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Biomimetic Synthetic Studies on the Bruceol Family of Meroterpenoid Natural Products

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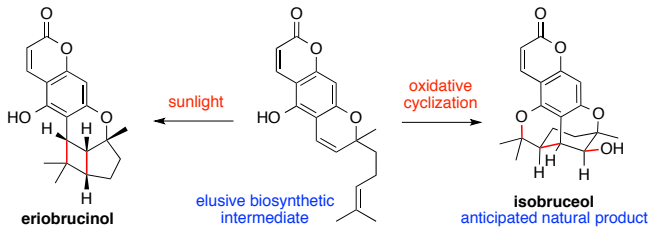
Abstract



A biomimetic approach to total synthesis can offer several benefits, including the development of cascade reactions for the rapid generation of molecular complexity, and guidance in the structure revision of old natural products and the anticipation of new ones. Herein, we describe how a biomimetic synthesis of bruceol, a pentacyclic meroterpenoid, led to the anticipation, isolation and synthesis of isobruceol. The key step in the synthesis of both bruceol and isobruceol was an intramolecular hetero-Diels-Alder reaction of an *o*-quinone methide that was formed by dearomatization of an electron-rich chromene. The synthesis of an elusive biosynthetic intermediate also allowed a concise synthesis of eriobrucinol via a photochemical [2+2] cycloaddition. Furthermore, some speculation on the biosynthesis of prenylated bruceol derivatives inspired the development of a Claisen/Cope/Diels-Alder cascade reaction. We also report the generation of halogenated bruceol derivatives, and the synthesis of several protobruceol natural products using singlet oxygen ene reactions.

Introduction

Australian plants of the *Philotheca* genus are a rich source of complex, polycyclic meroterpenoids (Figure 1).[1] These natural products generally feature coumarin ring systems (highlighted in red) derived from polyketide biosynthetic pathways, while the stereochemically rich "citran" and "cyclol" ring systems[2] (highlighted in blue) arise from the cyclization of terpene side chains. The

prototypical *Philotheca* meroterpenoid is bruceol (**1**), first isolated from *Philotheca brucei* (formerly known as *Eriostemon brucei*) by Jefferies *et al.* working at the University of Western Australia (UWA) in 1963.[3] The structure of bruceol was determined predominantly by X-ray crystallography, an early application of this technique towards the elucidation of a complex Australian natural product that was facilitated by the then recent appointment of Edward Maslen to the staff at UWA.[4] NMR spectroscopy was not used in the structure elucidation of bruceol, although a few peaks of a low resolution 60 MHz ^{1}H NMR spectrum were reported. The absolute configuration of naturally occurring (–)-bruceol was later determined by X-ray crystallography of chloroacetate and iodoacetate derivatives.[5] Several years later, in 1992, Waterman and co-workers believed they had re-isolated bruceol (**1**) from *Philotheca brucei*, and accordingly they published a full NMR analysis.[6] However, our synthesis of bruceol revealed that Waterman had in fact unwittingly isolated a new isomeric natural product that we termed isobruceol (**2**).[7] In isobruceol (**2**), the orientation of the citran ring system (highlighted in blue) to the coumarin ring system (highlighted in red) is opposite to that of bruceol (**1**). In addition to the synthesis of bruceol and isobruceol, we also isolated isobruceol from *Philotheca brucei*. Herein we present a full account of this work, alongside the synthesis of several related natural products. Deoxyisobruceol (**4**) was isolated from *Philotheca brucei* in 1981 by Jefferies *et al.*,[5] although a pre-emptive total synthesis was first reported by Crombie and Ponsford in 1968 (*vide infra*).[8] Initially, Crombie thought he had synthesised deoxybruceol (**3**), which has not yet been isolated from a natural source, but later X-ray studies revealed his synthesis of **4**.[9] Both structures **3** and **4** are therefore variously referred to as "deoxybruceol" in the previous literature, despite this name for the natural product **4** being a misnomer. To avoid further confusion, we strongly recommend use of the trivial names given in Figure 1. Several cyclobutane-containing pentacyclic natural products have also been isolated from *Philotheca brucei*, including eriobrucinol (**6**)[10] and iso-eriobrucinol A (**5**).[11] These meroterpenoids feature a "cyclol" ring system (highlighted in blue).

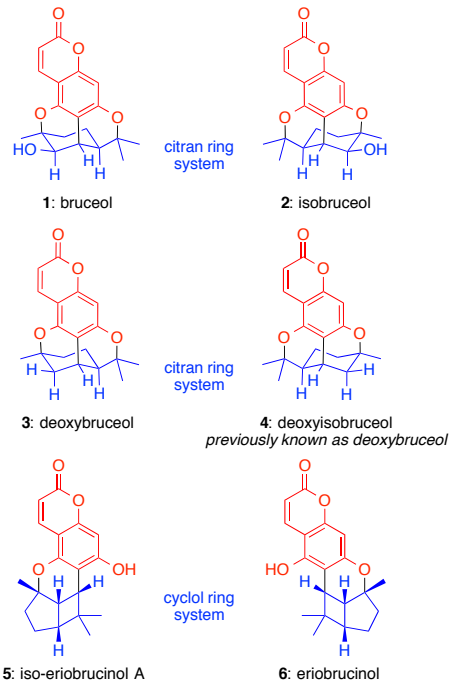
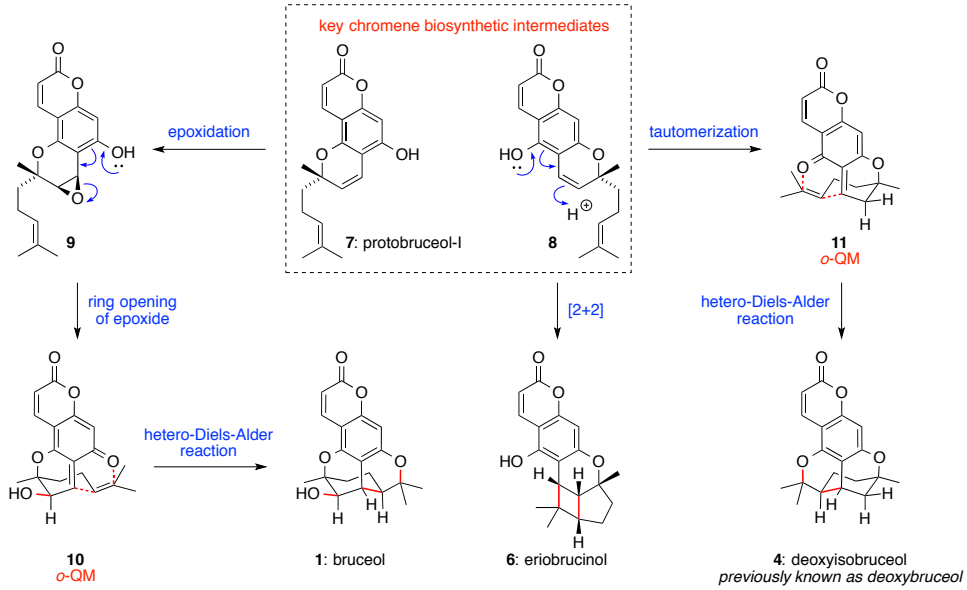


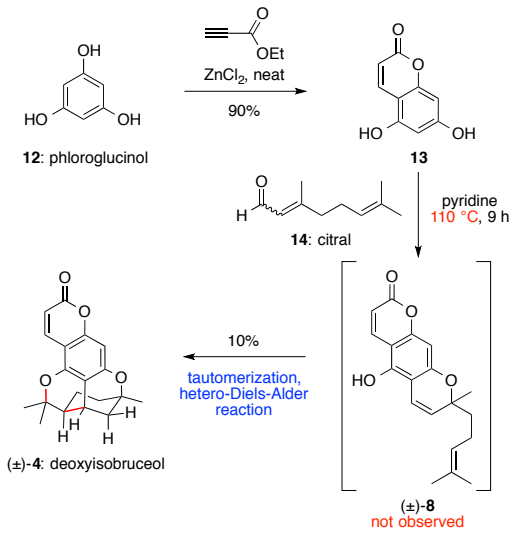
Figure 1. "Citran" and "cyclol" meroterpenoid natural products related to bruceol.

The biosynthetic pathways to most of the polycyclic meroterpenoids found in *Philotheca brucei* are proposed to start from an isomeric pair of tricyclic chromenes: protobruceol-I (**7**), which was isolated by Waterman in 1992,[12] and chromene **8**, which has yet to be isolated. The biosynthesis of bruceol (**1**) from protobruceol-I (**7**) has been previously proposed in review articles by Ghisalberti[1] and by Trauner.[13] In detail, the stereoselective epoxidation of **7** could give epoxide **9**, which could ring open to form the reactive *o*-quinone methide (*o*-QM) intermediate **10** (Scheme 1).[14] An intramolecular hetero-Diels-Alder reaction of **10** could then generate the polycyclic framework of bruceol (**1**).[15] In a similar manner, deoxyisobruceol (**4**) could be formed via tautomerization of chromene **8**, followed by intramolecular hetero-Diels-Alder reaction of the *o*-quinone methide **11**. Eriobrucinol (**6**), the prototypical cyclol natural product in the bruceol family, is presumably biosynthesized via an intramolecular [2+2] cycloaddition of chromene **8**.



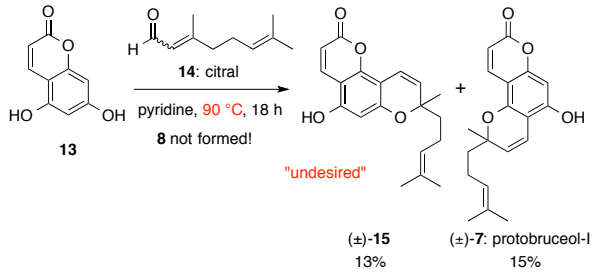
Scheme 1. Proposed Biosynthesis of Bruceol, Deoxyisobruceol and Eriobrucinol From a Pair of Isomeric Chromenes

Racemic deoxyisobruceol (**4**) was first synthesised in 1968 by Crombie and Ponsford in a classic work of biomimetic synthesis – and also natural product prediction, given that its isolation was not reported until several years later. Firstly, the synthesis of 5,7-dihydroxycoumarin (**13**) was achieved by the reaction between phloroglucinol (**12**) and neat ethyl propiolate in the presence of $ZnCl_2$ (Scheme 2).[16] The second, incredible step of the synthesis involved the condensation of **13** with citral (**14**) in pyridine at 110 ºC, which gave **(±)-4** in 10% isolated yield. It was initially assumed that Knoevenagel condensation of **13** with **14** followed by oxa-6π-electrocyclization of an intermediate *o*-quinone methide gave chromene **8** – a sequence often referred to as a "Crombie chromenylation". Chromene **8** could then undergo tautomerization followed by an intramolecular hetero-Diels-Alder reaction of a second *o*-quinone methide (**11**, Scheme 1) to give **4**. However, chromene **8** was never observed as an intermediate in, or a by-product of, this reaction.



Scheme 2. Crombie's Classic Total Synthesis of Racemic Deoxyisobruceol

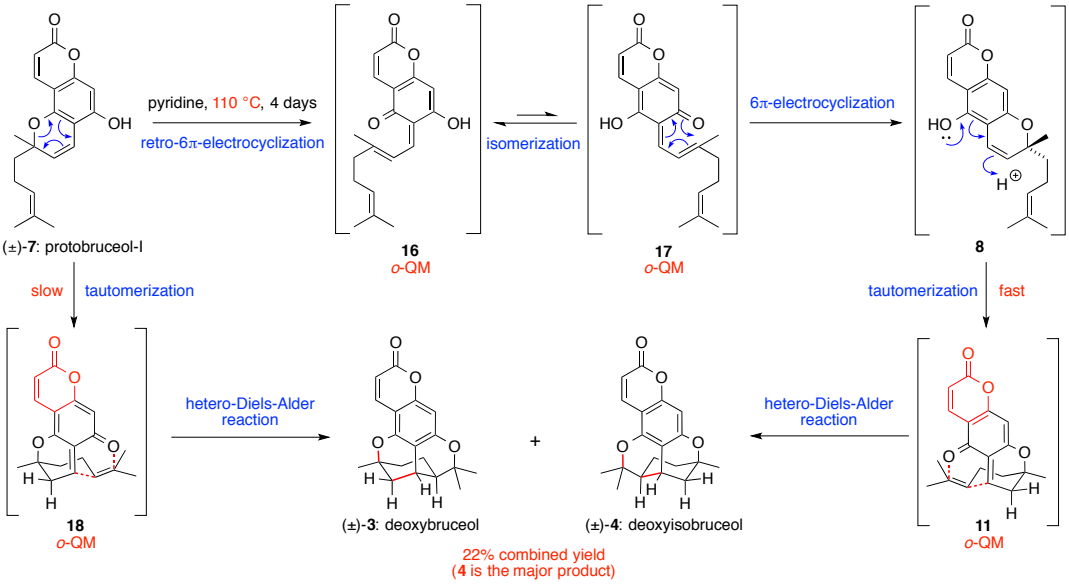
In fact, when the chromenylation of **13** was conducted at lower temperature (90 ºC), the only chromene products observed were **15** and protobruceol-I (**7**), in 13% and 15% yield respectively (Scheme 3). Crombie rationalised the regioselective synthesis of chromenes **15** and **7** in preference to **8** due to their formation via 6π-electrocyclization of stabilised *o*-quinone methide intermediates in which the partial aromaticity of the coumarin ring was maintained.



Scheme 3. Crombie's Synthesis of Protobruceol-I

To explain his synthesis of deoxyisobruceol (**4**) (Scheme 2), Crombie reasoned that protobruceol-I (**7**) must isomerize under the thermal reaction conditions to generate chromene **8** as an unobservable intermediate. This was proven by heating **7** in pyridine at reflux, which generated **4** as the major product (Scheme 4). Mechanistically, retro-6π-electrocyclization of **7** could form the stabilized *o*-quinone methide **16**, which retains the partially aromatic coumarin ring (highlighted in

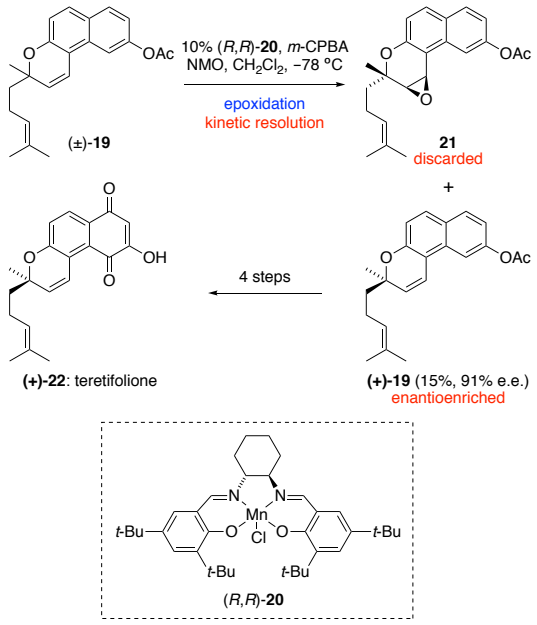
red). Isomerization of **16** could give the less stable *o*-quinone methide **17**, followed by chromene **8** via 6π-electrocyclization. Chromene **8** is more reactive than **7** with respect to tautomerization, as the resultant *o*-quinone methide **11** retains the aromatic character of the coumarin ring system (*c.f.* the less stable **18**). The tautomerization and hetero-Diels-Alder reaction of chromene **8** is therefore faster than that of **7**, and deoxyisobruceol (**4**) is the major product of the reaction in a good example of the Curtin-Hammett principle. In 2007, Lee and Kim reported a modified synthesis of **4** in 45% yield by condensation of **13** with **14** using catalytic ethylenediamine diaceatate (EDDA) in DMF, instead of pyridine.[17]



Scheme 4. Crombie's Thermal Rearrangement of Protobruceol-I

In order to build on Crombie's seminal work and achieve the first biomimetic synthesis of bruceol (**1**), we needed an oxidant capable of epoxidizing the chromene alkene of protobruceol-I (**7**) in the presence of the prenyl side chain. Our previous biomimetic synthesis of rhodonoids C and D used *m*-CPBA to epoxidize the prenyl side chain of a similar chromene meroterpenoid,[18] so this reagent was clearly unsuitable. Examination of the literature revealed that the Jacobsen-Katsuki epoxidation[19] performs well in the epoxidation of chromenes.[20] Furthermore, the Jacobsen-type chiral (salen)manganese(III)-complexes are known to epoxidize (*Z*)-1,2-disubstituted alkenes in preference to tri-substituted alkenes, such as the prenyl side chain. Indeed, Jacobsen has exploited

this chemoselectivity in a kinetic resolution of a chromene *en route* to the asymmetric synthesis of the meroterpenoid (+)-teretifolione B (**22**) (Scheme 5).[21] In this work, the racemic chromene **(±)-19** was treated with 10 mol % of the chiral (salen)Mn catalyst (*R,R*)-**20** in the presence of *m*-CPBA and NMO. To obtain **(+)-19** in good enantiopurity, the epoxidation had to be carried out to high conversion (approx. 80%), as the kinetic resolution occurred with high catalyst-induced selectivity but low substrate-induced selectivity. The presumed major epoxide product, **21**, was undesired and discarded in this process. However, in the case of our bruceol synthesis, a similar chromene epoxide would trigger the biomimetic cascade.

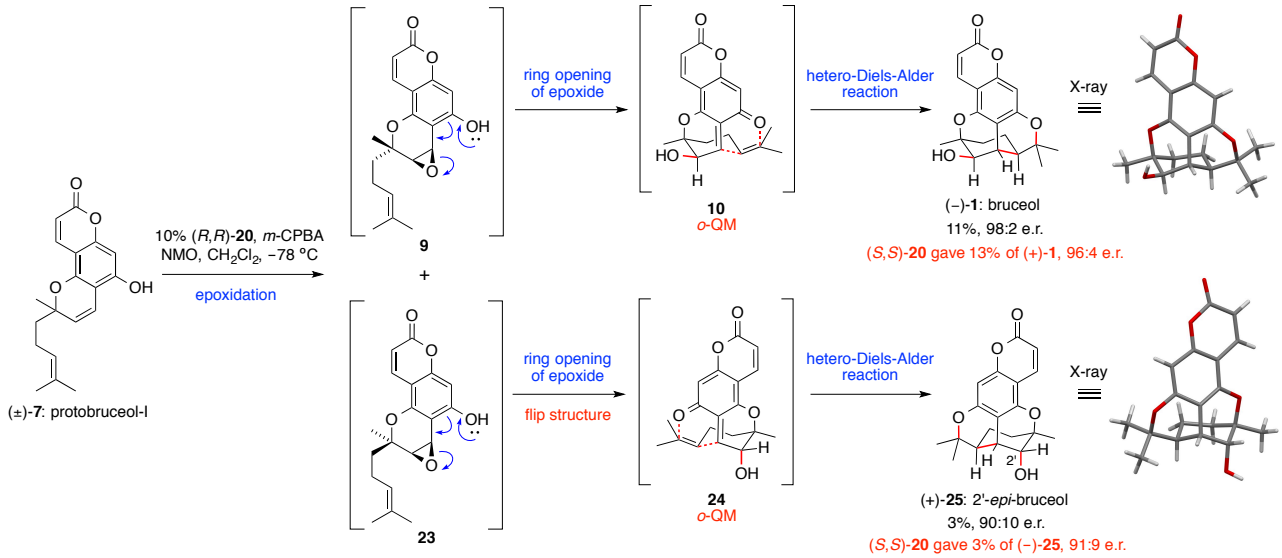


Scheme 5. Jacobsen's Kinetic Resolution of a Racemic Chromene Using an Asymmetric Epoxidation Strategy

Results and Discussion

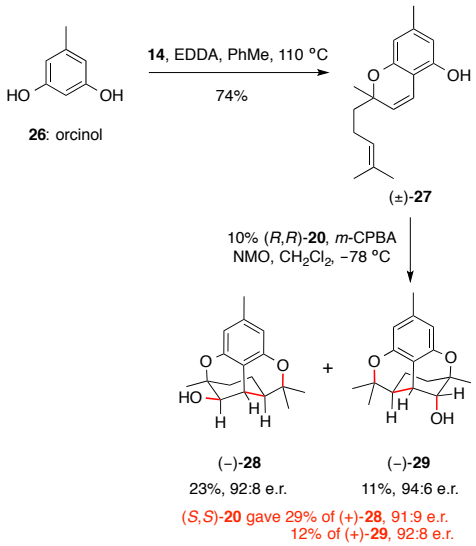
Before our attempts to synthesise bruceol, racemic protobruceol-I (**7**) was prepared in two steps and in multi-gram quantities according to Crombie's published procedures (Scheme 3). Treatment of **(±)-7** with 10 mol % of Jacobsen's catalyst (*R,R*)-**20** then gave **(–)-1** in a modest but reproducible yield of 11%, and in high enantiopurity (98:2 e.r.) (Scheme 6). This kinetic resolution presumably proceeds via a biomimetic cascade reaction involving ring opening of enantiopure epoxide **9**,

followed by an intramolecular hetero-Diels-Alder reaction of the resultant *o*-quinone methide **10**. Formation of 2'-*epi*-bruceol **(+)-25** was also observed in low yield during this reaction (3%, 90: 10 e.r.) via ring opening of the diastereomeric epoxide **23** and cyclization of *o*-quinone methide **24**, indicating the expected low substrate selectivity for the Jacobsen epoxidation. Use of (*S,S*)-**20** resulted in the formation of the unnatural enantiomer of bruceol, **(+)-1**, alongside **(–)-25**. However, careful comparison of the NMR spectra for synthetic bruceol (**1**) revealed that it did not quite match the NMR data for "bruceol" isolated by Waterman in 1992. Remarkably, we were able to obtain the original 1963 isolation sample of bruceol from the University of Western Australia, and its NMR spectra perfectly matched our synthetic material. We also obtained X-ray structures of both **1** and **25**. At this point, we thought it was likely that Waterman had isolated isobruceol (**2**), rather than bruceol (**1**).



Scheme 6. Biomimetic Total Synthesis of Bruceol

The low yield for the bruceol cascade could be due to overoxidation of the coumarin ring system, which gave rise to some highly polar, uncharacterised by-products. This conjecture was supported by the much higher yield for the epoxidation-cyclization cascades of the simpler chromene **(±)-27**, which was derived from chromenylation of orcinol (**26**) (Scheme 7).[18]



Scheme 7. A More Efficient Epoxidation-Cyclization Cascade of a Simpler Chromene

Having confirmed that synthetic bruceol (**1**) matched the original isolation sample in all characterisation data, we wanted to confirm our hypothesis that Waterman had isolated isobruceol (**2**), rather than bruceol. Initial attempts to synthesize isobruceol met with failure, so we conducted our own isolation experiments (Figure 2). Several kilograms of *Philotheca brucei* were collected from the Koolyanobbing Range (approx. 500 km east of Perth, Western Australia), and the plant material was extracted via two different methods. Firstly, a simple extraction of the plant material using Et_2O and purification by flash chromatography (after removal of volatile eucalyptol) gave an 11:1 mixture of bruceol (**1**) and isobruceol (**2**). Pure bruceol was easily obtained by crystallization, whereas purification of isobruceol required HPLC separation. Recrystallisation of isobruceol from $CHCl_3/Et_2O$ gave crystals suitable for X-ray analysis,[22] and its NMR spectra matched Waterman's data, thus confirming his isolation of **2** rather than **1**. The second extraction involved the pressurized hot water extraction (PHWE) method developed by Smith and co-workers, which uses an unmodified household espresso machine.[23] This method has recently been used to isolate coumarin natural products from Australian native plant species.[24] Application of the PHWE approach to *Philotheca brucei* gave a mixture of four known coumarin natural products – bruceol (**1**), isobruceol (**2**), hydroxyeriobrucinol (**30**) and isoimperatorin (**31**). **(–)-30** was particularly abundant (0.44% dry

weight of the plant material). Single crystal X-ray crystallography of **(–)-30** allowed its absolute configuration to be assigned as shown in Figure 1, which agrees with a previous tentative assignment.[25] We had hoped to discover chromene **8** to support our biosynthetic speculations, but ultimately our efforts were unsuccessful.

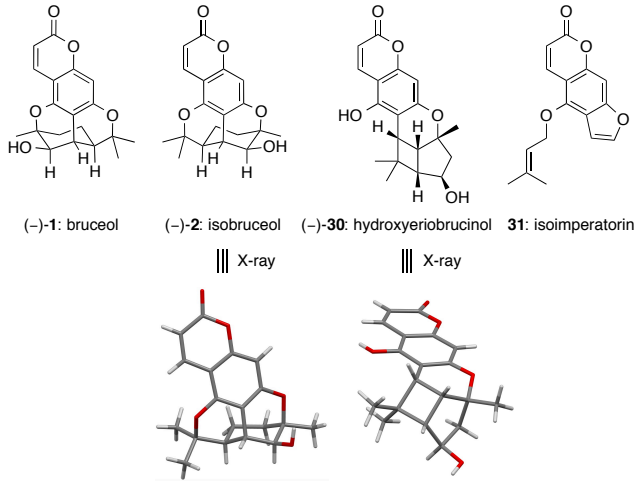
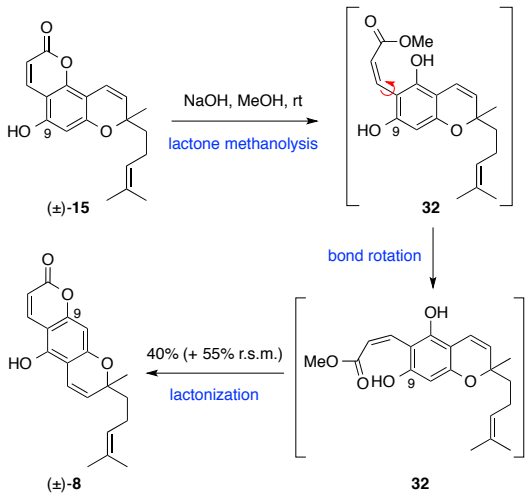


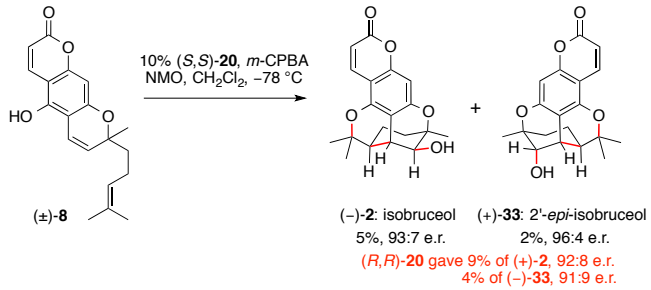
Figure 2. Coumarin natural products isolated from *Philotheca brucei* in this work.

Attempts to synthesise isobruceol (**2**) were thwarted by the impossibility of preparing its likely biosynthetic precursor **8** via the direct chromenylation of 5,7-dihydroxycoumarin (**13**) with citral (**14**), which gave only the regioisomeric chromenes **15** and **7** (Scheme 3). Indeed, we accumulated significant quantities of the undesired chromene **15** as we scaled up the synthesis of protobruceol-I (**7**). Eventually, we realised that chromene **15** could be isomerized to give **8** via lactone methanolysis to give **32**, followed by lactonization (Scheme 8).[26] This resulted in an equilibrium mixture of **15** and **8**, which was easily separated by flash chromatography.



Scheme 8. Isomerization of 15 to 8 Catalysed by Methoxide

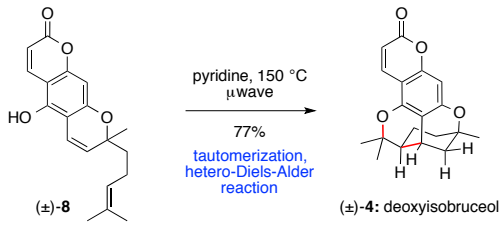
With convenient access to racemic chromene **8**, we could investigate its conversion into isobruceol (**2**) under Jacobsen epoxidation conditions (Scheme 9). Reaction of **(±)-8** with 10% (*S,S*)-**20** alongside *m*-CPBA and NMO as the stoichiometric oxidants formed **(–)-2** in 5% yield, alongside its C-2' epimer **(+)-33** in 2% yield. Although this kinetic resolution of **(±)-8** was low yielding, the products were obtained in good enantiopurity, and use of the opposite catalyst, (*R,R*)-**20**, gave access to **(+)-2** in 9% yield. Furthermore, NMR spectra for synthetic **2** perfectly matched our isolated natural product data.



Scheme 9. Biomimetic Synthesis of Isobruceol from Chromene 8

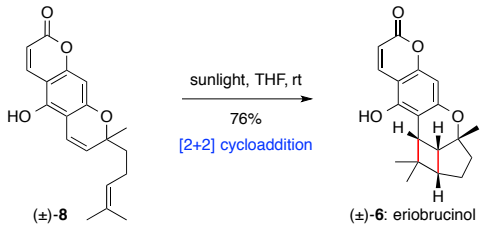
As shown in Scheme 1, chromene **8** is also a pivotal intermediate in the biosynthesis of deoxyisobruceol (**4**) and eriobrucinol (**6**), and this elusive intermediate was also proposed to be the direct precursor of **4** in Crombie's total synthesis (Scheme 4). In vindication of Crombie's mechanistic analysis, we showed that heating chromene **8** at 150 °C in pyridine gave **4** in 77% yield

(Scheme 10). Therefore, the low yield of **4** in Crombie's cascade is due to the inefficient interconversion between chromenes **7** and **8**, which results in a mixture of deoxybruceol and deoxyisobruceol products. On the other hand, the final tautomerization of **8** to give *o*-QM **11** followed by intramolecular hetero-Diels-Alder reaction is clearly an efficient reaction sequence.



Scheme 10. Biomimetic Synthesis of Deoxyisobruceol from Chromene 8

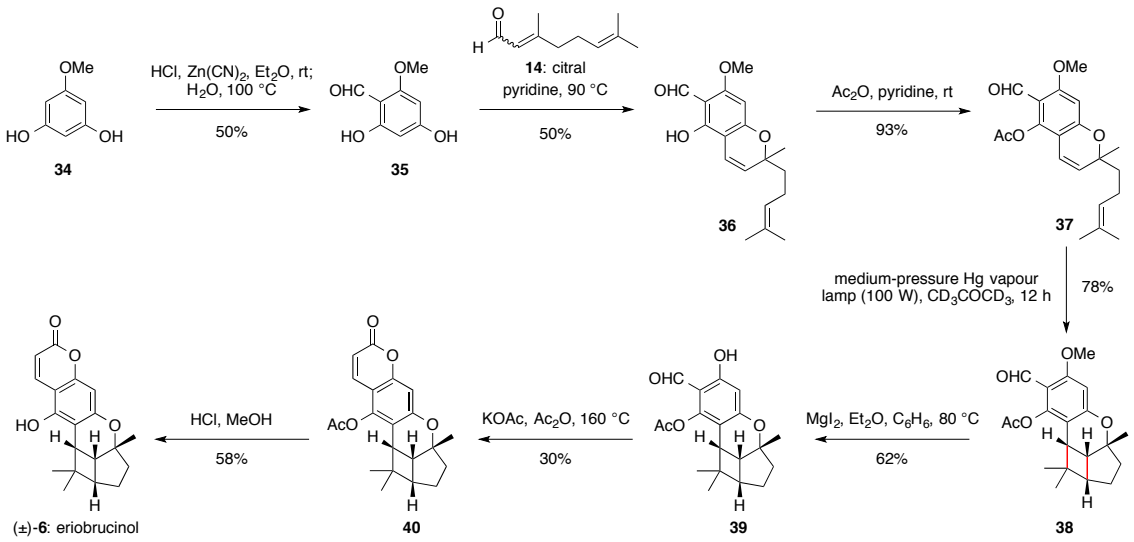
Exposure of a solution of chromene **8** in THF to direct sunlight resulted in the gradual formation of eriobrucinol (**6**) in good yield via a photochemical [2+2] cycloaddition (Scheme 11). Despite extensive work in this area, Crombie was unable to investigate the biomimetic conversion of **8** into eriobrucinol due to his failure to synthesise **8**. However, Crombie did achieve biomimetic, photochemical syntheses of the isomeric natural products, iso-eriobrucinols A and B (*vide infra*), and he also confirmed the structure of eriobrucinol (**6**) via a less direct total synthesis.[27]



Scheme 11. Photochemical Conversion of Chromene 8 into Eriobrucinol

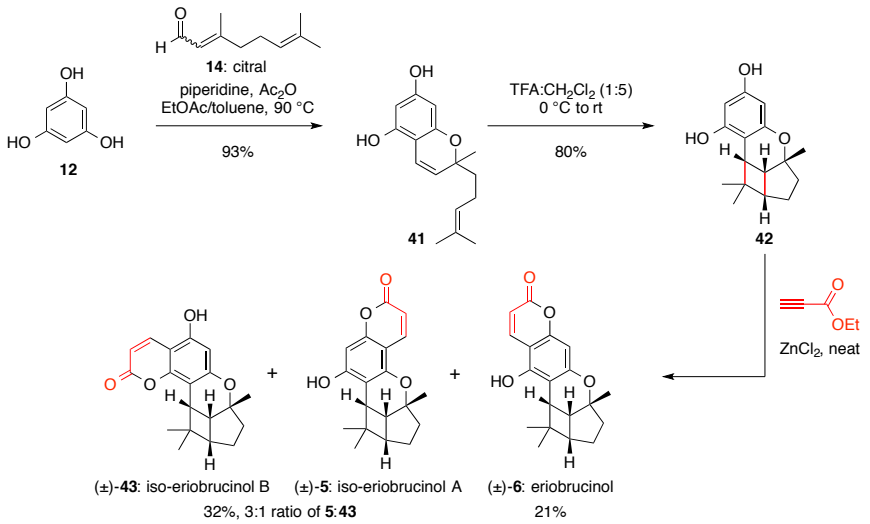
It is worth comparing our four-step total synthesis of eriobrucinol (**6**) from its direct biosynthetic precursor **8** with the first total synthesis by Crombie, and also with a more recent synthesis by Hsung and Tang. As shown in Scheme 12, Crombie's synthesis of eriobrucinol features an early stage chromenylation of 2,4-dihydroxy-6-methoxybenzaldehyde (**35**) to give chromene **36**, followed by acetylation and photochemical [2+2] cycloaddition to give **38**. The coumarin ring

system was then installed via a Perkin reaction, and a final deacetylation gave **6** in a total of seven steps from commercial starting materials.



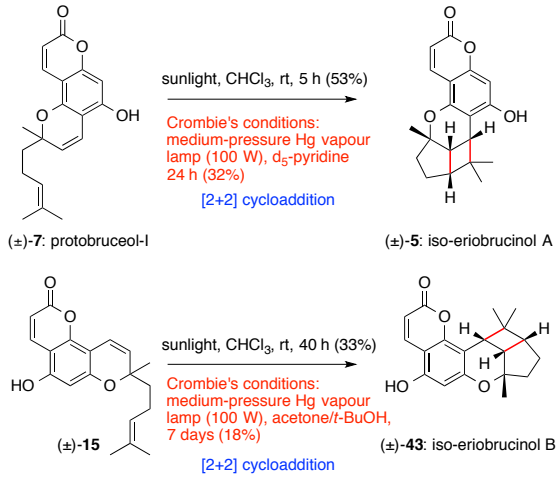
Scheme 12. Crombie's Total Synthesis of Eriobrucinol

Hsung *et al.* recently reported a divergent, three-step total synthesis of eriobrucinol (**6**) and the isomeric natural products iso-eriobrucinol A (**5**) and iso-eriobrucinol B (**43**) (Scheme 13).[28] Initial chromenylation of phloroglucinol (**12**) gave chromene **41**, which underwent acid catalysed [2+2] cycloaddition to give cyclobutene **42**. Late stage coumarin formation using $ZnCl_2$ in neat ethyl propiolate gave a 21% yield of **6** alongside a 32% yield of an inseparable 3:1 mixture of **5** and **43**.



Scheme 13. Hsung and Tang's Divergent Total Synthesis of Eriobrucinol and Iso-eriobrucinols A and B

Given the ease of the photochemical [2+2] cycloaddition of **8** on exposure to sunlight,[29] we investigated the solar photocyclizations of protobruceol-I (**7**) and chromene **15**, which resulted in the formation of iso-eriobrucinol A (**5**) and iso-eriobrucinol B (**43**) in 53% and 33% yield respectively (Scheme 14). Similar (but lower yielding) syntheses of iso-eriobrucinols A and B were achieved by Crombie, several years before their isolation, via irradiation with a 100 W medium-pressure mercury lamp.



Scheme 14. Biomimetic Synthesis of Iso-eriobrucinols A and B Using Sunlight

In 1994, a family of seven bruceol derivatives (**45-51**, Figure 3), each with an oxidized prenyl substituent at C-2', were isolated by Waterman and co-workers from *Philotheca myoporoides* (previously known as *Eriostemon myoporoides*).[30] *Philotheca myoporoides* is a flowering shrub that occurs widely along the east coast of Australia. The bruceol derivatives **45-51** are presumably formed via aerobic oxidation of "prenylbruceol" (**44**), although this biosynthetic intermediate and plausible "undiscovered natural product" has not yet been reported.

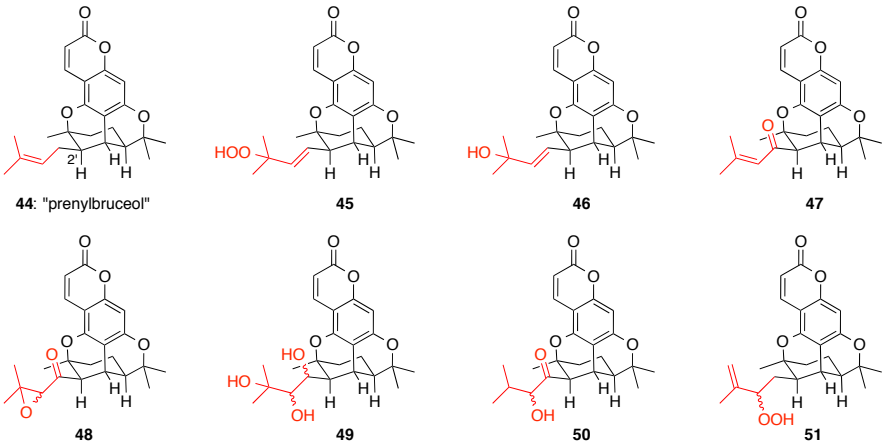
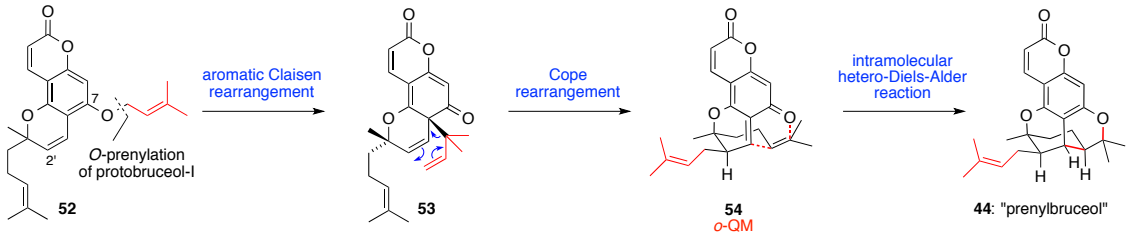


Figure 3. C-2' prenylated bruceol derivatives isolated from *Philotheca myoporoides*.

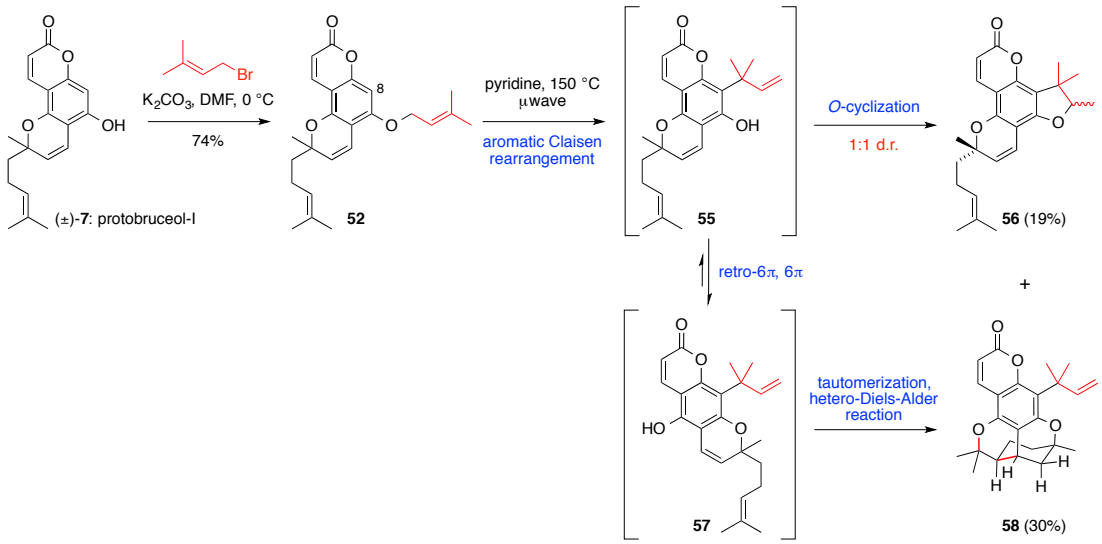
The origin of the prenyl side chain of **44** and its oxidized derivatives is biosynthetically intriguing. One possibility is a direct prenylation at C-2' of protobruceol-I (**7**) to initiate the hetero-Diels-Alder reaction of an intermediate *o*-QM. However, this would be an unusual site for a prenylation reaction, and we propose an alternative that invokes a more common aromatic prenyltransferase that could prenylate the C-7 phenol of protobruceol-I to give **52** (Scheme 15). The aromatic prenyl ether **52** could then undergo an aromatic Claisen rearrangement[31] to give **53**, followed by a Cope rearrangement to give *o*-QM **54**, and a final intramolecular hetero-Diels-Alder reaction to give "prenylbruceol" (**44**). Cascade cyclizations initiated by aromatic Claisen rearrangements have been proposed in the biosynthesis of several caged xanthone natural products.[32]



Scheme 15. Proposed Biosynthesis of "Prenylbruceol"

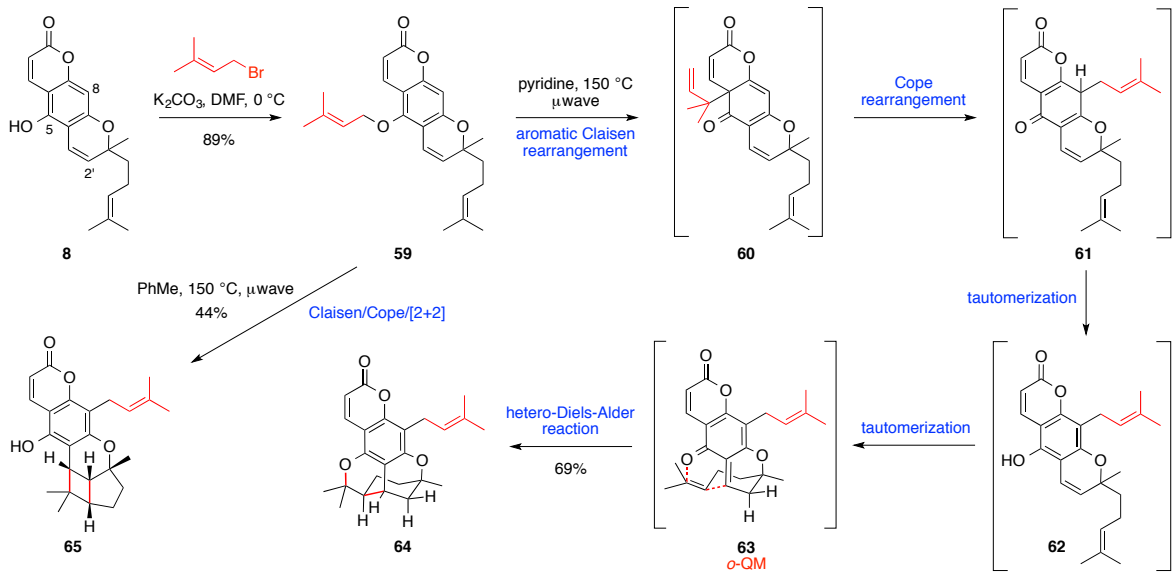
To investigate a biomimetic synthesis of **44**, prenylation of the free phenol of **7** was achieved under standard conditions to give **52** in good yield (Scheme 16). However, heating **52** in pyridine (150 °C in a microwave) formed benzofuran **56** (19%) and the bruceol derivative **58** (30%), rather than the

desired "prenylbruceol" (**44**). Perhaps unsurprisingly, the initial aromatic Claisen rearrangement shifted the prenyl group to the unhindered C-8 position to give **55**, which cyclized to give **56**. Alternatively, intermediate **55** isomerized to the more reactive chromene **57** via retro-6π-electrocyclization and 6π-electrocyclization, followed by tautomerization and intramolecular hetero-Diels-Alder reaction to give **58**, in a process that is analogous to the sequence outlined in Scheme 4.



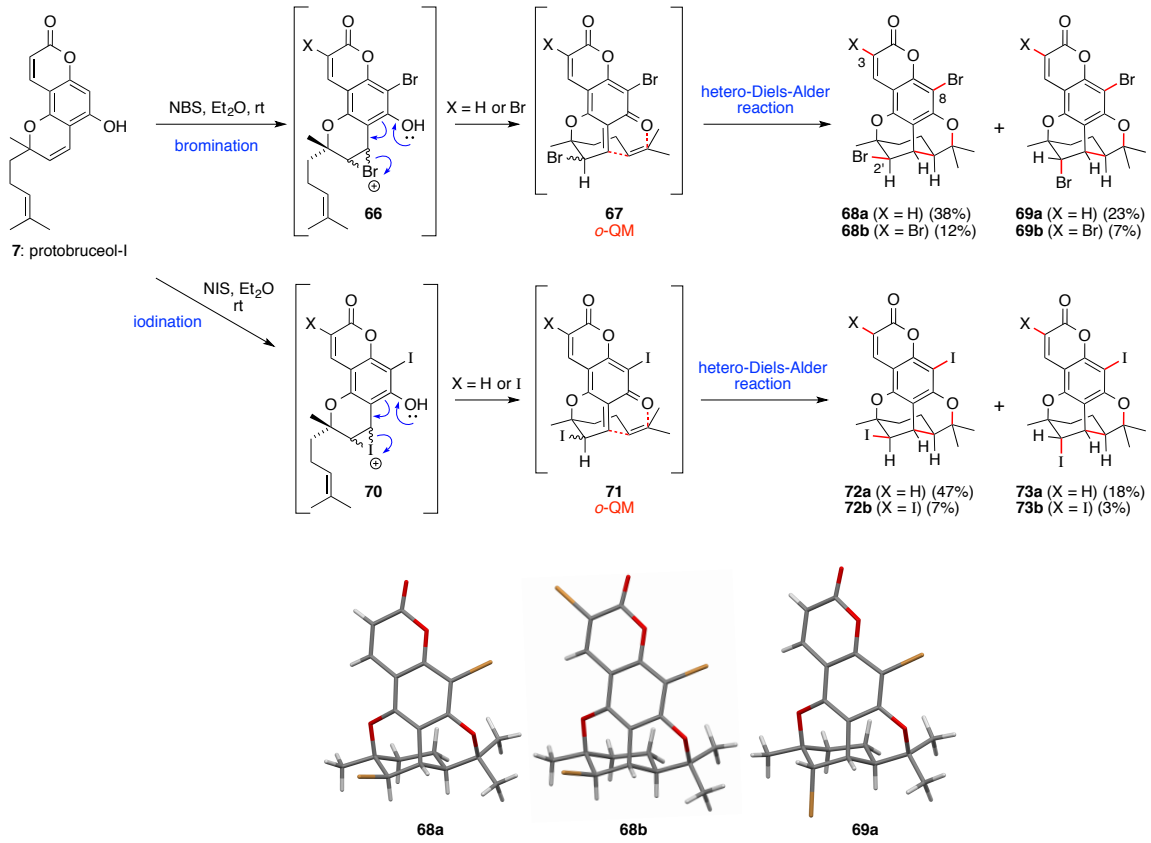
Scheme 16. Thermal Rearrangement of Prenylated Protobruceol-I

We also *O*-prenylated chromene **8** under standard conditions to give prenyl ether **59** (Scheme 17). In this substrate, there is no unhindered carbon atom adjacent to the C-5 prenyl ether for a facile aromatic Claisen rearrangement. However, we still did not observe migration of the prenyl substituent to C-2' of the chromene. Instead, under thermal conditions in pyridine **59** underwent successive Claisen and Cope rearrangements[33] to shift the prenyl group to C-8 of **61**, followed by aromatization and tautomerization to give *o*-QM **63**, and a final intramolecular hetero-Diels-Alder reaction to give **64**. Heating **59** in toluene instead of pyridine initiated a similar Claisen-Cope cascade, but with a terminating intramolecular [2+2] cycloaddition to give cyclobutane **64** favoured over the hetero-Diels-Alder reaction. Attempts to catalyse the desired Claisen-Cope cascade using a europium(III) catalyst were unsuccessful.[34]



Scheme 17. Synthesis of Prenylated Isobruceol Derivative 64 via a Claisen/Cope/Hetero-Diels-Alder Cascade Reaction and Synthesis of Prenylated Eriobrucinol Derivative 65 via a Claisen/Cope/[2+2] Cascade Reaction

Bromonium and iodonium-induced cyclizations of protobruceol-I (**7**) were also investigated, but these reactions were rather unselective (Scheme 18). Treatment of **7** with NBS in Et_2O generated a mixture of di- and tri-brominated citran products **68a**, **68b**, **69a** and **69b**. The major product **68a** (formed in 32% yield) has an equatorial bromine substituent at C-2' of the citran ring system, and a bromine substituent at C-8 of the coumarin ring system. Additional bromination at C-3 gave **68b** in 12% yield. Lack of diastereoselectivity of the initial bromonium ion formation resulted in significant formation of **69a** and **69b** (23% and 7% respectively), which both have an axial bromine substituent at C-2'. The structures of **68a**, **68b** and **69a** were elucidated using single crystal X-ray crystallography. Iodination of **7** with NIS in Et_2O gave a similar result, with a mixture of di- and tri-iodinated citran products **72a**, **72b**, **73a** and **73b** being formed.



Scheme 18. Bromination and Iodination of Protobruceol-I

Alongside protobruceol-I (**7**), the biosynthetic precursor to bruceol (**1**) and isoeriobrucinol A (**5**), Waterman discovered five oxidized chromene natural products **74**-**78** in the aerial parts of *Philotheca brucei* (Figure 4).[12] Protobruceol-II (**74**) and protobruceol-III (**75**) are presumably derived from reduction of their corresponding hydroperoxides (**76**) and (**77**), which in turn are probably formed via the addition of singlet oxygen[35] in a Schenck ene reaction.[36] The proposed structure of protobruceol-IV (**78**) bears the same regiochemistry as eriobrucinol (**6**), isobruceol (**2**), and their proposed precursor **8**.

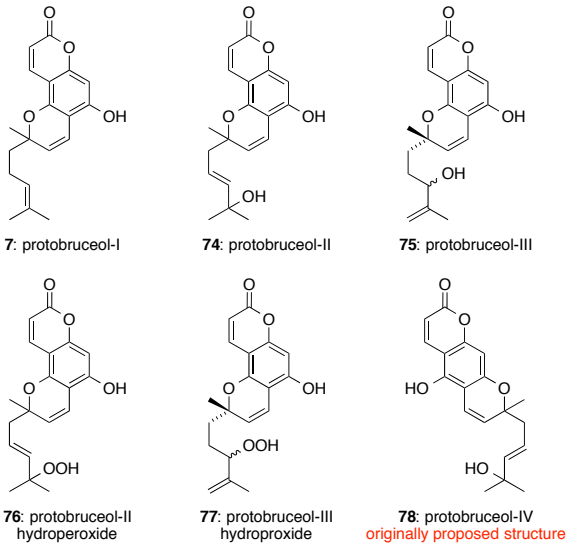
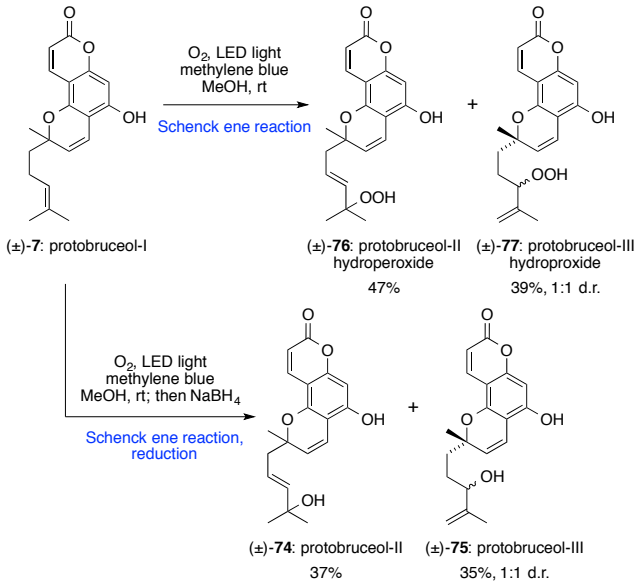


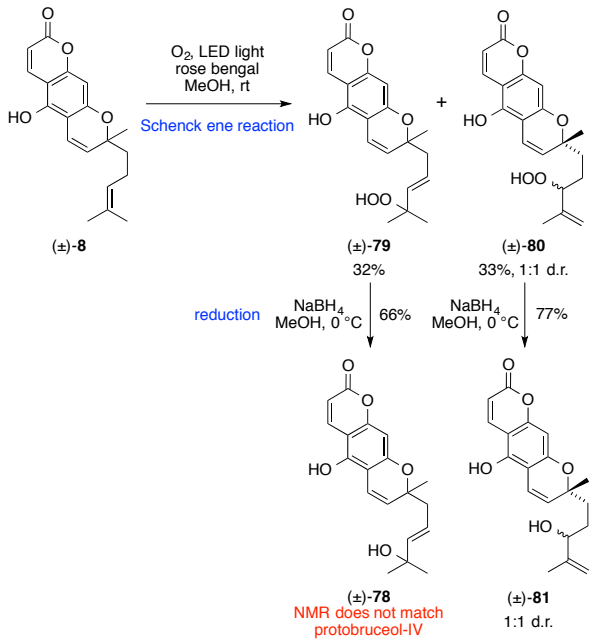
Figure 4. Protobruceol natural products.

Protobruceol-II hydroperoxide (**76**) and protobruceol-III hydroperoxide (**77**) were synthesised from **7** in 47% and 39% yield respectively by addition of singlet oxygen, generated *in situ* using methylene blue as a sensitiser (Scheme 19). Addition of $NaBH_4$ after the completion of the Schenck ene reaction afforded protobruceol-II (**74**) and protobruceol-III (**75**) in 37% and 35% yield resepectively. ^{1}H NMR spectra for these protobruceol natural products fully matched Waterman's isolation data.[12]



Scheme 19. Synthesis of Protobruceol-II, Protobruceol-III and their Hydroperoxides

After the straightforward synthesis of protobruceols **74**-**77**, our attention turned to the synthesis of protobruceol-IV (**78**) (Scheme 20). The one-pot procedure used to synthesise alcohols **74** and **75** proved less reliable with chromene **8** due to poor acid/base stability of this system, so instead we chose a two step method. Oxidation of chromene **8** gave hydroperoxides **79** (32%) and **80** (33%), which were separated by flash chromatography. Careful reduction of **79** using $NaBH_4$ gave **78** in 66% yield, whereas reduction of **80** gave **81** in 77% yield. Unfortunately, there were significant discrepancies between the ^1H NMR data of our synthetic **78** and that of natural protoisobruceol-IV. We therefore believe a structural revision is necessary for protobruceol-IV. However, with only ^1H NMR data reported by Waterman for protobruceol-IV, we were unable to determine its true strucure.



Scheme 20. Synthesis of the Proposed Structure of Protobruceol-IV

Conclusion

We have used biosynthetic speculation to guide the synthesis of several polycyclic meroterpenoids found in *Philotheca brucei* from a pair of isomeric chromenes. The synthesis of bruceol featured an oxidative cascade cyclization triggered by an asymmetric Jacobsen-Katsuki epoxidation of protobruceol-I, a process that was also a kinetic resolution. Discrepancies between the NMR spectra for synthetic bruceol and some published NMR data for natural bruceol led us to propose the

existence of isobruceol as a previously unrecognised natural product. This was confirmed by the isolation of isobruceol from *Philotheca brucei*, and its synthesis from an isomer of protobruceol-I. This chromene isomer, an elusive biosynthetic intermediate, was also directly converted into eriobrucinol via a photochemical [2+2] cycloaddition, and into deoxyisobruceol via a thermal hetero-Diels-Alder reaction. Further studies on some biosynthetically-intriguing prenylated derivatives of bruceol remain inconclusive, although we achieved a complex Claisen/Cope/Diels-Alder reaction sequence. In a general sense, this work shows that biosynthetic speculation can inspire the development of novel cascade reactions, and also aid the discovery of new natural products.

Experimental Section

General Information. All chemicals used were purchased from commercial suppliers and used as received. All reactions were performed under an inert atmosphere of N_2. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using aluminium sheets coated with silica gel. Visualization was aided by viewing under a UV lamp and staining with ceric ammonium molybdate stain followed by heating. All R_f values were measured to the nearest 0.05. Flash chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a digital melting point apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR was recorded using a 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) or a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). The solvent used for NMR spectra was $CDCl_3$ unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C NMR are reported in ppm relative to chloroform (δ 77.0). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All *J*-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Optical rotations were measured on a modular circular polarimeter.

Experimental Procedures. *Note:* Experimental information for compounds **1**, **2**, **7**, **8**, **15**, **22**, **25**, **28**, **29**, and **33** have been previously reported as part of the bruceol synthesis.[7]

Isolation of Bruceol (1) and Isobruceol (2). *Philotheca brucei* collected from the Koolyanobbing Range (approx. 500 km east of Perth, GPS location E749300 N6581700) (1.0 kg) was cut into a crude mulch and macerated in Et_2O (~3 L) for 5 days with intermittent stirring. The extract was filtered and concentrated to ~750 mL, then washed sequentially with 5% HCl (2 × 500 mL), 8% $NaHCO_3$ (2 × 500 mL), and 5% NaOH (2 × 500 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*, giving a green, fragrant oil. The volatiles (mostly eucalyptol) were removed by vacuum distillation. The residue was purified by sequential flash column chromatography on SiO_2 (10:1 → 1:1 petrol/EtOAc, then 2:1 petrol/EtOAc) to give a mixture of bruceol **1** and isobruceol **2** (500 mg, 11:1 in favour of **1**). The mixture was then recrystallised from petrol/EtOAc to afford pure **1** as colourless prisms (140 mg), and the residue was repurified by flash column chromatography to afford an enriched mixture of bruceol **1** and isobruceol **2** (300 mg, 4.5:1 in favour of **1**). Further recrystallization from petrol/EtOAc afforded more **1** as colourless prisms (36 mg, total of 176 mg, 0.018% w/w). The residue was repurified by flash column chromatography (2:1 petrol/EtOAc) to afford a further enriched mixture of bruceol **1** and isobruceol **2** (200 mg, 2:1 in favour of **1**). No more bruceol **1** in the residue could be removed by crystallization. The residue was then purified by semi-preparative reverse phase HPLC on an Ascentis ® C18 column (25 cm × 10 mm, 5 μm) (MeCN/H_2O, gradient elution) to afford isobruceol **2** as a white solid (11 mg, 0.0011% w/w). A single crystal was obtained by recrystallization from $CHCl_3/Et_2O$.

Data for **1**. R_f 0.20 (1:1 petrol/EtOAc); mp 197 – 209 °C (prisms from petrol/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.6 Hz, 1H), 6.46 (s, 1H), 6.17 (d, *J* = 9.6 Hz, 1H), 3.85 (dd, *J* = 8.4, 2.0 Hz, 1H), 2.93 (d, *J* = 2.4 Hz, 1H), 2.30 (ddd, *J* = 11.6, 5.4, 2.6 Hz, 1H), 2.12 (d, *J* = 8.4 Hz, 1H), 1.91 (dd, *J* = 15.6, 6.3 Hz, 1H), 1.58 (d, *J* = 2.5 Hz, 3H), 1.51 (ddd, overlapped, *J* = 16.2, 14.4,

7.6 Hz, 1H), 1.50 (s, 3H), 1.25 (ddd, *J* = 13.0, 7.0, 5.3 Hz 1H), 1.07 (s, 3H), 0.59 (tdd, *J* = 13.6, 11.7, 6.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 161.6, 160.5, 155.1, 151.4, 138.3, 111.2, 109.4, 104.0, 99.2, 85.5, 79.3, 70.9, 47.0, 36.8, 35.9, 29.5, 24.2, 23.9, 21.6; IR (neat) 3529, 3457, 2971, 1702, 1615, 1566, 1447, 1360, 1248, 1196; HRMS (ESI) Calculated for $C_{19}H_{19}O_5$ 327.1238 $[M-H]^-$, found 327.1235.

Data for **2**. R_f 0.20 (1:1 petrol/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 9.6 Hz, 1H), 6.51 (s, 1H), 6.14 (d, *J* = 9.5 Hz, 1H), 3.83 (s, 1H), 2.91 (t, *J* = 2.4 Hz, 1H), 2.32 (ddd, *J* = 11.7, 5.6, 2.7 Hz, 1H), 2.14 (s, 1H), 1.92 (dd, *J* = 15.5, 6.2 Hz, 1H), 1.62 (s, 3H), 1.50 (ddd, *J* = 15.0, 13.3, 7.2 Hz, 1H) 1.47 (s, 3H), 1.23 (dt, *J* = 13.2, 6.4 Hz, 1H), 1.07 (s, 3H), 0.56 (tdd, *J* = 13.6, 11.7, 6.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 161.8, 158.3, 154.7, 154.2, 138.1, 111.6, 110.1, 105.9, 97.3, 86.5, 79.3, 71.0, 47.4, 36.7, 36.2, 29.6, 24.4, 24.3, 21.6; IR (neat) 3422, 2925, 1718, 1617, 1568, 1446, 1387, 1338, 1315, 1258, 1214, 1193; HRMS (ESI) Calculated for $C_{21}H_{21}O_5$ 329.1384 $[M+H]^+$, found 329.1386.

Isolation of Hydroxyeriobrucinol (30) and Isoimperatorin (31). Dried and finely powdered *Philotheca brucei* (10.0 g) was mixed with sand (3.5 g), placed in the portafilter (sample compartment) of a conventional, unmodified espresso machine and extracted with 35% EtOH in water (2 × 100 mL). The process was repeated nine times (100 g total plant material). The combined extracts were concentrated to ~200 mL on a rotary evaporator (40 °C bath) and the aqueous phase was extracted with EtOAc (4 × 200 mL). The combined organic extracts were washed with brine (2 × 200 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was initially purified by flash column chromatography on SiO_2 (10:1 → 1:1 petrol/Et_2O, gradient elution) giving fractions containing a non-polar fragrant oil, shown to be mostly eucalyptol (254 mg), a brown oil containing a complex mixture of compounds (944 mg), and a mixture of (–)-bruceol (**1**), (–)-isobruceol (**2**), and (–)-hydroxyeriobrucinol (**30**) as well as other minor impurities (1.1 g). Flash column chromatography on SiO_2 (4:1 petrol/EtOAc) of the brown oil gave crude

isoimperatorin (**31**) as a brown solid (55 mg), which was recrystallised (petrol/EtOAc) to afford **31** as white needles (18.1 mg, 0.018% w/w). Data for **31**. R_f 0.40 (1:1 petrol/Et_2O); mp 98.2 – 99.2 °C (*lit.*[37] 110 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 9.8, 0.7 Hz, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.16 (t, *J* = 0.8 Hz, 1H), 6.96 (dd, *J* = 2.3, 1.0 Hz, 1H), 6.27 (d, *J* = 9.8 Hz, 1H), 5.54 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.92 (dt, *J* = 7.1, 0.9 Hz, 2H), 1.80 (s, 3H), 1.70 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 161.5, 158.3, 152.8, 149.1, 145.0, 140.0, 139.8, 119.2, 114.3, 112.7, 107.7, 105.2, 94.4, 69.9, 26.0, 18.4; IR (neat) 3026, 2997, 2667, 1603, 1507, 1460, 1443, 1286, 1238, 1229, 1179, 1039; HRMS (ESI) calculated for $C_{16}H_{15}O_4$ 271.0968 $[M+H]^+$, found: 271.0971. Trituration of the mixture containing **1**, **2**, and **30** with $CHCl_3$ (20 mL) gave (–)-hydroxyeriobrucinol (**30**) as a white powder (438 mg, 0.44% w/w). Data for **30**. R_f 0.15 (1:1 petrol/EtOAc); mp 245 – 249 °C (decomposes) (needles from EtOH); $[\alpha]_D^{25°C}$ −181 (MeOH, c = 1.0); ^{1}H NMR (500 MHz, d_5-pyridine) δ 8.29 (d, *J* = 9.6 Hz, 1H), 6.73 (s, 1H), 6.25 (d, *J* = 9.6 Hz, 1H), 4.51 (d, *J* = 5.0 Hz, 1H), 3.47 (d, *J* = 9.7 Hz, 1H), 2.92 (dd, *J* = 9.7, 7.5 Hz, 1H), 2.75 (d, *J* = 7.4 Hz, 1H), 2.52 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.25 (d, *J* = 13.9 Hz, 1H), 1.87 (s, 3H), 1.53 (s, 3H), 0.99 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, d_5-pyridine) δ 161.6, 158.7, 155.6, 154.9, 140.1, 111.1, 111.0, 105.1, 98.7, 85.6, 73.4, 57.2, 48.7, 39.0, 38.7, 36.6, 34.5, 29.9, 19.0; IR (neat) 3289, 2972, 2936, 1683, 1605, 1562, 1446, 1405, 1357, 1283, 1253, 1146, 1107; HRMS (ESI) calculated for $C_{19}H_{21}O_5$ 329.1384 $[M+H]^+$, found: 329.1384.

Deoxyisobruceol (4). A solution of **8** (43.3 mg, 0.139 mmol) in pyridine (1 mL) was heated to 150 °C by microwave for 30 min. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on SiO_2 (3:1 petrol/EtOAc) to afford deoxyisobruceol (**4**) as a colourless oil (33.5 mg, 77%). Data for **4**: R_f 0.35 (2:1 petrol/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.5 Hz, 1H), 6.44 (s, 1H), 6.11 (d, *J* = 9.5 Hz, 1H), 2.90 – 2.84 (m, 1H), 2.24 (ddd, *J* = 13.4, 4.7, 3.2 Hz, 1H), 2.13 (ddd, *J* = 11.6, 5.4, 2.8 Hz, 1H), 1.91 (dd, *J* = 13.4, 1.7 Hz, 1H), 1.81 (ddd, *J* = 14.9, 5.6, 3.4 Hz, 1H), 1.60 (s, 3H), 1.47 (ddd, *J* = 15.1, 13.1, 6.8 Hz, 1H), 1.42 (s, 3H),

1.30 (dt, *J* = 12.8, 6.0 Hz, 1H), 1.07 (s, 3H), 0.64 (tdd, *J* = 13.4, 11.6, 6.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 162.0, 159.8, 154.6, 153.6, 138.3, 112.4, 110.7, 105.1, 96.9, 86.5, 76.4, 46.2, 37.3, 34.8, 29.6, 28.8, 28.0, 24.2, 22.0; IR (neat) 2975, 2933, 1728, 1616, 1568, 1445, 1355, 1258, 1138, 1125, 1071; HRMS (ESI) calculated for $C_{19}H_{20}O_4Na$ 335.1254 $[M+Na]^+$, found: 335.1259.

Eriobrucinol (6). A solution of **8** (25 mg, 0.80 mmol) in THF (2 mL) was placed in direct sunlight for 6 h. The solvent was removed and the residue was purified by flash column chromatography on SiO_2 (2:1 petrol/EtOAc) to afford eriobrucinol (**6**) as a yellow oil (18.9 mg, 76%). Data for **6**: R_f 0.25 (2:1 petrol/EtOAc); mp 163 – 165 °C (from toluene) (*lit.*[10] = 185 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.7 Hz, 1H), 6.46 (s, 1H), 6.15 (d, *J* = 9.6 Hz, 1H), 5.40 (s, 1H), 3.08 (d, *J* = 9.7 Hz, 1H), 2.66 (dd, *J* = 9.7, 7.6 Hz, 1H), 2.48 (t, *J* = 7.5 Hz, 1H), 1.96 – 1.87 (m, 1H), 1.75 – 1.67 (m, 1H, overlapped), 1.75 – 1.61 (m, 2H, overlapped), 1.45 (s, 3H), 1.41 (s, 3H), 0.79 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 162.1, 157.8, 154.6, 151.3, 138.9, 111.0, 107.1, 103.2, 99.0, 84.7, 46.4, 39.1, 38.7, 37.3, 35.6, 34.6, 27.4, 25.7, 18.2; IR (neat) 3225, 2949, 1690, 1615, 1445, 1205, 1355, 1278, 1137, 1109, 1082; HRMS (ESI) calculated for $C_{19}H_{21}O_4$ 313.1434 $[M+H]^+$, found: 313.1438.

Iso-eriobrucinol A (5). A solution of protobruceol-I (**7**) (80.0 mg, 0.256 mmol) in $CHCl_3$ (2 mL) was placed in direct sunlight for 5 h. The solvent was removed and the residue was purified by flash column chromatography on SiO_2 (2:1 petrol/EtOAc) to afford isoeriobrucinol A (**5**) as a white solid (42.5 mg, 53%). Data for **5**: R_f 0.30 (neat Et_2O); ^{1}H NMR (500 MHz, d_5-pyridine) δ 8.09 (d, *J* = 9.6 Hz, 1H), 6.61 (s, 1H), 6.27 (d, *J* = 9.6 Hz, 1H), 4.92 (br s, 1H), 3.34 (d, *J* = 9.6 Hz, 1H), 2.56 (dd, *J* = 9.6, 7.5 Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 1H), 2.04 (td, *J* = 12.6, 7.5 Hz, 1H), 1.72 – 1.64 (m, overlapped, 2H), 1.57 (ddd, *J* = 13.7, 12.3, 7.6 Hz, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 0.98 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, d_5-pyridine) δ 162.2, 162.1, 156.1, 151.7, 140.0, 110.2, 109.2, 104.2, 95.6, 85.4, 47.1, 39.9, 39.2, 38.5, 37.0, 34.3, 27.9, 26.4, 18.5; IR (neat) 3212, 2959, 1679, 1595, 1572, 1440, 1397, 1366, 1258, 1229, 1137, 1084; HRMS (ESI) calculated for $C_{19}H_{20}O_4Na$ 335.1254 $[M+Na]^+$, found: 335.1261.

Iso-eriobrucinol B (43). A suspension of **15** (60.0 mg, 0.192 mmol) in $CHCl_3$ (2 mL) was placed in direct sunlight for a total of 40 h over the course of 5 days. The mixture was diluted with $CHCl_3$ (3 mL) and filtered to afford isoeriobrucinol B (**43**) as a pale yellow solid (19.9 mg, 33%). Data for **43**: R_f 0.30 (neat Et_2O); ^1H NMR (500 MHz, d_5-pyridine) δ 8.31 (d, J = 9.5 Hz, 1H), 6.63 (s, 1H), 6.29 (d, J = 9.5 Hz, 1H), 3.30 (d, J = 9.6 Hz, 1H), 2.50 (dd, J = 9.7, 7.3 Hz, 1H), 2.31 (t, J =7.4 Hz, 1H), 2.02 (td, J = 12.8, 7.8 Hz, 1H), 1.64 – 1.57 (m, 1H), 1.56 (s, 3H), 1.53 – 1.45 (m, 1H), 1.37 (s, 3H), 0.87 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, d_5-pyridine) δ 161.8, 158.4, 155.9, 155.5, 140.5, 110.4, 104.8, 103.7, 100.7, 85.3, 47.2, 39.6, 39.0, 37.9, 36.2, 34.2, 28.0, 26.2, 18.6; IR (neat) 3331, 2938, 1686, 1606, 1498, 1455, 1356, 1263, 1135, 1108; HRMS (ESI) calculated for $C_{19}H_{21}O_4$ 313.1434 $[M+H]^+$, found: 313.1435.

Prenyl ether 52. To a solution of protobruceol (**7**) (999 mg, 3.20 mmol) in DMF (40 mL) at 0 °C was added K_2CO_3 (1.33 g, 9.59 mmol), followed by prenyl bromide (0.41 mL, 3.5 mmol). The reaction was stirred at 0 °C for 5 min, then warmed to room temperature and stirred for a further 2 h. The mixture was diluted with brine (50 mL) and extracted with EtOAc (5 × 50 mL). The combined organic extracts were washed with brine (5 × 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (8:1 petrol/EtOAc) to afford **52** as a pale yellow oil (900 mg, 74%). Data for **52**: R_f 0.45 (5:1 petrol/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, J = 9.6 Hz, 1H), 6.67 (d, J = 10.1 Hz, 1H), 6.14 (d, J = 9.6 Hz, 1H), 5.48 (d, J = 10.2 Hz, 1H), 5.45 (t, J = 6.6, 1H), 5.08 (t, J = 7.3 Hz, 1H), 4.57 (d, J = 6.6 Hz, 2H), 2.15 – 2.07 (m, 2H), 1.80 (s, 3H), 1.80 – 1.67 (m, overlapped, 2H), 1.76 (s, 3H), 1.65 (s, 3H), 1.55 (s, 3H), 1.42 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.8, 157.7, 155.9, 150.6, 138.83, 138.75, 132.1, 126.5, 123.9, 119.0, 116.9, 111.1, 106.7, 103.6, 92.6, 80.3, 65.9, 41.3, 26.6, 26.0, 25.8, 22.8, 18.5, 17.8; IR (neat) 2791, 2915, 1733, 1614, 1597, 1437, 1377, 1137, 1107; HRMS (ESI) calculated for $C_{24}H_{29}O_4$ 381.2060 $[M+H]^+$, found 381.2062.

Chromene 56 and Citran 58. A solution of **52** (44.6 mg, 0.117 mmol) in pyridine (5 mL) was heated to 150 °C in a microwave reactor for 1 h. The solvent was removed *in vacuo* and the residue

was purified by flash column chromatography on SiO_2 (8:1 → 3:1 petrol/EtOAc, gradient elution) to afford chromene **56** as a clear and colourless oil (8.3 mg, 19%). Further elution gave citran **58** as a light yellow solid (13.5 mg, 30%).

Data for **56**. R_f 0.40 (5:1 petrol/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 9.6 Hz, 1H), 6.48 (d, *J* = 10.0 Hz, 1H), 6.07 (d, *J* = 9.7 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.08 (t, *J* = 7.2 Hz, 1H), 4.48 (qd, *J* = 6.6, 1.8 Hz, 1H), 2.10 (tt, *J* = 11.3, 6.5 Hz, 2H), 1.82 – 1.67 (m, 2H), 1.65 (s, 3H), 1.56 (s, 3H), 1.52 (d, *J* = 1.5 Hz, 3H), 1.42 (s, 3H), 1.39 (d, *J* = 6.6 Hz, 3H), 1.25 (d, *J* = 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 161.42, 161.41, 158.22, 158.21, 151.2, 150.58, 150.56, 139.4, 132.1, 127.0, 126.9, 123.89, 123.88, 116.47, 116.46, 114.24, 114.23, 109.9, 103.60, 103.59, 101.79, 101.77, 91.17, 91.16, 80.5, 44.1, 41.4, 41.3, 26.68, 26.65, 25.8, 25.7, 25.6, 22.81, 22.78, 21.4, 21.3, 17.8, 14.40, 14.37 (Note: more than 24 ^{13}C signals are observed as **56** is a 1:1 mixture of diastereoisomers); IR (neat) 2968, 2926, 1733, 1623, 1603, 1584, 1435, 1380, 1345, 1313, 1136, 1093, 1093; HRMS (ESI) calculated for $C_{24}H_{29}O_4$ 381.2060 $[M+H]^+$, found 381.2062.

Data for **58**. R_f 0.25 (5:1 petrol/EtOAc); mp 170.9 – 172.3 °C (prisms from EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.5 Hz, 1H), 6.31 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.08 (d, *J* = 9.5 Hz, 1H), 4.90 (dd, *J* = 17.4, 1.2 Hz, 1H), 4.86 (dd, *J* = 10.6, 1.3 Hz, 1H), 2.88 – 2.84 (m, 1H), 2.18 (ddd, *J* = 13.2, 4.8, 3.1 Hz, 1H), 2.08 (ddd, *J* = 11.7, 5.4, 2.7 Hz, 1H), 1.85 (dd, *J* = 13.2, 1.6 Hz, 1H), 1.76 (ddd, *J* = 15.2, 5.1, 2.9 Hz, 1H), 1.66 (s, 3H), 1.65 (s, 4H), 1.58 (s, 3H), 1.47 – 1.41 (m, overlapped, 1H), 1.40 (s, 3H), 1.29 (dt, *J* = 12.8, 5.9 Hz, 1H), 1.06 (s, 3H), 0.64 (tdd, *J* = 13.5, 11.7, 6.2 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 161.9, 158.9, 152.4, 151.5, 149.7, 138.8, 115.3, 112.2, 110.1, 108.3, 105.1, 85.6, 76.2, 46.7, 41.1, 37.4, 34.9, 29.7, 29.6, 29.4, 28.9, 28.5, 24.2, 22.2; IR (neat) 2975, 2931, 1707, 1638, 1596, 1561, 1458, 1428, 1335, 1310, 1273, 1166, 1136; HRMS (ESI) calculated for $C_{24}H_{29}O_4$ 381.2060 $[M+H]^+$, found 381.2063.

Prenyl ether 59. To a solution of **8** (151 mg, 0.484 mmol) in DMF (10 mL) at 0 °C was added K_2CO_3 (201 mg, 1.45 mmol), followed by prenyl bromide (0.06 mL, 0.53 mmol). The reaction mixture was stirred at 0 °C for 5 min, then warmed to room temperature and stirred for a further 1 h.

The reaction was quenched with 1 M HCl (2 mL) and diluted with water (10 mL). The mixture was extracted with Et_2O (3 × 15 mL) and the combined organic extracts were washed with brine (5 × 15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (8:1 petrol/EtOAc) to afford **59** as a pale yellow oil (165 mg, 89%). Data for **59**: R_f 0.35 (5:1 petrol/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.6 Hz, 1H), 6.62 (d, *J* = 10.1 Hz, 1H), 6.53 (s, 1H), 6.17 (d, *J* = 9.6 Hz, 1H), 5.64 (d, *J* = 10.1 Hz, 1H), 5.51 (t, *J* = 7.5 Hz, 1H), 5.07 (t, *J* = 6.7 Hz, 1H), 4.46 (d, *J* = 7.4 Hz, 2H), 2.14 – 2.03 (m, 2H), 1.80 – 1.74 (m, overlapped, 1H), 1.76 (s, 3H), 1.68 – 1.62 (m, overlapped, 1H), 1.65 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.42 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 161.4, 158.0, 155.7, 151.9, 140.2, 139.3, 132.2, 129.4, 123.7, 119.2, 116.9, 112.0, 111.9, 108.1, 100.6, 80.0, 73.0, 41.6, 26.9, 26.0, 25.8, 22.8, 18.2, 17.8; IR (neat) 2973, 1736, 1615, 1599, 1564, 1449, 1380, 1367, 1316, 1196, 1136, 1079; HRMS (ESI) calculated for $C_{24}H_{29}O_4$ 381.2060 $[M+H]^+$, found 381.2061

Citran 64. A solution of **59** (23.5 mg, 0.0617 mmol) in pyridine (5 mL) was heated to 150 °C in a microwave reactor for 30 min. The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography on SiO_2 (5:1 petrol/EtOAc) to afford **64** as a pale yellow oil (16.3 mg, 69%). Data for **64**: R_f 0.20 (5:1 petrol/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.5 Hz, 1H), 6.10 (d, *J* = 9.4 Hz, 1H), 5.27 (t, *J* = 7.7 Hz, 1H), 3.43 (d, *J* = 7.5 Hz, 2H), 2.86 (br s, 1H), 2.24 (ddd, *J* = 13.3, 4.8, 3.2 Hz, 1H), 2.09 (ddd, *J* = 11.7, 5.5, 2.8 Hz, 1H), 1.88 (dd, *J* = 13.3, 1.6 Hz, 1H), 1.82 (s, 3H), 1.74 (ddd, *J* = 14.9, 5.5, 2.7 Hz, 1H), 1.67 (s, 3H), 1.58 (s, 3H), 1.46 (ddd, *J* = 13.2, 8.7, 6.7 Hz, 1H), 1.43 (s, 3H), 1.29 – 1.24 (m, 1H), 1.03 (s, 3H), 0.59 (tdd, *J* = 13.5, 11.7, 6.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.3, 157.6, 151.7, 151.3, 138.6, 131.8, 122.2, 112.1, 110.5, 110.0, 105.1, 86.0, 76.1, 46.6, 37.5, 34.9, 29.7, 29.0, 28.3, 26.0, 24.2, 22.2, 21.4, 18.1; IR (neat) 2975, 2927, 1724, 1606, 1573, 1442, 1338, 1270, 1239, 1214, 1187, 1166, 1142, 1124; HRMS (ESI) calculated for $C_{24}H_{29}O_4$ 381.2060 $[M+H]^+$, found 381.2062.

Cyclol 65. A solution of **59** (28.7 mg, 0.0754 mmol) in toluene (10 mL) was heated to 150 °C in a microwave reactor for 1.5 h. The solvent was removed *in vacuo* and the residue was purified by

flash column chromatography on SiO_2 (5:1→ 3:1 petrol/EtOAc) to afford **65** as a yellow solid (12.7 mg, 44%). Data for **65**: R_f 0.10 (5:1 petrol/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 9.6 Hz, 1H), 6.16 (d, *J* = 9.6 Hz, 1H), 5.22 (t, *J* = 7.5 Hz, 1H), 4.64 (br s, 1H), 3.45 (d, *J* = 7.4 Hz, 2H), 3.03 (d, *J* = 9.7 Hz, 1H), 2.67 (t, *J* = 8.5 Hz, 1H), 2.47 (t, *J* = 7.2 Hz, 1H), 1.91 – 1.86 (m, 1H), 1.83 (s, 3H), 1.73 – 1.64 (m, overlapped, 3H), 1.66 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 0.77 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 162.0, 155.1, 152.0, 148.8, 138.8, 131.7, 122.1, 111.5, 111.1, 106.3, 102.8, 84.5, 46.3, 39.0, 38.5, 37.2, 35.9, 34.7, 27.5, 26.0, 25.7, 21.8, 18.3, 18.2; HRMS (ESI) calculated for $C_{24}H_{29}O_4$ 381.2060 $[M+H]^+$, found 381.2059.

Bromination of 7. To a solution of **7** (195 mg, 0.624 mmol) in Et_2O (10 mL) was added NBS (333 mg, 1.87 mmol) at room temperature for 10 min. The reaction mixture was quenched with $Na_2S_2O_3$, filtered through Celite, flushed with Et_2O (20 mL) and concentrated *in vacuo*, and the residue was purified by flash chromatography on SiO_2 (8:1 → 3:1 petrol/EtOAc, gradient elution) to afford **69b** (23 mg, 7%), **69a** (68 mg, 23%), **68b** (41 mg, 12%) and **68a** (111 mg, 38%).

Data for **69b**: R_f 0.45 (2:1 petrol/EtOAc); mp 206 – 208 °C (white needles from petrol/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 4.71 (dd, *J* = 4.4, 2.0 Hz, 1H), 3.11 (dd, *J* = 4.4, 2.7 Hz, 1H), 2.75 (ddd, *J* = 11.7, 5.5, 2.7 Hz, 1H), 2.10 (ddd, *J* = 15.7, 13.0, 7.1 Hz, 1H), 1.74 (dd, *J* = 15.6, 6.5 Hz, 1H), 1.63 (s, 3H), 1.61 (s, 3H), 1.35 (dt, *J* = 13.2, 6.3 Hz, 1H), 1.13 (s, 3H), 0.63 (ddt, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.4, 159.1, 153.5, 152.5, 141.6, 115.4, 109.5, 108.0, 94.3, 91.1, 82.2, 55.5, 44.1, 38.7, 34.4, 31.8, 30.1, 27.1, 23.8; IR (neat) 2979, 2939, 1739, 1611, 1554, 1454, 1433, 1372, 1433, 1372, 1348, 1295, 1240, 1117; HRMS (ESI) calculated for $C_{19}H_{18}Br_3O_4$ 546.8750 $[M+H]^+$, found: 546.8746.

Data for **69a**: R_f 0.35 (2:1 petrol/EtOAc); mp 210 – 212 °C (white needles from petrol/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.7 Hz, 1H), 6.21 (d, *J* = 9.6 Hz, 1H), 4.72 (dd, *J* = 4.5, 2.1 Hz, 1H), 3.11 (dd, *J* = 4.5, 2.7 Hz, 1H), 2.75 (ddd, *J* = 11.8, 5.5, 2.6 Hz, 1H), 2.10 (ddd, *J* = 15.6, 13.0, 7.1 Hz, 1H), 1.73 (dd, J = 15.6, 6.5 Hz, 1H), 1.64 (s, 3H), 1.59 (s, 3H), 1.35 (dt, *J* = 13.3, 6.3 Hz, 1H), 1.14 (s, 3H), 0.67 (tdd, *J* = 14.0, 12.4, 6.4 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ

160.6, 156.3, 151.8, 150.7, 137.9, 112.4, 112.1, 105.1, 92.1, 88.3, 79.3, 53.4, 41.7, 36.3, 31.9, 29.3, 27.7, 24.5, 21.3; IR (neat) 2980, 1736, 1612, 1560, 1461, 1431, 1390, 1356, 1240, 1185, 1126 1080; HRMS (ESI) calculated for $C_{19}H_{19}Br_2O_4$ 468.9645 $[M+H]^+$ found: 468.9645.

Data for **68b**: R_f 0.25 (2:1 petrol/EtOAc); mp 185 – 187 °C (petrol/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 4.42 (d, *J* = 1.9 Hz, 1H), 3.28 (t, *J* = 2.2 Hz, 1H), 2.42 (ddd, *J* = 11.8, 5.4, 2.7 Hz, 1H), 2.12 (dd, *J* = 15.6, 6.0 Hz, 1H), 1.66 (m, overlapped, 1H), 1.65 (s, 3H), 1.56 (s, 3H), 1.39 (dt, *J* = 13.1, 6.0 Hz, 1H), 1.10 (s, 3H), 0.70 (tdd, *J* = 13.7, 11.7, 6.1 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.2, 157.0, 150.9, 149.6, 139.3, 110.9, 107.0, 105.7, 92.0, 88.1, 78.4, 53.7, 49.0, 39.3, 37.9, 29.6, 27.8, 24.5, 22.1; IR (neat) 1737, 1611, 1431, 1367, 1241, 1138, 1012; HRMS (ESI) calculated for $C_{19}H_{18}Br_3O_4$ 546.8750 $[M+H]^+$, found: 546.8742

Data for **68a**: R_f 0.20 (2:1 petrol/EtOAc); mp 175 – 177 °C (white needles from petrol/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.6 Hz, 1H), 6.23 (d, *J* = 9.6 Hz, 1H), 4.42 (d, *J* = 1.8 Hz, 1H), 3.28 (t, *J* = 2.3 Hz, 1H), 2.40 (ddd, *J* = 11.7, 5.4, 2.8 Hz, 1H), 2.11 (ddd, *J* = 15.6, 6.1, 1.4 Hz, 1H), 1.69 – 1.61 (m, overlapped, 1H), 1.64 (s, 3H), 1.54 (s, 3H), 1.38 (dt, *J* = 12.6, 5.5 Hz, 1H), 1.10 (s, 3H), 0.72 (tdd, *J* = 13.6, 11.6, 6.1 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.7, 151.7, 150.4, 138.2, 112.0, 110.5, 105.3, 92.1, 87.8, 78.0, 54.0, 49.1, 39.3, 37.9, 29.6, 27.9, 24.4, 22.1; IR (neat) 2980, 2937, 1731, 1612, 1561, 1460, 1429, 1394, 1366, 1317, 1283, 1260, 1194, 1127; HRMS (ESI) calculated for $C_{19}H_{19}Br_2O_4$ 468.9645 $[M+H]^+$, found: 468.9644.

Iodination of 7. To a solution of chromene **7** (200 mg, 0.640 mmol) in THF (15 mL) at 0 °C was added NIS (360 mg, 1.60 mmol) in one portion. The mixture was stirred at 0 °C for 10 min then quenched with $Na_2S_2O_3$ (~1 g) and filtered through a pad of Celite, flushed with CH_2Cl_2 (20 mL) The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on SiO_2 (8:1 → 2:1 petrol/EtOAc, gradient elution) to afford **73b** as an off white solid (13.8 mg, 3%), **73a** as a white solid (63.8 mg, 18%), **72b** as a light brown solid (28.9 mg, 7%), and **72a** as a pale orange solid (171 mg, 47%).

Data for **73b**: R_f 0.55 (2:1 petrol/EtOAc); mp 163 – 171 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 4.88 (dd, *J* = 4.3, 2.3 Hz, 1H), 3.06 – 3.03 (m, 1H), 2.70 (ddd, *J* = 11.7, 5.5, 2.7 Hz, 1H), 2.20 (ddd, *J* = 15.7, 13.0, 7.1 Hz, 1H), 1.78 (dd, *J* = 15.9, 6.6 Hz, 1H), 1.67 (s, 3H), 1.64 (s, 3H), 1.34 (dt, *J* = 12.9, 6.2 Hz, 1H), 1.15 (s, 3H), 0.73 – 0.62 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.4, 157.6, 154.4, 151.5, 146.5, 112.2, 106.7, 89.0, 80.1, 79.4, 65.0, 44.5, 37.7, 33.5, 32.4, 30.2, 29.3, 24.8, 21.5; IR (neat) 2925, 2853, 1728, 1608, 1424, 1343, 1293, 1139, 1119; HRMS (ESI) calculated for $C_{19}H_{17}I_3O_4$ 690.8334 $[M+H]^+$, found: 690.8332.

Data for **73a**: R_f 0.45 (2:1 petrol/EtOAc); mp 143 – 153 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 9.5 Hz, 1H), 6.18 (d, *J* = 9.7 Hz, 1H), 4.90 (dd, *J* = 4.2, 2.4 Hz, 1H), 3.04 (dd, *J* = 4.2, 2.6 Hz, 1H), 2.69 (ddd, *J* = 11.7, 5.5, 2.6 Hz, 1H), 2.18 (ddd, *J* = 15.5, 13.0, 7.1 Hz, 1H), 1.76 (ddd, *J* = 15.9, 13.0, 6.1 Hz, 1H), 1.65 (s, 4H), 1.63 (s, 3H), 1.33 (dt, *J* = 13.2, 6.3 Hz, 1H), 1.14 (s, 3H), 0.68 (tdd, *J* = 13.6, 11.7, 6.3 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.9, 158.9, 154.3, 152.5, 137.8, 112.1, 105.1, 88.6, 79.0, 65.3, 44.5, 37.7, 33.91, 33.86, 32.4, 30.3, 29.3, 24.7, 21.5; IR (neat) 2976, 2933, 1730, 1606, 1556, 1457,1423, 1384, 1355, 1317, 1271,1239, 1200, 1185, 1117; HRMS (ESI) calculated for $C_{19}H_{18}I_2O_4$ 564.9367 $[M+H]^+$, found: 564.9365.

Data for **72b**: R_f 0.25 (2:1 petrol/EtOAc); mp 140 – 145 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 4.57 (d, *J* = 1.7 Hz, 1H), 3.39 (t, *J* = 2.2 Hz, 2H), 2.39 (ddd, *J* = 11.7, 5.5, 2.8 Hz, 1H), 2.16 (dd, *J* = 15.5, 6.0 Hz, 1H), 1.71 (ddd, *J* = 15.4, 13.2, 6.7 Hz, 1H), 1.64 (s, 3H), 1.53 (s, 3H), 1.47 (dt, *J* = 14.9, 6.1 Hz, 1H), 1.10 (s, 3H), 0.73 (tdd, *J* = 13.6, 11.7, 6.1 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.3, 157.6, 154.4, 150.6, 146.7, 112.2, 110.9, 106.9, 78.4, 65.6, 49.6, 41.7, 36.4, 33.9, 31.2, 29.7, 24.7, 22.3, 14.3; IR (neat) 2925, 1729, 1542, 1448, 1424, 1344, 1293, 1237, 1134, 1119, 1086; HRMS (ESI) calculated for $C_{19}H_{17}I_3O_4$ 690.8334 $[M+H]^+$, found: 690.8328.

Data for **72a**: R_f 0.20 (2:1 petrol/EtOAc); mp 123 – 130 °C (decomposition); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 9.6 Hz, 1H), 6.21 (d, *J* = 9.6 Hz, 1H), 4.58 (d, *J* = 1.7 Hz, 1H), 3.38 (t, *J* = 2.2 Hz, 1H), 2.39 (ddd, *J* = 11.7, 5.4, 2.8 Hz, 1H), 2.13 (ddd, *J* = 15.4, 6.2, 1.3 Hz, 1H), 1.70 (ddd, *J* =

15.4, 13.2, 6.9 Hz, 1H), 1.62 (s, 3H), 1.50 (s, 3H), 1.46 (dt, *J* = 13.0, 6.1 Hz, 1H), 1.09 (s, 3H), 0.73 (tdd, *J* = 13.5, 11.6, 6.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 161.0, 159.8, 154.3, 151.6, 138.2, 112.1, 110.7, 105.3, 88.0, 78.1, 65.9, 49.6, 41.7, 36.4, 34.3, 31.2, 29.7, 24.6, 22.3; IR (neat) 2978, 2935, 1724, 1606, 1557, 1455, 1422, 1387, 1357, 1131; HRMS (ESI) calculated for $C_{19}H_{18}I_2O_4$ 564.9367 $[M+H]^+$, found: 564.9369.

Protobruceol-II hydroperoxide (76) and protobruceol-III hydroperoxide (77). To a solution of protobruceol-I (**7**) (80.0 mg, 0.256 mmol) in MeOH (10 mL) was added methylene blue (0.9 mg, 0.003 mmol). O_2 was bubbled through the resultant solution while it was irradiated with LED light for 15 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on SiO_2 (8:1 → 7:1 CH_2Cl_2/EtOAc) to afford protobruceol-III hydroperoxide (**77**) as a pale yellow oil (34.6 mg, 39%, d.r. 1:1). Further elution afforded protobruceol-II hydroperoxide (**76**) as a pale yellow oil (41.8 mg, 47%).

Data for protobruceol-III hydroperoxide **77**: R_f 0.20 (6:1 CH_2Cl_2/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 8.05 (br s, 1H), 7.97 (dd, *J* = 9.6, 1.4 Hz, 1H), 6.70 (dd, *J* = 10.1, 1.3 Hz, 1H), 6.62 (s, 1H), 6.13 (dd, *J* = 9.6, 1.2 Hz, 1H), 5.47 (dd, *J* = 10.1, 1.2 Hz, 1H), 5.02 (q, *J* = 1.6 Hz, 1H), 5.00 (s, 1H), 4.30 (td, *J* = 6.4, 2.8 Hz, 1H), 1.90 – 1.76 (m, 2H), 1.76 – 1.60 (m, overlapped, 2H) 1.70 (dd, *J* = 5.0, 1.3 Hz, 3H), 1.42 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 163.1, 156.5, 155.4, 150.97, 150.94, 143.3, 143.2, 139.7, 126.1, 126.1, 117.2, 114.9, 114.8, 110.2, 106.0, 103.40, 103.39, 95.8, 89.5, 80.2, 80.1, 37.31, 37.2, 26.8, 26.6, 25.5, 25.3, 17.38, 17.36 (Note: more than 19 ^{13}C signals are observed as **77** is a 1:1 mixture of diastereoisomers); IR (neat) 3263, 2973, 1691, 1638, 1615, 1594, 1442, 1364, 1263, 1208, 1187, 1141, 1086; HRMS (ESI) calculated for $C_{19}H_{21}O_6$ 345.1333 $[M+H]^+$, found: 345.1334.

Data for protobruceol-II hydroperoxide **76**: R_f 0.15 (6:1 CH_2Cl_2/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (brs, 1H), 7.98 (d, *J* = 9.6 Hz, 1H), 6.70 (d, *J* = 10.0 Hz, 1H), 6.60 (s, 1H), 6.13 (d, *J* = 9.6, 1H), 5.71 (dt, *J* = 15.9, 7.2 Hz, 1H), 5.59 (d, *J* = 15.8 Hz, 1H), 5.50 (d, *J* = 10.1 Hz, 1H), 2.46 (d, *J* = 7.2 Hz, 2H), 1.47 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ

163.0, 156.5, 155.4, 151.1, 139.7, 137.9, 126.0, 125.2, 117.2, 110.2, 106.3, 103.2, 95.8, 82.3, 79.9, 44.4, 26.8, 24.5, 24.3; IR (neat) 3267, 2978, 2933, 1692. 1638, 1615, 1594, 1443, 1363, 1259, 1141, 1095; HRMS (ESI) calculated for $C_{19}H_{21}O_6$ 345.1333 $[M+H]^+$, found: 345.1333.

Protobruceol-II (74) and protobruceol-III (75). To a solution of protobruceol-I (**7**) (66.8 mg, 0.214 mmol) in MeOH (15 mL) was added methylene blue (3.1 mg, 0.0097 mmol). O_2 was bubbled through the resultant solution while it was irradiated with LED light for 26 h. $NaBH_4$ (150 mg, 3.96 mmol) was added and the mixture was stirred for a further 1.5 h. The reaction was quenched by addition of 1 M HCl solution (10 mL) and diluted with brine (10 mL). The resultant mixture was then extracted with Et_2O (5 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (3:2 → 1:1 petrol/EtOAc) to afford protobruceol-III (**75**) as a clear colourless oil (24.5 mg, 35%). Further elution gave protobruceol-II (**74**) as a clear colourless oil (25.8 mg, 37%).

Data for protobruceol-III (**75**): R_f 0.17 (6:1 CH_2Cl_2/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 7.94 (d, *J* = 9.5 Hz, 1H), 6.67 (dd, *J* = 10.1, 1.3 Hz, 1H), 6.58 (s, 1H), 6.08 (dd, *J* = 9.5, 1.5 Hz, 1H), 5.47 (d, *J* = 10.1 Hz, 1H), 4.95 (s, 1H), 4.86 (q, *J* = 1.7 Hz, 1H), 4.12 (ddd, *J* = 15.5, 8.1, 5.1 Hz, 1H), 1.86 (td, *J* = 9.8, 9.0, 3.6 Hz, 1H), 1.71 (d, *J* = 5.2 Hz, 3H), 1.42 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.3, 156.94, 156.92, 155.3, 150.9, 146.8, 146.7, 139.9, 126.2, 126.1, 117.1, 117.0, 112.0, 111.9, 109.7, 106.11, 106.10, 103.1, 95.6, 80.24, 80.22, 76.09, 76.07, 37.3, 37.1, 29.04, 28.97, 26.7, 17.72, 17.68 (Note: more than 19 ^{13}C signals are observed as **75** is a 1:1 mixture of diastereoisomers); IR (neat) 3246, 3005, 2971, 1708, 1638, 1615, 1595, 1443, 1365, 1299, 1262, 1141, 1085; HRMS (ESI) calculated for $C_{19}H_{21}O_5$ 329.1384 $[M+H]^+$, found: 329.1383.

Data for protobruceol-II (**74**): R_f 0.13 (6:1 CH_2Cl_2/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 7.96 (d, *J* = 9.6 Hz, 1H), 6.68 (d, *J* = 10.1 Hz, 1H), 6.55 (s, 1H), 6.09 (d, *J* = 9.5 Hz, 1H), 5.72 – 5.64 (m, 1H), 5.63 (d, *J* = 15.6 Hz, 1H), 5.48 (d, *J* = 10.1 Hz, 1H), 2.42 (d, *J* = 7.1 Hz, 1H), 1.45 (s, 3H), 1.25 (s, 3H), 1.22 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.2, 156.9, 155.3,

151.1, 141.9, 139.9, 125.9, 121.0, 117.3, 109.7, 106.4, 103.0, 95.6, 79.9, 71.5, 44.0, 29.7, 29.6, 26.6; IR (neat) 3211, 2974, 2930, 1708, 1615, 1444, 1365, 1299, 1259, 1208, 1181, 1141, 1096; HRMS (ESI) calculated for $C_{19}H_{21}O_5$ 329.1384 $[M+H]^+$, found: 329.1385.

Hydroperoxides 79 and 80. To a solution of **8** (500 mg, 1.60 mmol) in MeOH (45 mL) was added rose bengal (15.0 mg, 0.0160 mmol). O_2 was bubbled through the resultant solution while it was irradiated with LED light for 18 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on SiO_2 (6:1 $\rightarrow$ 4:1 CH_2Cl_2/EtOAc, gradient elution) to afford **80** as a pale yellow oil (181 mg, 33%, d.r. 1:1). Further elution afforded **79** as a pale yellow oil (178 mg, 32%).

Data for **80**: R_f 0.25 (5:1 CH_2Cl_2/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9.7 Hz, 1H), 6.65 (d, *J* = 10.1 Hz, 1H), 6.34 (s, 1H), 6.13 (dd, *J* = 9.6, 1.1 Hz, 1H), 5.57 (d, *J* = 10.1 Hz, 1H), 5.29 (s, 2H), 5.04 – 5.00 (m, 1H), 4.99 (s, 1H), 4.29 (t, *J* = 6.6 Hz, 1H), 1.83 – 1.51 (m, overlapped, 4H) 1.70 (s, 3H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.52, 157.83, 157.76, 155.9, 148.79, 148.78, 139.6, 128.3, 128.2, 115.94, 115.91, 114.8, 114.8, 110.6, 105.9, 105.8, 104.1, 104.0, 97.6, 97.6, 89.5, 89.4, 79.7, 79.5, 37.4, 37.1, 27.0, 26.7, 25.5, 25.2, 17.4 (Note: more than 19 ^{13}C signals are observed as **80** is a 1:1 mixture of diastereoisomers); IR (neat) 3319, 2973, 1767, 1686, 1615, 1567, 1453, 1405, 1354, 1303, 1196, 1139, 1081; HRMS (ESI) calculated for $C_{19}H_{21}O_6$ 345.1333 $[M+H]^+$, found: 345.1334.

Data for **79**: R_f 0.20 (5:1 CH_2Cl_2/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.6 Hz, 1H), 7.58 (s, 1H), 6.69 (d, *J* = 10.1 Hz, 1H), 6.34 (s, 1H), 6.13 (dd, *J* = 9.6, 1.3 Hz, 1H), 5.67 (dt, *J* = 15.9, 7.0 Hz, 1H), 5.63 – 5.56 (m, 2H), 2.46 (dd, *J* = 14.0, 7.1 Hz, 1H), 2.39 (dd, *J* = 14.0, 6.9 Hz, 1H), 1.43 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.4, 157.9, 155.9, 148.8, 139.6, 137.9, 128.0, 125.2, 116.1, 110.7, 106.2, 104.1, 97.5, 82.4, 79.4, 44.5, 26.8, 24.5, 24.2; IR (neat) 3316, 2979, 1692, 1616, 1567, 1454, 1406, 1355, 1196, 1140, 1084, 975; HRMS (ESI) calculated for $C_{19}H_{21}O_6$ 345.1333 $[M+H]^+$, found: 345.1333.

Proposed structure for protobruceol-IV (78). To a solution of **79** (44.6 mg, 0.130 mmol) in MeOH (5 mL) was added $NaBH_4$ (7.3 mg, 0.17 mmol) in one portion, and the reaction mixture was stirred at 0 °C for 5 min. Further $NaBH_4$ (7.3 mg, 0.168 mmol) was added, then the reaction was quenched with 1 M HCl solution (0.5 mL) at 0 °C and diluted with brine (10 mL). The mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (neat Et_2O) to afford protobruceol IV (**78**) as a pale yellow oil (27.9 mg, 66%). Data for **78**: R_f 0.25 (neat Et_2O), 0.05 (2:1 petrol/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 9.7 Hz, 1H), 6.68 (d, J = 10.1 Hz, 1H), 6.29 (s, 1H), 6.08 (d, J = 9.7 Hz, 1H), 5.63 – 5.60 (m, 2H), 5.54 (d, J = 10.1 Hz, 1H), 2.41 (dd, J = 13.3, 5.1 Hz, 1H), 2.33 (dd, J = 13.4, 4.9 Hz, 1H), 1.40 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.7, 158.1, 155.8, 149.2, 142.0, 140.0, 127.6, 121.0, 116.5, 110.2, 106.7, 104.3, 97.3, 79.4, 71.4, 44.2, 29.8, 29.5, 26.7; IR (neat) 3331, 2974, 1699, 1615, 1567, 1452, 1355, 1138; HRMS (ESI) calculated for $C_{19}H_{21}O_5$ 329.1384 $[M+H]^+$, found: 329.1383.

Allylic alcohol 81. To a solution of **80** (96.5 mg, 0.280 mmol) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (19.0 mg, 0.504 mmol). The reaction was stirred at 0 °C for 5 minutes, then was diluted with brine (5 mL) and quenched with 1 M HCl (0.8 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on SiO_2 (neat Et_2O) to afford **81** as a yellow oil (70.4 mg, 77%, d.r. 1:1). Data for **81**: R_f 0.30 (neat Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 9.6, 1H), 6.66 (d, J = 10.1 Hz, 1H), 6.28 (s, 1H), 6.09 (d, J = 9.4 Hz, 1H), 5.54 (d, J = 10.2 Hz, 1H), 4.93 (s, 1H), 4.84 (br d, J = 5.2 Hz, 1H), 4.10 – 4.05 (m, 1H), 1.84 – 1.57 (m, overlapped, 4H), 1.69 (s, 3H), 1.38 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.7, 157.92, 157.91, 155.8, 149.1, 146.9, 146.7, 139.9, 128.1, 116.1, 112.0, 111.8, 110.3, 106.1, 106.0, 104.2, 97.3, 79.7, 76.11, 76.09, 37.4, 37.1, 29.1, 29.0, 27.0, 26.8, 17.73, 17.69 (Note: more than 19 ^{13}C signals are observed as **81** is a 1:1 mixture of diastereoisomers); IR (neat)

3307, 2972, 1691, 1615, 1567, 1453, 1354, 1235, 1139, 1080, 1081; HRMS (ESI) calculated for $C_{19}H_{21}O_5$ 329.1384 $[M+H]^+$, found: 329.1385.

Supporting Information

Supplementary information is available free of charge, in the online version, at https://

Copies of ^1H, $^{13}C\{^1H\}$, COSY, ^1H–^{13}C HSQC and ^1H–^{13}C HMBC NMR for all new compounds and X-ray data for **30**, **68a**, **68b**, and **69a**.

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