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Extension of the Eschenmoser Sulfide Contraction/Iminoester Cyclization Method to the Synthesis of Tolyporphin Chromophore

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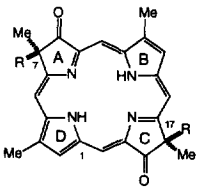
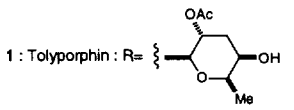
***Abstract** : Tolyporphin chromophore **2** has been synthesized by performing a double-retroaldol/oxidation sequence on an octahydroporphyrin precursor **18** prepared by using the Eschenmoser sulfide-contraction/iminoester-condensation method.* © 1997 Elsevier Science Ltd.

Tolyporphin (**1**) was isolated in 1992 by Moore and co-workers from the lipophilic extract of the blue-green microalga *Tolypothrix nodosa*.[1] Spectroscopic analysis indicates that tolyporphin is a modified unsymmetrical porphyrin containing ketones at C.8 and C.18 and two identical β-linked *C*-glycosyl units at C.7 and C.17.[2] This compound, which potentiates the cytotoxicity of adriamycin or vinblastine in SK-VLB cells at doses as low as 1 μg/ml, is characterized as a multidrug resistance (MDR) reversing agent.[3,4] In this communication, we report a synthesis of a chromophore model of tolyporphin, 3,7,7,12,17,17-hexamethyl-8,18 dioxobacteriochlorin (**2**).





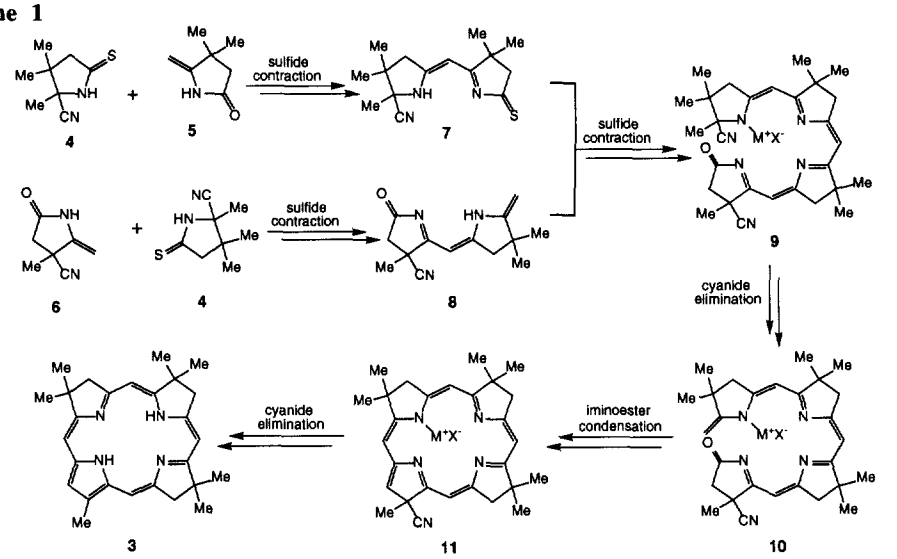
2 : Chromophore Model : R=Me

The sulfide contraction method developed by Eschenmoser[5,6] during the vitamin B_{12} synthesis has emerged as an important carbon-carbon bond-forming process for the synthesis of numerous complex corrin, chlorin, and porphyrin systems. Eschenmoser's synthesis of pyrrocorphin **3**,[7] which incorporates three sulfide contractions and one iminoester condensation reaction, illustrates his general strategy (Scheme 1).

With several modifications, this method appears to be applicable to the synthesis of tolyporphin.[8] Eschenmoser sulfide contraction and iminoester cyclization would allow us to assemble the octahydroporphyrin **18** from the four monocyclic precursors (cf. Scheme 2). In order to extend the Eschenmoser methodology directly to the present case, we chose to place a protecting group "X" at C.3 and C.12, which, upon elimination, would yield the tetrahydroporphyrin **19**. Oxidation of **19** would then give the chromophore **2** of tolyporphin. Two important issues in this approach are the appropriate selection of the "X" group in **18** to serve in the critical

double elimination reaction to give **19**, and the choice of oxidation conditions to selectively effect transformation of **19** to **2**. We decided to test the feasibility of this approach as outlined in Scheme 2.

Scheme 1

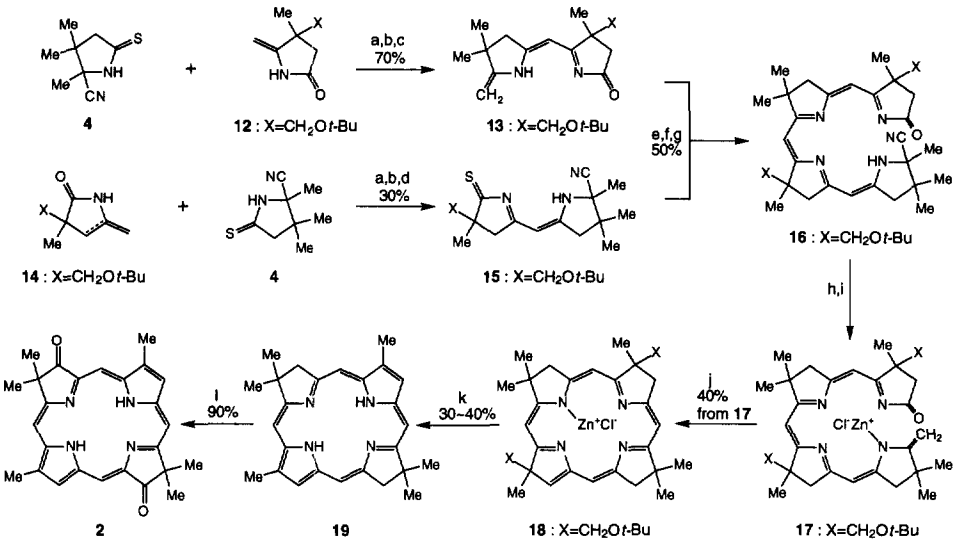


Several ester, nitrile, and protected hydroxymethyl derivatives were screened as "X" group candidates. The nitrile group, which is known to smoothly undergo elimination in the final stage of Eschenmoser's pyrrocorphin synthesis (cf. **11**→**3** in Scheme 1), was tested first. However, during attempted exocyclic eneamide formation, premature elimination of cyanide from **15** (X=CN) and **16** (X=CN) made further elaboration of these substrates impossible, and this protecting group was abandoned. In addition, carboxymethyl (X=CO_2Me) and carboxyethyl (X=CO_2Et) derivatives suffered hydrolysis and decarboxylation under these same conditions. Methoxymethyl derivatives (X=CH_2OMe) circumvented the elimination problem, allowing preparation of octahydroporphyrin **18** (X=CH_2OMe). However, all attempts to cleave the methyl ether in **18** (X=CH_2OMe) failed, and recourse to a more labile protected hydroxymethyl group was necessary.

Based on these preliminary results, *tert*-butyloxymethyl was chosen as the protecting group "X". The Eschenmoser approach was used to assemble the octahydroporphyrin **18** from monocyclic precursors. Base-mediated coupling of the eneamide **12**[9] with the thiolactam **4**[10] in the presence of NIS, followed by sulfide contraction with triethyl phosphite, furnished a bicyclic intermediate in 70% overall yield. Similarly, the coupling of **14**[9] with **4** gave the corresponding bicyclic intermediate in 30% overall yield. The eneamide **14** exists as a mixture of *exo* and *endo* enamide forms, which apparently results in the lower coupling yield. The sulfide contraction method was once again used to couple **13** with **15** to yield the tetracyclic lactam **16**. Upon exposure to Meerwein reagent, the non-symmetrical precorphin **17**, obtained by extrusion of cyanide from **16**, underwent an iminoester condensation/cyclization reaction to produce the octahydroporphyrin **18**.

Finally, the octahydroporphyrin zinc corphin **18** was subjected to the crucial double elimination step. Upon successive treatment with TFA, *t*-BuOK/*t*-BuOH, and 20% aq. HCl, this substrate underwent *t*-butyl ether cleavage, double retroaldol/autoxidation reaction, and demetallation in one pot to furnish the tetrahydroporphyrin **19** as a crystalline green solid in 30~40% overall yield (Scheme 2).

Scheme 2



Reagents and conditions: (a) NIS (1 eq.), DBU (2 eq.), CH_3CN, 3 h, r.t. (b) $(EtO)_3P$, xylenes (1:4), 23 h, 125 °C. (c) *t*-BuOK/*t*-BuOH, 3 h, 85 °C. (d) Lawesson's reagent, toluene, 3 h, 80 °C. (e) NIS (1 eq.), DBU (4 eq.), CH_3CN, 3 h, r.t. (f) $CdCl_2$, $NaHCO_3$, PPh_3, CH_3CN, 4 h, r.t. (g) KCN, MeOH, 10 min., r.t. (h) *t*-BuOK/*t*-BuOH, 15 min., 80 °C. (i) $Zn(ClO_4)_2$, MeOH, r.t. (j) Et_3OBF_4, CH_2Cl_2, *i*-Pr_2NEt, 20 h, r.t. (k) (1) TFA, anisole, 1 h, r.t., (2) MeOH, 10 min., (3) *t*-BuOK/*t*-BuOH, 15 min., (4) 20% HCl, 1 min, r.t. (l) CrO_3·dimethyl pyrazole, CH_2Cl_2, r.t.

A number of oxidants, including Pt(0)/O_2, DDQ, MCPBA/dimethyl dioxirane, and benzoyl peroxide/O_2, were tested to achieve conversion of **19** to the tolyporphin chromophore model **2** without success. However, it was found that the desired oxidation could be effected cleanly by titrating a CH_2Cl_2 solution of **19** with a 0.01M CH_2Cl_2 solution of CrO_3·dimethylpyrazole complex.[11] The chromophore model **2**[12] was isolated as a purple solid in 90% yield, which exhibited a virtually identical UV spectrum to that of tolyporphin (**1**). In addition, ^{1}H- and ^{13}C-NMR chemical shifts of the porphyrin ring atoms coincided closely with those reported for tolyporphin. The structural framework and the location of the carbonyl groups in **2** were verified by a combination of ^{1}H-^{13}C correlation HMQB and HMQC spectroscopy. It is interesting to note that oxidation took place exclusively at the desired positions and that one of the two sites was oxidized much faster than the other, although the structure of the mono-oxidation product is not conclusively established at this time.

In conclusion, the synthetic route outlined provides novel access to unsymmetrical tetrahydroporphyrins and related compounds, and its application to a total synthesis of tolyporphin (**1**) is in progress.

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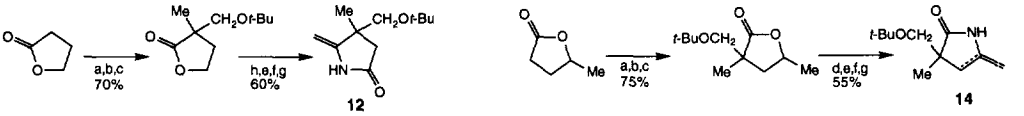
8. For an alternative approach to dioxobacteriochlorins from porphyrins, see Pandey, R. K.; Isaac, M.; MacDonald, I.; Medforth, C. J.; Senge, M. O.; Dougherty, T. J.; Smith, K. M. *J. Org. Chem.* **1997**, *62*, 1463.

9. The monocyclic precursors **12** and **14** were synthesized as outlined below.



Reagents and conditions: (a) LDA, THF; MeI, -78 °C. (b) LDA, THF, H_2CO,-78 °C. (c) isobutylene, H_2SO_4, CH_2Cl_2, r.t., 16 h. (d) LAH, THF, r.t. (e) $RuCl_3 \cdot H_2O$, H_2O, MeCN, CCl_4, r.t. (f) EtO_2CCl, Et_3N, THF, r.t. (g) xylenes-azeotrope, 160 °C. (h) MeLi, Et_2O, -78 °C→0 °C.

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12. Spectroscopic data of **2**: MS (FAB; m/z) 426 (M^+, 100%); UV (MeOH) λ_{max} 399 nm, 479, 503, 547, 615, 646, 678; ^1H NMR (500 MHz, C_6D_6) δ 1.86 ppm (s, 3H), 1.90 (s, 3H), 3.09 (s, 3H), 3.13 (s, 3H), 8.35 (s, 1H), 8.40 (s, 1H), 8.70 (s, 1H), 8.89 (s, 1H), 9.91 (s, 1H), 10.06 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 13.1 ppm, 23.5, 23.7, 50.0, 50.1, 95.5, 96.9, 97.1, 99.0, 126.5, 127.2, 136.2~137.9 (4 signals), 167.5 (2 signals), 209.6 (2 signals).

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