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Visible Light Photoredox Catalysis Enables the Biomimetic Synthesis of Nyingchinoids A, B and D, and Rasumatranin D

Jacob D. Hart, Laura Burchill, Aaron J. Day, Christopher G. Newton, Christopher J. Sumby, David M. Huang and Jonathan H. George*

Abstract: The total synthesis of nyingchinoids A and B has been achieved via successive rearrangements of a 1,2-dioxane intermediate that was assembled using a visible light photoredox catalysed aerobic [2+2+2] cycloaddition. Nyingchinoid D was synthesised by a competing [2+2] cycloaddition. Based on NMR data and biosynthetic speculation, we proposed a structure revision of the related natural product rasumatranin D, which was confirmed through total synthesis. Under photoredox conditions, we observed the conversion of a cyclobutane into a 1,2-dioxane via retro-[2+2] cycloaddition followed by aerobic [2+2+2] cycloaddition.

The renaissance of visible light photoredox catalysis during the past decade has significantly enhanced the toolkit of organic synthesis through the improved ability to access radicals and radical ions under mild conditions.[1] However, the application of photoredox catalysis to the total synthesis of natural products has been relatively slow, with most examples to date involving the reductive generation of alkyl radicals or photocatalysed [4+2] and [2+2] cycloadditions.[2] Herein, we report the first total synthesis application of a photocatalytic aerobic [2+2+2] cycloaddition as the key step of a biomimetic route to nyingchinoid[3] and rasumatranin[4] meroterpenoid natural products.
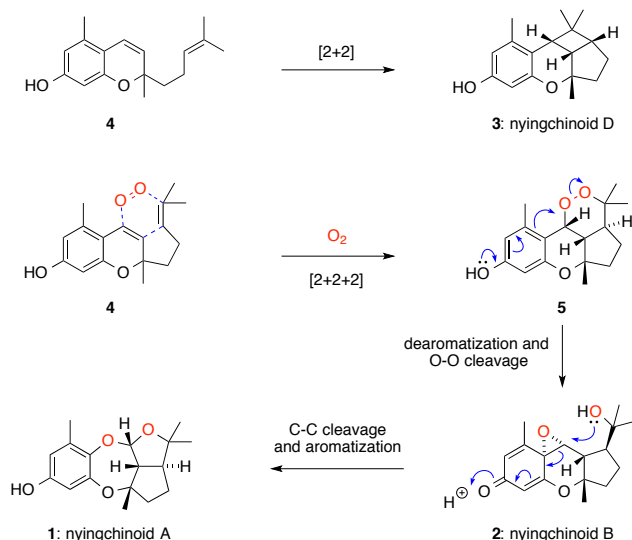

Scheme 1. Proposed biosynthesis of nyingchinoids A, B and D.

Nyingchinoids A-H are a family of polycyclic meroterpenoids isolated from *Rhododendron nyingchiense* by Hou and co-

workers, with each natural product identified as a scalemic mixture by chiral HPLC.[3] We were particularly interested in the biosynthetic relationships between nyingchinoids A (**1**), B (**2**) and D (**3**) and a possible biosynthetic precursor, chromene **4** (Scheme 1). While nyingchinoid D (**3**) is most likely derived from an intramolecular, photochemical [2+2] cycloaddition of **4**, the biosynthetic origin of nyingchinoids A (**1**) and B (**2**) is less obvious. We propose that 1,2-dioxane **5** is an undiscovered natural product or biosynthetic intermediate that links chromene **4** to **1** and **2**. The 1,2-dioxane **5** could arise via a [2+2+2] cycloaddition between oxygen and the chromene and prenyl alkenes of **4**. Intramolecular dearomatization of **5** driven by cleavage of the weak O-O bond could then form **2**.[5] Nucleophilic attack at the epoxide of **2** by the newly formed tertiary alcohol could then rearomatize the system via an unusual C-C bond scission to give **1**.

In biosynthesis, the aerobic [2+2+2] cycloaddition has only been proposed to occur in the formation of gracilioethers A and H,[6] although this reaction has not yet been successfully applied in a total synthesis of these,[7] or any other, 1,2-dioxane natural products. The majority of 1,2-dioxane natural products are biosynthesised via [4+2] cycloadditions between 1,3-dienes (of either terpene or polyketide origin) and singlet oxygen, a reaction that is amenable to biomimetic synthesis.[8] The biomimetic synthesis of 1,2-dioxane natural products has also been achieved using cascade radical cyclizations that incorporate triplet oxygen.[9]

As a synthetic method, the photocatalytic aerobic [2+2+2] cycloaddition of electron-rich 1,1-disubstituted styrenes to give 1,2-dioxanes using 9,10-dicyanoanthracene (DCA) as the photocatalyst was first reported by Gollnick.[10] Synthesis of bicyclic endoperoxides via aerobic [2+2+2] cycloaddition of electron-rich bis(styrene) substrates was later disclosed by Miyashi, again using DCA as the photocatalyst.[11] More recently, the scope of the aerobic [2+2+2] cycloaddition was significantly extended by Yoon to include less electron-rich bis(styrene) substrates using Ru(bpz)$_3$$^{2+}$ as an efficient photocatalyst.[12] Most recently, and most relevantly to this work, Nicewicz showed that the use of triarylpyrylium salts as organic photocatalysts allowed the aerobic [2+2+2] cycloaddition of dienes bearing one styrene and one aliphatic alkene (Scheme 2).[13]
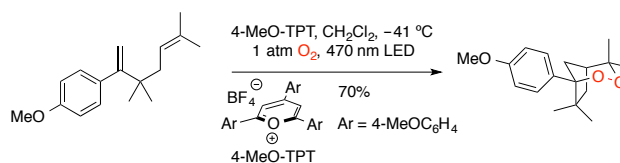
Scheme 2. Nicewicz's photocatalysed cyclization-endoperoxidation cascade of a tethered diene using a triarylpyrylium catalyst. 4-MeO-TPT = 2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate.

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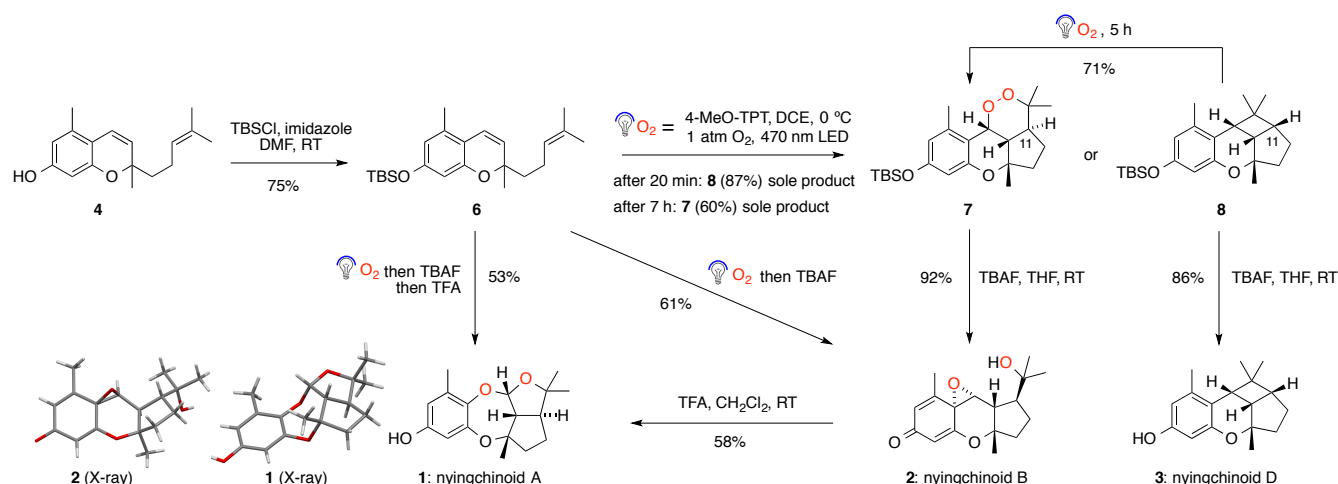
Scheme 3. Biomimetic synthesis of nyingchinoids A, B and D. TBSCl = *tert*-butyldimethylsilyl chloride, DMF = *N,N*-dimethylformamide, DCE = 1,2-dichloroethane, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

Our biomimetic synthesis of nyingchinoids A, B and D is outlined in Scheme 3. Racemic chromene **4** was first synthesised in one step by condensation of orcinol with citral according to a known procedure.[14] We then attempted to convert chromene **4** into 1,2-dioxane **5** using various oxidation protocols. Firstly, exposure of **4** to conditions known to generate singlet oxygen (e.g. Rose Bengal sensitiser, O_2, MeOH, visible light) gave products exclusively formed by oxidation of the prenyl side chain, rather than the electron-rich chromene.[15] Secondly, attempts to oxidise **4** to a phenoxy radical in the presence of O_2 resulted in degradation of starting material.[16] We therefore protected **4** as TBS-ether **6**, which we thought could be oxidised to a radical cation under photoredox conditions. Treatment of **6** with a slightly modified version of Nicewicz's conditions for pyrylium photoredox catalysed aerobic [2+2+2] cycloaddition (2 mol% 4-MeO-TPT photocatalyst, DCE, 0 °C, 1 atm O_2, 470 nm LED) gave, after 20 min, cyclobutane **8** as the only product observed in the ^{1}H NMR spectrum of the reaction mixture.[17] After purification, **8** was obtained in 87% yield. Deprotection of **8** using TBAF in THF gave nyingchinoid D (**3**) in 86% yield. However, on repeating this [2+2] cycloaddition we noticed the gradual formation of the desired 1,2-dioxane **7** (as a single diastereoisomer) when the reaction was run for extended time periods. After 7 h, **7** was obtained in 60% yield. No reaction was observed in either the absence of photocatalyst or blue LED light. Treatment of **7** with TBAF formed nyingchinoid B (**2**) in 92% yield via intramolecular dearomatization of the intermediate phenoxide anion.[18] Acid catalysed rearrangement of **2** using TFA in CH_2Cl_2 then gave nyingchinoid A (**1**) in 58% yield. Next, we investigated some telescoped reactions of chromene **6** to form **1** and **2** in one-pot procedures. Pleasingly, photoredox catalysed aerobic [2+2+2] cycloaddition of **6** followed by addition of TBAF gave **2** in 61% yield, while addition of TBAF followed by TFA gave **1** in 53% yield. The latter transformation of **6** into **1** involves the construction of 2 rings, 3 stereocentres, 4 C-O bonds and 1 C-C bond, alongside the scission of 1 O-O bond and 1 C-C bond.

Our experimental results clearly demonstrate that the photoredox catalyzed [2+2] cycloaddition of **6** is reversible using the 4-MeO-TPT photocatalyst. Indeed, re-subjecting cyclobutane **8** to this catalyst under aerobic conditions formed 1,2-dioxane **7** in 71% yield, with inversion of the relative configuration at C-11 indicating that full cycloreversion had taken place before the [2+2+2] cycloaddition. In previous studies of photocatalytic, intermolecular [2+2] cycloadditions of electron-rich styrenes, Yoon has observed significant cycloreversion of the cyclobutane products when using the highly oxidizing photocatalyst $Ru(bpz)_3^{2+}$.[19] A mechanistic cycle for the aerobic [2+2+2] cycloaddition of **6** that incorporates a reversible [2+2] cycloaddition is outlined in Scheme 4. The 4-MeO-TPT photocatalyst is first activated by blue LED light to give an excited state capable of oxidizing the electron-rich chromene **6** to give radical cation **9**. 5-exo-trig cyclization of **9** generates the diasteromeric, distonic radical cations **10** and **12**. Diastereomer **10** has the correct relative configuration to undergo further cyclization to give the cyclobutane radical cation **11**, followed by reduction to give cyclobutane **8** as the overall kinetic product of the reaction. Diastereomer **12** is unable to undergo reductive cyclization in this manner, so it is trapped by $^3O_2$ to give **14** via the peroxy radical cation **13**. Single electron reduction of **13** then gives 1,2-dioxane **7** as the thermodynamic product. Re-oxidation of **8** by the excited photocatalyst could regenerate radical cation **9** via retro-[2+2] cycloaddition of **11**, thus allowing the kinetic product **8** to be "recycled" to give **7** via radical cation **12**. The high oxidation potential of the excited state of 4-MeO-TPT$^+$ (+1.74 V) is presumably required to oxidize **8** prior to cycloreversion. This stepwise mechanistic pathway is supported by computational modeling using density functional theory, which shows that both 5-exo-trig cyclizations of radical cation **9** are reversible and confirms **7** as the thermodynamic product, but indicates that the system becomes kinetically trapped as **11** instead of forming **12** (see the Supporting Information for full details).
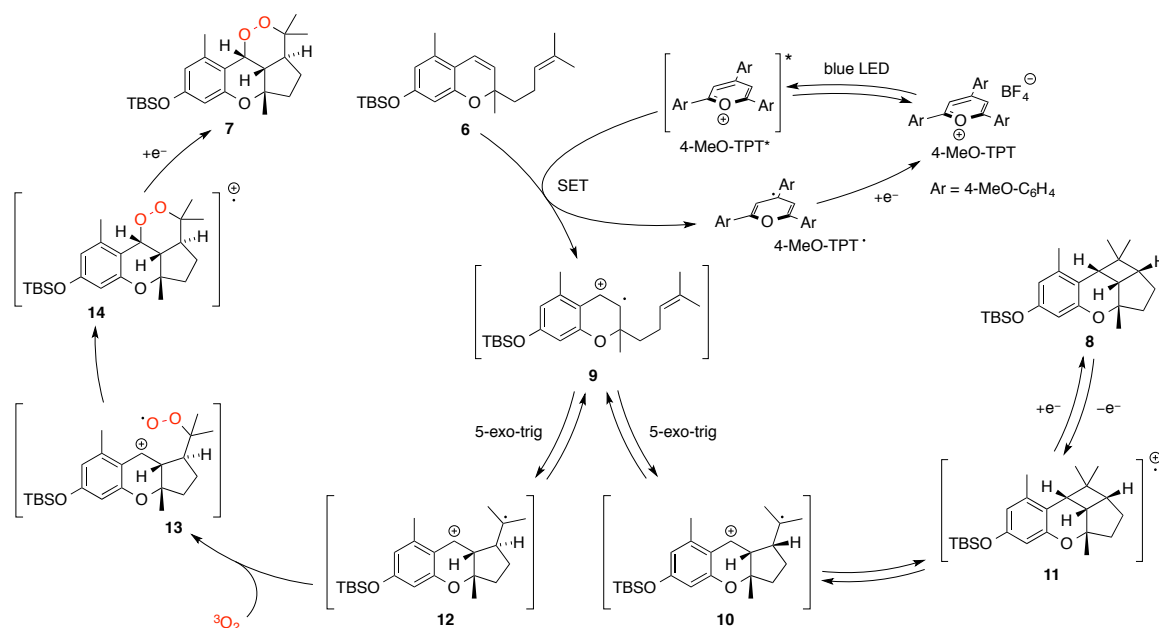
Scheme 4. Proposed mechanistic cycle for the photocatalysed cyclization of chromene **6** to give 1,2-dioxane **7** and cyclobutane **8**.

Finally, we compared the NMR spectra of nyingchinoid A (**1**), whose structure has been unequivocally proven by X-ray crystallography, with that of the related natural product rasumatranin D, which suggested that the previously proposed structure **15** was incorrect (Figure 1).[4] We believed that the substitution pattern of the aromatic ring and the relative configuration at C-11 of rasumatranin D should be reassigned as structure **16**, in line with the structure of nyingchinoid A. The coupling constant of 14 Hz between H-3 and H-11, and the absence of an nOe interaction, indicates a *trans* relationship at this ring junction of **16**. Furthermore, the co-isolation of the cyclobutane natural product **17** alongside rasumatranin D suggested a common chromene biosynthetic precursor with the same aromatic substitution pattern as the nyingchinoids.[20]
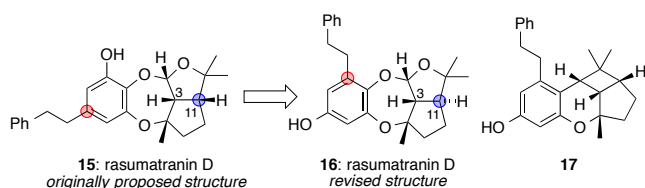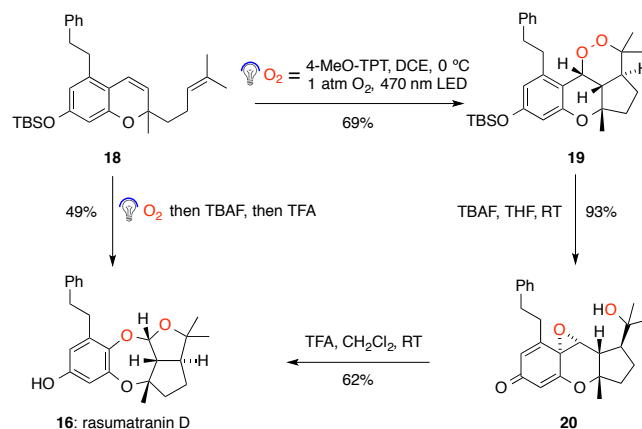
natural rasumatranin D, thus confirming the structure revision. The synthesis of rasumatranin D was significantly streamlined by conducting a one-pot conversion of **18** into **16** in 49% yield.

Scheme 5. Biomimetic synthesis of rasumatranin D.

Figure 1. Proposed structure revision of rasumatranin D.

Our synthesis of the revised rasumatranin D structure **16** is outlined in Scheme 5. Firstly, **18** was synthesised by TBS-protection of a known chromene.[21] Visible light photoredox catalysed aerobic [2+2+2] cycloaddition of **18** then gave 1,2-dioxane **19**. Treatment of **19** with TBAF formed the nyingchinoid B analogue **20** (presumably an undiscovered natural product), which gave rasumatranin D (**16**) on exposure to TFA. NMR data for **16** showed excellent agreement with the published data for

In conclusion, we have achieved the biomimetic synthesis of nyingchinoids A, B and D, and the revised structure of rasumatranin D, using [2+2] and [2+2+2] cycloadditions that were initiated by oxidation of electron-rich chromenes. The use of visible light mediated photoredox catalysis to oxidize these substrates enabled the cycloadditions to be telescoped with further rearrangements in multi-step, one-pot procedures. The predisposed, highly diastereoselective, biomimetic synthesis of nyingchinoids A and B from a common chromene intermediate gives good insight into the biosynthesis of these natural products, which is supported by the structure revision of rasumatranin D. Furthermore, we observed for the first time the conversion of a

cyclobutane into a 1,2-dioxane via a photocatalysed retro-[2+2] cycloaddition / aerobic [2+2+2] cycloaddition cascade reaction.

Acknowledgements

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Entry for the Table of Contents

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4 C-O, 1 C-C bonds formed
1 O-O, 1 C-C bonds broken
2 rings, 3 stereocentres formed
1 ring expansion

nyingchinoid A

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