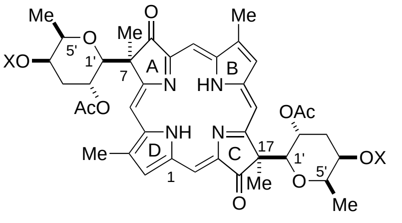
Total Synthesis of the Proposed Structure of (+)-Tolyporphin A *O,O*-Diacetate[**]

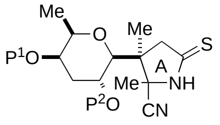
Thomas G. Minehan and Yoshito Kishi*

In 1992 Moore and co-workers reported that the lipophilic extract of the cyanophyte microalga *Tolypothrix nodosa* reverses multidrug resistance (MDR)[1] in a vinblastine-resistant subline of a human ovarian adenocarcinoma line[2a] and that most of this activity was accounted for by an unusual porphyrin, tolyporphin A. Based on extensive spectroscopic studies, the structure of tolyporphin A was suggested to be **1a**.[2a] Subsequently, eight additional tolyporphins B–I were also isolated and found to possess varying degrees of anti-MDR activity.[2b] Structurally, tolyporphin A, the representative member of this class of natural products, consists of an unsymmetrical dioxobacteriochlorin core with quaternary centers at C7 and C17 containing β-linked C-glycosides.



1a (X=H) : "tolyporphin A"
1b (X=Ac) : "tolyporphin-A-*O,O*-diacetate"

Intrigued by their unique structures and biological activity, we undertook synthetic studies on the tolyporphins. Specifically, we were interested in assembling the tolyporphin skeleton from the monocyclic precursors **2**–**4**. An obvious advantage of this approach is that the ring-C precursor is identical to the ring-A precursor (i.e., **2**). The synthesis of the chromophore model[3] demonstrated the feasibility of this approach: The sulfide contraction/iminoester-cyclization method of Eschenmoser and co-workers[4] was adopted to assemble an octahydroporphyrin precursor, which was then subjected to a double-retroaldol/oxidation sequence to form the chromophore of the tolyporphins. Here we report an extension of this route to the successful total synthesis of the proposed structure of (+)-tolyporphin A *O,O*-diacetate (**1b**), and demonstrate that a structural revision is required for this class of natural products.



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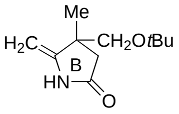

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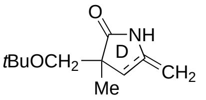

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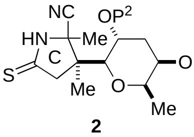

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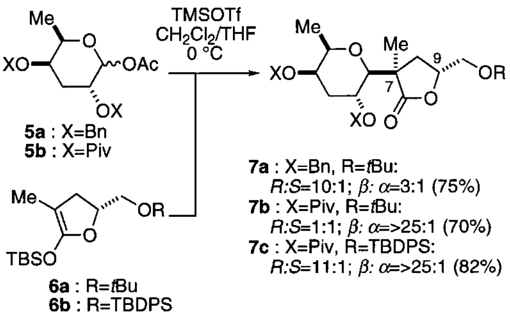
Recognizing that the tolyporphins contain C-glycoside substructures, we planned to synthesize the ring-A precursor **2** from an appropriate carbohydrate such as 3,6-dideoxy-D-xylose. In this connection, one needs to pay attention to two structural characteristics of **2**: the β-C-glycosidic bond and the quaternary carbon atom adjacent to the anomeric center. We have recently demonstrated that sterically hindered β-C-glycosides can be synthesized by Lewis acid promoted addition of silyl ketene acetals to carbohydrate 1-*O*-acetates.[5] The remaining question is then how to control the stereochemistry at the quaternary carbon atom in the C-glycosidation. It was conceivable that placement of an additional chiral center in the nucleophile would influence the facial selectivity of the reaction. We were specifically interested in silyl ketene acetals containing a protected hydroxymethyl group at C9 for two reasons: 1) Optimization of the stereoselectivity in the C-glycosidation could be achieved by tuning the steric bulk of the protecting group, and 2) the hydroxymethyl group could be removed after the glycosidation by an oxidative diol cleavage. Under the assumption that the carbohydrate adds preferentially to the lactone from the face opposite to the chiral directing group, it was anticipated that an (*R*)-silyl ketene acetal such as **6**[6] (see Scheme 1) would give rise to a product C-glycoside with the correct configuration at C7.[7]

Reaction of bis(benzyl ether) **5a** with *tert*-butyl-substituted **6a** in the presence of TMSOTf in CH_2Cl_2/THF (10/1) at 0 °C gave a product mixture with an *R*:*S* selectivity of 10:1 at the quaternary center, but with a β:α selectivity of only 3:1 at the anomeric position (Scheme 1).[8] It has been previously shown that β selectivity can be dramatically enhanced by placement of an acyl protecting group such as acetate at C2 of the carbohydrate; however, yields by this method often suffer because of by-product formation arising from glycosidation at the carbonyl carbon atom of the acyl group.[5] We hoped that with a quaternary center at the α carbon atom of the ester protecting group, the undesired side reaction might be suppressed for steric reasons.[9] This possibility was tested



Scheme 1. Reaction of **5** and **6** to provide **7**. Bn = benzyl, Piv = pivaloyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butylsilyl, TMSOTf = trimethylsilyl trifluoromethanesulfonyl.

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[*] Prof. Dr. Y. Kishi, T. G. Minehan
Department of Chemistry and Chemical Biology
Harvard University
Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-5150
E-mail: kishi@chemistry.harvard.edu

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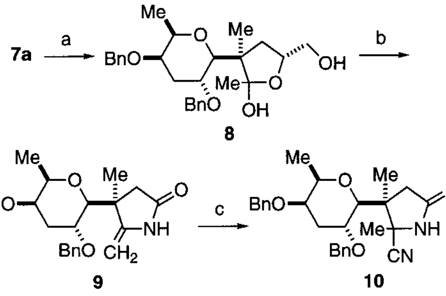
with the 2,4-bis-*O*-pivalate **5b**; glycosidation of **5b** with **6a** gave β-substituted C-glycosides in high yield, but with no diastereoselectivity at the quaternary center. Gratifyingly, however, glycosidation of **5b** with TBDPS-protected **6b** produced C-glycoside **7c** in 82 % yield, with virtually exclusive β selectivity and an *R*:*S* selectivity of 11:1 at C7.

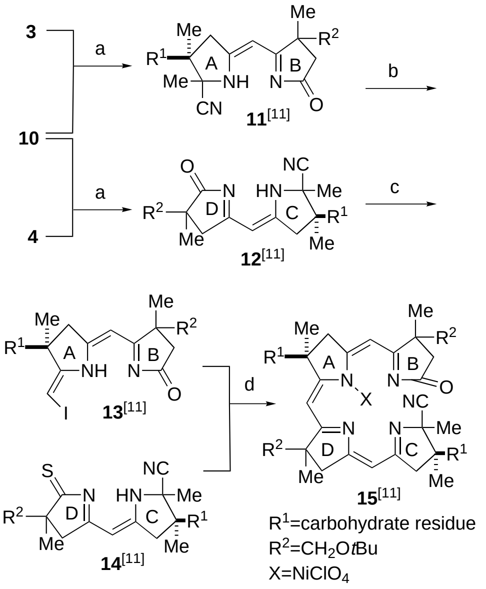
Considering the compatibility of protecting groups with the reagents and reaction conditions encountered in the remaining synthetic steps, we identified the optimum protecting groups of the carbohydrate moiety to be benzyl ethers (i.e., $P^1 = P^2 = Bn$ in **2**). However, attempts to switch the pivalate ester groups of **7c** to the corresponding benzyl ether moieties met with limited success.[10] Thus, in spite of the poorer β selectivity in the C-glycosidation, material through-put was most effectively secured with C-glycoside **7a** (Scheme 2). The hydroxymethyl group used for control of the stereochemistry at C7 was easily removed by treatment of ketol alcohol **8** with $Pb(OAc)_4$. Subsequent oxidation, amide formation, and dehydration delivered eneamide **9**. The acylenamine group in **9** was protected as its HCN adduct and thionated with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) to furnish thiolactam **10**.



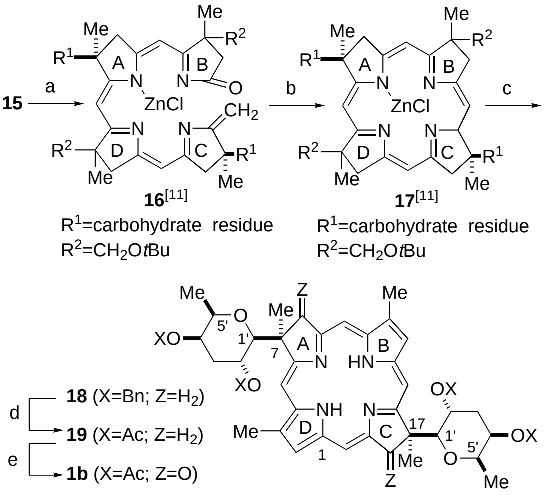
Scheme 2. Synthesis of thiolactam **10**. a) 1. Trifluoroacetic acid (TFA), CH_2Cl_2, room temperature (RT); 2. MeLi, THF, −78 °C (92 %); b) 1. $Pb(OAc)_4$, CH_2Cl_2, $NaHCO_3$, RT; 2. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, H_2O, RT; 3. EtO_2CCl, Et_3N, THF, RT; NH_3, RT; 4. xylenes, reflux (70 % from **8**); c) 1. KCN, MeOH, 60 °C (70 %); 2. Lawesson's reagent, toluene, 80 °C (98 %).

The precorphin–metal complex **15**[11, 12] was efficiently assembled from **3**,[3] **4**,[3] and **10** by sequential Eschenmoser reactions as in the model series (Scheme 3).

Transformation of **15** to exo-eneamide–zinc complex **16** was accomplished smoothly by demetalation followed by cyanide elimination and remetalation in one pot (Scheme 4). This air-, moisture-, and light-sensitive intermediate was subjected immediately to the iminoester cyclization conditions optimized for the chromophore model;[3] treatment of **16** with excess (10 equiv) Et_3OBF_4 or Et_3OPF_6 in the presence of Hünig base (ethyldiisopropylamine; 5 equiv) in CH_2Cl_2 at room temperature for two days, with addition of methanol (1.7 equiv) after the first day, indeed gave the desired cyclized corphin **17**[13] in approximately 20 % yield. The extreme sensitivity of the reaction mixture to both air and moisture made it difficult to obtain the product reproducibly; the yield varied from 20 % down to 0 %. However, replacement of the Meerwein salt with MeOTf led to significant improvements in yields (50–60 %) and reproducibility.[14] This experiment demonstrates that MeOTf[15] not only effectively methylates the lactam oxygen atom, but is also compatible with the other functional groups present.



Scheme 3. Synthesis of **15**. a) 1. *N*-Iodosuccinimide (NIS), *t*BuOK, *t*BuOH, C_6H_6, RT; 2. $(EtO)_3P$, xylenes, 125 °C (65 % over two steps); b) 1. *t*BuOK, *t*BuOH, 85 °C; 2. I_2, K_2CO_3, CH_2Cl_2, 0 °C (80 % over two steps); c) Lawesson's reagent, toluene, 80 °C (89 %); d) 1. diazabicyclo[5.4.0]undec-7-ene (DBU, 4 equiv), CH_3CN, RT; 2. $Ni(ClO_4)_2$, PPh_3, CH_3CN, RT (50 % over two steps).



Scheme 4. Synthesis of **1b**. a) 1. KCN, MeOH, RT; 2. *t*BuOK, *t*BuOH, RT; $Zn(ClO_4)_2$, MeOH, RT; b) MeOTf (6.8 equiv), pentamethylpiperidine (4.6 equiv), CH_2Cl_2, RT, 20 h; MeOH (1.75 equiv), RT, 20 h (50 % from **15**); c) TFA, anisole, dimedone, RT; MeOH, RT; *t*BuOK, *t*BuOH; 20 % HCl, RT (55 %); d) 1. $ZnCl_2$, EtSH, CH_2Cl_2, RT; 2. Ac_2O, pyridine, RT (98 %). e) $CrO_3 \cdot$ dimethyl pyrazole/CH_2Cl_2/0 °C (30–40 %).

Conversion of corphin **17** into tetrahydroporphyrin **18** took place in a moderate overall yield of 30 %. This one-pot, three-step transformation involved *tert*-butyl ether deprotection, double-retroaldol reaction/autoxidation, and demetalation. Spectroscopic analysis of the crude reaction mixture suggested that formaldehyde generated in the retroaldol process had been trapped by the chlorin, leading to some of the observed by-products. Thus, it was speculated that a formaldehyde scavenger might improve both the yields and reproducibility of the reaction; indeed, addition of excess dimedone improved the yield to 55% with excellent reproducibility.[16] The benzyl ethers in **18** were removed under Fujita conditions[17] to yield a tetraol, which was directly acetylated to give tetraacetate **19**. The structure of **19** was established by spectroscopic data (high-resolution mass spectrometry (HR-MS), UV, ^{1}H NMR); in particular, ^{1}H – ^{1}H COSY and ^{1}H – ^{1}H NOESY experiments unambiguously established the proton assignments and connectivities.[18]

The final double allylic oxidation[3] to form dioxobacteriochlorin **1b** was carried out in a stepwise manner.[19] Titration of a solution of **19** in CH_2Cl_2 with a 0.05 M solution of $CrO_3 \cdot$ dimethylpyrazole[20] in CH_2Cl_2 showed clean formation of an approximately 1:1 mixture of A- and C-ring monoketones (thin-layer chromatography and ^{1}H NMR spectroscopy); however, continued titration resulted in complete decomposition of the substrates. Curiously, when the monoketones were isolated, purified, and resubjected to the same oxidation conditions, the desired **1b** was isolated in 30 – 40% overall yield from **19**. The structure of **1b** was fully supported by spectroscopic data (HR-MS, UV, ^{1}H NMR). However, upon comparison of ^{1}H NMR spectra, it became evident that the synthetic material was different from the authentic sample prepared from natural (+)-tolyporphin A.[21, 22] In the following communication,[18] we present evidence that (+)-tolyporphin A is most likely described by the structure in which the configurations at both quaternary centers C7 and C17 are opposite to those in the originally proposed structure **1a**.

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[6] The (*R*)-silyl ketene acetals **6a**, **b** were prepared from (*R*)-5-oxotetrahydrofuran carboxylic acid (U. Ravid, R. M. Silverstein, L. R. Smith, *Tetrahedron* **1978**, *34*, 1449) in four steps: 1. $BH_3 \cdot Me_2S$, THF, RT; 2. TBDPS-Cl. imidizole, CH_2Cl_2 or *t*BuOH, H_2SO_4, $MgSO_4$, CH_2Cl_2; 3. lithium diisopropylamide (LDA), THF, −78 °C; MeI, hexamethyl phosphoramide (HMPA); 4. LDA, THF, −78 °C; TBS-Cl, HMPA.

[7] For the stereochemical assignment of the quaternary centers, see reference [18].

[8] Satisfactory spectroscopic data were obtained for all new compounds reported: T. G. Minehan, Ph.D. Thesis, Harvard University, **1998**.

[9] Glycosidation of substrates having less reactive acyl carbonyl groups such as the bis-*O*-benzoate and the bis-*O*-*para*-methoxybenzoate corresponding to **5** was also tested, but the major product in each case was still found to arise from C–C bond formation at the carbonyl carbon atom of the acyl group at C2.

[10] Base hydrolysis followed by acid work-up yielded three lactones. Treatment with methyllithium or diisobutyl aluminum hydride (DIBAL-H) yielded a ketal or acetal involving the alcohol groups of C9 and C2; attempted hydrolysis of the resultant acetal or ketal failed under a wide range of acidic conditions. Efforts to incorporate "removable" α-quaternary ester protecting groups, for example the α,α-dimethyllevulinoyl group, also met with limited success.

[11] The product at this stage was a mixture of diastereomers due to the chiral centers at C3, C6, C12, and/or C16.

[12] Because of its extreme sensitivity to light, purification and manipulation of the cadmium precorphin complex corresponding to **15** presented technical difficulties, resulting in poor overall yields; thus, the nickel-containing substrate was used for further elaboration.

[13] Eschenmoser and co-workers have suggested[4] that this cyclization involves three distinct steps: 1) a slow reaction of the lactam carbonyl with the alkylating reagent, 2) a proton-catalyzed isomerization of the double bonds in the precorphin structure, and 3) an electrocyclic ring closure. The addition of methanol serves to release a controlled amount of "catalytic protons" into the reaction medium.

[14] The MeOTf method was also more effective for the precorphin cyclization in the synthesis of the chromophore model: 55% (MeOTf) versus 40% (Et_3OBF_4).[3]

[15] For general reactivity of MeOTf, see *Encyclopedia of Reagents for Organic Synthesis* (Ed.: L. A. Paquette), Wiley, New York, **1995**, pp. 3617 ff, and references therein.

[16] The addition of dimedone was also shown to be more effective for the double retroaldol reaction in the syntheis of the chromophore model: 60% (with dimedone) versus 30 – 40% (without dimedone).[3]

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[19] For previous dioxobacteriochlorin/dioxoisobacteriochlorin syntheses, see a) R. K. Pandey, M. Isaac, I. MacDonald, C. J. Medforth, M. O. Senge, T. J. Dougherty, K. M. Smith, *J. Org. Chem.* **1997**, *62*, 1463; b) C. J. Aucken, F. J. Leeper, A. R. Battersby, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2099; J. Micklefield, M. Beckmann, R. L. Mackman, M. H. Block, F. J. Leeper, A. R. Battersby, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2123; c) F.-P. Montforts, F. Romanowski, J. W. Bats, *Angew. Chem.* **1989**, *101*, 471; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 480.

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[21] We gratefully thank Dr. Michèle Prinsep, University of Waikato, New Zealand, for kindly providing a sample of natural tolyporphin A. Acetylation of tolyporphin A is known to form tolyporphin A *O,O*-diacetate.[2a]

[22] To confirm this result, **1b** was further converted (K_2CO_3, MeOH, RT, 70%) into the corresponding tetraol and compared with (+)-tolyporphin D prepared from natural tolyporphin A. Upon comparison of ^{1}H NMR spectra, the synthetic material was once again found not to match the authentic sample.