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. Resveratrone 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-labeling applications.\(^4, 5\) 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”.\(^4\) 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 employed 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...
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′ = 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 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 (RP[16], 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).

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...
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-resveratrole (2-iso) and resveratrole (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, 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 resveratrole 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. 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-resveratrole (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-resveratrole 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 · resveratrole · total synthesis

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Manuscript received: April 28, 2022
Revised manuscript received: May 30, 2022