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A Chemoenzymatic Total Synthesis of the Protoilludane Aryl Ester (+)-Armillarivin

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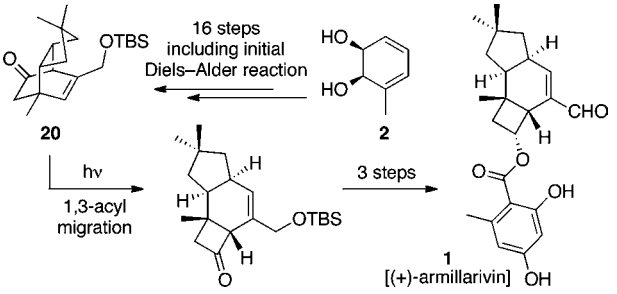
ABSTRACT



The title natural product, 1, has been synthesized in 20 steps from the enantiomerically pure *cis*-1,2-dihydrocatechol 2, itself obtained through the whole-cell biotransformation of toluene. The pivotal steps in the reaction sequence involve a Diels–Alder cycloaddition reaction between diene 2 and cyclopentenone (3) and the photochemically promoted 1,3-acyl rearrangement of the bicyclo[2.2.2]oct-4-en-1-one 20 derived from the cycloadduct 4.

The significant biological properties and distinctive perhydrocyclobuta[*e*]indene framework associated with the protoilludane class of sesquiterpenoid natural products have attracted considerable attention since the late 1960s when the first member of the class was isolated and characterized by McMorris.[1] New members continue to be identified[2] and some of these display properties likely to be of commercial significance, particularly in veterinary settings.[3,4] There is a rich history of synthetic approaches to the protoilludanes, perhaps the most popular and effective involving photochemically promoted [2+2] cycloaddition or cobalt-mediated [2+2+2] cyclization processes.[2] The majority of such approaches have provided the racemic forms of the target natural products. While the photochemically promoted 1,3-acyl rearrangement of cyclopentannulated bicyclo[2.2.2]oct-4-en-1-ones has been explored as a means of obtaining the carbocyclic framework of protoilludanes,[5,6] to date it has not been deployed in a total synthesis of any one of these natural products. Herein, therefore, we now report the successful implementation of such an approach in the enantioselective total synthesis of the protoilludane aryl ester (+)-armillarivin (**1**, Figure 1), the first member of this subclass of sesquiterpenoid natural product to be so obtained (by any means). Compound **1** was originally isolated from the acetone extract of artificially cultured mycelium *Armillaria mellea* (Vahl. Ex Fr) Quel. (Tricholomataceae) and its structure established using ^{1}H and ^{13}C NMR spectroscopies.[7] It has since been isolated from *Armillaria tabescens*, a pathogenic basidiomycete that causes root disease in a range of commercially significant plants.[8]

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(4) Assante, G.; Dallavalle, S.; Martino, P. A. *J. Antibiot.* **2013**, *66*, 43–45.

(5) (a) Singh, V.; Porinchu, M. *J. Chem. Soc., Chem. Commun.* **1993**, 134. (b) Singh, V.; Sharma, U. *J. Chem. Soc., Perkin Trans. 1* **1998**, 305.

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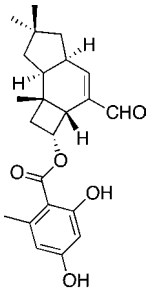


1

Figure 1. Structure of compound **1**.

The synthetic sequence leading to the substrate required for the pivotal 1,3-acyl rearrangement is shown in Scheme 1 and starts with the high-pressure promoted Diels–Alder reaction between the enzymatically derived and enantiomerically pure *cis*-1,2-dihydrocatechol **2**[9] and cyclopent-2-en-1-one (**3**). The adduct **4**[10] (70%) so-formed was converted into the corresponding acetonide **5**[10] (98%) under standard conditions and this was, in turn, transformed into the corresponding *gem*-dimethylated derivative **6**[10] (95%) using established techniques. Deletion of the carbonyl moiety contained within the last compound involved its initial lithium aluminum hydride-promoted reduction to the corresponding alcohol **7**[10] (99% of an 11:1 mixture of epimers), the xanthate ester derivative, **8**,[10] of which was subjected to a Barton–McCombie deoxygenation reaction using tri-*n*-butyltin hydride and thus providing alkene **9**[10] (50% from **7**). Hydroboration/oxidation of the last compound using the borane-dimethylsulfide complex then alkaline hydrogen peroxide afforded a mixture of the regioisomeric and chromatographically separable alcohols **10** (39%) and **11** (36%). Various attempts to improve the regioselectivity of this reaction using other hydroborating agents failed. Compound **11** was oxidized to the corresponding ketone **12** (91%)[11] using the oxammonium salt derived from 4-*N*-AcetylTEMPO[12] and this was, in turn, converted into the corresponding nonaflate **13** (90%) under standard conditions. Compound **13** was readily engaged in a Pd^0-catalyzed carboxyamination reaction using a combination of CO and methoxy(methyl)amine[13] and thereby providing the Weinreb amide **14** (98%). Treatment of compound **14** with $LiAlH_4$ then afforded the corresponding allylic alcohol **15** (89%).[14] Hydrolytic cleavage of the acetonide residue associated with this last compound was achieved using acidified DOWEX-50 resin in aqueous methanol and the resulting triol **16** (70%) selectively protected as the mono-TBS ether **17** (80%) using TBS-Cl in the presence of imidazole. Selective oxidation of the hydroxyl group remote from the bridgehead methyl group within compound **17** could be achieved using the sterically demanding oxammonium salt obtained by the *p*-TsOH-promoted disproportionation of 4-acetamido-TEMPO[12] and by such means the acyloin **18** was obtained in 92% yield. The readily derived benzoate **19** (96%) was then subjected to reaction with samarium diiodide[15] and thus affording, through a reductive deoxygenation process, the target bicyclo[2.2.2]oct-4-en-1-one **20**. This was obtained in 98% yield.

The alcohol **10** produced through hydroboration/oxidation of alkene **9** as shown in Scheme 1 could also be converted into the substrate **20** required for the pivotal photochemical rearrangement reaction. Thus, as shown in Scheme 2, oxidation of compound **10** to the corresponding ketone **21** (87%) followed by reaction of the derived enolate with Mander's reagent[16] afforded the β-hydroxy-α,β-unsaturated ester **22** (73%) that was readily converted into the corresponding triflate **23** (72%)[17] or diethylphosphate **24** (78%) by treatment with triflic anhydride/Hünig's base or $ClPO(OEt)_2$/triethylamine, respectively. Reaction of the former product with formic acid in the presence of a Pd^0 catalyst and tri-*n*-butylamine[17] or of the latter product with lithium dimethylcuprate[18] afforded the deoxygenated ester **25** in 85% and 77% yields, respectively. Finally, reduction of compound **25** with DIBAL-H afforded the allylic alcohol **15** (95%) that could be converted into compound **20** by the means defined in the later parts of Scheme 1.

The pivotal 1,3-acyl migration reaction was carried out (Scheme 3) by irradiating a dichloromethane solution of substrate **20** with a high-pressure mercury lamp for 1.5 h at 0 °C and thereby generating the desired product **26** (23% or 57% brsm). This was accompanied by small quantities of cyclopropane **27** (5% or 12% brsm), diene **28** (7% or 17% brsm) and the oxa-di-π-methane rearrangement[19] product **29** (3% or 7% brsm). The first two of these byproducts, viz. compounds **27** and **28**, presumably arise

(9) Bon, D. J.-Y. D.; Lee, B.; Banwell, M. G.; Cade, I. A. *Chim. Oggi* **2012**, *30* (No. 5, Chiral Technologies Supplement), 22.

(10) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A. *Tetrahedron* **2004**, *60*, 535.

(11) The structures of compounds **12** and **1** were confirmed by single-crystal X-ray analysis (CCDC Nos. 919145 and 919146, respectively). Details are provided in the Supporting Information.

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

(13) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054.

(14) In the original synthetic plan this Weinreb amide was to be subjected to a late-stage (and direct) reduction to the corresponding aldehyde (and thus installing this moiety as required in target **1**). However, it transpired that this amide residue is converted into the corresponding demethoxylated amide upon exposure to samarium diiodide.

(15) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

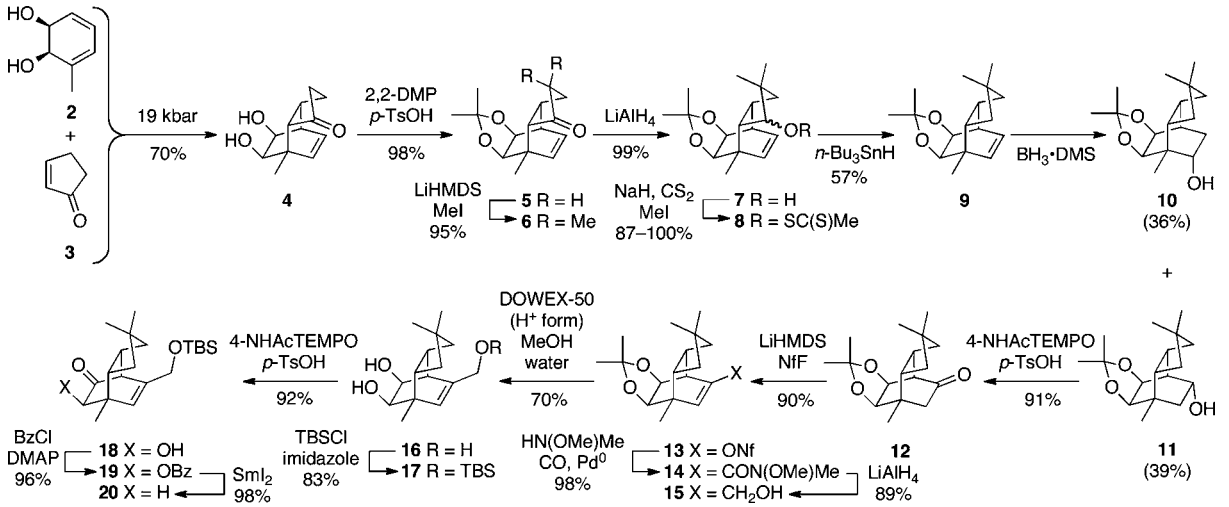
(16) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, 169.

(17) Ramachandran, S. A.; Kharul, R. K.; Marque, S.; Soucy, P.; Jacques, F.; Chênevert, R.; Deslongchamps, P. *J. Org. Chem.* **2006**, *71*, 6149.

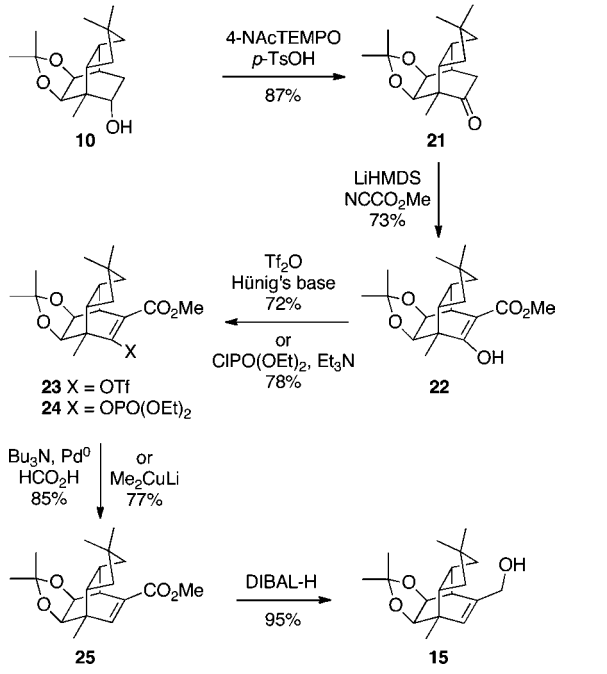
(18) For examples of the organocuprate-mediated reductions of enol phosphates, see: (a) Ishihara, T.; Maekawa, T.; Yamasaki, Y.; Ando, T. *J. Org. Chem.* **1987**, *52*, 300. (b) Paquette, L. A.; Dahnke, K.; Doyon, J.; He, W.; Wyant, K.; Friedrich, D. *J. Org. Chem.* **1991**, *56*, 6199.

(19) For a very recent review of the oxa-di-π-methane rearrangement, see:Rao, V. J.; Srinivas, K. In *CRC Handbook of Organic Photochemistry and Photobiology*, 3rd ed; Griesbeck, A. G., Oelgemöller, M., Ghetti, F., Eds.; CRC Press: Boca Raton, FL, 2012; Chapter 22, pp 527–548.

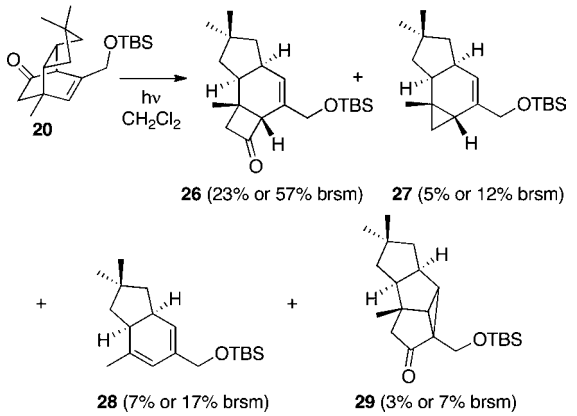
Scheme 1



Scheme 2



Scheme 3



through loss of CO and ketene, respectively, from the primary photoproduct **26**. The *s*-cissoid nature of the diene substructure associated with compound **28** was confirmed through its ready engagement in a Diels–Alder cycloaddition reaction with the potent dienophile 1-phenyltriazoline-2,5-dione (PTAD).[20]

With the key perhydrocyclobuta[*e*]indene **26** to hand, completion of the synthesis of the target natural product, **1**, ultimately proved to be a relatively straightforward matter (Scheme 4). Thus, the former compound was reduced stereoselectively, and in the desired manner, by treating it with $LiAlH_4$ and thus affording the *endo*-alcohol **30** (78%) through delivery of hydride to the more accessible *exo*-face of the precursor ketone. Coupling of compound **30** with the readily prepared acid **31**[21] was accomplished using DCC in combination with DMAP and the ester **32** (60%) so-formed was oxidized directly to (+)-armillarivin (**1**) (70%) upon exposure to the oxammonium salt derived from *p*-TsOH-promoted disproportionation of 4-acetamido-TEMPO. The spectral data derived from this synthetically generated sample of compound **1** were in complete accord with the assigned structure but final confirmation of this came from a single-crystal X-ray analysis.[11] The

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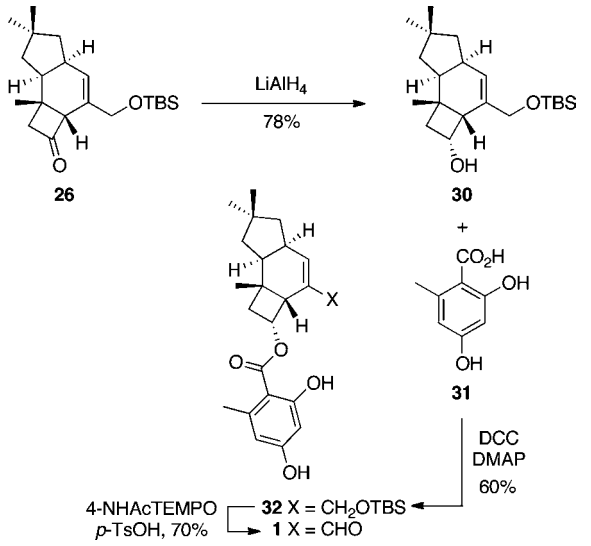
Scheme 4



derived ORTEP is shown in Figure 2. A comparison of the ^{1}H and ^{13}C NMR spectral data recorded on the natural product[7] with those arising from the present study established that these were in complete accord with one another (see Table S1, Supporting Information). Furthermore, the specific rotations derived from the two samples of compound **1** were in excellent agreement {$[\alpha]_D$ = +134.0 (*c* 0.5, $CHCl_3$) vs $[\alpha]_D$ = +136.6 (*c* 0.465, $CHCl_3$)[7]} as were the corresponding melting points (176−181 °C vs 169−172 °C[7]).

The present study has identified a new means by which protoilludane natural products can be synthesized and thereby offering the prospect of being able to access many more members of this fascinating class of compound. The use of the enantiomerically pure metabolite **2** as the starting material in the synthesis reported here serves to further emphasize the utility of this readily available compound as a chiron for the construction of a range of terpenoid compounds.[9,22]

(22) Bon, D. J.-Y. D.; Banwell, M. G.; Ward, J. S.; Willis, A. C. *Tetrahedron* **2013**, *69*, 1363.

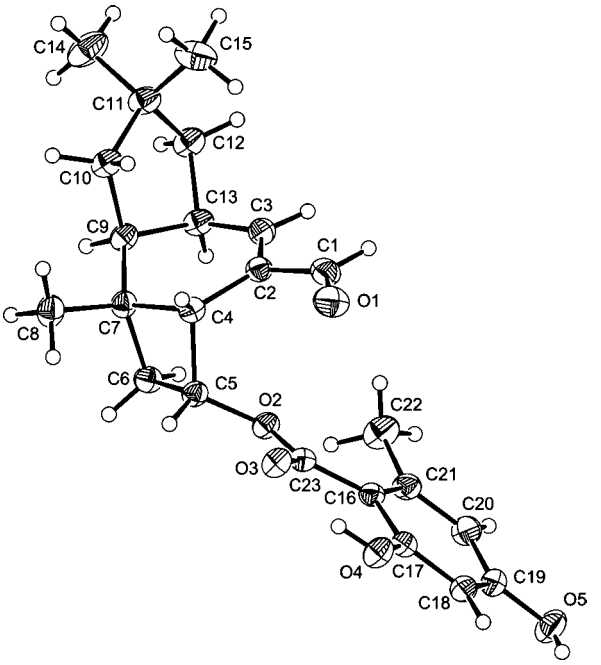


Figure 2. ORTEP derived from the single-crystal X-ray analysis of compound **1** (CCDC No. 919146) with labeling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

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Supporting Information Available. Full experimental procedures; comparison of the ^{13}C and ^{1}H NMR data recorded on synthetically derived **1** with those reported for (+)-armillarivin; data derived from the single-crystal X-ray analyses of compounds **1** and **12** and ORTEP of compound **12**; and ^{1}H and ^{13}C NMR spectra of compounds **1**, **10**−**22**, **24**−**30** and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.