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Total Synthesis of (±)-Biphyscion

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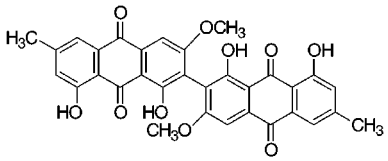
ABSTRACT



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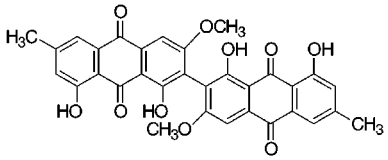
A regiospecific total synthesis of (±)-biphyscion (1) is described. A novel aspect of the plan was construction of the bianthraquinone ring system from a biphenyl intermediate through the use of a one-pot, double isobenzofuranone condensation.

Although a large number of naturally occurring bianthraquinones have been identified,[1] there has been only modest synthetic work on this class of compounds.[2] In conjunction with our interest in developing new routes to these natural products, we have explored a one-pot, double isobenzofuranone annelation[3] on the biphenyl **6b** (Scheme 2), and in so doing, have accomplished the first total synthesis of the 7,7′-linked bianthraquinone biphyscion (**1**).[4]



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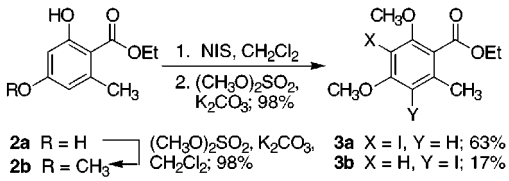
As shown in Scheme 2, an initial goal of the plan was preparation of the symmetrical biphenyl **4** through Ullman coupling of the protected iodoresorcinol **3a**. To maximize the yield of the needed iodoresorcinol **3a**, iodination of **2a** and its acetoxy and methyl ether derivatives was studied (Scheme 1).[5] The 4-methoxy derivative **2b**, prepared in 96% yield through regioselective methylation [$(CH_3O)_2SO_2/K_2CO_3/CH_2Cl_2$] of **2a**, proved to be the best substrate. Iodination (NIS, CH_2Cl_2, rt) of **2b** consistently gave a 2.8:1 ratio of the 3-iodo to 5-iodo compounds, **3a** and **3b**. The iodo isomers could be separated; however, it proved experimentally

Scheme 1



(1) (a) For an extensive list on naturally occurring bianthraquinones, see: ; Academic Press: New York, 1971; Vol. I, Chapter 5. (b) Thompson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Chapman and Hall: New York, 1987; Vol. 3, Chapter 3.

(2) Only two examples of bianthraquinone syntheses have been reported, and both were based on the use of emodin or a derivative thereof. Ullman reaction of the trimethyl ether derivative of 5-bromoemodin was employed to synthesize the 5,5′-linked bianthraquinone skyrin: Tanaka, O.; Kaneko, C. *Chem. Pharm. Bull.* **1955**, *3*, 284. Biomimetic coupling of emodin with $K_3Fe(CN)_6$ affords an unnatural 4,7′-linked bianthraquinone (30%) and a trace (0.28%) of the 5,5-linked bianthraquinone, skyrin: Kato, T.; Hozumi, T. *Chem. Pharm.* **1972**, *20*, 1574.

(3) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. For use of this reaction in natural products syntheses, see: Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098. Hauser, F. M.; Prasanna, S. *Tetrahedron* **1984**, *40*, 4711. Hauser, F. M.; Chakrapani, S.; Ellenberger, W. P. *J. Org. Chem.* **1991**, *56*, 5248. Hauser, F. M.; Tommassi, R. A. *J. Org. Chem*, **1991**, *56*, 5758. Hauser, F. M.; Zhou, M. *J. Org. Chem.* **1996**, *61*, 5722. Hauser, F. M.; Xu, Y. *Org. Lett*. In press.

(4) Gluchoff, K.; Arpin, N.; Dangy-Caye, M.; Lebreton, P.; Steglich, W.; Töpfer, E.; Pourrat, M.; Regerat, F.; Deruaz, D. *C. R. Seances Acad. Sci., Ser. 3* **1972**, *274*, 1739. Steglich, W.; Töpfer-Petersen, E.; Reininger, W.; Gluchoff, K.; Arpin, N. *Phytochemistry* **1972**, *11*, 3299.

(5) The details of this study will be published elsewhere.

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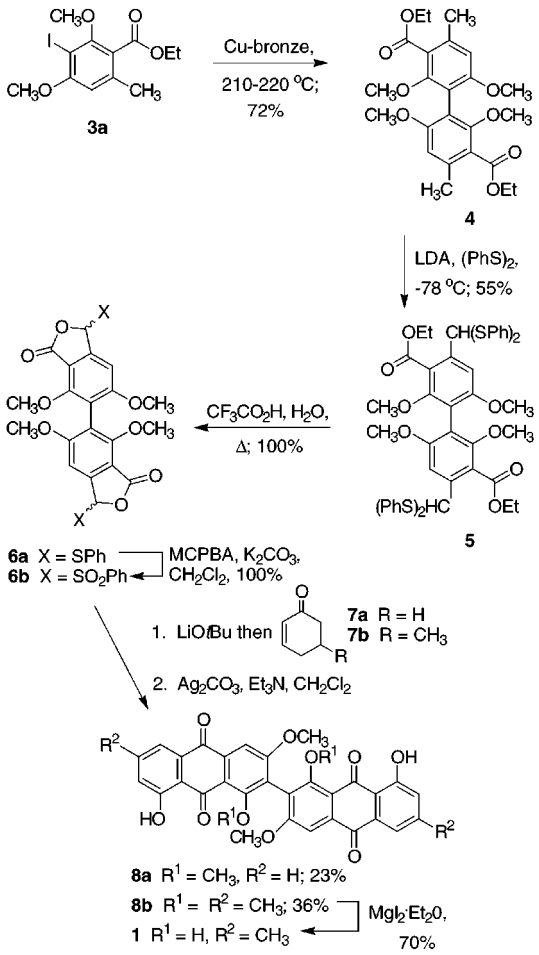
expeditious to effect methylation [$(CH_3O)_2SO_2$, K_2CO_3, acetone] of the mixture and then perform chromatographic separation of the isomers. The overall yield of the iodoresorcinol **3a** from the resorcinol **2a** was 63%.

Although steric hindrance can be a problem in Ullman reactions,[6] coupling of **3a** with copper bronze proceeded as expected to afford the biphenyl **4** in good yield (73%) (Scheme 2). Fabrication of phenylsulfonyl isobenzofuranone

Scheme 2



fragments from the *o*-methyl carboxylate functionalities in **4** proved to be challenging, and several methods were explored for this key construction. Ultimately, it was found that brief treatment of **4** with 6 equiv of LDA (5 min, −78 °C) and 4.4 equiv of $(PhS)_2$ consistently afforded the tetrathiophenylated product **5** in 55% yield.[7] Longer reaction times gave less of the tetrathiophenylated product and more of the di- and trithiophenylated products.

Brief treatment of **5** with CF_3CO_2H/H_2O provided a quantitative yield of the 3-thiophenylated biphthalide **6a** as a mixture of diastereoisomers in a 1:2:1 ratio. The biphthalide **6a** was oxidized (MCPBA, K_2CO_3, CH_2Cl_2)[8] to the sulfone **6b** (100% yield).[9,10] Since the chirality at two of the three chiral centers in **6b** would be lost in the next step, the diastereomeric mixture was used in further transformations. The dianion of **6b**, generated with 4 equiv of Li*O*t*Bu*, was reacted with the cyclohexenone **7a**. Analysis of the ^{1}H NMR spectrum of the initially received condensation product, as well as TLC, indicated that a complex mixture had been formed. Nevertheless, we decided to explore oxidative transformation of the hydroanthracene intermediate, since this might afford some insight into the reaction outcome. To this end, we employed the procedure previously developed by us to specifically accomplish this type of oxidative conversion.[11] We were quite pleased to discover that treatment of the condensation product with Ag_2CO_3 on Celite in the presence of Et_3N afforded the expected bianthraquinone **8a** in 23% yield.

Having established that the double condensation can be used to construct bianthraquinones, we undertook preparation of the naturally occurring bianthraquinone biphyscion (**1**). As in the previous sequence, the dianion of **6b** was generated with 4 equiv of Li*O*t*Bu* and then reacted with the cyclohexenone **7b**. Oxidation (Ag_2CO_3 on Celite, Et_3N, CH_2Cl_2) of the bihydroanthracene condensation intermediate gave the bianthraquinone **8b** in 36% yield. Regiospecific demethylation of **8b** with MgI_2[12] afforded biphyscion (**1**) in 70% yield. The ^{1}H and ^{13}C NMR spectra were identical with those reported for biphyscion (**1**).

Acknowledgment. This work was generously supported by the National Cancer Institute and the National Institute of General Medical Sciences of the National Institutes of Health (CA 18141)

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(7) Hauser, F. M.; Rhee, R. P.; Weinreb, S. M.; Dodd, J. H. *Synthesis* **1980**, 73.

(8) The use of a buffered medium is crucial to obtaining a high yield of the sulfone. Without K_2CO_3, the yield was only 70%.

(9) The diastereoisomeric ratio was unaltered during oxidation.

(10) The sulfone diastereoisomers were separated. The ^{1}H and ^{13}C NMR spectra of the most polar and the least polar isomers indicated that they were C-2 symmetric. The isomer of intermediate polarity gave ^{1}H and ^{13}C spectra indicating that all the protons and all the carbons were different.

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