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Synthesis of the Potent Antimalarials Calothrixin A and B

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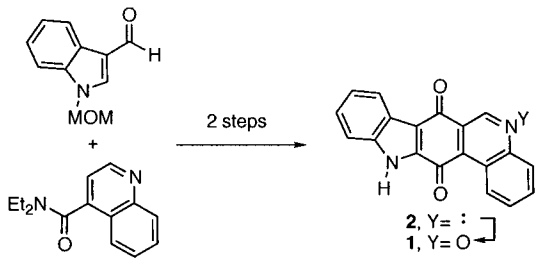
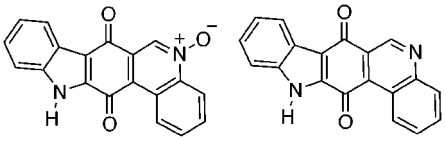
ABSTRACT



A concise synthesis of calothrixins A (1) and B (2) that confirms their assigned structures and affords straightforward synthetic access to them is reported.

In 1999 Rickards, Smith, and colleagues reported[1] the isolation and structure determination of calothrixin A (**1**) and B (**2**). Both compounds have exceptional (nanomolar) antimalarial activity, and their utility in that regard is currently under evaluation.



1 **2**

The structure assigned to **1** is based on an X-ray crystallographic determination. The structure assignment for **2** is based on a careful consideration of the similarities and differences of the spectra of **1** and **2**, but the two have not been interconverted. While two natural products that both have a $C_{19}N_2$ core and co-occur are likely to have the same skeleton, it is not necessary.

To our knowledge the calothrixins are the only known naturally occurring members of this pentacyclic ring system. These considerations, taken with our continuing interest[2] in the synthesis of heteroaromatic natural products and the minor reservations expressed above about the structure of

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(2) See: Kelly, T. R.; Fu, Y.; Sieglen, J. T.; De Silva H. *Org. Lett.* **2000**, *2*, 2351 and references therein.

(3) (a) Kelly, T. R.; Echavarren, A.; Chandrakumar, N. S.; Köksal, Y. *Tetrahedron Lett.* **1984**, *25*, 2127. (b) Kelly, T. R.; Bell, S. H.; Ohashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 6471. (c) Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522. (d) Kelly, T. R.; Kim, M. H. *J. Org. Chem.* **1992**, *57*, 1595. (e) Kelly, T. R.; Walsh, J. J. *J. Org. Chem.* **1992**, *57*, 6657. (f) Kelly, T. R.; Xu, W.; Sundaresan, J. *Tetrahedron Lett.* **1993**, *34*, 6173. (g) Kelly, T. R.; Xu, W.; Ma, Z.; Li, Q.; Bhushan, V. *J. Am. Chem. Soc.* **1993**, *115*, 5843. (h) Kelly, T. R.; Xie, R. L. *J. Org. Chem.* **1998**, *63*, 8045.

(4) For reviews, see: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(5) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457.

(6) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104.

(7) Work, T. S. *J. Chem. Soc.* **1942**, *429*, 431.

(8) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442.

(9) See Supporting Information.

(10) The ^{1}H NMR and UV−vis spectra of synthetic **2** are in excellent agreement with those reported for the natural product. Our[9] ^{13}C NMR data are in good, but not perfect, agreement with those reported. We attribute the minor (all less than 1 ppm) differences to variations in the water content (or pH) of our DMSO-d_6 ^{13}C NMR solution and that of Rickards et al. A ^{13}C NMR spectrum of synthetic **2** subsequently recorded in Prof. Rickards's laboratory is in much better agreement with the original[1] data. Direct TLC comparisons (including cospotting) of synthetic **2** with natural **2** showed the two are indistinguishable (we thank Professor Rickards for recording the ^{13}C NMR spectrum and carrying out TLC comparisons; NMR spiking experiments were precluded by the paucity of the natural material available).

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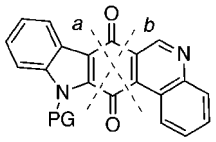
2, led us to undertake its synthesis. We now report the first total synthesis of **2**, the demonstration that the structure of naturally occurring **2** is correctly assigned, and the conversion of **2** to **1**.

Our past success[3] with ortho lithiation-based strategies for total synthesis encouraged us to consider such an approach to **2**. The two retrosyntheses suggested in Figure 1 appeared



3

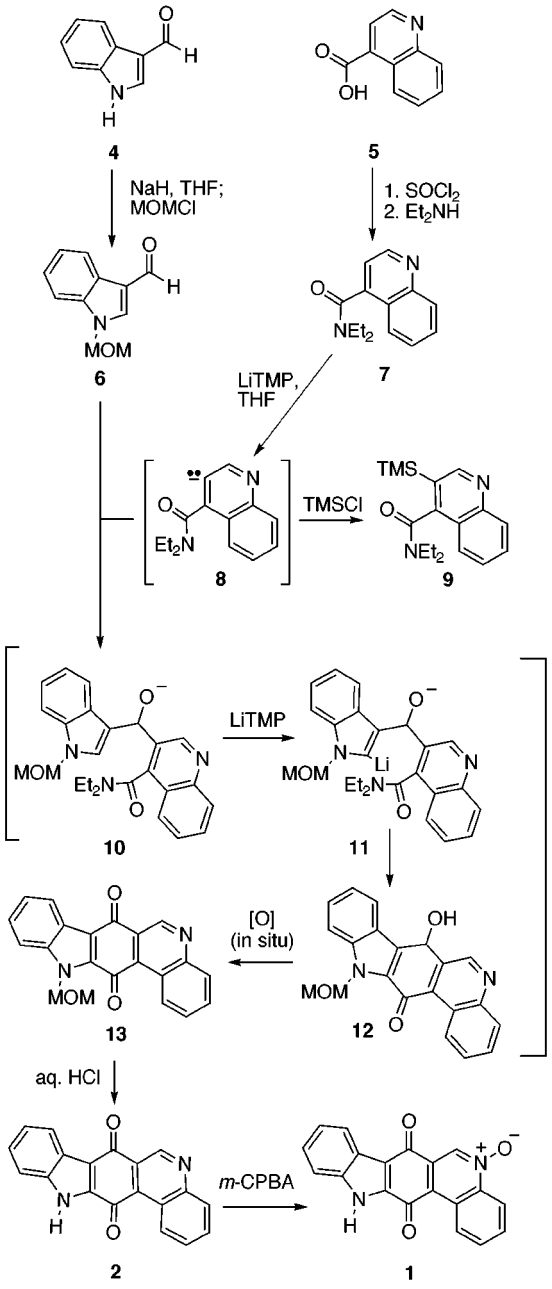
Figure 1. Retrosynthetic analysis of **3**.

particularly attractive because they offered the prospect of achieving a highly convergent synthesis from two relatively simple precursors. In fact, we now report a total synthesis of **2** in which the longest linear sequence is only two steps from known compounds (four steps from commercially available materials).

In pursuing the retrosyntheses in Figure 1, a search of the literature[4] led to a report in which Watanabe and Snieckus[5] demonstrated that the strategy implicit in retrosynthesis *b* is a viable one, at least when applied to simpler targets. In the present instance, however, the reaction conditions reported by Watanabe and Snieckus totally failed to give any of **3**. An extensive examination of reaction conditions was required before the synthesis of **3** was reduced to practice.

The synthesis is summarized in Scheme 1. The known **6**[6] and **7**,[7] each prepared in a one-pot operation from commercially available materials **4** and **5**, were coupled, again in a one-pot operation, to give **13** (≅ **3**) directly. None of the putative intermediates **8**, **10**, **11**, or **12** shown in Scheme 1 was isolated, but the choice of lithium tetramethylpiperidide (LiTMP) as base was crucial. The base used to metalate the amide in the original report (*s*-BuLi) failed with **7**; *t*-BuLi was equally useless under a variety of conditions. Attempts to deprotonate **7** with lithium hexamethyldisilazide (pK_a of amine = 29.5)[8] led to no detectable reaction with **6**. The more basic lithium diisopropylamide (LDA, pK_a of amine = 35.7)[8] resulted in the production of small amounts of **13**. The still more basic (pK_a of amine = 37.3)[8] LiTMP was most effective. The reaction of **7** with LDA and LiTMP behaved as if an equilibrium was being established [quenching of ostensibly **8**, prepared using either LDA or LiTMP, with TMSCl gave good yields of the TMS quinoline amide **9**, but this normally near-instantaneous reaction was slow, requiring several hours for consumption of **7**/**8**, as judged by thin-layer chromatography (any **8** present would have been detected as **7**)]. Accordingly, use of excess rather than stoichiometric LiTMP in the deprotonation of **7** was examined. The optimized conditions[9] enlisted 4 equiv of LiTMP in the deprotonation of **7**, without the need to add an

Scheme 1. Synthesis of Calothrixins A and B



additional equivalent in the subsequent step involving the deprotonation of **10**.

Even with all the optimization, the yield of **13** from **7** is only 12% [26% if one uses 0.4 equiv of **6** and calculates the yield based on **6** (using 1 equiv of **6** does not improve the yield based on **7**)]. However, the route is extremely concise, and the main step is amenable to operation on at least a gram scale. Furthermore, after removal of the MOM protecting group (74%), the sequence serves to confirm the structure assigned to **2**.[10] In addition, selective oxidation of the pyridine nitrogen of synthetic **2** with *m*-CPBA affords **1** (71%), whose spectra are in excellent agreement with those reported for natural **1**.

In conclusion, we provide very short syntheses of calo-

thrixins A and B that confirm the assigned structures and afford straightforward synthetic access to them and, in principle, their analogues.

Acknowledgment. We thank Professor Rickards[1] for providing spectra of natural **1** and **2** and for the TLC and NMR comparison of natural **2** with synthetic **2**.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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