A Second-Generation Chemoenzymatic Total Synthesis of Platencin

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The identification of new antibiotics showing efficacy against the rapidly growing number of drug-resistant bacteria is becoming a worldwide priority in medicine and healthcare. Among the recently identified molecules displaying novel modes of antibacterial action, one of the most promising is platencin (Figure 1). This was isolated from the microorganism *Streptomyces platensis* (see the original *Synlett* article for references).

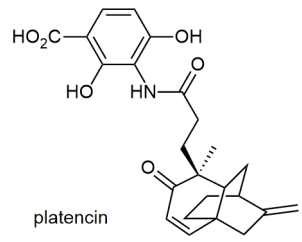


Figure 1

The work reported in this paper from Professor Martin Banwell's group at the Australian National University (Canberra, Australia) is an outgrowth of the group's broader studies on the application of a class of metabolites known as the *cis*-1,2-dihydrocatechols to the chemical synthesis of biologically active natural products and related compounds.[1] Professor Banwell explained that *cis*-1,2-dihydrocatechols of the general form **1** (Figure 2) are produced in >99.9% enantiomeric excess and often on a kilogram or greater scale through the dihydroxylation of the corresponding aromatic by the enzyme toluene dioxygenase (TDO) in a whole-cell biotransformation process. TDO can be overexpressed in genetically engineered organisms such as *E. coli* JM109 (pDTG601).[2]

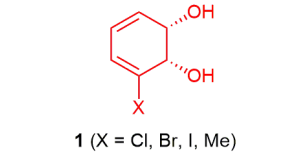


Figure 2

The synthetic utility of 'diols' of the general form **1** has been highlighted by a number of groups.[2] Representative natural products and/or their analogues that the Banwell Group have prepared from this type of starting material are shown in Figure 3.[1]

Professor Banwell explained: "A key and normally early-stage transformation that is used in many of the synthetic sequences is the Diels–Alder cycloaddition reaction. This produces a bicyclo[2.2.2]octene that can be manipulated in various ways." Significantly, by controlling the facial selectivity of the cycloaddition reaction (*viz.* whether the dienophile – e.g. cyclopentenone – adds to the same face of diene **1** as occupied by the hydroxyl groups or to the opposite one), either enantiomeric form of the bicyclo[2.2.2]octane framework can be produced.[3] Professor Banwell said: "Selectivity can be achieved by using either the free diol (in which case the *syn*-adduct **2** is formed preferentially) or, for example, the readily derived acetonide **3** (with the result that the *anti*-adduct **4** is now formed almost exclusively) (Scheme 1). So, simply by controlling the facial selectivity of these addition processes either enantiomeric form of highly utilitarian carbocyclic frameworks can be obtained from the *same* enantiomeric form of a precursor.[2] This concept applies to other cycloaddition processes as well.[4]"

"Immediately upon seeing the structure of the carbocyclic core of platencin (a cyclohexannulated bicyclo[2.2.2]octenone) in a 2007 *Chemical & Engineering News* article[5] reporting on the isolation and structural elucidation of this natural product, we thought it could be assembled via a type-1 intramolecular Diels–Alder (IMDA) reaction wherein a dienophile was tethered to the diene component of the *cis*-1,2-dihydrocatechol," said Professor Banwell. He continued: "In our original investigations of this approach we made an appropriate triene through Negishi cross-coupling of the acetonide **3** (X = I) of diol **1** (X = I) with organozinc **5** (Scheme 2).[6] Remarkably, when product triene **6**, which contains an unactivated dieneophile, was heated in refluxing toluene, the anticipated IMDA reaction took place to give adduct **7** (mixture of epimers at the oxygen-bearing carbon) as the major product. This adduct could be elaborated in a fairly straightforward manner to enone **8**, an advanced intermediate associated with Nicolaou's original total synthesis of the natural product.[7]"

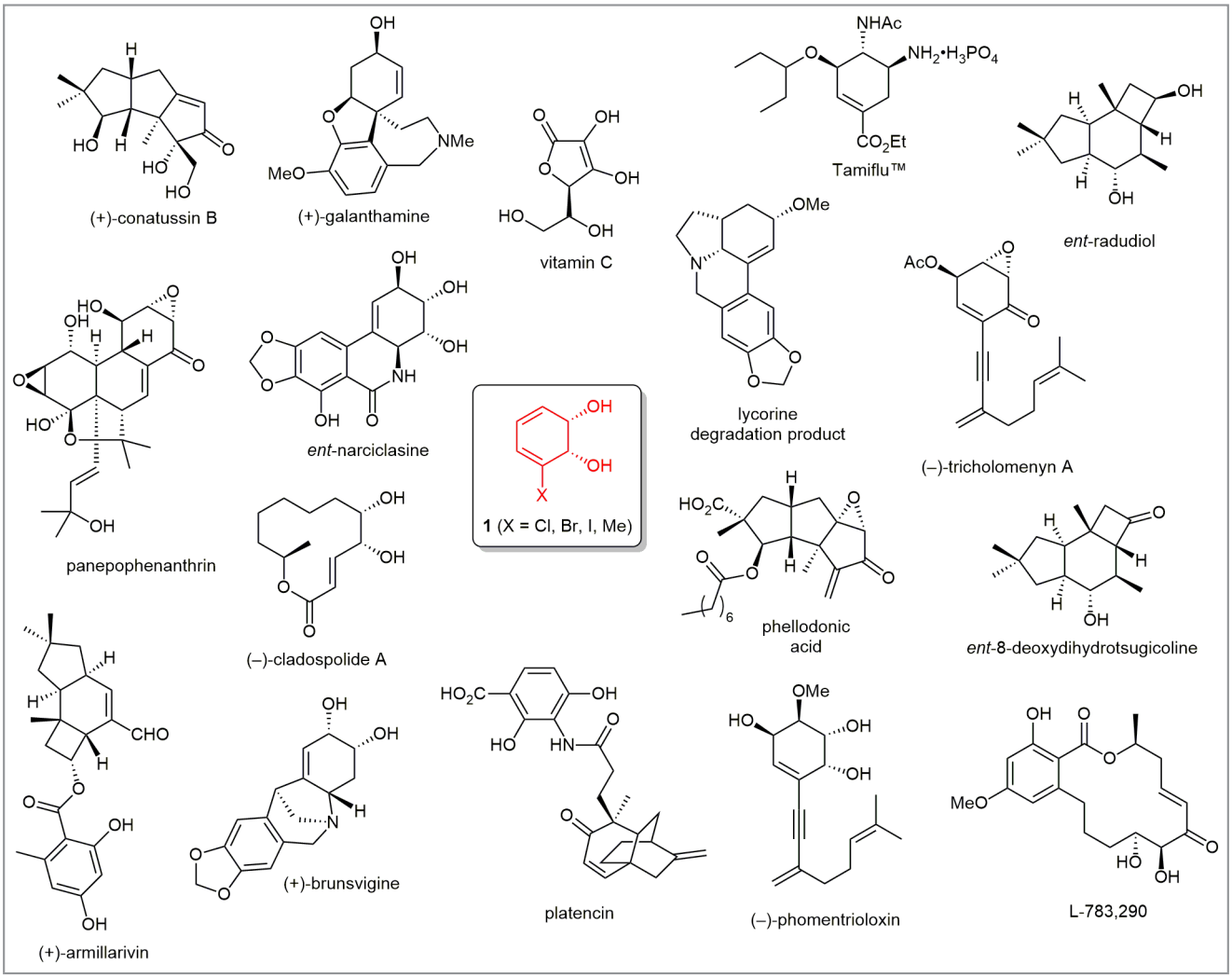
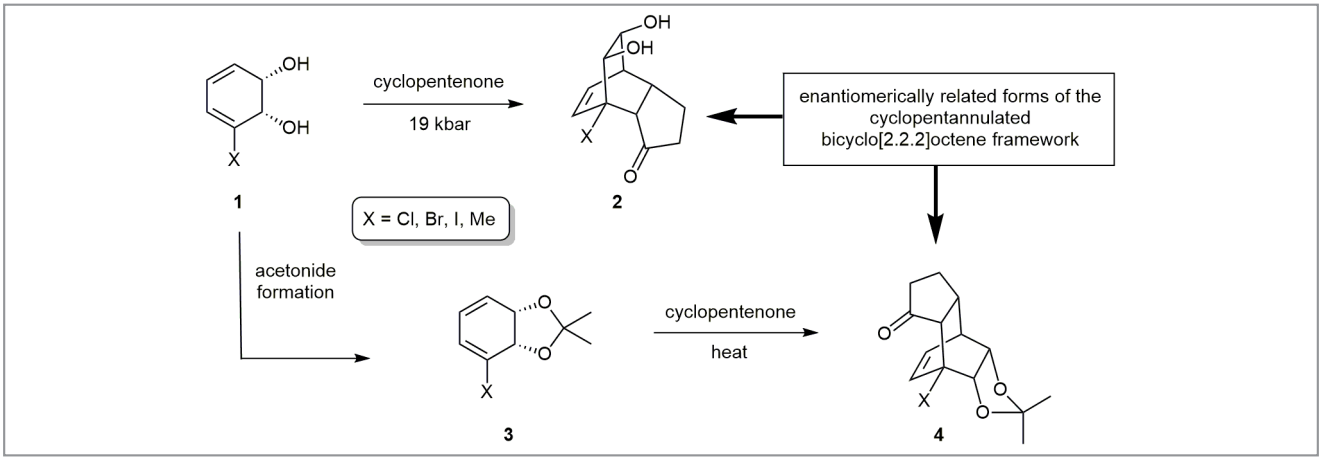
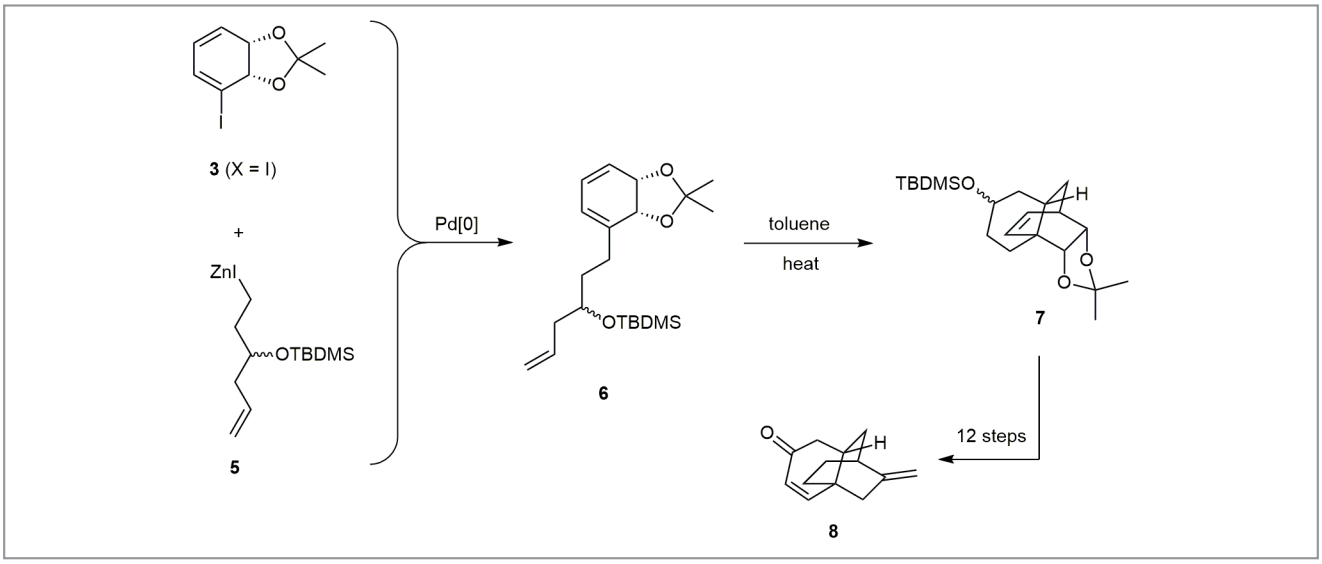


Figure 3

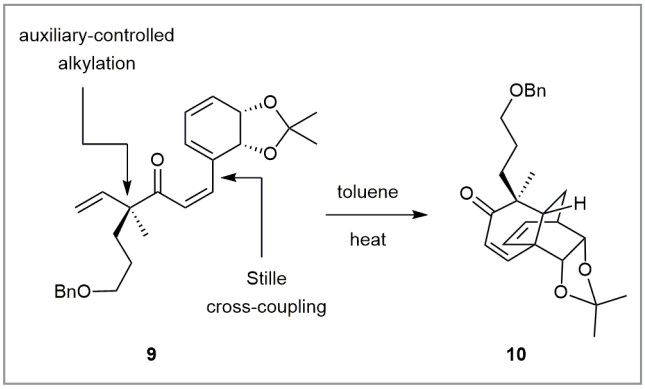


Scheme 1



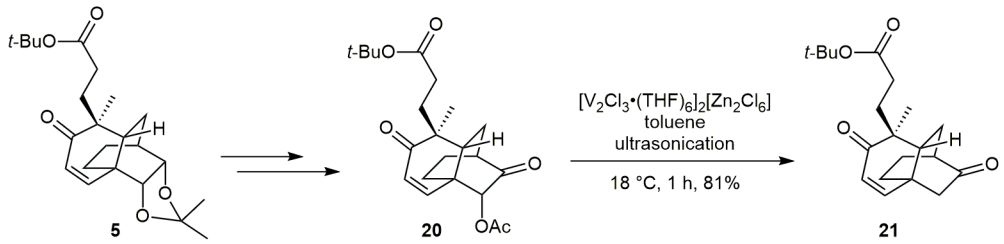
Scheme 2

In a variation on the IMDA route to the platencin core, the group recently reported[8] what Professor Banwell describes as a first-generation chemoenzymatic total synthesis of platencin (Scheme 3). The substrate involved in the key step associated with this approach was the tetra-ene **9** where the associated side chain, now embodying a stereogenic center that had been established through the use of a chiral auxiliary, was attached to the diene core using Stille cross-coupling chemistry. Professor Banwell remarked: "Once again, the IMDA reaction served the synthesis well – it proceeded very effectively in refluxing toluene to provide adduct **10** incorporating much more of the functionality of platencin than did the original IMDA product **7**." He continued: "However, the undoing of this first-generation chemoenzymatic total synthesis was a protecting group problem. The benzyl ether residue within compound **10** could never be cleaved without accompanying removal of both C=C double bonds – we wanted to remove just the non-conjugated one and not the enone-based one. The end result is that extra steps had to be introduced into the reaction sequence so as to re-establish the enone C=C bond that we had taken so much trouble to install in the first place."



Scheme 3

In the work just reported in *Synlett*[9] the group sought to exploit the best aspects of their two earlier syntheses[6,8] by re-preparing the original and readily accessible IMDA adduct **7** and then manipulating this in ways that had not been explored in the lead up to their original publication. "Educated by a seminal 2009 publication from the Nicolaou group,[10] we were able to elaborate this adduct to compound **5** shown in Scheme 4," explained Professor Banwell, continuing: "So, 'conventional' manipulations of this last compound got us to acetate **20** shown in Scheme 4 but we then encountered one of our perennial problems, accessing (from overseas sources) high-quality samarium metal so as to make the corresponding iodide (as needed in the reductive deoxygenation reaction that we hoped would deliver compound **21**). After a desperate search through the literature we became aware of the distinctly under-appreciated studies of Torii and co-workers[11] who showed that certain readily prepared vanadium complexes can act in the same way as SmI_2." To the authors' delight, the conversion **20** → **21** proceeded smoothly using this 'new' reagent under ultrasonication conditions. With good quantities of compound **21** to hand as a result of the 'discovery' of this vanadium-based reagent (according to Professor



Scheme 4

Banwell, perhaps the most important aspect of their work reported in *Synlett*) the completion of the synthesis of platencin proceeded smoothly.

Professor Banwell said: "While this second-generation synthesis has some advantages over the first, when our long-time colleague Tomas Hudlicky became aware of our most recent work he immediately saw an opportunity for improvement and so we are now collaborating on the development of what we hope will be a third-generation approach and one that might be able to 'beat' probably the very best synthesis of platencin reported thus far by Mulzer and co-workers.[12]"

A major motivation for the Banwell group in pursuing the sort of studies reported in the *Synlett* paper is the desire to identify platencin analogues that are even more effective than the natural product. The group feels that they have not yet succeeded in this regard, but some of the biological test results obtained through screening a plethora of compounds arising from their synthesis program encourage them to persist.

Going back to the IMDA aspects of their work, Professor Banwell said: "We are intrigued by the ease with which these processes work even though there is no formal activation of the dienophile. We think there is a different form of activation involved in these cases and one that involves a 'pinching' of the diene as a result of its annulation with the proximate acetonide residue." He concluded: "Whether or not this seemingly unconventional mode of activation can be exploited in many other settings remains to be seen. Certainly, we have already used it in the targeted synthesis of members of the sterpurene class of natural products.[13]"

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About the authors

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Rehmani N. Muhammad was born and raised in Punjab Province of Pakistan. He completed his Masters in chemistry at The Islamia University Bahawalpur (Pakistan) then joined the Department of Collegiate Education of the Government of Pakistan. He has been working as Assistant Professor of Chemistry there since 2002. He joined the Banwell Group in 2010 as a PhD candidate and his research focus is on the synthesis of natural products of biological interest. He has interests in law, medicine and computing and secured an LLB (with distinction) in an earlier phase of his career.

Dr. A. G. Draffan

Alistair G. Draffan graduated from the University of Glasgow (UK) with BSc(Hons) in chemistry before conducting PhD research under the supervision of Professor Alan Armstrong at the University of Nottingham (UK) where he developed new methodologies for selective intramolecular epoxidation. Alistair has more than 15 years of experience in medicinal chemistry and pharmaceutical R&D, particularly in the field of novel anti-infective drugs.

Prof. M. G. Banwell

Martin G. Banwell gained his PhD in 1979 after studying under Professor Brian Halton at the Victoria University of Wellington (New Zealand). Following post-doctoral studies with Leo Paquette at the Ohio State University (USA) he moved to the University of Adelaide (South Australia) as a Senior Teaching Fellow. In 1981 he took up an appointment as a Lecturer in Chemistry at the University of Auckland (New Zealand) and then moved to an equivalent position at the University of Melbourne (Australia) in 1986. In 1995 he was appointed a Senior Fellow in the Research School of Chemistry at the Australian National University in Canberra (Australia) where he remains and now holds the rank of Professor.

Dr. A. C. Willis

Anthony C. Willis was born in Perth (Western Australia). He obtained his PhD from the University of Western Australia in 1977 for work performed under the direction of Professor Allan White. He then pursued post-doctoral studies at Simon Fraser University in Vancouver (Canada), with Professor Fred Einstein before returning to Australia in 1985 to a crystallography position within the Research School of Chemistry at the Australian National University in Canberra.