ORGANIC LETTERS

2000
Vol. 2, No. 15
2351−2352

Synthesis of an Orange Anthrathiophene Pigment Isolated from a Japanese Bryozoan

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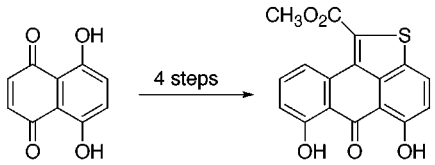
Received May 30, 2000

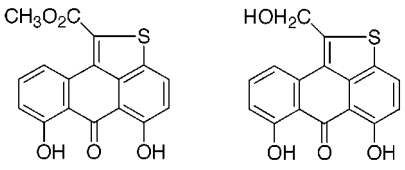
ABSTRACT



7 1

A short, regiospecific synthesis of the naturally occurring anthrathiophene 1 from naphthazarin (7) is described.

In 1993, a group of scientists at Sankyo Co. Ltd. in Tokyo reported[1] the isolation and structure elucidation of two naturally occurring anthrathiophenes. These compounds were isolated from a deep-red-colored bryozoan that is ubiquitous on the Japanese seacoast and assigned structures **1** and **2**.

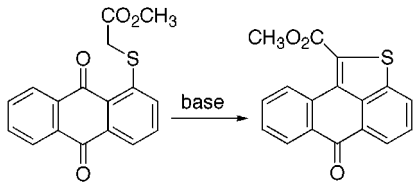


1 **2**

Compounds **1** and **2** have not been interconverted. The structure assigned for **2** is based on an X-ray crystallographic determination. The structure of **1** is somewhat less certain; it depends partly on the spectral similarity of **1** to **2** and a tacit and reasonable (but not necessary) expectation that, because **1** and **2** both possess a $C_{16}S$ skeleton and co-occur, they are likely to have the same skeleton.

To our knowledge, **1** and **2** are the only naturally occurring members of the 6*H*-anthra[1,9-*bc*]thiophene ring system and neither has been previously synthesized. These considerations, taken with our continuing interest[2] in the synthesis of heteroaromatic natural products and the reservations expressed above about the structure of **1**, led us to undertake its synthesis. We now report the first synthesis of **1** and the demonstration that the structure of naturally occurring **1** is correctly assigned.

The scant prior literature[3] on construction of the parent 6*H*-anthra[1,9-*bc*]thiophene ring system encouraged a strategy involving as the final step the base-catalyzed Knoevenagel-type cyclization of **3** to **4**. Historically,[3] compounds



3 **4**

such as **3** have been prepared by reaction of an anthraquinone bearing a sulfur substituent at the 1-position with chloroac-

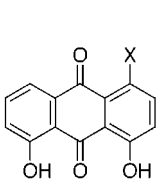
† Undergraduate research participant.

(1) Shindo, T.; Sato, A.; Kasanuki, N.; Hasegawa, K.; Sato, S.; Iwata, T.; Hata, T. *Experientia* **1993**, *49*, 177.

(2) For recent examples, see (a) Kelly, T. R.; Chamberland, S.; Silva, R. A. *Tetrahedron Lett.* **1999**, *40*, 2723. (b) Kelly, T. R.; Fu, Y.; Xie, R. L. *Tetrahedron Lett.* **1999**, *40*, 1857. (c) Kelly, T. R.; Moiseyeva, R. L. *J. Org. Chem.* **1998**, *63*, 3147 and earlier work cited therein.

10.1021/ol006127a CCC: $19.00
Published on Web 06/22/2000

etate. We chose to explore an alternate (and more convergent) strategy involving the nucleophilic aromatic substitution of **5**, where X is a good leaving group, with an α-mercaptoacetate. Concerns existed, however, as to whether the two acidic phenolic protons in the real substrates (**5** and **6**) would interfere with the requisite enolate formation and/or substitution reaction.



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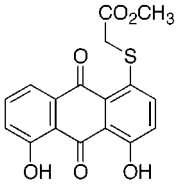
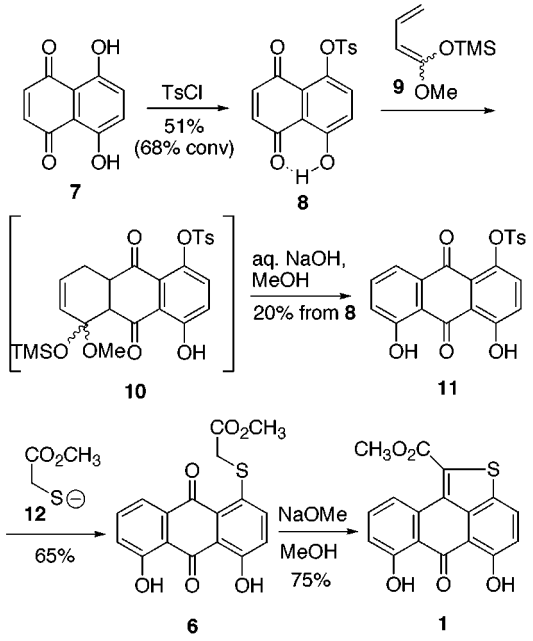
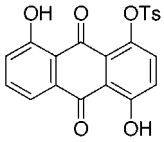


6

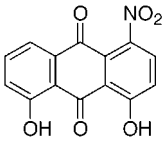
Those worries proved unwarranted, and a short regiospecific route to **1** has been achieved. The synthesis is summarized in Scheme 1. Tosylate **11** was regioselectively prepared in two operations from naphthazarin (**7**). Monotosylation of **7** gave **8**, which, as anticipated on the basis of extrapolation of earlier[4] findings from these laboratories, underwent a regiospecific Diels−Alder reaction with diene **9**[5] to give **11** via **10**. None of the undesired regioisomer **13** was detected.

Scheme 1





13



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Treatment of quinone tosylate **11** with methyl mercaptoacetate (**12**) and potassium carbonate in THF resulted in the desired nucleophilic aromatic substitution to give **6**; the latter was then cyclized in good yield to **1** with methanolic methoxide. As a result of the paucity (3 mg) of natural **1** originally isolated, direct comparison of synthetic and natural **1** was not possible, but synthetic **1** gave ^{1}H NMR, IR, and UV spectra in good agreement with spectra obtained[1] for natural **1**.

The less than satisfying yield of the Diels−Alder reaction between **8** and **9** may be due to the known[5] tendency of **9** to exhibit multiple reaction paths with dienophiles. Consequently, a more readily accessible substitute for **11** was sought. Nitroanthraquinone **14** is a known compound.[6] The preparation of **14** is not regiospecific, but it can nonetheless be achieved in one step by nitration of 1,8-dihydroxyanthraquinone. Nitro groups usually serve as activating substituents, not leaving groups, in nucleophilic aromatic substitutions, but the participation of nitrite ion as a leaving group in such reactions is not unknown.[7] In fact, the reaction of **14** with **12** gives **6** in 51% yield.

In conclusion, we describe the first synthesis of the naturally occurring **1**. The synthesis is short and regiospecific and affirms the structure assignment.

Acknowledgment. We thank Dr. A. Sato[1] for providing spectra of natural **1**.

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

OL006127A

(3) (a) Krollpfeiffer, V. F.; Schneider, K. L.; Wibner A. *Justus Liebigs Ann. Chem.* **1950**, *566*, 139. (b) Fries, K.; Schurmann, G. *Chem. Ber*. **1919**, *52*, 2170.

(4) For a leading reference, see: Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, R. N., Jr.; King, P. F.; Lyding, J. M.; Tsang, W.-G.; Vaya, J. *Tetrahedron* **1984**, *40*, 4569.

(5) Brassard, P.; Savard, J. *Tetrahedron* **1984**, *40*, 3455.

(6) Antonello, C.; Uriarte, E.; Palumbo, M. *Arch. Pharm. (Weinheim, Ger.)* **1989**, *322*, 541.

(7) The removal of isomeric contaminants in the purification of the explosive TNT provides one example: Fieser, L. F.; Fieser, M. *Advanced Organic Chemistry* Reinhold: New York, 1963; p 682.