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Total Synthesis of the Photoprotecting Dipyrrolobenzoquinone (+)-Terreusinone

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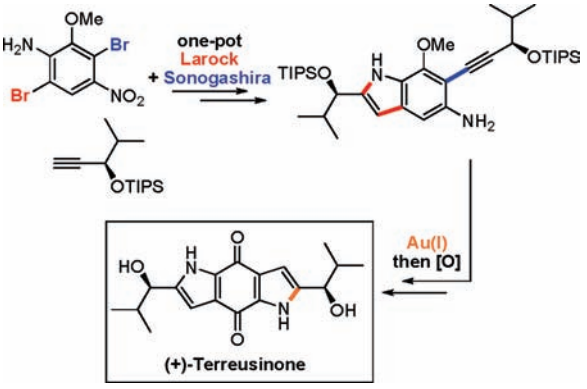
ABSTRACT

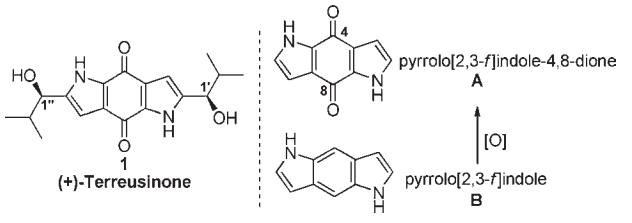


The first synthesis of (+)-terreusinone 1, a dipyrrolobenzoquinone with a potent UV-A protecting capability, is described. Key transformations include a one-pot Larock indolization–Sonogashira coupling reaction and the hydroamination of an unsubstituted *ortho*-alkynylaniline catalyzed by a cationic gold(I) complex. The synthesis proceeds in eight steps from commercially available starting materials, confirming the structure and absolute configuration of the natural product.

Terreusinone (**1**) is a dipyrrolobenzoquinone isolated from the algicolous marine fungus *Aspergillus terreus* in 2003 (Scheme 1).[1] Terreusinone contains a pyrrolo[2,3-*f*]indole-4,8-dione ring system (**A**) that is unique among natural products. Moreover, terreusinone was shown to exhibit significant UV-A protecting properties, implying **1** may serve to protect the host organism from the harmful effects of solar UV radiation.[2] Significantly, the UV-A protecting capability of **1** ($ED_{50} \approx 200\ \mu m$) is stronger than that of oxybenzone ($ED_{50} = 350\ \mu m$), a compound widely used in sunscreens, suggesting **1** (and analogues thereof) may have potential dermatological and biomedical applications.

The configuration of the stereocenters at C1′/C1″ in **1** were assigned as (*R*).[1] A short time later, subjecting **1** to a desymmetrizing microbial oxidation further confirmed the *C*2-symmetrical structure **1**.[3]

Scheme 1. Terreusinone (**1**) and Heterocyclic Motifs **A** and **B**



Successful syntheses of compounds bearing the dipyrrolobenzoquinone **A** include the flash vacuum pyrolysis of a

(1) Lee, S. M.; Li, X. F.; Jiang, H.; Cheng, J. G.; Seong, S.; Choi, H. D.; Son, B. W. *Tetrahedron Lett*. **2003**, *44*, 7707–7710.

(2) For a review on UV-A protecting natural products: Gao, Q.; Garcia-Pichel, F. *Nat. Rev. Microbiol*. **2011**, *9*, 791–802.

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(4) Qiao, G. G. H.; Meutermans, W.; Wong, M. W.; Träubel, M.; Wentrup, C. *J. Am. Chem. Soc*. **1996**, *118*, 3852–3861.

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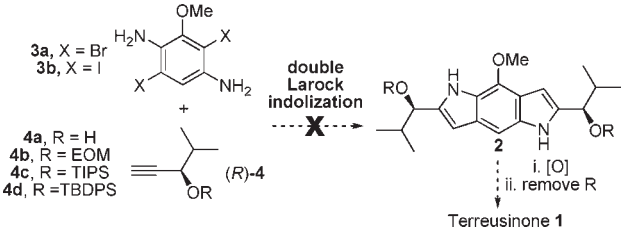
diketopiperazine,[4] the reaction of a series of activated methylene derivatives with 3,6-diamino-2,5-dibromobenzoquinones[5] or *p*-chloranil,[6] and the reaction of 1,2-amino alcohols with indoloquinones followed by acid mediated cyclization and oxidation.[7] These methods require harsh conditions,[4–7] afford heavily substituted products,[5,6] or proceed in a nonregioselective manner.[7] Furthermore, due to the nature of the substrates involved, none of these methods can be applied to the synthesis of dipyrrolobenzoquinones with chiral substituents on the heterocyclic ring(s), as observed in **1**. Broadly speaking, the simplest synthesis of dipyrrolobenzoquinones of type **A** is via the oxidation of its benzenoid derivative, pyrrolo[2,3-*f*]indole **B** (Scheme 1). Much like dipyrrolobenzoquinones **A**, the literature syntheses of pyrroloindoles **B** possess narrow scope and none have incorporated chiral substituents onto the heterocyclic core.[8]

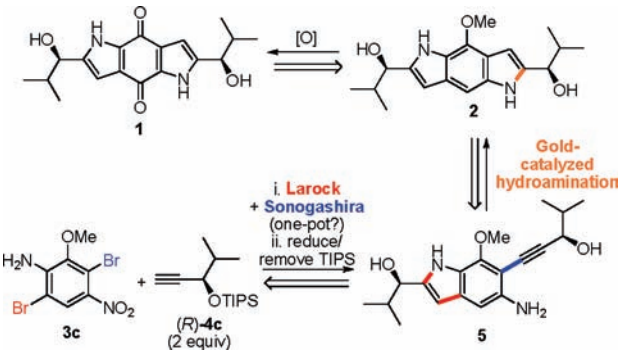
Scheme 2. Failed Double Larock Indolization Approach



As alluded to in the above, the aim was to construct terreusinone **1** by the late stage oxidative demethylation of the pyrroloindole **2** (Scheme 2). The palladium-catalyzed reaction between *ortho*-haloanilines and terminal alkynes (Larock indolization) is a highly reputable procedure for constructing 2-substituted indoles,[9] and as such, we envisaged that pyrroloindole **2** be constructed using a double Larock indolization of a halogenated 1,4-dianiline (**3a** or **3b**) with the chiral, secondary propargylic alcohols (*R*)-**4a**–**d**. Unfortunately, despite attempting a plethora of reaction conditions and various combinations of **3a**–**b**/**4a**–**d**, no pyrroloindole **2** was ever observed (Scheme 2). Although the full details are not discussed herein, knowledge of this failed approach is necessary when considering the modified, ultimately successful synthesis of (+)-**1** detailed henceforth.

A new retrosynthesis of terreusinone **1** was devised whereby the two heterocyclic rings would be installed in separate synthetic steps (Scheme 3). In this revised route, the synthesis of **1** would conclude with the late stage oxidative demethylation of pyrroloindole **2** which will in turn be constructed by a gold-catalyzed[10,11] hydroamination of *ortho*-alkynylaniline **5**. In keeping with the original proposal, the highly substituted indole **5** would be constructed using a Larock indolization. At this planning stage, it was apparent that the modified catalytic system[12] that facilitates the use of aryl bromides[13] in the Larock indolization may also promote Sonogashira coupling.[14] Accordingly, **5** could be assembled by a novel one-pot Larock indolization–Sonogashira coupling reaction between the dibromide **3c** and 2 equiv of the silylated propargylic alcohol (*R*)-**4c**,[15] followed by reduction (Scheme 3).

Scheme 3. Revised Approach to (+)-Terreusinone



Focus turned toward assembling the coupling partners **3c** and (*R*)-**4c** to assess the viability of the proposed

(6) Shindy, H. A.; El-Maghraby, M. A.; Eissa, F. M. *Dyes Pigm.* **2002**, *52*, 79–87.

(7) (a) Rives, A.; Delaine, T.; Legentil, L.; Delfourne, E. *Tetrahedron Lett.* **2010**, *50*, 1128–1130. (b) Rives, A.; Le Calvé, B.; Delaine, T.; Legentil, L.; Kiss, R.; Delfourne, E. *Eur. J. Med. Chem.* **2010**, *45*, 343–351.

(8) Previous syntheses of pyrrolo[2,3-*f*]indoles (**B**) rely on classical indolization reactions, see: Japp–Murray: (a) Yamashkin, S. A. *Khim. Geterotsikl. Soedin.* **1995**, 55–57. Fischer:(b) Park, I.-K.; Suh, S.-E.; Lim, B.-Y.; Cho, C.-G. *Org. Lett.* **2009**, *11*, 5454–5456. Leimgruber–Batcho:(c) Berlin, A.; Bradamante, S.; Ferraccioli, R.; Pagani, G. A.; Sannicolò, F. *J. Chem. Soc. Chem. Commun.* **1987**, 1176–1177. Bischler: (d) Prasad, G. K. B.; Burchat, A.; Weeratunga, G.; Watts, I.; Dmitrienko, G. I. *Tetrahedron Lett.* **1991**, *32*, 5035–5038. Madelung:(e) Chen, H. Z.; Jin, Y. D.; Xu, R. S.; Peng, B. X.; Desseyn, H.; Janssens, J.; Heremans, P.; Borghs, G.; Geise, H. J. *Synth. Met.* **2003**, *139*, 529–534. The Rh(I)-catalyzed hydroamination of *ortho*- alkynylaniline furnishes the pyrrolo[2,3-*f*]indole heterocyclic system in poor yield (20%): (f) Clentsmith, G. K. B.; Field, L. D.; Messerle, B. A.; Shasha, A.; Turner, P. *Tetrahedron Lett.* **2009**, *50*, 1469–1471.

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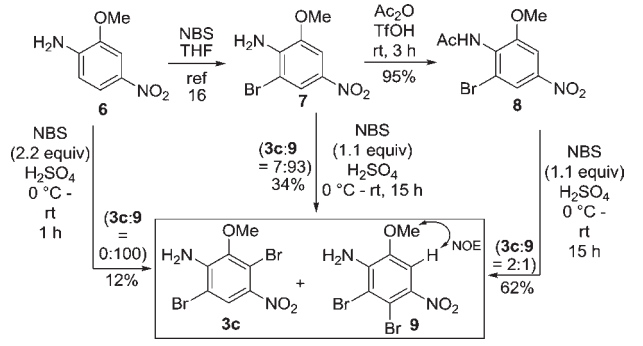
(11) Gold(I): Wang, C.; Widom, J.; Petronijevic, F.; Burnett, J. C.; Nuss, J. E.; Bavari, S.; Gussio, R.; Wipf, P. *Heterocycles* **2009**, *79*, 487–520.

one-pot Larock indolization–Sonogashira coupling reaction and the synthesis of dibromide **3c** was the initial task. Although commercially available 2-methoxy-4-nitroaniline **6** underwent successful dibromination with NBS in sulfuric acid, the undesired 1,2-dibromide **9** was isolated as the sole product in poor yield, as determined by NOE experiments (Scheme 4).[17] In light of this disappointing result, a two-step dibromination was considered. Thus, the known bromide **7**[16] underwent successful bromination (NBS, H_2SO_4), affording dibromides **3c** and **9**, again heavily favoring the undesired regioisomer **9** (93:7) (Scheme 4). However, acetylation of bromide **7** gave **8** that, upon exposure to the conditions used previously (NBS, H_2SO_4), underwent bromination with concomitant acetate hydrolysis, giving bromides **3c** and **9**, pleasingly favoring regioisomer **3c** in a 2:1 ratio (Scheme 4).

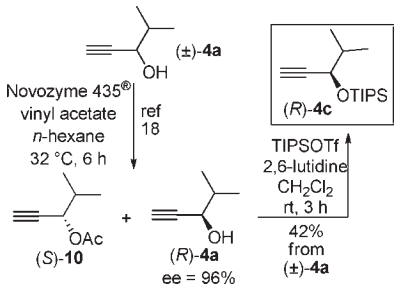
Racemic propargylic alcohol (±)-**4a** was subjected to kinetic resolution (Novozyme 435, vinyl acetate)[18] followed by silylation, delivering (*R*)-**4c** (Scheme 5). The enantiomeric excess of (*R*)-**4a** showed a slight improvement

Scheme 4. Synthesis of Dibromide **3c**



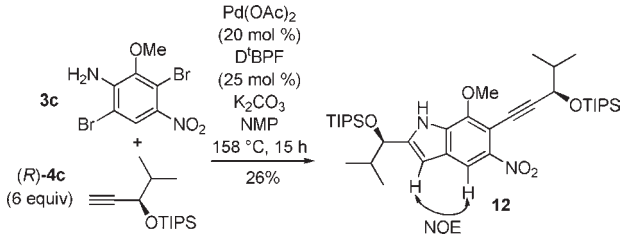
(96%) against the literature value (93%),[18] determined by Mosher's ester analysis.[17]

Scheme 5. Synthesis of (*R*)-**4c**



Upon subjecting dibromide **3c** and an excess of (*R*)-**4c** to Senanayake's modified Larock indolization conditions,[12a] both the Larock indolization and Sonogashira coupling successfully occurred, furnishing indole **12** in 26% yield (Scheme 6). ^{1}H and ^{13}C NMR spectroscopy showed only one diastereomer of **12** was present,[17] indicating the stereochemical integrity in (*R*)-**4c** had been retained in the product. The desired regiochemical outcome of the Larock indolization was confirmed by NOE studies.[17,19] Despite the poor yield of this step, it did accomplish the formation of three key bonds (2 × C–C, 1 × C–N) in a single operation. Moreover, there are limited examples of Larock indolizations with *ortho*-bromoanilines[12] and copper-free Sonogashira couplings[14] with aryl bromides, so achieving both of these transformations in a single step represents a significant accomplishment. Extending the utility of this reaction as a novel one-pot synthesis of alkynyl indoles is currently under investigation in our laboratory.

Scheme 6. One-Pot Larock Indolization–Sonogashira Coupling



(12) (a) Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129–4132. (b) Shimamura, H.; Breazzano, S. P.; Garfunkle, J.; Kimball, F. S.; Trzupek, J. D.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 7776–7783. (c) Cui, X.; Li, J.; Fu, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2008**, *49*, 3458–3462. (d) Batail, N.; Dufaud, V.; Djakovitch, L. *Tetrahedron Lett.* **2011**, *52*, 1916–1918.

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(15) Model studies indicated that triisopropylsilyl protected alkynol **4c** was the best substrate for the Larock indolization.

(16) Tietze, L. F.; Looft, J.; Feuerstein, T. *Eur. J. Org. Chem.* **2003**, 2749–2755.

(17) See Supporting Information for full details.

(18) Raminelli, C.; Comasseto, J. V.; Andrade, L. H.; Porto, A. L. M. *Tetrahedron: Asymmetry* **2004**, *15*, 3117–3122.

(19) There is only one example of a Larock indolization proceeding with complete reversal in regioselectivity: Nishikawa, T.; Wada, K.; Isobe, M. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 2273–2278.

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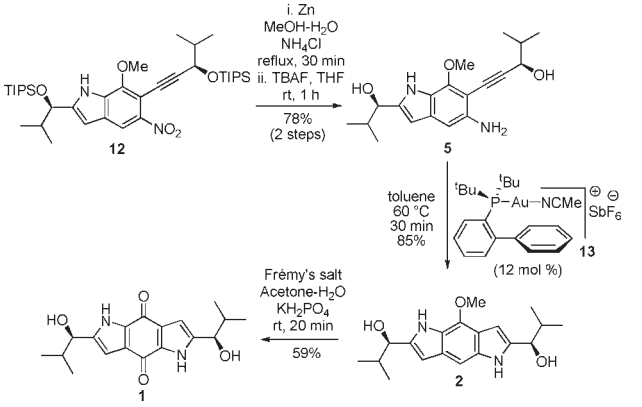
Nitro group reduction in **12** followed by TBAF-mediated silyl ether cleavage delivered the *ortho*-alkynylaniline **5**, setting the scene for the key hydroamination (Scheme 7).

Various acid metal-based catalytic systems are known to catalyze the hydroamination of unsubstituted *ortho*-alkynylanilines to indoles.[20] However, the field of gold catalysis has increased exponentially over the past few years[21] and in contrast to many of the aforementioned methods,[20] the catalysts involved are typically air- and moisture-stable and reactions can be performed in an open flask under mild conditions. Initial attempts to effect the desired transformation of **5** to **2** with all of the gold(III)[10] and gold(I)[11] catalysts reported to facilitate the synthesis of indoles from *ortho*-alkynylanilines failed, primarily due to the instability of the substrate **5**. In a final attempt, we turned to Echavarren's cationic gold(I) complex[22] (acetonitrile)-[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate **13**. Upon exposing **5** to 12 mol % of complex **13** in toluene at 60 °C, pyrroloindole **2** was isolated in excellent yield after 30 min (Scheme 7). This result demonstrates a novel application of complex **13**, extending its utility in organic synthesis.[22]

Scheme 7. Total Synthesis of (+)-Terreusinone **1**



Upon oxidation of **2** with Frémy's salt under buffered conditions, (+)-terreusinone **1** was obtained in good yield. The NMR spectroscopic data[17] and optical rotation {$[\alpha]_D^{21}$+43.7 (*c* 0.16, MeOH); lit.,[1] $[\alpha]_D$+47 (*c* 0.3, MeOH)} of synthetic **1** were in excellent agreement with the literature,[1] confirming the structure and absolute configuration of the natural product. Unfortunately, we were unable to establish contact with the authors of the isolation report[1] and obtain an authentic sample of natural (+)-**1**.

In conclusion, this report describes the first synthesis of the photoprotecting dipyrrolobenzoquinone natural product (+)-terreusinone. This synthesis is noteworthy for a one-pot Larock indolization−Sonogashira coupling reaction and the hydroamination of a delicate, unsubstituted *ortho*-alkynylaniline **5** catalyzed by Echavarren's cationic gold(I) complex **13**. The overall route proceeds in eight steps, furnishing sufficient quantities of (+)-**1** that allows further study of its photoprotecting properties, details of which shall be reported in due course.

Acknowledgment. We thank the Royal Society of New Zealand Marsden Fund for supporting this work.

Supporting Information Available. Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146–6148. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *11*, 1694–1702. (c) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452–5455. (d) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455–5459. (e) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306–6316. (f) Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6152–6155. (g) Jiménez-Núñez, E.; Molawi, K.; Echavarren, A. M. *Chem. Commun.* **2009**, 7327–7329. (h) Menon, R. S.; Findlay, A. D.; Bissember, A. C.; Banwell, M. G. *J. Org. Chem.* **2009**, *74*, 8901–8903. (i) Solorio, C. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 11881–11883. (j) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3517–3519. (k) Solorio-Alvarado, C. R.; Wang, Y.-H.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952–11955. (l) Rao, W.-D.; Susanti, D.; Chan, P. W.-H. *J. Am. Chem. Soc.* **2011**, *133*, 15248–15251. (m) Barabe, F.; Levesque, P; Korobkov, I.; Barriault, L. *Org. Lett.* **2011**, *13*, 5580–5583.