

Total Synthesis of Resveratrone and *iso*-Resveratrone

Stefan Fritsch, Nazli Aldemir, Jan Balszuweit, Kevin Bojaryn, Jens Voskuhl,* and Christoph Hirschhäuser*^[a]

Dedicated to the memory of Prof. Dr. Carsten Schmuck.

The first total synthesis of resveratrone and *iso*-resveratrone based on an epoxide olefination approach is described. The pivotal reaction proceeds by insertion of the lithiated epoxide into a boronic ester and subsequent *syn*-elimination. Resvera-

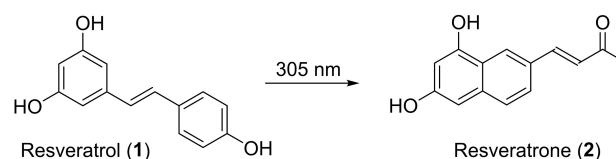
trone has been described to have remarkable photophysical properties, including two-photon absorption. Therefore, an azide derivative has been prepared to allow for use as a biological label.

Introduction

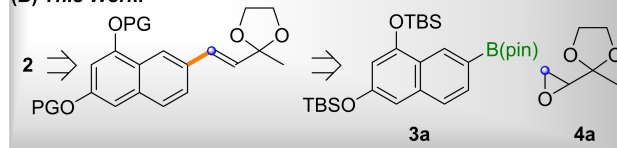
Resveratrol (**1**) is a naturally occurring phenol produced by a variety of plants in response to external pathogens.^[1] It has gained some notoriety as a potentially "healthy" ingredient in red wine,^[2] although resveratrol's lifespan-enhancing effects are strongly debated.^[3] In 2012, Kim and co-workers have reported that resveratrol (**1**) reacts to resveratrone (**2**) under UV irradiation as shown in Scheme 1A.^[4] Resveratrone (**2**) is a highly fluorescent compound that can undergo two-photon absorption, making it interesting for bio-labelling applications.^[4a, 5] More recently, the photo-switchability between **1** and **2** has been utilized by Voskuhl, Giese and co-workers for the preparation of light-responsive liquid crystals.^[6] In his 2012 publication, Kim stated: "It will be interesting to see if this relatively simple molecule can be synthesized without resorting to a photochemical reaction".^[4a] Beyond this challenge, a total synthesis of resveratrone (**2**) appeared desirable as it provides opportunities for structural modification and might avoid the extensive late stage purification by advanced chromatography techniques, which is necessary when **2** is prepared directly from **1**.

For reasons of stability, we assumed that a protected resveratrone derivative, in which the acidic character is suppressed, would be a desirable precursor (Scheme 1B). For the pivotal formation of the aryl-vinyl bond, we envisioned the use of an epoxide olefination, which would require boronate **3a** and the literature-known epoxide **4a**^[10] as suitable precursors. The epoxide olefination method em-

(A) Photochemical Generation of Resveratrone (Kim 2012)

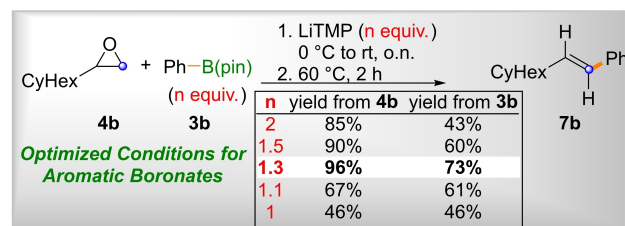
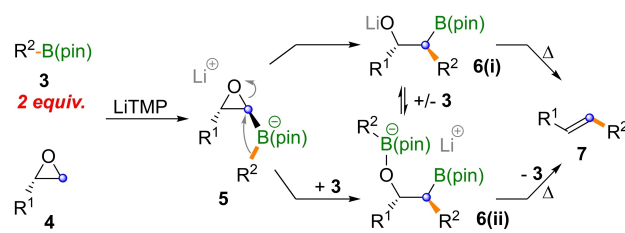


(B) This Work:



Scheme 1. Resveratrone (**2**) from resveratrol (**1**) and key disconnection (PG = protecting group, TBS = *tert*-butyldimethylsilyl).

ployed was reported by us in 2019,^[9] utilizing epoxides such as **4**, or even their more highly substituted congeners. Epoxides of type **4** can be lithiated in the presence of boronic esters,^[7] thus forming *ate*-complexes (**5**), which can undergo 1,2-metallate rearrangements to β -alkoxy boronates (**6**; Scheme 2).^[9] Stereospecific *syn*-elimination delivers alkenes



Scheme 2. Epoxide olefination and optimization of reaction conditions for aromatic boronates (LiTMP = lithium tetramethylpiperide, pin = pinacol).

[a] S. Fritsch, N. Aldemir, J. Balszuweit, K. Bojaryn, Prof. Dr. J. Voskuhl, Dr. C. Hirschhäuser
Organic Chemistry and Center for Nanointegration Duisburg-Essen (CeNIDE)
University of Duisburg-Essen
Universitätsstr. 5-7
45117 Essen (Germany)
E-mail: christoph.hirschhaeuser@uni-due.de
jens.voskuhl@uni-due.de

Supporting information for this article is available on the WWW under <https://doi.org/10.1002/open.202200098>

© 2022 The Authors. Published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

of type **7** as well as their tri- and tetrasubstituted congeners upon iterative application. The synthesis of resveratrone sets up an interesting challenge for this method, as it usually requires the use of two equivalents of the boronic ester **3**. As, in this case, the boronic ester would be the valuable 1,3,7-substituted dinaphthol **3a**, this was not attractive. We thus first set out to optimize the epoxide olefination for aromatic boronates of type **3** on the simple test system **7b**.

Results and Discussion

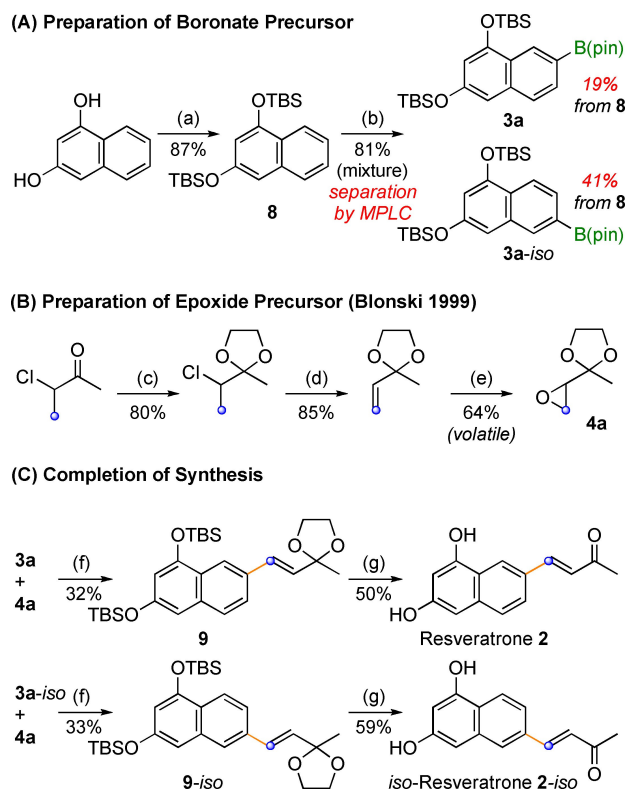
Our earlier attempts to reduce the amount of alkylboronic ester necessary for epoxide insertion below two equivalents were unsuccessful.^[9] This was attributed to the formation of ate complexes such as **6(ii)**, which could arise either directly from **5** – excess boronate facilitates epoxide opening – or by simple complexation of the alkoxide **6(i)**. For $R^2 = \text{alkyl}$, this leads to the consumption of two equivalents of boronic ester per lithiated epoxide. However, for aromatic boronates, the subsequent elimination occurs comparatively swiftly, so that excess boronate **3** might be re-liberated before the lithiated epoxide decomposes. Thus, by slowly raising the temperature overnight, the required excess of phenyl boronic ester **3b** was reduced substantially and the best results for the synthesis of alkene **7b** from cyclohexyl oxirane **4b** were obtained when 1.3 equivalents of **3b** were employed. Based on these encouraging results, we set out to synthesize resveratrone **2** as shown in Scheme 3.

For this, the required 1,3,7-dinaphthol derivative **3a** was prepared as shown in Scheme 3A. TBS protection of 1,3-dinaphthol^[11] yielded **8** and subsequent Hartwig-Miyaura borylation delivered **3a**.^[12] Both reactions proceeded in excellent yield, but, as expected, borylation of **8** furnished a 1:1 mixture of **3a** and its isomer **3a-iso**. Separation of the regioisomers was readily achieved by MPLC (RP¹⁸, MeOH/H₂O 9:1) and their structures were assigned by NOESY NMR experiments (see Supporting Information). Interestingly, **3a** started to decompose under MPLC conditions,^[13] while its regioisomer **3a-iso** remained intact. While this reduced the yield of **3a** to 19%, isolating **3a-iso** with a purity of more than >90% became reasonably easy this way.

In order to complete the synthesis of resveratrone, the required epoxide **4a** was prepared as described by Blonski and co-workers (Scheme 3B).^[10] As shown in Scheme 3C, epoxide olefination to **9** and **9-iso** as well as subsequent deprotection to resveratrone (**2**) and *iso*-resveratrone (**2-iso**) proceeded in moderate yields.

Given the instability of **3a** under MPLC conditions and the resulting ease with which **3a-iso** can be obtained, we decided to briefly investigate the photophysical properties of *iso*-resveratrone (**2-iso**) in comparison to resveratrone (**2**).

It was found that both compounds **2** and **2-iso** showed quite similar emission profiles, which were in good agreement with those reported in literature. Both compounds revealed the same emission maximum at 571 nm irrespective of their slight deviations in excitation spectra (Figure 1).



Scheme 3. (a) TBSCl (3.0 equiv.), imidazole (3.5 equiv.), DCM, rt, 16 h; (b) B_2Pin_2 (2.0 equiv.), $[Ir(COD)(OMe)_2]$ (0.04 equiv.), dtbpy (0.06 equiv.), *n*-hexane, reflux, 16 h; (c) *p*TsOH (0.02 equiv.), $(HOCH_2)_2$, Ph-H, 80 °C, 16 h; (d) KOH, $(HOCH_2)_2$, 130 °C, 3 h; (e) Oxone (5 equiv.), $NaHCO_3$ (10 equiv.) acetone, 3 d; (f) **9** (1.3 equiv.), LiTMP (2.0 equiv.), THF 0 °C to rt, overnight, 60 °C, 2 h; (g) 1. TBAF, THF, 0 °C, 3 h, 2. HCl (2 m in H₂O), THF, overnight, rt (COD = cyclooctadiene, dtbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl).

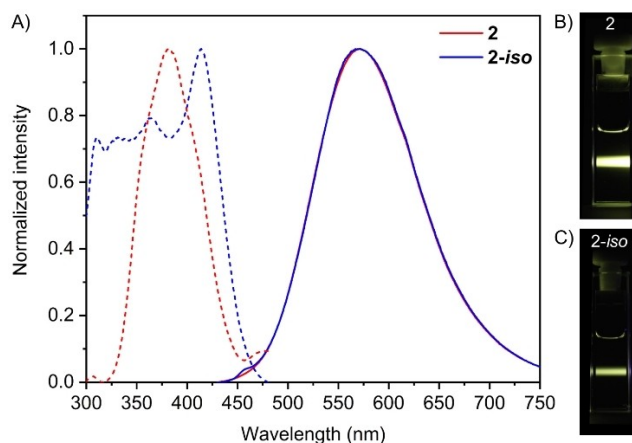
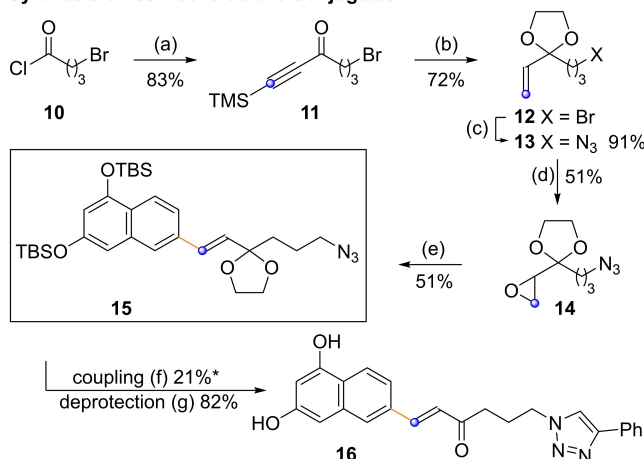


Figure 1. A) Excitation (dashed) and emission (solid) spectra of **2** and **2-iso** in methanol, $c = 100 \mu M$. B) $100 \mu M$ **2** in MeOH under UV light excitation ($\lambda_{ex} = 405 \text{ nm}$), C) $100 \mu M$ **2-iso** in MeOH under UV light excitation ($\lambda_{ex} = 405 \text{ nm}$).

Having established a reliable route to this interesting fluorophore and its photochemically related regioisomer, we applied it to the synthesis of the azide-functionalized derivative **15**, which we identified as a potentially interesting compound for molecular labelling (Scheme 4). Starting from acid chloride

Synthesis of *iso*-Resveratrone Conjugates

Scheme 4. (a) AlCl₃ (1.30 equiv.), (TMSC)₂, DCM, 0 °C to rt; (b) 1. (HOCH₂)₂, pTsOH (0.07 equiv.), 16 h, 85 °C, 2. TBAF, THF, 1 h 0 °C to rt, 3. Lindlar cat. (0.05 equiv.), H₂ (1 atm.), pyridine, 16 h, rt. (c) NaN₃ (3.00 equiv.), DMF, 16 h, rt; (d) oxone (5.00 equiv.) NaHCO₃ (10 equiv.), acetone, 0 °C to rt, 4 d; (e) LiTMP (2.00 equiv.), **3a-iso** (1.50 equiv.) 0 °C to rt 24 h, 60 °C 2 h; (f) CuSO₄ (0.10 equiv.), sodium ascorbate (0.20 equiv.), THF, H₂O, 2 d, rt; (g) HCl^{aq} (1 M), THF, 16 h, rt. (*) Yield of click product without deprotected side products.

10, an AlCl₃-mediated reaction with bis-TMS-acetylene yielded **11** in 83% yield. Acetal cleavage, desilylation and Lindlar reduction required only minimal workup. Bromide **12** was isolated in 72% overall yield, before reaction with NaN₃ delivered **13** in 91% yield. Epoxidation with oxone delivered the epoxide required for olefination in 51% yield.

Given the ease with which **3a-iso** can be prepared combined with the related photochemical properties of *iso*-resveratrone (**2-iso**) and resveratrone (**2**), olefination was conducted with 1.5 equivalents of **3a-iso**. The suitably protected, click-ready fluorophore **15** was obtained in 51% yield. Coupling and deprotection of **15** was tested with phenylacetylene. However, under aqueous click-coupling conditions,^[14] partial cleavage of the TBS groups took place, leading to only 21% of the click-product being isolated, deprotection of which yielded **16**.

Conclusions

In summary, we have reported the first total synthesis of resveratrone using the epoxide olefination as a key transformation. The amount of necessary boronate for the epoxide olefination can be reduced to 1.3 equiv. for aromatic boronates (**3**), which is a vital improvement for sequences that require the coupling of valuable boronic esters such as **3a**. A reoccurring challenge in the preparation of such substituted naphthalene derivatives lies in the lack of selectivity upon functionalization of 1,3-dinaphthol derivatives.^[15] This was also seen in the preparation of **3a**. However, separation from the regioisomer **3a-iso** was achieved by MPLC. Partial decomposition of **3a** made **3a-iso**, and thus *iso*-resveratrone (**2-iso**), more readily accessible.

First photochemical experiments point towards a comparable behavior of **2-iso**, so we applied our route to the synthesis of the click-ready *iso*-resveratrone derivative **15**, which will hopefully serve the community as a useful labelling tool.

Acknowledgements

We gratefully acknowledge funding from the Deutsche Forschungsgemeinschaft (DFG).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

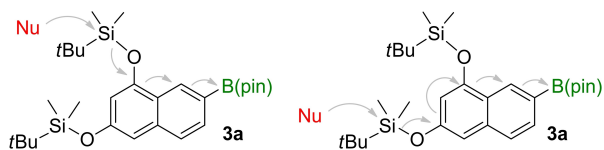
The data that support the findings of this study are available in the supplementary material of this article.

Keywords: epoxide · fluorescence label · olefination · resveratrone · total synthesis

- [1] S. Quideau, D. Deffieux, C. Douat-Casassus, L. Pouységu, *Angew. Chem. Int. Ed.* **2011**, *50*, 586–62; *Angew. Chem.* **2011**, *123*, 610–646.
- [2] S. Bradamante, L. Barengi, A. Villa, *Cardiovasc. Drug Rev.* **2004**, *22*, 3, 169–188.
- [3] A. Sahebkar, C. Serban, S. Ursoniu, N. D. Wong, P. Muntner, I. M. Graham, D. P. Mikhailidis, M. Rizzo, J. Rysz, L. S. Sperling, G. Y. H. Lip, M. Banach, *Int. J. Cardiol.* **2015**, *189*, 47–55.
- [4] a) I. Yang, E. Kim, J. Kang, H. Han, S. Sul, S. B. Park, S. K. Kim, *Chem. Commun.* **2012**, *48*, 3839–3841; *Emergence of fluorescence upon irradiation of 1 had been reported before:* b) J. P. Roggero, C. Garciaparrilla, *Sci. Aliments* **1995**, *15*, 411–422.
- [5] I. Yang, J. W. Lee, S. Hwang, J. E. Lee, E. Lim, J. Lee, D. Hwang, C. H. Kim, Y.-S. Keum, S. K. Kim, *J. Photochem. Photobiol. B* **2017**, *166*, 52–57.
- [6] M. Blanke, J. Balszuweit, M. Saccone, C. Wölper, D. D. Jiménez, M. Mezger, J. Voskuhl, M. Giese, *Chem. Commun.* **2020**, *56*, 1105–1108.
- [7] a) D. M. Hodgson, N. J. Reynolds, S. J. Coote, *Tetrahedron Lett.* **2002**, *43*, 7895–7897; b) D. M. Hodgson, E. H. M. Kirton, S. M. Miles, S. L. M. Norsikian, N. J. Reynolds, S. Coote, *J. Org. Biomol. Chem.* **2005**, *3*, 1893–1904.
- [8] K. Bojaryn, S. Fritsch, C. Hirschhäuser, *Org. Lett.* **2019**, *21*, 2218–2222.
- [9] *Previous reports on the insertion of lithiated epoxides into boronic esters:* a) M. Shimizu, T. Fujimoto, H. Minezaki, T. Hata, T. Hiyama, *J. Am. Chem. Soc.* **2001**, *123*, 6947–6948; b) E. Vedrenne, O. A. Wallner, M. Vitale, F. Schmidt, V. K. Aggarwal, *Org. Lett.* **2009**, *11*, 165–168; c) E. Alwedi, L. N. Zakharov, P. R. Blakemore, *Eur. J. Org. Chem.* **2014**, *2014*, 6643–6648; d) K. Bojaryn, C. Hoffmann, F. R. Struth, C. Hirschhäuser, *Synlett* **2018**, *29*, 1092–1094; *Previous reports on Olefinations with Epoxide based carbenoids:* e) D. M. Hodgson, M. J. Fleming, S. J. Stanway, *J. Am. Chem. Soc.* **2004**, *126*, 12250–12251; f) D. M. Hodgson, M. J. Fleming, S. J. Stanway, *J. Org. Chem.* **2007**, *72*, 4763–4773; g) D. M. Hodgson, P. G. Humphreys, M. J. Fleming, *J. Org. Synth.* **2008**, *85*, 1.
- [10] P. Page, C. Blonski, J. Périé, *Bioorg. Med. Chem.* **1999**, *7*, 1403–1412.
- [11] R. Meier, S. Strych, D. Trauner, *Org. Lett.* **2014**, *16*, 2634–2637.
- [12] a) T. Ishiyama, K. Ishida, N. Miyaura, *Tetrahedron* **2001**, *57*, 9813–9816; b) A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412–443; c) J. P. Fischer, J. Bradford, J. F. Blake, R. J. Hinklin, M. Macedonio, E. J. Hicken, M. J. Chicarelli, J. J. Gaudino, G. P. A. Vigers, L. E. Burgess, M. A. Marx, J. G. Christensen, M. R. Lee, P. Savechenko, H. J. Zecca, *Preparation*

of substituted pyridopyrimidines as *KRas* G12C inhibitors for treating cancer, *PCT international Application*, 2017, WO 2017201161.

[13] The preferred decomposition of **3a** can be rationalized via the vinylogous positioning of the boronic ester:



[14] F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210–216.

[15] J. Winkelblech, S.-M. Li, *ChemBioChem* **2014**, *15*, 1030–1039.

Manuscript received: April 28, 2022

Revised manuscript received: May 30, 2022