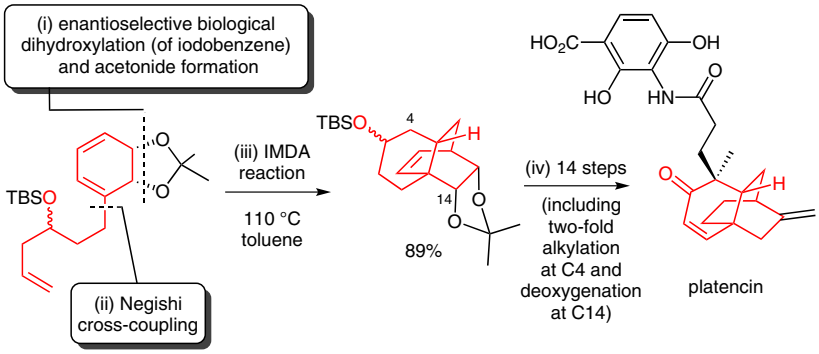
A Second-Generation Chemoenzymatic Total Synthesis of Platencin

Rehmani N. Muhammad[a]
Alistair G. Draffan[b]
Martin G. Banwell*[a]
Anthony C. Willis[a]

[a] Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia
Martin.Banwell@anu.edu.au
[b] Biota Scientific Management Pty Ltd, Melbourne, VIC 3168, Australia

Dedicated to Professor Steve Ley on the occasion of his 70th birthday and in appreciation of the inspirational leadership he has provided to the discipline



Received: 01.10.2015
Accepted after revision: 14.10.2015
Published online: 05.11.2015
DOI: 10.1055/s-0035-1560814; Art ID: st-2015-d0783-l

Abstract A total synthesis of the potent antibacterial agent platencin is described. The reaction sequence used involves, as starting material, an enantiomerically pure *cis*-1,2-dihydrocatechol derived from the whole-cell biotransformation of iodobenzene. Simple chemical manipulations of this metabolite provide a triene that engages in a thermally promoted intramolecular Diels–Alder reaction to establish the octahydro-2*H*-2,4a-ethanonaphthalene core of platencin.

Key words antibacterial, cross-coupling, cycloaddition, natural product, total synthesis

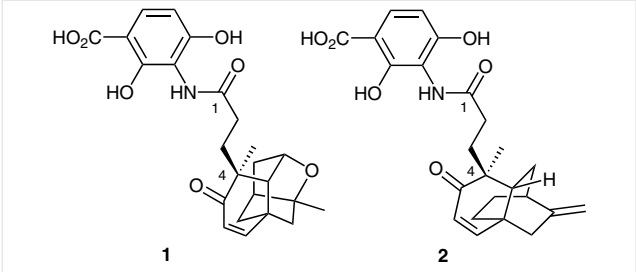


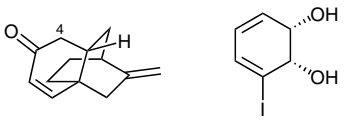
Figure 1 Platensimycin (**1**) and platencin (**2**)

The rapidly accelerating emergence of highly drug resistant and multidrug-resistant bacteria, often described as superbugs, is a source of great concern and such that various commentators suggest the world is sliding into a 'post-antibiotic era' with potentially apocalyptic consequences.[1,2] A range of possible solutions to this profoundly challenging situation has been suggested,[2] not the least being the identification of new, structurally unusual antibacterial agents displaying novel modes of action. Despite the impediments involved,[2c] there have been some successes in this regard. Of particular note is the isolation and structural elucidation of the *Streptomyces platensis*-derived compounds platensimycin (**1**) and platencin (**2**) and their identification as potent and selective inhibitors of certain enzymes associated with the type II bacterial fatty acid biosynthetic (FASII) pathway (Figure 1).[3]

As a result of their enzyme-inhibitory properties, compounds **1** and **2** display particularly efficacious *in vitro* activities against, for example, vancomycin-resistant *Enterococus faecalis* (VREF), methicillin-resistant *Staphylococcus aureus* (MRSA), and extensively drug-resistant *Mycobacterium tuberculosis*.[3] While there has been debate about the likely clinical benefit of FASII inhibitors such as **1** and **2** in the presence of potentially 'recruitable' extracellular fatty acids, evidence is now emerging of their utility *in vivo*.[4] Accordingly, platensimycin (**1**) and platencin (**2**) are regarded as important new leads in the development of urgently required and clinically effective next-generation antibacterial agents.[3,4]

As part of a range of programs directed towards the identification of clinically useful analogues,[5] various studies have focussed on establishing total syntheses of platensimycin (**1**) and platencin (**2**).[6–10] In 2008, we reported[7] a synthesis of the tricyclic enone **3** (Figure 2), an advanced intermediate in Nicolaou's original total synthesis[6a] of platencin (**2**). The starting material used in our study was the enantiomerically pure *cis*-1,2-dihydrocatechol (**4**) obtained through a whole-cell biotransformation of iodobenzene using a genetically engineered microorganism *E. coli* JM109 (pDTG601) that overexpresses the enzyme toluene dioxygenase.[11] Over a number of simple steps,[7] including a Negishi cross-coupling reaction, compound **4** was converted into a triene that participated in a thermally induced intra-

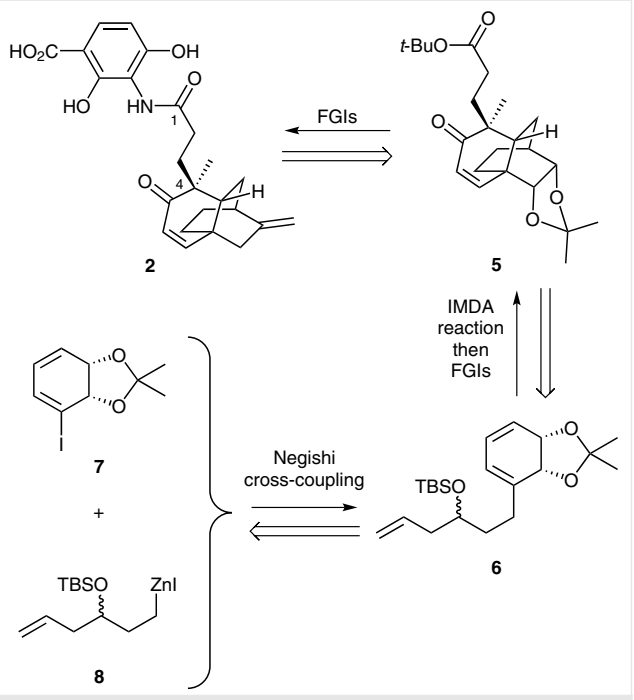
molecular Diels–Alder (IMDA) reaction, thus affording the tricarbocyclic framework embodied within compounds **2** and **3**.



3 4

Figure 2 Enone **3** and diol **4**

A difficulty associated with this approach was the limited amount of intermediate **3** available by such means. Furthermore, introducing the required C4 methyl and propionic acid groups in an efficient and stereocontrolled manner proved problematic. In an attempt to address these issues, we recently reported[9] an alternate IMDA-based approach that delivered a more highly functionalised form of compound **3** and one that could be converted, over a further thirteen steps, into platencin. However, significant functional group incompatibilities were encountered in this first chemoenzymatic total synthesis of the title natural product. Given the deficiencies associated with both of our previous routes we pursued a second-generation chemoenzymatic total synthesis. As a result, we have established, and now report, a more concise as well as a regio- and stereocontrolled pathway to compound **2** that exploits key elements of our earlier approach to enone **3**.



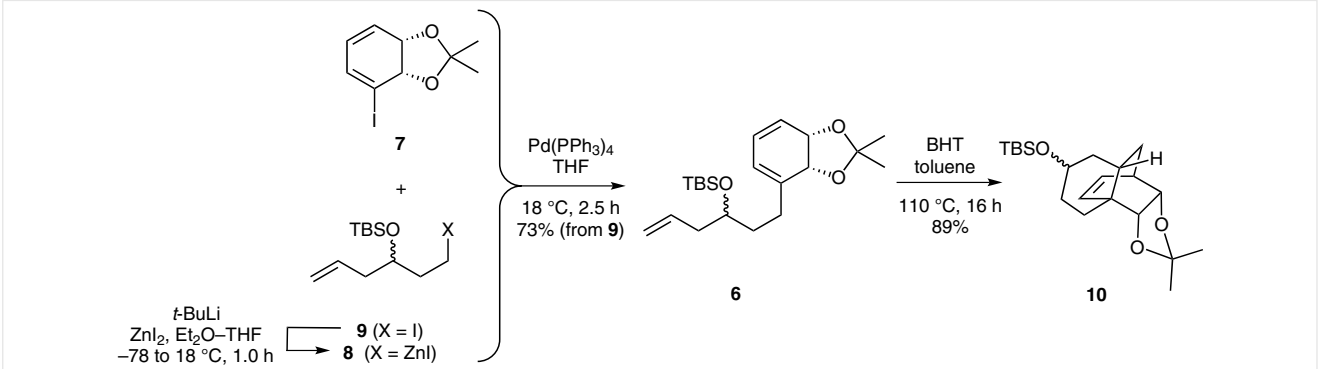
Scheme 1 Retrosynthetic analysis of platencin (**2**)

The retrosynthetic analysis employed in the present study is shown in Scheme 1 and anticipated that target **2** could be prepared, through straightforward functional group interconversions (FGI), from ester **5** that would itself be formed by employing, as a first step, our previously reported[7] IMDA reaction of the triene **6** and then elaborating the resulting adduct into the pivotal subtarget **5**. In our original studies[7] we showed that the substrate **6** required for the crucial IMDA reaction could be obtained through Negishi cross-coupling of the iodide **7** with the easily generated organozinc species **8**. Compound **7** is the readily accessible[12–14] acetonide derivative of *cis*-1,2-dihydrocatechol (**4**),[15] while the iodide precursor to compound **8** can be produced in just four steps from diallyl alcohol.[7]

The opening stage of the present synthesis involved, as we have shown previously but repeat here for the sake of completeness, conversion (Scheme 2) of the known[8] and racemic iodide **9** into the organozinc species **8** by successive treatment of the former compound with *t*-butyllithium and then zinc iodide between –78 and 18 °C followed by cross-coupling of the latter with iodide **7** in the presence of $Pd(Ph_3P)_4$. By such means, the triene **6**[7] was obtained as a 1:1 mixture of diastereoisomers in 73% yield (from **9**). While rather acid sensitive, when a toluene solution of compound **6** containing butylated hydroxytoluene (BHT – added to suppress oxidative degradation of the substrate) was heated at 110 °C for 16 hours, the corresponding mixture of diastereoisomeric Diels–Alder adducts **10**[7,16] was obtained in 89% combined yield.

The means for converting the diastereoisomeric forms of compound **10** into the ester **5** are shown in Scheme 3 and involved, as a first step, treating the former compound with tetra-*n*-butylammonium fluoride (TBAF) in THF at 18 °C. The β-epimeric form of compound **10**[7] (embodying an *endo*-configured TBSO group) was converted into the corresponding alcohol **11**[7] over 56 hours and in 86% yield, while the notionally more hindered α-epimer[7] took just 16 hours to react under the same conditions and afforded the anticipated alcohol in 97% yield.

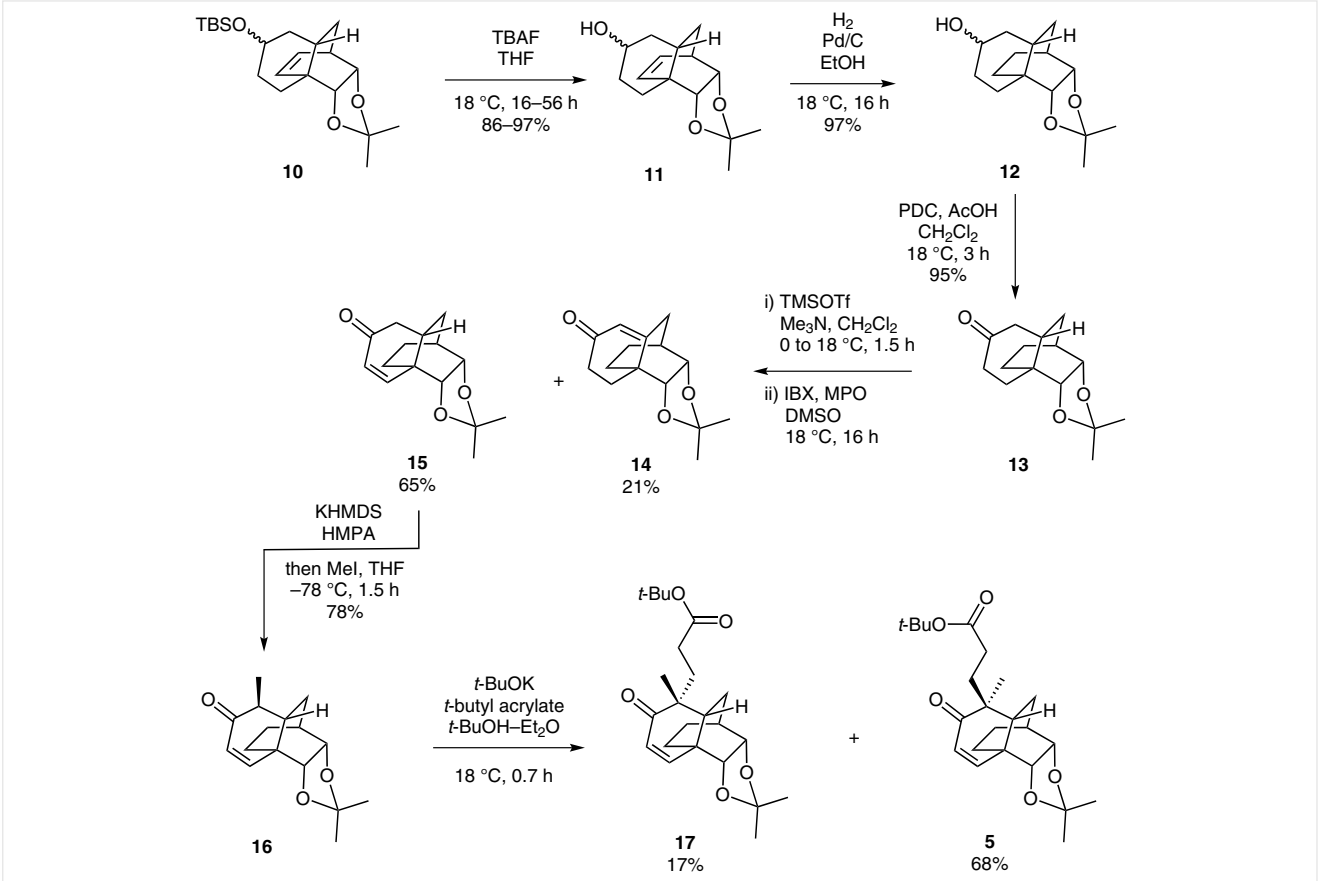
Hydrogenation of alcohol **11** (as a mixture of epimers) at atmospheric pressures using 10% palladium on carbon as catalyst and ethanol as solvent afforded the corresponding mixture of saturated alcohols **12**[7] in (97% combined yield) and this was oxidised to the corresponding ketone **13**[17] (95%) using pyridinium dichromate (PDC). In order to generate the enone required for the twofold α-alkylation reaction that would deliver subtarget **5**, compound **13** was treated with trimethylsilyl triflate (TMSOTf) in the presence of trimethylamine. The ensuing mixture of silyl enol ethers was exposed to *o*-iodoxybenzoic acid (IBX) in the presence of 4-methoxypyridine-*N*-oxide (MPO)[18] and thereby affording a (flash) chromatographically separable mixture of enones **14** (21%) and **15** (65%). The spectroscopic data derived from these products were in complete accord with the assigned structures, and that of the former was confirmed



Scheme 2 Assembly of the tricyclic core of platencin via the IMDA reaction of triene **6**

by single-crystal X-ray analysis.[19] Treatment of compound **15** with potassium hexamethydisilazide (KHMDS) and trapping of the ensuing enolate at –78 °C with methyl iodide afforded compound **16** (78%), and the structure of this product was also confirmed by single-crystal X-ray analysis.[19] Following protocols reported by Nicolaou *et al.*,[6b] compound **16** was treated with *t*-BuOK and *tert*-butyl acrylate, producing a mixture of the epimeric esters **17** (17%) and **5** (68%) that could only be separated by (semi-preparative) HPLC techniques.

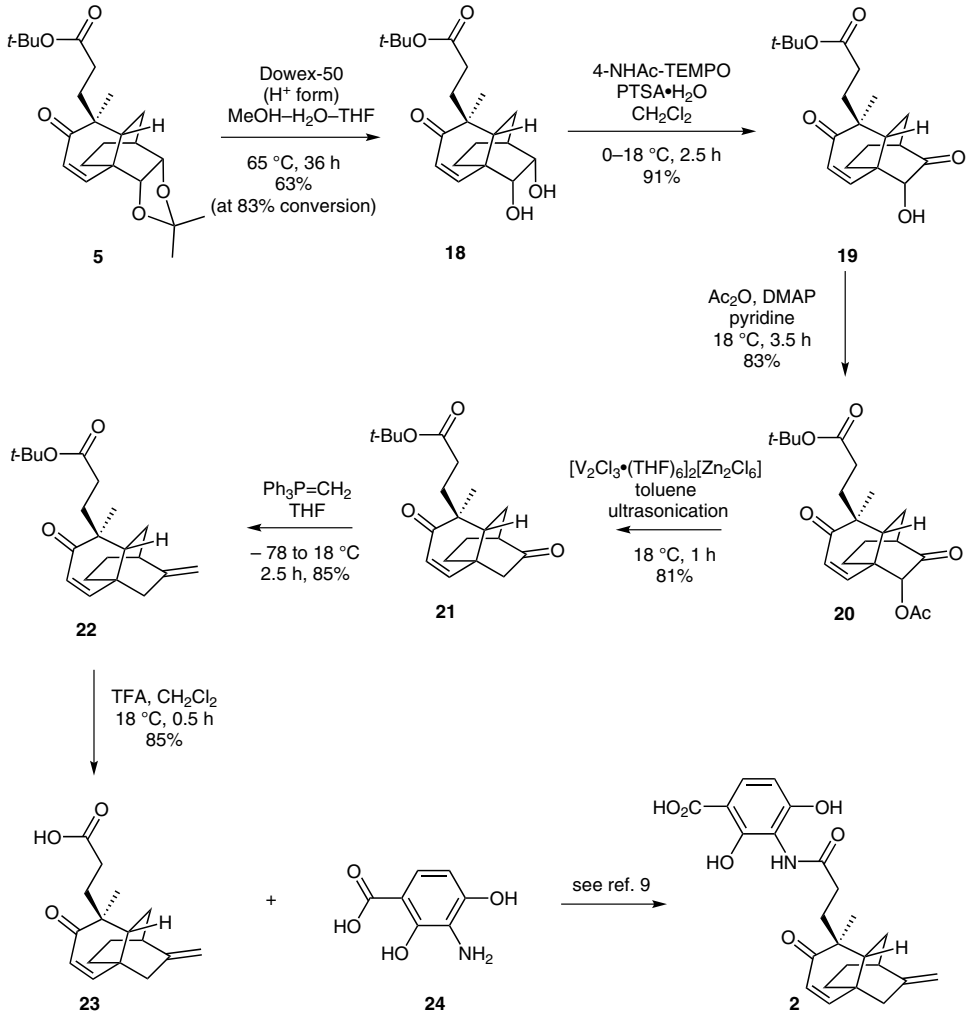
The reaction sequence used to convert ester **5** into platencin (**2**) is shown in Scheme 4 and parallels that employed in our first-generation route to the natural product.[9] Thus, the acetonide residue associated with compound **5** was cleaved using acid-activated Dowex-50 resin in a metha-



Scheme 3 Conversion of the IMDA adduct **10**into ester **5**

nol–water–THF mixture at 65 °C and, after 36 hours, a 63% yield (at 83% conversion) of the required diol **18** was realised. Regioselective oxidation of the hydroxyl group remote from the cyclohexenone substructure within compound **18** could be achieved using the sterically demanding oxammonium salt derived from the *p*-toluenesulfonic acid (PTSA)-promoted disproportionation of 4-acetamido-TEMPO[20] and the acyloin **19** (91%) thus obtained. As the first step in the removal of the remaining hydroxyl group within compound **19** this was converted into the corresponding acetate **20** (83%) under standard conditions. Reductive cleavage of the newly introduced ester residue was most conveniently achieved using the readily prepared but distinctly underutilised vanadium(II) complex $[V_2Cl_3{\cdot}(THF)_6]_2[Zn_2Cl_6]$ first introduced for this purpose by Torii and co-workers over two decades ago.[21–23] The reaction proceeded rapidly under ultrasonication conditions and afforded dione **21**[5a] in 81% yield. Selective methylenation of the nonconjugated ketone carbonyl moiety within compound **21** was achieved using the Wittig reagent under carefully controlled conditions,[9] to afford the previously reported ester **22**[6b] in 85% yield. In contrast to observations of Nicolaou and co-workers,[6b] it was found that the *t*-butyl ester moiety within this last compound could be cleaved using trifluoroacetic acid (TFA, at 18 °C for 0.5 h) without any accompanying conversion of the exocyclic olefin to its endocyclic isomer. Platencinic acid (**23**)[6,8,9,24] was thus formed in ca. 85% yield. The spectroscopic data derived from this material were in complete accord with those reported by both our group[9] and by others.[6,8] Because we have previously[9] coupled this last compound with aniline **24**[9] to form platencin (**2**) in 42% yield, the present work constitutes a formal synthesis of the title natural product.

The route to platencin (**2**) described here exploits the capacity, as reported in our earlier studies,[7] of the readily accessible and enantiomerically pure triene **6** to engage in an IMDA reaction and thereby generate the tricarbocyclic framework of the natural product. The value of the work



Scheme 4 End game: conversion of ester **5** into platencin (**2**)

detailed above lies in the defining of a method by which cycloadduct **10** can be elaborated to platencinic acid (**23**), an immediate precursor to platencin and itself a naturally occurring compound.[24] The present route is slightly shorter than our first-generation chemoenzymatic synthesis of platencin. However, it remains wanting because of an inability to install the enone double bond in a completely regiocontrolled manner and a failure to fully control the stereoselectivity of the Michael addition reaction (**16** → **5**) that establishes the C4 quaternary carbon centre. The second issue is the more problematic because of the need to resort to tedious HPLC techniques to separate the diastereoisomeric product esters **5** and **17** (see Scheme 3). Efforts focussed on addressing such matters as well as exploiting the protocols reported here for the purposes of preparing platencin analogues are under investigation.

Acknowledgment

We thank the Australian Research Council and the Institute of Advanced Studies for financial support including the provision of a scholarship to R.N.H.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560814.

References and Notes

(1) (a) Hancock, R. E. W. *Nat. Rev. Drug Discov.* **2007**, *6*, 28. (b) Appelbaum, P. C. *J. Antimicrob. Chemther.* **2012**, *67*, 2062. (c) Shapiro, S. *J. Antibiot.* **2013**, *66*, 371. (d) Tommasi, R.; Brown, D. G.; Walkup, G. K.; Manchester, J. I.; Miller, A. A. *Nat. Rev. Drug Discov.* **2015**, *14*, 529.

(2) (a) Payne, D. J.; Gwynn, M. N.; Holmes, D. J.; Pompliano, D. L. *Nat. Rev. Drug Discov.* **2007**, *6*, 29. (b) Lewis, K. *Nature (London, U.K.)* **2012**, *485*, 439. (c) Lewis, K. *Nat. Rev. Drug Discov.* **2013**, *12*, 3781. (d) Reardon, S. *Nature (London, U.K.)* **2015**, *521*, 402. (e) Garber, K. *Nat. Rev. Drug Discov.* **2015**, *14*, 445.

(3) For some reviews, see: (a) Tiefenbacher, K.; Mulzer, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 2548. (b) Palanichamy, K.; Kaliappan, K. P. *Chem. Asian J.* **2010**, *5*, 668. (c) Martens, E.; Deamin, A. L. *J. Antibiot.* **2011**, *64*, 705. (d) Saleem, M.; Hussain, H.; Ahmed, I.; van Ree, T.; Krohn, K. *Nat. Prod. Rep.* **2011**, *28*, 1534. (e) Allahverdiyev, A. M.; Bagirova, M.; Abamor, E. S.; Ates, S. C.; Koc, R. C.; Miralogu, M.; Elcicek, S.; Yaman, S.; Unal, G. *Infect. Drug. Resist.* **2013**, *6*, 99.

(4) Parson, J. B.; Yao, J.; Frank, M. W.; Rock, C. O. *Antimicrob. Agents Chemother.* **2015**, *59*, 849; and references cited therein.

(5) See, for example: (a) Leung, G. Y. C.; Li, H.; Toh, Q.-Y.; Ng, A. M.-Y.; Sum, R. J.; Bandow, J. E.; Chen, D. Y.-K. *Eur. J. Org. Chem.* **2011**, 183. (b) Plesch, E.; Bracher, F.; Krauss, J. *Arch. Pharm.* **2012**, *345*, 657. (c) Krauss, J.; Plesch, E.; Clausen, S.; Bracher, F. *Sci. Pharm.* **2014**, *82*, 501; and references cited therein.

(6) (a) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1780. (b) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J.; Kar, M. *J. Am. Chem. Soc.* **2009**, *131*, 15909.

(7) Austin, K. A. B.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2008**, *10*, 4465.

(8) Tiefenbacher, K.; Mulzer, J. *J. Org. Chem.* **2009**, *74*, 2937.

(9) Chang, E. L.; Schwartz, B. D.; Draffan, A. G.; Banwell, M. G.; Willis, A. C. *Chem. Asian J.* **2015**, *10*, 427.

(10) (a) Moustafa, G. A. I.; Saku, Y.; Aoyama, H.; Yoshimitsu, T. *Chem. Commun.* **2014**, *50*, 15706. (b) Wang, J. W.; Sun, W.-B.; Li, Y. Z.; Wang, X.; Sun, B.-F.; Lin, G.-Q.; Zou, J.-P. *Org. Chem. Front.* **2015**, *2*, 674; and references cited therein.

(11) 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) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta* **1999**, 32-35. (b) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Voegtle, M. *Pure Appl. Chem.* **2003**, *75*, 223. (c) Johnson, R. A. *Org. React.* **2004**, *63*, 117. (d) Hudlicky, T.; Reed, J. W. *Synlett* **2009**, 685. (e) Bon, D. J.-Y. D.; Lee, B.; Banwell, M. G.; Cade, I. A. *Chim. Oggi* **2012**, *30*, 22; Chiral Technologies Supplement. (f) Rinner, U. *Chiral Pool Synthesis: Chiral Pool Syntheses from cis-Cyclohexadiene Diols*, In *Comprehensive Chirality*; Carreira, E. M.; Yamamoto, H., Eds.; **2012**, Vol. 2: 2, 40.

(12) Entwistle, D. A.; Hudlicky, T. *Tetrahedron Lett.* **1995**, *36*, 2591.

(13) For general procedures for the preparation of acetonides of this type, see: Hudlicky, T.; Boros, E. E.; Olivo, H. F.; Merola, J. S. *J. Org. Chem.* **1992**, *57*, 1026.

(14) These types of acetonides are prone to dimerization: Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W. *Synlett* **1991**, 741.

(15) Boyd, D. R.; Sharma, N. D.; Byrne, B.; Hand, M. V.; Malone, J. F.; Sheldrake, G. N.; Blacker, J.; Dalton, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1935.

(16) For some key earlier studies on the Diels–Alder cycloaddition reactions of *cis*-1,2-dihydrocatechol derivatives, see: (a) First example, used for proof of structure: Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J. *Biochemistry* **1970**, *9*, 1626. (b) First application in synthesis, singlet oxygen as dienophile: Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735. (c) First IMDA reaction: Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem.* **1989**, *54*, 4239. (d) Downing, W.; Latouche, R.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2613. (e) Mahon, M. F.; Molloy, K.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O.; Winders, J. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1255.

(17) Detailed experimental protocols for the synthesis of all new compounds and the spectroscopic data derived from them are provided in the Supporting Information.

(18) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 996.

(19) Details of this X-ray analysis, including the derived ORTEP, are provided in the Supporting Information.

(20) This protocol is based on one first described by Ma and Bobbitt: Ma, Z.; Bobbitt, J. M. *J. Org. Chem.* **1991**, *56*, 6110.

(21) Inokuchi, T.; Kawafuchi, H.; Torii, S. *Chem. Lett.* **1992**, 1895.

(22) **Procedure for the Reductive Deoxygenation of Compound 20**
A solution of freshly prepared $VCl_3{\cdot}(THF)_3$[23] (210 mg, 0.56 mmol) in dry toluene (2.5 mL) maintained at 18 °C was treated with freshly activated Zn dust (37 mg, 0.56 mmol) and the ensuing mixture irradiated in an ultrasonic bath (B2500R-DTH model from Branson) for 0.33 h. After this time a solution of acetate **20** (109 mg, 0.28 mmol) in toluene (1.5 mL) was added and sonication continued for 0.66 h. The reaction mixture was

then diluted with EtOAc (5.0 mL) and passed through a short plug of TLC-grade silica gel that was washed with EtOAc (3 × 5 mL). The combined filtrates were washed with H_2O (1 × 10 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:4 v/v EtOAc–hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.4), compound **21**[5a] (75 mg, 81%) as a white foam. A full spectroscopic data set for this compound is provided in the Supporting Information.

(23) Manzer, L. E. *Inorg. Synth.* **1982**, *21*, 135.
(24) Smanski, M. J.; Yu, Z.; Casper, J.; Lin, S.; Peterson, R. M.; Chen, Y.; Wendt-Pienkowski, E.; Rajski, S. R.; Shen, B. *Proc. Natl. Acad. Sci., U.S.A.* **2011**, *108*, 13498.