6b** + **7b** → **8c**, synthetic efficiency was most effectively secured via *C*-glycoside **8a** since utilization of this precursor mininized the number of synthetic operations required to access **3**. On the basis of these considerations, we planned the synthesis of the revised ring-A (and ring-C) precursor **12** via the *C*-glycosidation of **6a** with **9**, the antipode of **7b** (Scheme 2).

Scheme 2



a. TMSOTf, CH_2Cl_2-THF (10:1), 0 °C. b. TBAF-HOAc, THF (60% overall [8]). c. i. MeLi, THF, -78→-20 °C. ii. $Pb(OAc)_4$, CH_2Cl_2. iii. $NaClO_2$, $(Me)_2C{=}CH_2$, CH_2Cl_2. iv. EtO_2CCl, Et_3N, THF, then NH_3. v.180 °C, xylenes. vi. KCN, MeOH. vii. Lawesson's reagent, toluene, 80 °C (47% from **11**).

C-Glycosidation of the acetate **6a**[7,8] with (*S*)-silyl ketene acetal **9**[9] in the presence of TMSOTf and 4 Å molecular sieves (powder) in a 10:1 mixture of CH_2Cl_2 and THF at 0 °C yielded the desired *C*-glycoside **10** as the major product. This transformation was observed to proceed with 3:1 stereoselectivity at C.1′ and 10:1 stereoselectivity at C.7. These stereoselectivities were virtually identical to those observed for the case of **6a** + **7a** → **8a**. Desilylation, followed by removal of the undesired minor stereoisomers by chromatography, afforded pure crystalline *C*-glycoside **11** in 60% overall yield from **6a**.[8] The *C*-glycoside **11** was then converted to the ring-A precursor **12** in seven steps[3] in 47% overall yield.

The stereochemical assignment of **11**, and consequently of **12**, was initially made through NMR analysis: (1) the

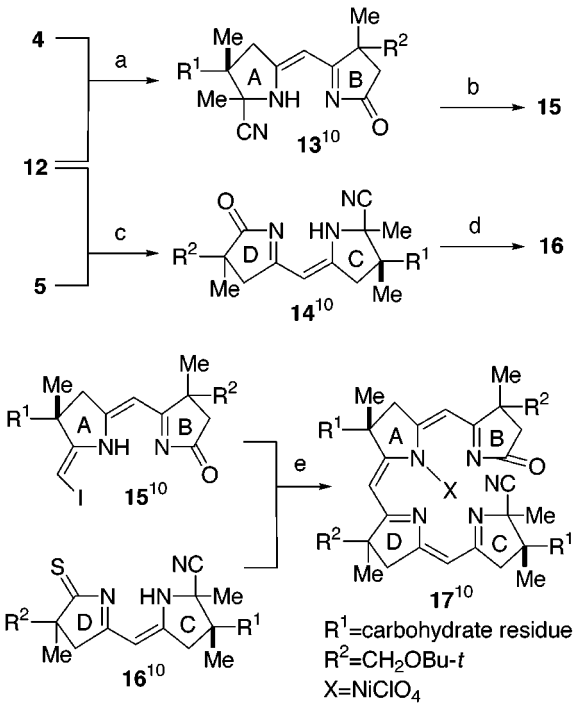
(5) The numbering used in ref 2a is adopted in this paper.
(6) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*. 6811.
(7) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*. 6815.

(8) The crude acetate **6a**, prepared from the corresponding methyl α-glycoside by treatment with Ac_2O−HOAc (3:1) and catalytic H_2SO_4 at 0 °C was used for this *C*-glycosidation. The 60% yield of **11** was based on the methyl α-glycoside used.
(9) (*S*)-Silyl ketene acetal was prepared from L-(*S*)-glutamic acid in five steps by using the known procedure for the (*R*)-series, see: Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449 and ref 3.

vicinal spin coupling constant $J_{1',2'}$ was determined to be 9.2 Hz for **11** and 1.3 Hz for the C.1′ stereoisomer of **11**, thereby establishing the C.1′ stereochemistry, and (2) the ^{1}H NMR spectra showed the thiolactam **12** obtained from **11** to be the stereoisomer of thiolactam **3**, thereby concluding the C.7 stereochemistry. Nevertheless, as the stereochemical assignment of tolyporphin A ultimately depended on the stereochemistry installed in the *C*-glycosidation, the structure of **11** was conclusively determined via X-ray analysis.

Following the protocols previously established, the ring-A (and -C), -B, and -D precursors **12**, **4**,[6] and **5**[6] were assembled to yield the precorphin−metal complex **17** (Scheme 3) and

Scheme 3

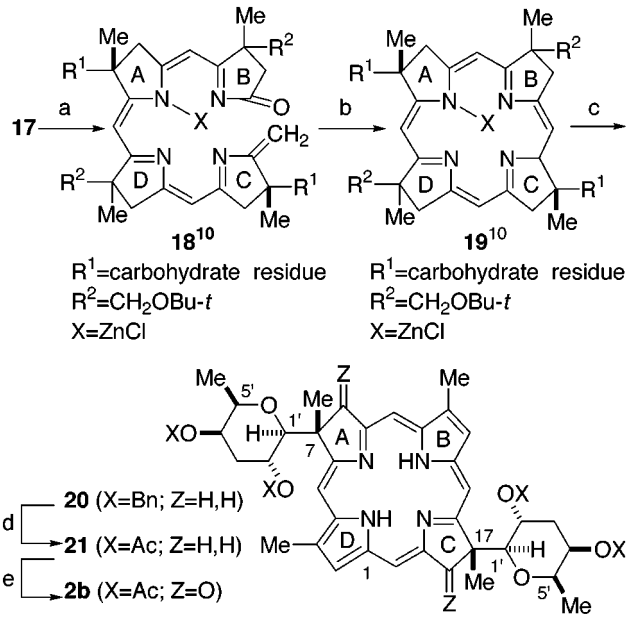


a. i. **4**, NIS, *t*-BuOK, *t*-BuOH, benzene. ii. $(EtO)_3P$, xylenes, reflux. b. i. *t*-BuOK, *t*-BuOH, reflux. ii. I_2, K_2CO_3, CH_2Cl_2, 0 °C (52% from **12**). c. i. **5**, NIS, *t*-BuOK, *t*-BuOH, benzene. ii. $(EtO)_3P$, xylenes, reflux. d. Lawesson's reagent, toluene, reflux (68% from **12**). e. i. DBU, CH_3CN. ii. $Ni(ClO_4)_2$, Ph_3P, CH_3CN, 80 °C (65% from **15** and **16**).

then the bacteriochlorin tetrabenzyl ether **20** (Scheme 4). It should be noted that the synthesis summarized in Schemes 3 and 4[10] was carried out with a mixture of diastereomers due to the stereogenic centers at C.3, C.6, C.12, and/or C.16 up to the bacteriochlorin **20**, which was the first stereochemically homogeneous compound after **11**. The bright-green bacteriochlorin **20** was isolated by preparative TLC [silica gel; hexane−ethyl acetate (2:1, buffered with 1% triethylamine)] in a comparable overall yield from **11** as in the previous synthesis of the initially proposed structure of tolyporphin A.[3]

(10) The product at this stage was a mixture of diastereomers due to the chiral centers at C.3, C.6, C.12, and/or C.16.

Scheme 4



a. i. KCN, MeOH. ii. *t*-BuOK, *t*-BuOH. iii. $Zn(ClO_4)_2 \cdot 6H_2O$, MeOH. b. MeOTf (6.5 eq.), pempidine (4.6 eq.), 24 h, then MeOH (1.7 eq.), 24 h (48% from **17**). c. i. TFA, dimedone, Bu_3P, anisole. ii. MeOH. iii. *t*-BuOK, *t*-BuOH. iv. 20% HCl (42%). d. i. $ZnCl_2$, EtSH, CH_2Cl_2. ii. Ac_2O, Py (90% from **20**). e. $CrO_3 \cdot$DMP (0.1M), CH_2Cl_2, 0 °C (30%[11]).

The synthesis of tolyporphin A *O*,*O*-diacetate was completed via debenzylation of **20**, followed by acetylation and double allylic oxidation, to furnish **2b** as a dark-purple solid. This double allylic oxidation was first employed in the synthesis of the chromophore model of toylporphin A,[6] but its application to the synthesis of **1b** met with substantial difficulty. This problem was eventually overcome via a two-

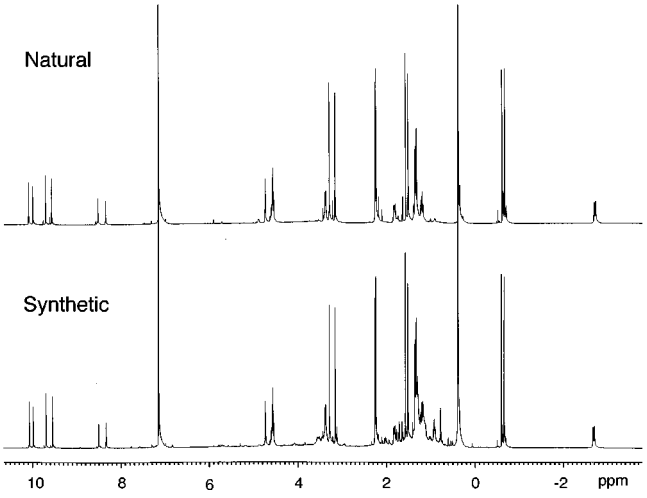


Figure 2. ^{1}H-NMR spectra (500 MHz, C_6D_6) of natural and synthetic tolyporphin A *O*,*O*-diacetates.

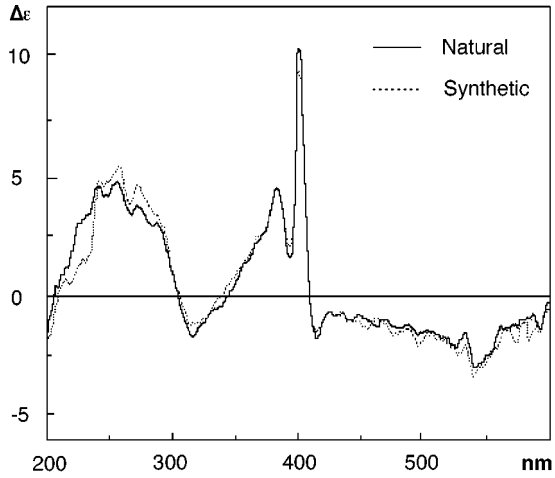


Figure 3. CD spectra (CH_2Cl_2) of natural and synthetic tolyporphin A *O*,*O*-diacetates.

step allylic oxidation.[3] Interestingly, it was found that substrate **21** behaved toward the oxidant in a fashion analogous to that of the chromophore model, to give synthetic tolyporphin *O*,*O*-diacetate (**2b)** as a dark-purple solid in a single step.[11]

Extensive chromatographic and spectroscopic studies [TLC, HR-MS, UV, ^{1}H NMR (Figure 2)] showed the synthetic *O*,*O*-diacetate **2b** to be identical to the *O*,*O*-diacetate derived from natural tolyporphin A,[12] unambiguously establishing the stereochemistry of tolyporphin A as the revised structure **2a**. In addition, the CD spectra (Figure 3) demonstrated that the synthetic *O*,*O*-diacetate **2b** possessed the same absolute configuration as the *O*,*O*-diacetate derived from natural tolyporphin A. Since the acetate **6a** was prepared from 3,6-dideoxy-D-galactopyranose,[6] the absolute configuration of tolyporphin A is represented by the structure **2a**. Strictly speaking, the structural conclusions from the current work should be limited to tolyporphin A, but we speculate these conclusions can be applied to other members of this class of natural products as well.

Acknowledgment. We thank Mr. G. Topalov for the X-ray analysis of **11** and Dr. J. Guo in the Nakanishi group at Columbia University for the measurements of CD spectra of **2b**. Financial support from the National Institutes of Health (CA 22215) is gratefully acknowledged.

Supporting Information Available: Experimental procedures summarized in Scheme 2, 3, and 4, spectroscopic data, and an ORTEP drawing of **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) TLC analysis showed that the oxidation was very clean but the isolated yield was only around 30%.

(12) We gratefully thank Dr. Michèle Prinsep for kindly providing a sample of natural tolyporphin A. Acetylation of tolyporphin A is known to form tolyporphin A *O*,*O*-diacetate (**2b**).