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# Chemoenzymatic pathways for the synthesis of biologically active natural products

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## Abstract

The whole-cell biotransformation of mono-nuclear aromatic compounds using certain genetically-engineered micro-organisms that over-express the enzyme toluene dioxygenase (TDO) allows for the large scale production of compounds known as *cis*-1,2-dihydrocatechols. These metabolites, which are normally obtained in enantiomerically pure form, can be manipulated, by chemical means, in a range of distinct (and predictable) ways with the result that they have proven to be especially versatile starting materials for the assembly of a range of structurally diverse and biologically active systems. Herein we describe, on a case-by-case basis, the recent applications of various combinations of TDO-mediated and chemical steps in so-called chemoenzymatic total syntheses of a range of organic compounds with therapeutic potential.

## Introduction

Chemical space (*viz.* the space spanned by all possible small molecules and chemical compounds) is essentially infinite.[1] The challenge, then, has been to access the most meaningful or useful parts of it. Nature has provided critical inspirations. So, 3.8 billion years of evolution has produced a global molecular library of unsurpassed size, structural diversity and functional value – our planet's chemome.[2,3,4] Humankind has sought to "mine" this bioactive molecule resource for its benefit and such endeavors have been spectacularly successful as evidenced by the existence of the remarkable array of medicines, materials and agrochemicals that underpin society as we know it today. As a result the world we live in has been transformed. This is evidenced by our exploitation of drugs with household names such as penicillin, morphine and Taxol®. There are many additional but perhaps less well-known examples. For instance, organ transplant surgery would fail completely without the post-operative application of the chemome-derived anti-rejection drugs such FK506 and cyclosporin A.[5] Similarly, a significant number of agents that control agricultural pests, and so helping to ensure both the security and efficiency of world food production, have also come from Nature/the global chemome.[6]

Despite such successes, enormous challenges remain. So-called unmet scientific and societal needs include those arising from the development of resistance to current therapies (perhaps seen most prominently in the area of antibiotics[7]) and, in the

agrochemical sector, pest-control agents.[8] In addition, there is a desperate need for small molecule entities that provide, *inter alia*, effective control of neurodegenerative diseases and diabetes in a globally aging population, for ones that treat certain types of refractory cancers and for others that effectively modulate mammalian and other immune systems.

After forays into areas such as combinatorial chemistry,[9] major players in the pharmaceutical industry, sometimes in partnerships with Government-funded agencies, are returning to interrogation of the chemome (or at least portions thereof) as a means for productively probing chemical and thence biological space.[10] There are a number of reasons for such moves[10] including the recognition that, for example, the current pharmaceutical industry is built on <10% of the biosynthetic capacity of the microbial world, one that continues to show a remarkable ability to deliver biologically relevant small molecules.[11]

Occurring in tandem with these trends is the emergence of a plethora of new techniques and concepts concerned with the generation of biologically relevant molecular diversity involving the use of, *inter alia*, techniques of *de novo* biosynthesis for producing functionally annotated chemome components,[12] the creation of new metabolic pathways,[12] synthetic fermentation,[13] and activity-directed synthesis.[14] Simultaneously, new synergies are being recognized between *in vitro*, *in vivo* and *in silico* studies of drug metabolism [15] and thus allowing for much more efficient/rapid assessments of the utility of certain compounds as molecular probes, drugs and/or agrochemicals.

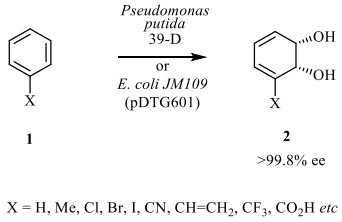
The development of new methods and protocols for effecting the chemical synthesis of biologically active natural products and various analogues remain important parts of the range of activities concerned with exploiting components of the global chemome for therapeutic and other purposes. At least two motivations drive such efforts, the first being the need to address issues of supply. Thus, it is often the case that secondary metabolites[2] are only available in miniscule amounts from their natural source with the result that insufficient material is available for development purposes. Chemical synthesis is often the best method for addressing such issues. Secondly, truly useful chemical syntheses offer the capacity to generate analogues of the natural product that would not normally be available through manipulation of the natural product itself.

This article, which is based on a lecture presented by the senior author at the University of Sydney as part of the RSNSW's 2014 Liversidge Award, details work being undertaken at the Australian National University on the exploitation of certain chemoenzymatic methods for the synthesis of biologically active natural products and their analogues. The work is presented according to the class of natural product being targeted as well as the structural and chemical relationships between them.

## Results and discussion

The term chemoenzymatic synthesis used in this article, and elsewhere,[16] refers to the assembly of target compounds using a combination of chemical and enzymatic techniques. While there are many variations on this theme that reflect the extraordinarily diverse range of chemical and enzymatic transformations available these days, the specific form of the latter that applies here involves the whole-cell biotransformation of a range of simple and readily available aromatic compounds of the general form **1** (**Scheme 1**) into the corresponding *cis*-1,2-dihydrocatechols (**2**).[16] When genetically engineered micro-organisms such as *E. coli* JM109 (pDTG601)[17] are used for such

purposes, these metabolites can be readily produced at kilogram scales and are often obtained in >99.95 enantiomeric excess (ee). In the illustrated cases the enzyme responsible for these conversions is toluene dioxygenase (TDO) but a number of related ones are known including biphenyl dioxygenase, naphthalene dioxygenase and toluate dioxygenase. The end result is that a remarkable suite of *cis*-1,2-dihydrocatechols and related metabolites is known - these number in the many hundreds at the present time.[16c] Given the capacities to produce numerous mutants, and thus expand the range of substrates that can be biotransformed, the possible extensions of such processes would appear to be vast. A further fascinating aspect of them is the "chemoselectivities" they can display. So, for example, styrene (**1**, X = $CH{=}CH_2$) is converted into the triene **2** (X = $CH{=}CH_2$), a process wherein the aromatic ring is oxidised in preference to the exocyclic olefin, a functional group selectivity that cannot be achieved by any of the strictly chemical methods known at the present time.[18]




**Scheme 1**

The utility of the *cis*-1,2-dihydrocatechols (**2**) as starting materials in chemical synthesis has taken some time to be recognised in a broader sense. Various groups, especially those led by Ley in the UK[19] and Hudlicky in North America,[16a,d] have carried out the pioneering work in the area. Such studies established the reactivity "patterns" shown in **Figure 1** as well as attendant hazards arising from the dehydrative re-aromatisation of these substrates[20] and the propensity of certain derivatives, most notably the corresponding acetonides, to engage in normally unproductive Diels-Alder (DA) dimerization reactions.[21]

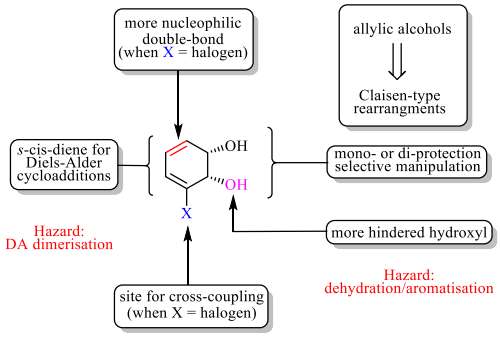



**Figure 1**

Our own contributions in the area began in the late 1980s[22] and in the intervening period we have been able to establish a series of total syntheses (**Figure 2**) that emphasise the extraordinary range of natural product targets available through manipulation of these metabolites. Some specific examples arising from our recent research are discussed on a case-by-case basis in the following sections.

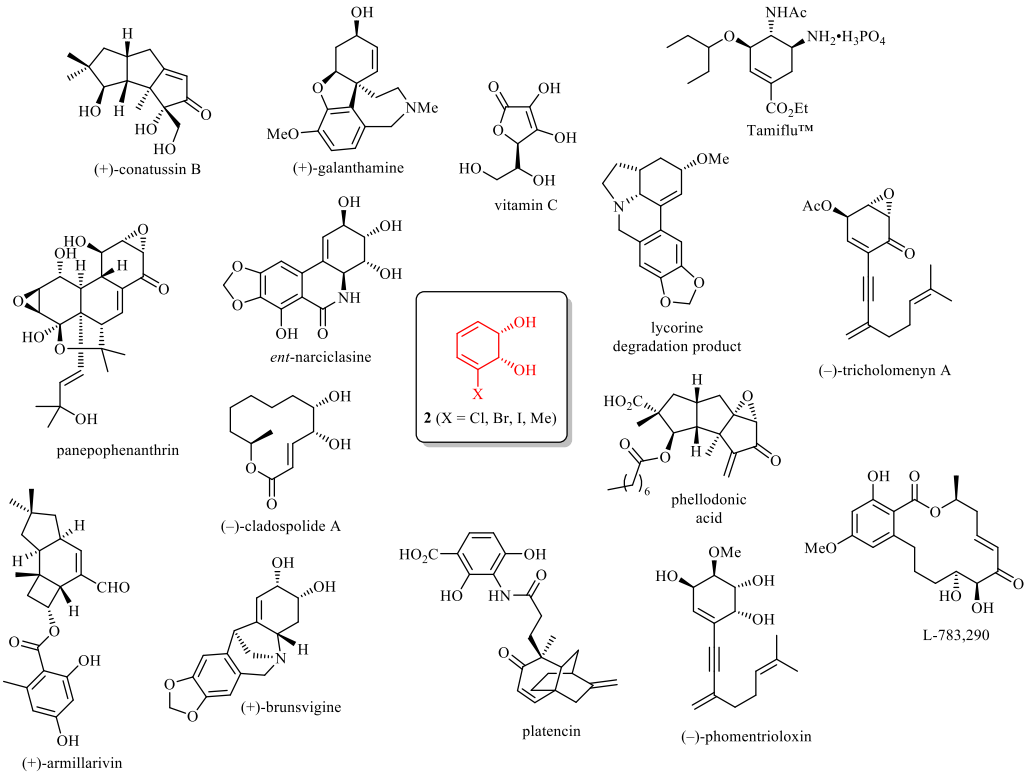



**Figure 2**

## The Ribisins

Ribisins A-D were isolated by Fukuyama and co-workers from *Phellinus ribis* (Schmach.) Quél (Hymenochaetaceae),[23] a fungus used in traditional medicine for various purposes. Using a range of spectroscopic methods they were assigned structures **3**-**6** (**Figure 3**), respectively, and shown to enhance neurite outgrowth in PC12 cells at *ca.* 1 μM concentrations. As such they have potential for development as agents for the treatment of certain neurological disorders.

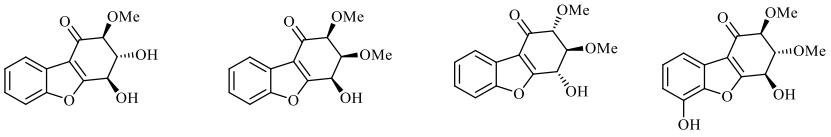
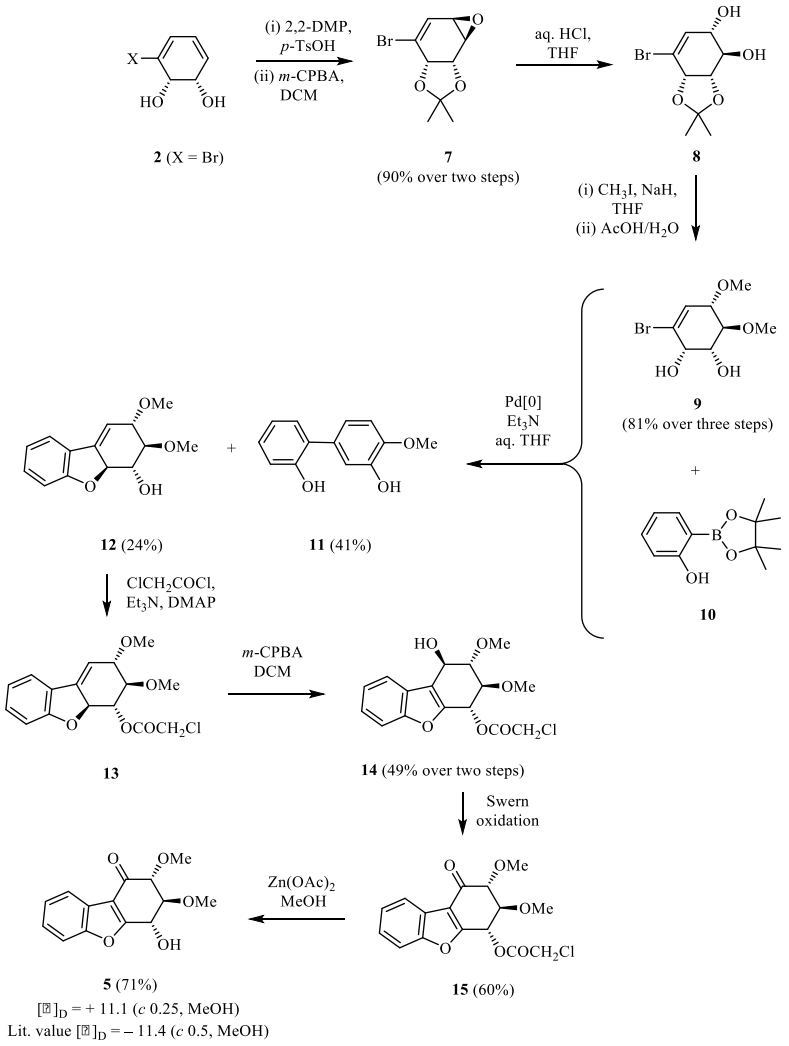


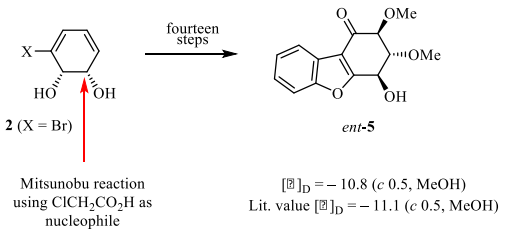

**Figure 3**

Given the structural resemblance of the polyoxygenated cyclohexane ring of these natural products to the *cis*-1,2-dihydrocatechols **2** (X = Br) we sought a means for effecting the relevant chemical conversions. The route used for establishing a synthesis of compound **5**, the structure assigned to ribisin C and the most active compound in the series, is shown in **Scheme 2**.[24]




**Scheme 2**

The opening stages of this reaction sequence are typical of the manner in which the *cis*-1,2-dihydrocatechols can be manipulated and involve the initial conversion of compound **2** (X = Br) into the corresponding acetonide and the regio- and stereo-selective epoxidation of the latter to give the oxirane **7**. Treatment of compound **7** with aqueous mineral acid resulted in a regioselective ring-opening reaction to afford the *trans*-diol **8** that could be bis-*O*-methylated under conventional conditions and the resulting acetonide was then cleaved, again under conventional conditions, to give the *cis*-diol **9** that embodies most of the key elements of the Eastern hemisphere of target **3**. Compound **9** could be engaged in a Suzuki-Miyaura cross-coupling reaction with the commercially available boronate ester **10** and two products thereby formed, namely the bis-phenol **11** and the dihydrobenzofuran **12**. Product **12** is presumably formed through cyclisation of the initially produced cross-coupling product while congener **11** arises from successive loss of the elements of water and methanol (no particular order implied) from the same intermediate. The lone hydroxyl group within compound **11** could be protected as the corresponding α-chloro-acetate **13**, a necessary step because of the looming introduction of a second hydroxyl group as the precursor to the ketone moiety. The use of the α-chloroacetate as a protecting group proved essential as in the final step of the reaction sequence attempts to remove the less labile parent acetate resulted in decomposition of the substrate. Epoxidation of compound **13** using *m*-chloroperbenzoic acid (*m*-CPBA) led, presumably *via* spontaneous rearrangement of the initially formed oxirane, to the benzofuran alcohol **14** that could be oxidised to the corresponding ketone **15** under Swern conditions. Cleavage of the α-chloroacetate residue within this last compound was accomplished using zinc acetate in methanol and thus forming the target compound **5**. While all the usual spectroscopic data acquired on compound **5** matched those reported for ribisin C, the specific rotation derived from the synthetic material was of the same magnitude but the opposite sign to that reported for the natural product. The implications are clear – the structure of ribisin C is represented by structure *ent*-**5** rather than **5**. Since we required an authentic sample of ribisin C (*ent*-**5**) for biological testing, a synthesis of it was pursued. This could be achieved (**Scheme 3**) using the same starting material and many of the same transformations as employed in generating its enantiomer (**5**). A key step of the fourteen-stage reaction sequence involved the inversion of configuration at C3 within a derivative of compound **2** (X = Br) using Mitsunobu chemistry. As a result ribisin C was obtained and all of the derived data, including the specific rotation, matched those reported for the natural product.




**Scheme 3**

Extensions of this sort of chemistry enabled the synthesis of all of the structures originally assigned to the ribisins and thus revealed that while ribisins A and D are constituted as originally described[23] that attributed to congener B is, like C, incorrect.[25] The true structures of all the ribisins are shown in **Figure 4** with the corrected stereocentres within compounds B (**16**) and C (*ent*-**5**) highlighted in red. Extensive biological evaluations of the ribisins and the range of

congeners prepared during the course of our synthetic studies are now underway.

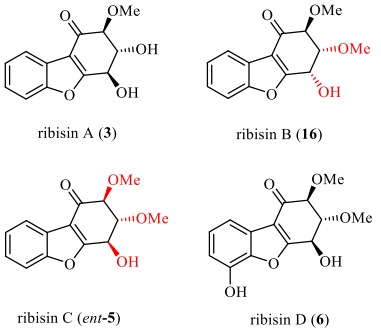



**Figure 4**

### Analogues of Galanthamine

Ribisin D (**6**) bears a "provocative" structural resemblance to the ABC ring-system of the alkaloid galanthamine (**17**) that is used in many countries for the symptomatic treatment of Alzheimer's disease (**Figure 5**).[26] As such we were prompted to explore means by which the chemistry described above could be adapted so as to produce compounds bearing greater similarities to galanthamine (or, in the first instance at least, the enantiomer thereof).

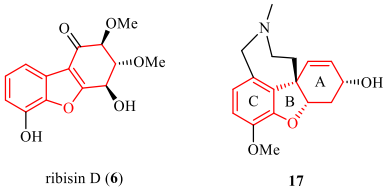
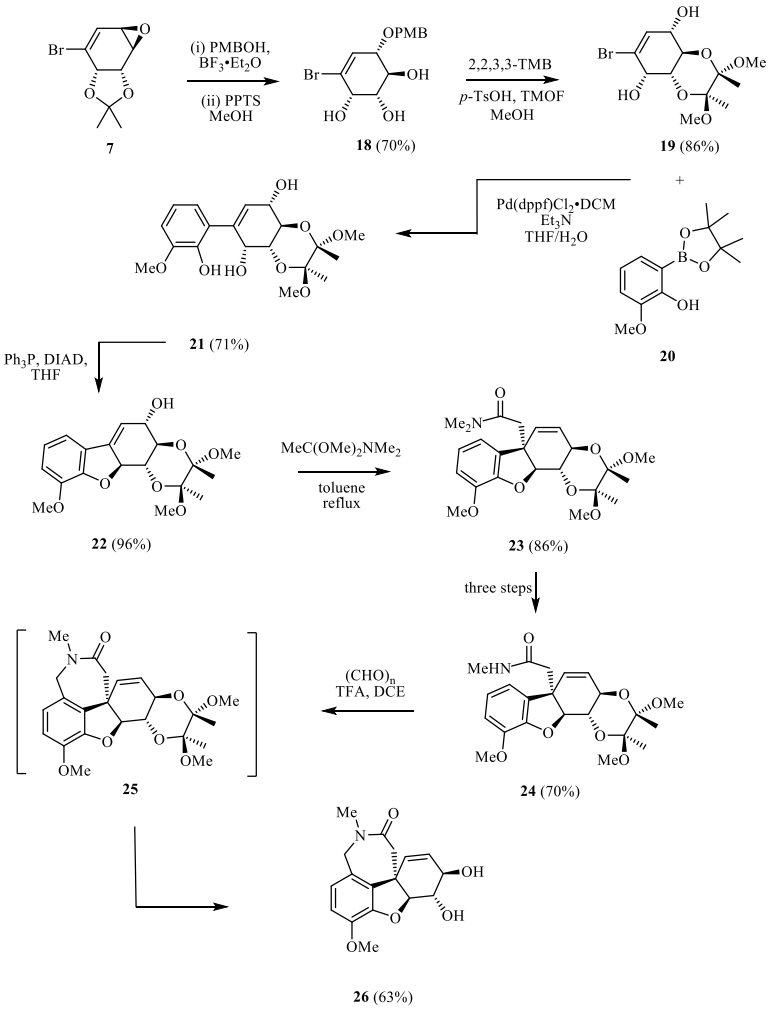



**Figure 5**

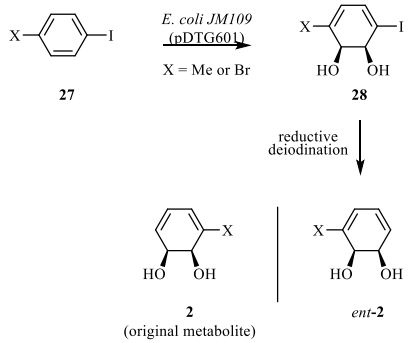
An efficient reaction sequence leading to a dioxygenated derivative of *ent*-galanthamine is shown in **Scheme 4**[27] and involves an initial reaction of the abovementioned oxirane **7** with *p*-methoxybenzyl alcohol (*p*-MBOH) in the presence of boron trifluoride diethyl etherate to generate the anticipated addition product that upon treatment, in a second step, with methanol containing pyridinium *p*-toluenesulfonate (PPTS) affords triol **18**. This last compound could be converted into the corresponding Ley ketal **19**[28] through treatment with 2,2,3,3-tetramethoxybutane (2,2,3,3-TMB) in the presence of *p*-toluenesulfonic acid (*p*-TsOH)/trimethyl orthoformate (TMOF) and Suzuki-Miyaura cross-coupling of this with the boronate ester **20** (produced directly from *o*-methoxyphenol using a C-H functionalization protocol) afforded the arylated cyclohexene **21**. This last compound that was itself engaged in an intramolecular Mitsunobu reaction using di-*iso*-propyl azodicarboxylate (DIAD) to afford the dihydrobenzofuran **22**.

Despite the potential for aromatisation (through simple double-bond migration), compound **22** could be engaged in an Eschenmoser-variant of the Claisen rearrangement reaction using the dimethyl acetal of *N*,*N*-dimethylacetamide[29] and thus affording the angularly substituted ABC-ring analogue **23** of *ent*-galanthamine. Over three conventional steps compound **23** could be converted into its mono-methylated counterpart **24**. The last compound participated in a Pictet-Spengler cyclisation reaction on exposure to a mixture of paraformaldehyde and trifluoroacetic acid (TFA) and the presumably first-formed product **25** underwent cleavage of the Ley acetal residue to give diol **26** as the only isolable product of reaction. Compound **26**, representing a dioxygenated derivative of *ent*-galanthamine (*ent*-**17**), and various congeners that have been prepared using related reaction sequences are currently being subjected to evaluation as inhibitors of the neurologically significant enzyme acetylcholine esterase (AChE).




**Scheme 4**

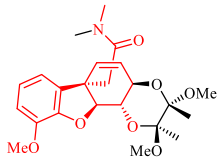
It is worth noting, at this point, that the enantiomer of certain of the *cis*-1,2-dihydrocatechols described above are also available.[30] So, for example, biotransformation of *p*-iodotoluene or *p*-iodobromobenzene [**27a** (X = Me) and **27b** (X = Br), respectively] (**Scheme 5**) using *E. coli* JM109 (pDTG601) affords metabolite **28** that upon exposure to dihydrogen in the presence of palladium on carbon undergoes hydrogenolytic cleavage of the associated C-I bond and thus delivering either *cis*-1,2-dihydrocatechol *ent*-**2** (X = Me) or *ent*-**2** (X = Br).



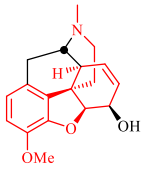

**Scheme 5**

## The Opiates

Morphine and its congener codeine are members of opiate family. They are used extensively for the management of pain and represent the most widely applied and highest grossing medicines in the world today.[31] Their structural complexity means that for the moment, at least, opiates such as morphine are obtained from natural sources and then derivatized by simple chemical means so as to produce related drugs. Nevertheless, much progress has been made in terms of developing commercially viable total syntheses of these systems. Hudlicky and co-workers have defined the current "gold standard" in the area.[32] Given the tantalising structural resemblance between the readily available compound **23** and *ent*-codeine (**29**) (**Figure 6**) we are now attempting to modify the synthesis of the former so as to access the latter. This will likely involve introducing the necessary additional two-carbon unit by using a variant of boronate ester **20** and completing the synthesis of the less functionalised cyclohexane ring within target **29** using an intramolecular $S_N'$ reaction that simultaneously cleaves the Ley acetal subunit.




**23**



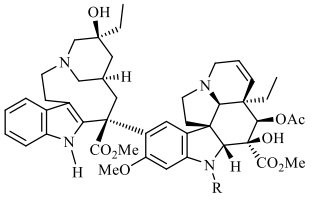

**29**
*(ent*-codeine)

**Figure 6**

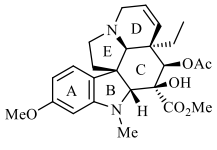
## Vinblastine, Vincristine and Vindoline

Vinblastine (**30**) and vincristine (**31**) (**Figure 7**) are indole-indoline-based alkaloids derived from various plant sources, perhaps most notably the Madagascan rosy periwinkle.[33] They are used in the clinical treatment of non-Hodgkin's lymphomas as well as testicular, breast and lung cancers. These compounds are derived *in vivo* from the significantly more abundant and co-occurring alkaloid vindoline (**32**). Given the development of direct, chemically based and "bio-inspired" methods for effecting the conversion of this simpler compound into alkaloids **30** and **31**, vindoline has become the focus of considerable attention as a synthetic target.[34]

Our own efforts in this area have been inspired by the observation (**Figure 8**)[35] that the mutant organism *P. putida* BGXM1 can effect, in an enantioselective fashion, the whole-cell biotransformation of abundant *m*-ethyltoluene (**33**) into the carboxylic acid diol **34** that bears a striking resemblance to the highly functionalised C-ring of vindoline. Accordingly, a recent focus of some of our work in the area of chemoenzymatic synthesis has been on identifying methods for converting this metabolite into vindoline (**32**) and thence into vinblastine (**30**) and vincristine (**31**).




**30** (R=Me)
**31** (R=CHO)




**32**

Madagascan rosy periwinkle

**Figure 7**

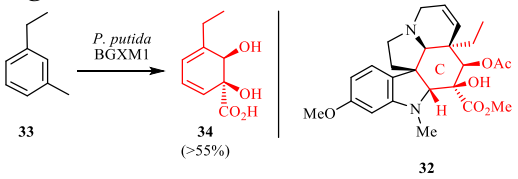
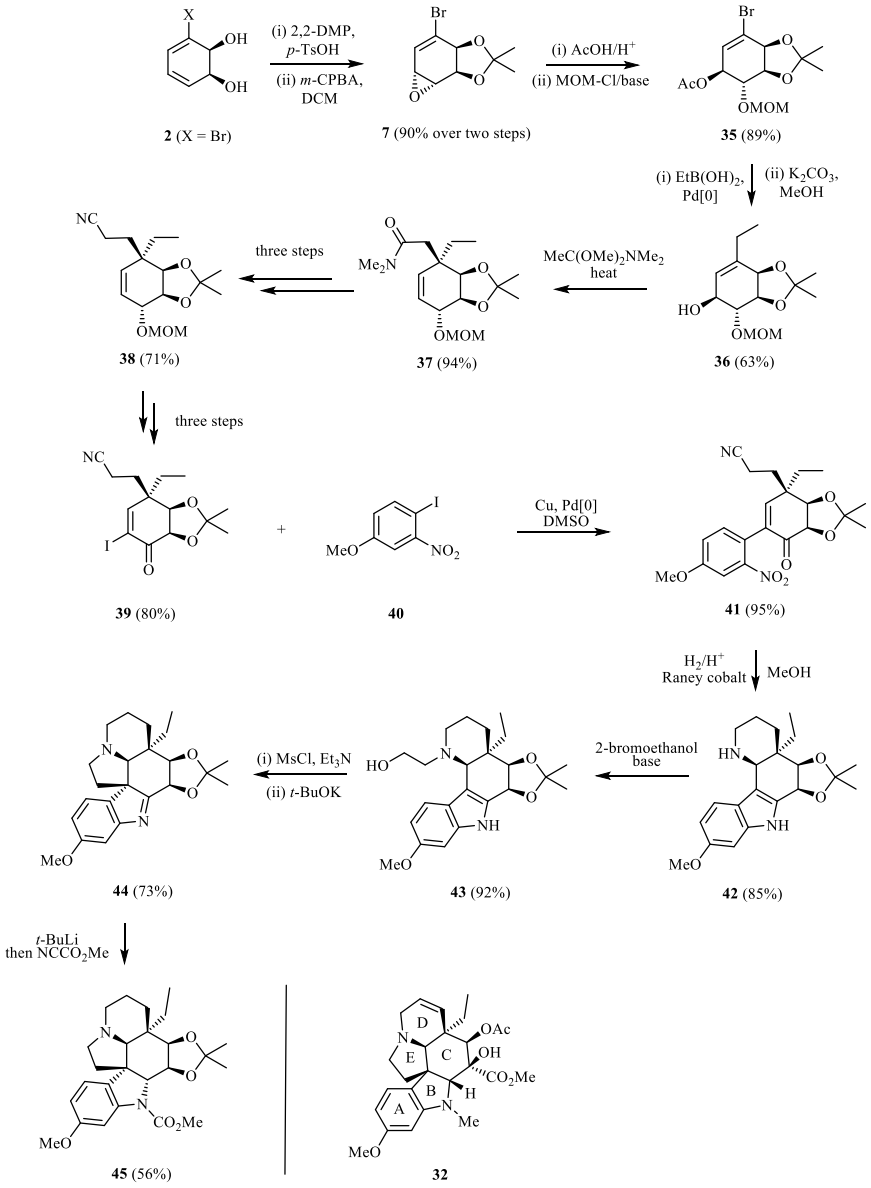



**Figure 8**

The model study outlined in **Scheme 6** has provided encouragement.[36] Thus, the *cis*-1,2-dihydrocatechol **2** (X = Br), representing a model for congener **34**, was converted, by the means described earlier, into the oxirane **7**. Treatment of this last compound with acetic acid in the presence of mineral acid afforded a *trans*-diol mono-ester that was protected under standard conditions as the corresponding MOM-ether and thus affording compound **35** that could be cross-coupled with ethyl boronic acid in the presence of a Pd[0] catalyst to give, after completing cleavage of the acetate residue using methanolic potassium carbonate, the allylic alcohol **36**. This last compound was engaged in a sluggish Eschenmoser-Claisen rearrangement reaction to give amide **37**, the side-chain of which could be elaborated, over three steps, into the nitrile **38**. Over a further three conventional steps this was converted into the α-iodocyclohexenone **39** that itself served as a substrate for a palladium-catalysed Ullmann cross-coupling reaction[37] with *o*-iodonitroarene **40** and so delivering the α-arylated cyclohexenone **41**. On exposure to dihydrogen in the presence of Raney cobalt[38] and a proton source compound **41** engaged in a series of chemoselective reductions and two cyclisation reactions with the result that the tetracyclic compound **42** was formed. The completion of the synthesis of the pentacyclic framework of vindoline proved straightforward and involved reaction of the last compound with 2-bromoethanol in the presence of base, mesylation of the resulting alcohol **43** and treatment of the sulfonate ester so formed with potassium *tert*-butoxide to generate the isoindole **44**.

In an effort to introduce the carbomethoxy group associated with alkaloid **32**, compound **44** was subjected to successive treatment with *tert*-butyllithium then Mander's reagent ($NCCO_2Me$).[39] However, rather than obtaining the hoped-for *C*-carbomethoxylated imine, carbamate **45** was produced, presumably by a pathway whereby the *tert*-butyllithium acts as a hydride source[40] with the resulting indoline anion then reacting (at nitrogen) with the added electrophile. Efforts are now underway to adapt these chemistries so as to convert metabolite **34** into vindoline. The most challenging issue associated with doing so will be finding a means for introducing the C-C double bond incorporated within the D-ring of target **32**.




**Scheme 6**

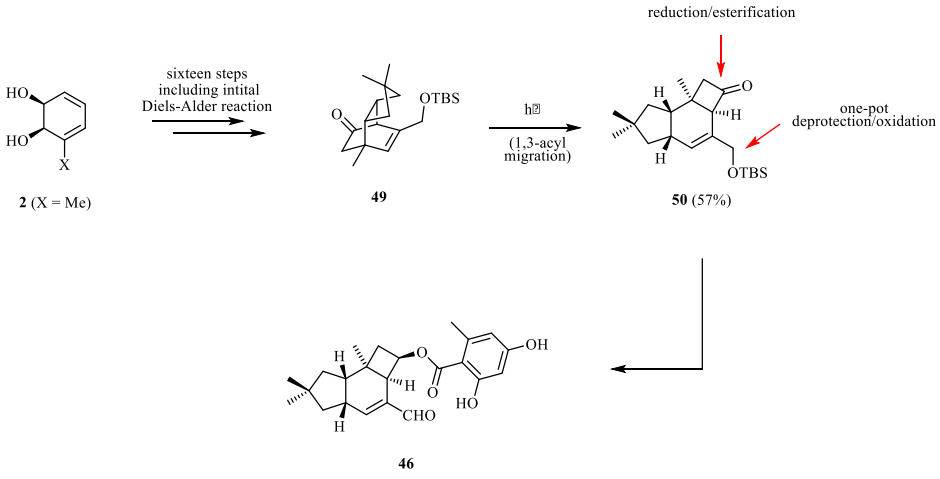
## The Protoilludanes

The title sesquiterpenes embody a distinctive tricyclic framework wherein a central cyclohexane ring is annulated, in an angular arrangement, to both a four- and a five-membered ring.[41] The protoilludane aryl ester (+)-armillarivin (**46**) (**Figure 9**) has been found in the edible sugar mushroom *Armillaria mellea*[42] while representative additional natural products in this family include **47**[43] and **48**[44] that are derived from the saprotrophic wood decomposing fungus *Granulobasidium vellereum* (Ellis & Cragin) Jülich.


**Figure 9**

In 2013 we described the first and thus far only total synthesis of (+)-armillarivin.[45] A key element of our approach (**Scheme 7**) was an initial high-pressure promoted and completely regio- and stereo-selective Diels-Alder reaction between the *cis*-1,2-dihydrocatechol **2** (X = Me) and cyclopentenone.[46] Relatively conventional but rather extensive manipulations of the resulting adduct lead to the cyclopentannulated bicyclo[2.2.2]octenone **49** that engaged, as a second pivotal step of the synthesis, in a photochemically-promoted 1,3-acyl migration reaction (Givens rearrangement)[47] to afford the tricyclic isomer **50**. This last compound, which embodies the tricyclic protoilludane framework, was readily manipulated over just three steps to deliver (+)-armillarivin. The structure of this synthetically produced material was confirmed by single-crystal X-ray analysis and all the derived spectroscopic data, including specific rotation, matched those reported for the natural product.

Subjection of the acetonide derivative of compound **2** (X = Me) to a Diels-Alder reaction with cyclopentenone affords, *via* addition of the dienophile to the face of the diene opposite to that "occupied" by the hydroxyl groups, cyclopentannulated bicyclo-[2.2.2]octenones that are enantiomerically related to those obtained by the pathway described immediately above. In essence, then, by controlling the facial selectivity of such cycloaddition reactions either enantiomeric form of the relevant Diels-Alder adduct can be obtained.




**Scheme 7**

By such means we have recently been able to complete total syntheses of the enantiomeric forms of the protoilludanes **47** and **48**[48] and thus confirming, for the first time, the structures assigned to them.

## Platencin

The Diels-Alder cycloaddition chemistry involving *cis*-1,2-dihydrocatechols as the 4π-component can be effectively extended to intramolecular variants. This is perhaps best exemplified in our recently completed first- and second-generation chemoenzymatic syntheses of platencin (**51**),[49,50] a compound isolated from *Streptomyces platensis* MA7327 that acts as a potent and dual inhibitor of FabH and FabF, key enzymes associated with fatty acid biosynthesis in bacteria (**Figure 10**).[51] By virtue of its novel structure and modes of action, platencin is regarded as an important new lead in the development of urgently needed, next-generation anti-bacterial agents.[52]

In our first generation synthesis of compound **51** (**Scheme 8**),[49] the acetonide derivative, **52**, of the *cis*-1,2-dihydrocatechol **2** (X = I) was engaged in a Stille cross-coupling reaction with the *Z*-configured alkenylstannane **53** to give the tetra-ene **54**. Substrate **53** was prepared in a straightforward manner with the stereochemistry at the quaternary carbon centre being controlled through the agency of a chiral auxiliary.

While compound **54** failed to engage in an intramolecular Diels-Alder (IMDA) reaction, the readily derived ketone **55** did so when heated in refluxing toluene and thus affording, in stereochemically pure form, adduct **56** embodying the tricarbocyclic core of platencin. Over a further thirteen steps compound **56** could be converted into (–)-platencin (**51**).

Some of these steps were needed to deal with functional group incompatibilities, an issue that has been addressed, albeit in a modest way, through our recently disclosed second-generation synthesis.[50] In a developing collaboration with the Hudlicky group at Brock University (Canada), efforts are now focussed on a third-generation approach.

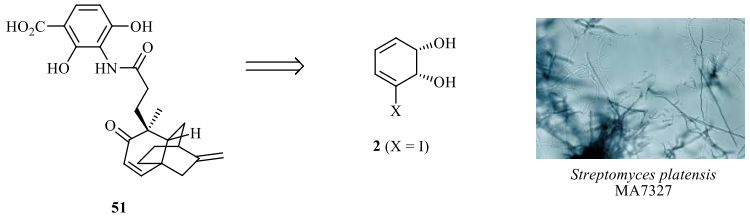
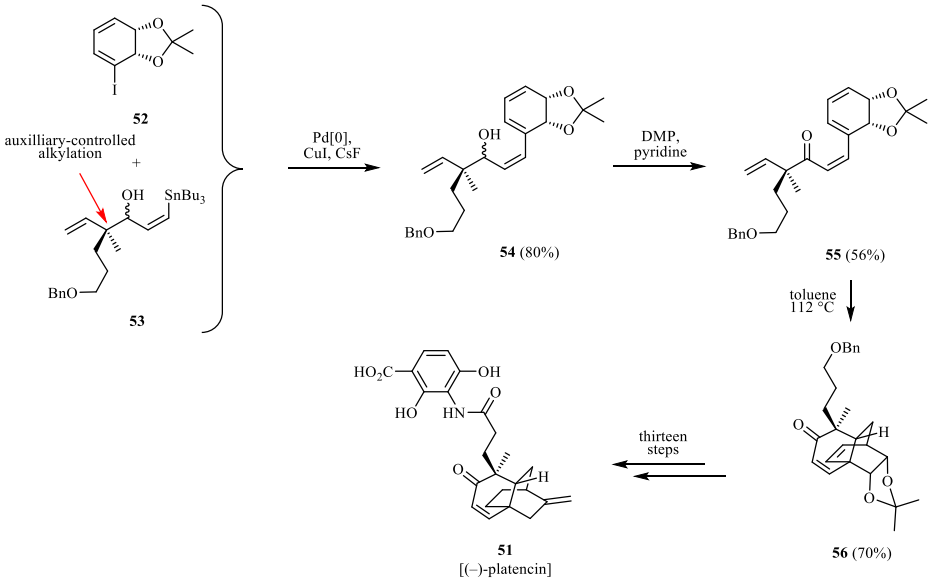



**Figure 10**




**Scheme 8**

## Conclusions

Enzymes have an almost unparalleled capacity to transform simple organic substrates into synthetically more valuable ones, especially enantiomerically pure compounds (EPCs). Through the use of various genetic engineering, gene shuffling and directed evolution techniques the opportunities to expand upon the existing "library" of metabolites seem almost infinite. Furthermore, pathway-engineering techniques provide a capacity to produce (mutant) organisms that effect, through the orchestrated action of a series of enzymes, multistep transformations. The conversion of *m*-ethyltoluene (**33**) into compound **34**[35] is a case in point and wherein both mono-oxygenases and dioxygenases act in concert to produce a potentially high-value metabolite. When combined with the power of chemical synthesis (as manifest in the techniques of chemoenzymatic synthesis), such bio-transformations provide a powerful tool kit for preparing a wide range of compounds of biological relevance. Ironically, perhaps, while microbiologists have a remarkable capacity to generate a diversity of low molecular weight metabolites (and often at multi-kilogram or larger scale) and synthesis chemists have an almost insatiable appetite for new synthons, the often siloed nature of academic research activities results in less than desirable overlap of the relevant sets of expertise. Changing this situation can only benefit both disciplines.

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## References and notes

1.J. L. Reymond, *Acc. Chem. Res.*, 2015, **48**, 722.
2.The term chemome is used here in the sense defined by Wender (see ref. 3) and taken to mean that vast collection of secondary metabolites produced by the planet's flora and fauna.
3.P. A. Wender, *Nat. Prod. Rep.*, 2014, **31**, 433.
4.The term "terpenome" has been introduced to define that subset of the chemome that is terpenoid in origin: M. B. Quin, C. M. Flynn and C. Schmidt-Dannert, *Nat. Prod. Rep.*, 2014, **31**, 1449.
5.See, for example, H. van Hattum and H. Waldmann, *J. Am. Chem. Soc.*, 2014, **136**, 11853; (b) S. Rizzo and H. Waldmann, *Chem. Rev.*, 2014, **114**, 4621; (c) M. E. Maier, *Org. Biomol. Chem.*, 2015, **13**, 5302.
6.B. C. Gerwick and T. C. Sparks, *Pest Manag. Sci.*, 2014, **70**, 1169.
7.M. A. T. Blaskovich, J. Zuegg, A. G. Elliot and M. A. Cooper, *ACS Infect. Dis.*, 2015, **1**, 285.
8.R. F. Service, *Science*, 2013, **341**, 1329.
9.A very limited number of drugs has thus far emerged from the *de novo* applications of combinatorial chemistry techniques: D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2012, **75**, 311.
10. (a) E. Kellenberger, A. Hofmann and R. J. Quinn, *Nat. Prod. Rep.*, 2011, **28**, 1483; (b) J. L. Fox, *Nat. Biotech.*, 2014, **32**, 305; (c) A. L. Harvey, R. Edrada-Ebel and R. J. Quinn, *Nat. Rev. Drug Discov.*, 2015, **14**, 111; (d) M. Pascolutti, M. Campitelli, B. Nguyen, N. Pham, A.-D. Gorse and R. J. Quinn, *PLoS ONE*, 2015, **10**, e0120942.
11. J. R. Doroghazi, J. C. Albright, A. W. Goering, K.-S. Ju, R. R. Haines, K. A. Tchalukov, D. P. Labeda, N. L. Kelleher and W. W. Metcalf, *Nature Chem. Biol.*, 2014, **10**, 963.
12.X. Zhu, J. Liu and W. Zhang, *Nat. Chem. Biol.*, 2015, **11**, 115.
13.Y. Huang and J. W. Bode, *Nat. Chem.*, 2014, **6**, 877.
14.G. Karageorgis, S. Warriner and A. Nelson, *Nat. Chem.*, 2014, **6**, 872.
15.J. Kirchmair, A. H. Göller, D. Lang, J. Kunze, B. Testa, I. D. Wilson, R. C. Glen and G. Schneider, *Nat. Rev. Drug Discov.*, 2015, **14**, 387.
16.For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see: (a) T. Hudlicky, D. Gonzalez and D. T. Gibson, *Aldrichimica Acta*, 1999, **32**, 35; (b) M. G. Banwell, A. J. Edwards, G. J. Harfoot, K. A. Jolliffe, M. D. McLeod, K. J. McRae, S. G. Stewart and M. Voegtle, *Pure Appl. Chem.*, 2003, **75**, 223; (c) R. A. Johnson, *Org. React.*, 2004, **63**, 117; (d) T. Hudlicky and J. W. Reed, *Synlett,* 2009, 685; (e) D. J.-Y. D. Bon, B. Lee, M. G. Banwell and I. A. Cade, *Chimica Oggi,* 2012, **30**, No. 5, (Chiral Technologies Supplement), 22; (f) U. Rinner, Chiral Pool Synthesis: Chiral Pool Syntheses from *cis*-Cyclohexadiene Diols In: E. M. Carreira and H. Yamamoto, (Eds) *Comprehensive Chirality*, 2012, **2**, 240.
17.G. J. Zylstra and D. T. Gibson, *J. Biol. Chem.*, 1989, **264**, 14940.
18.The chemical dihydroxylation of benzene has been reported as a means of preparing the cyclitol (±)-pinitol: P. M. J. Jung, W. B. Motherwell and A. S. Williams, *Chem. Commun.*, 1997, 1283.
19. See, for example, S. V. Ley, F. Sternfeld and S. Taylor, *Tetrahedron Lett.*, 1987, **28**, 225.
20.(a) S. M. Brown and T. Hudlicky, in Organic Synthesis: Theory and Applications, 1992, JAI Press Inc., Greenwich, Connecticut, 1992, vol. II, 113; (b) D. R. Boyd, J. Blacker, B. Bryne, H. Dalton, M. V. Hand, S. C. Kelly, R. A. More O'Ferrall, S. N. Rao, N. D. Sharma and G. N. Sheldrake, *J. Chem. Soc., Chem. Commun.*, 1994, 313.
21.These types of acetonides are prone to dimerization: (a) S. V. Ley, A. J. Redgrave, S. C. Taylor, S. Ahmed and D. W. Ribbons, *Synlett*, 1991, 741; (b) T. Hudlicky, E. E. Boros, H. F. Olivo and J. S. Merola, *J. Org. Chem.*, 1992, **57**, 1026.
22. M. G. Banwell, *Org. Prep. Proced. Int.*, 1989, **21**, 255.
23. Y. Liu, M. Kubo and Y. Fukuyama, *J. Nat. Prod.*, 2012, **75**, 2152.
24. P. Lan, M. G. Banwell, J. S. Ward and A. C. Willis, *Org. Lett.*, 2014, **16**, 228.
25. P. Lan, M. G. Banwell and A. C. Willis, *J. Org. Chem.*, 2014, **79**, 2829.
26. For points-of-entry into the relevant literature

see: (a) J. Nugent, E. Matoušová and M. G. Banwell, *Eur. J. Org. Chem.*, 2015, 3771; (b) M. G. Banwell, J. Buckler, C. J. Jackson, P. Lan, X. Ma, E. Matoušová and J. Nugent J. – Devising New Syntheses of the Alkaloid Galanthamine, a Potent and Clinically Deployed Inhibitor of Acetylcholine Esterase in *Strategies and Tactics in Organic Synthesis* (Ed. M. Harmarta), 2015 **11**, 29.

27. J. N. Buckler, E. S. Taher and M. G. Banwell, unpublished observations.
28. S. V. Ley, D. K. Baeschlin, D. J. Dixon, A. C. Foster, S. J. Ince, H. W. M. Priepke and D. J. Reynolds, *Chem. Rev.*, 2001, **101**, 53.
29. For a relevant application of this process see M. G. Banwell, X. Ma, O. P. Karunaratne and A. C. Willis, *Aust. J. Chem.*, 2010, **63**, 1437.
30. (a) D. R. Boyd, N. D. Sharma, S. A. Barr, H. Dalton, J. Chima, G. Whited, R. Seemayer, *J. Am. Chem. Soc.*, 1994, **116**, 1147; (b) C. C. R. Allen, D. R. Boyd, H. Dalton, N. D. Sharma, I. Brannigan, N. A. Kerley, G. N. Sheldrake, S. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1995, 117.
31. For relevant background accounts see: (a) L. D. Kapoor, *Opium Poppy: Botany, Chemistry, and Pharmacology*, Food Products Press, New York, 1997; (b) M. Booth, *Opium: A History*, St. Martin's Press, New York, 1998.
32. J. W. Reed and T. Hudlicky, *Acc. Chem. Res.*, 2015, **48**, 674 and references cited therein.
33. (a) M. E. Kuehne and I. Marko, *The Alkaloids*, 1990, **37**, 77; (b) H. L. Pearce, *The Alkaloids*, 1990; **37**, 145; (c) N. Neuss and M. N. Neuss, *The Alkaloids*, 1990, **37**, 229.
34. J. E. Sears and D. L. Boger, *Acc. Chem. Res.*, 2015, **48**, 653.
35. M. G. Banwell, A. J. Edwards, D. W. Lupton and G. Whited, *Aust. J. Chem.*, 2005, **58**, 14.
36. L. V. White and M. G. Banwell, *J. Org. Chem.*, 2016, **81**, 1617.
37. M. G. Banwell, M. T. Jones and T. A. Reekie, *Chem. N. Z.*, 2011, **75**, 122.
38. M. G. Banwell, M. T. Jones, T. A. Reekie, B. D. Schwartz, S. H. Tan and L. V. White, *Org. Biomol. Chem.*, 2014, **12**, 7433.
39. S. R. Crabtree, W. L. A. Chu and L. N. Mander, *Synlett,* 1990, 169.
40. G. B. Bennett, W. J. Houlihan and R. B. Mason, *J. Organomet. Chem.*, 1975, **99**, 185.
41. For a recent and comprehensive review of the area, see P. Siengalewicz, J. Mulzer and U. Rinner, *Eur. J. Org. Chem.*, 2011, 7041.
42. (a) J. S. Yang, Y. L. Su, Y. L. Wang, X. Z. Feng, D. Q. Yu, and X. T. Liang, *Yaoxue Xuebao (Acta Phamaceutica Sinica),* 1991, **26**, 117; (b) P. Cremin, D. M. X. Donnelly, J.-L. Wolfender and K. Hostettmann, *J. Chromatogr. A*, 1995, **710**, 273; (c) D. M. X. Donnelly, T. Konishi, O. Dunne and P. Cremin, *Phytochem.,* 1997, **44**, 1473.
43. C. L. Nord, A. Menkis, R. Vasaitis and A. Broberg, *Phytochem.*, 2013, **90**, 128.
44. C. L. Nord, A. Menkis, C. Lendel, R. Vasaitis and A. Broberg, *Phytochem.*, 2014, **102**, 197.
45. B. D. Schwartz, E. Matoušová, R. White, M. G. Banwell and A. C. Willis, *Org. Lett.*, 2013, **15**, 1934.
46. See, for example, M. G. Banwell, K. A. B. Austin and A. C. Willis, *Tetrahedron*, 2007, **63**, 6388.
47. For a review of this and related photochemically-promoted rearrangements see M. G. Banwell and D. J.-Y. D Bon, Applications of the Di-π-Methane and Related Rearrangement Reactions in Chemical Synthesis in *Molecular Rearrangements in Organic Synthesis* (Ed. C. M. Rojas), 2015, 261.
48. E. L. Chang, B. Bolte, P. Lan, A. C. Willis and M. G. Banwell, J. Org. Chem., 2016, **81**, 2078.
49. E. L. Chang, B. D. Schwartz, A. G. Draffan, M. G. Banwell and A. C. Willis, *Chem. Asian J.*, 2015, **10**, 427.
50. R. N. Muhammad, A. G. Draffan, M. G. Banwell, M. G. and A. C. Willis, *Synlett*, 2016, **27**, 61.
51. For useful reviews of this topic see (a) K. Tiefenbacher and J. Mulzer, *Angew. Chem. Int. Ed.*, 2008, **47**, 2548; (b) K. Palanichamy and K. P. Kaliappan, *Chem. Asian J.*, 2010, **5**, 668; (c) E. Martens and A. L. Deamin, *J. Antibiot.,* 2011, **64**, 705; (d) M. Saleem, H. Hussain, I. Ahmed, T. van Ree, and K. Krohn, *Nat. Prod. Rep.*, 2011, **28**, 1534; (e) A. M. Allahverdiyev, M. Bagirova, E. S. Abamor, S. C. Ates, R. C. Koc, M. Miralogu, S. Elcicek, S. Yaman and G. Unal, *Infect. Drug. Resist.* 2013, **6**, 99.
52. (a) R. E. W. Hancock, *Nat. Rev. Drug Discov.*, 2007, **6**, 28; (b) P. C. Appelbaum, *J. Antimicrob. Chemother.*, 2012, **67**, 2062; (c) S. Shapiro, *J. Antibiot.*, 2013, **66**, 371; (d) R. Tommasi, D. G.

Brown, G. K. Walkup, J. I. Manchester and A. A. Miller, *Nat. Rev. Drug Discov.*, 2015, **14**, 529.

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