

Chemoenzymatic Synthesis of
(+)-Aspicilin from Chlorobenzene

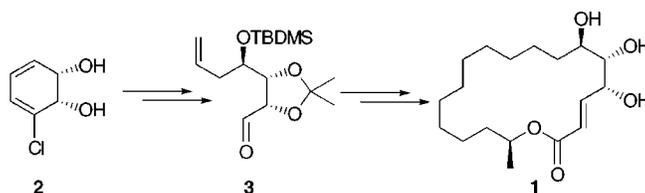
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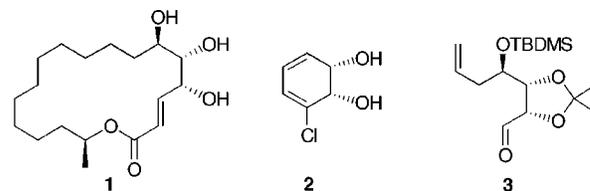
ABSTRACT



The enantiomerically pure *cis*-1,2-dihydrocatechol **2**, which is obtained by microbial oxidation of chlorobenzene, has been converted, via intermediate **3**, into the natural product (+)-aspicilin (**1**).

The macrocyclic lactone (+)-aspicilin (**1**) is a crystalline solid that was first isolated in 1900¹ by Hesse from a lichen of the *Lecanoraceae* family, but it was not until 1973 that Huneck and co-workers² deduced, by application of various spectroscopic methods, the basic structure of this material. In 1985 both the relative and absolute stereochemistries associated with (+)-aspicilin were finally established through a combination of X-ray crystallographic, degradation, and synthesis studies.³ No significant biological properties have been attributed to (+)-aspicilin, but the synthetic challenges presented by the presence of three contiguous stereogenic centers within an 18-membered macrocyclic ring system have prompted a significant number of efforts to develop total syntheses of the compound.⁴ It is against this background

that we now report a chemoenzymatic synthesis of the title compound wherein the pivotal stereochemical triad, as embodied within intermediate **3**, has been constructed from



the *cis*-1,2-dihydrocatechol **2**. Starting material **2** is available in enantiomerically pure form (>99.8% ee) and a large quantity by whole-cell-mediated dihydroxylation of chlorobenzene using a genetically engineered strain of *Echerichia coli* [JM109 (pDTG601)] which overexpresses the toluene dioxygenase (TDO) enzyme system.⁵ The present work serves to further highlight the considerable utility of such microbial oxidation products for the synthesis of polyoxygenated secondary metabolites and their congeners.⁶

Our initial attempts to prepare target **1** from compound **2** are shown in Scheme 1 and involved, as the first step,

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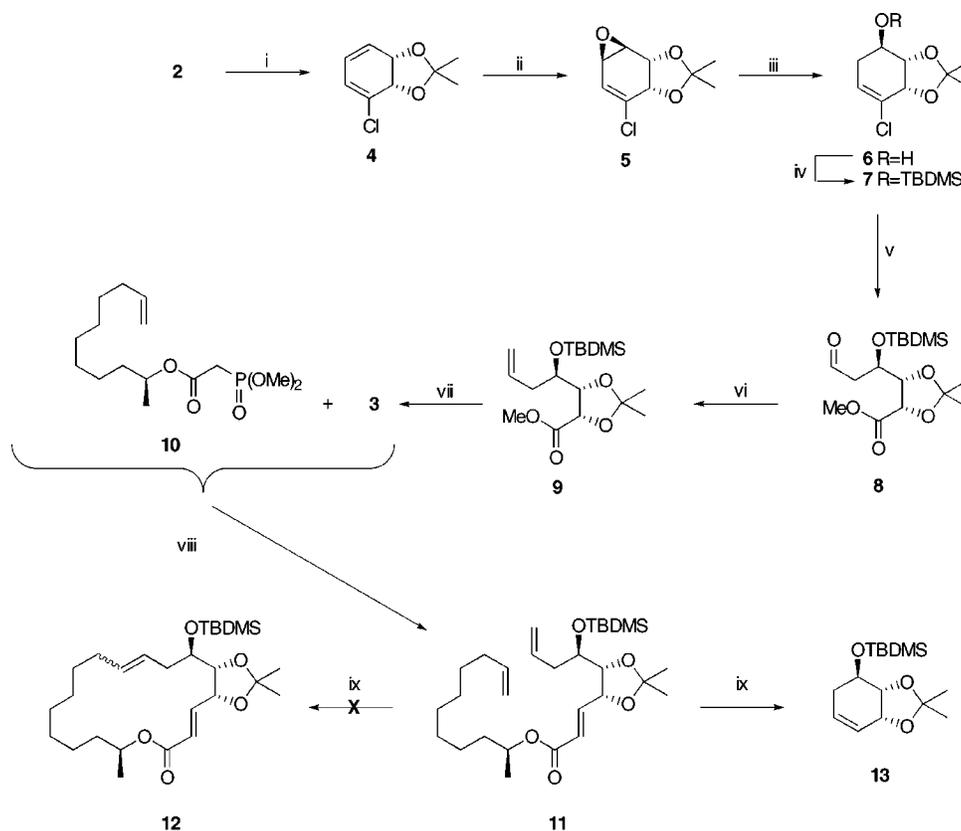
(5) Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem.* **1989**, *264*, 14940.

(1) Hesse, O. *J. Prakt. Chem.* **1900**, *62*, 430. (b) Hesse, O. *J. Prakt. Chem.* **1904**, *70*, 449.

(2) Huneck, S.; Schreiber, K.; Steglich, W. *Tetrahedron* **1973**, *29*, 3687.

(3) Quinkert, G.; Heim, N.; Bats, J. W.; Oschkinat, H.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 987.

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Scheme 1^a

^a Reagents and conditions: (i) $\text{Me}_2\text{C}(\text{OMe})_2$ (excess), *p*-TsOH (catalyst), 18 °C, 1 h; (ii) *m*-CPBA (1.0 molar equiv), CH_2Cl_2 , 0 to 18 °C, 15 h; (iii) DIBAL-H (2.0 molar equiv of a 1 M solution in hexane), Et_2O , -40 to -20 °C, 1 h; (iv) TBDMS-Cl (2.0 molar equiv), imidazole (2.5 molar equiv), DMF, 18 °C, 8 h; (v) ozone (excess), MeOH, -78 °C, 0.16 h then NaBH_4 (2.0 molar equiv), 0 °C, 0.5 h; (vi) $\text{Ph}_3\text{P}=\text{CH}_2$ (2.0 molar equiv), THF, 0 to 18 °C, 2 h; (vii) DIBAL-H (1.1 molar equiv of a 1 M solution in hexane), hexane, -78 °C, 0.75 h; (viii) compound **10** (1.5 molar equiv), NaH (1.5 molar equiv), THF, 0 °C, 0.5 h, then compound **3** (1.0 molar equiv), 0 °C, 1 h; (ix) $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ (10 mol %), CH_2Cl_2 , 18 °C, 4 h.

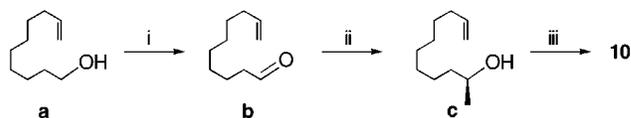
conversion of the latter compound into the well-known⁷ acetonide derivative **4** (97%). Regio- and diastereoselective epoxidation of diene **4** was achieved with *m*-chloroperbenzoic acid (*m*-CPBA), and oxide **5**⁷ (92%) thereby obtained was subjected to reductive cleavage with diisobutylaluminum hydride (DIBAL-H) in diethyl ether. The ensuing alcohol **6** {87%,⁸ $[\alpha]_{\text{D}} -55$ (*c* 1.5)⁹} was converted, by standard methods, into the corresponding *tert*-butyldimethylsilyl (TBDS) ether **7** {91%, mp 36–39 °C, $[\alpha]_{\text{D}} -30$ (*c* 1.4)} which was subjected to cleavage with ozone in methanol followed by in situ reduction of the intermediate peroxidic material with sodium borohydride. The resulting ester–aldehyde **8** was somewhat unstable and, therefore, immediately submitted to standard Wittig–methylenation conditions. Alkene **9**

{71% from compound **7**, $[\alpha]_{\text{D}} +23$ (*c* 1.7)} thus formed was treated with DIBAL-H and thereby afforded the pivotal aldehyde **3**¹⁰ {83%, $[\alpha]_{\text{D}} -17$ (*c* 2.8)}. In anticipation of following the closing stages associated with Hatakeyama's recently reported^{4i,11} synthesis of (+)-aspicilin, compound **3** was treated with the phosphonoacetate **10**^{12,13} and in this

(10) Selected spectral data for compound **3**: ¹³C NMR (75 MHz, CDCl_3) δ 200.9 (CH), 133.9 (CH), 117.8 (CH_2), 110.4 (C), 81.2 (CH), 80.6 (CH), 70.2 (CH), 38.0 (CH_2), 27.0 (CH_3), 25.9 (CH_3), 25.1 (CH_3), 18.2 (C), -4.1 (CH_3) and -4.3 (CH_3); ¹H NMR (300 MHz, CDCl_3) δ 9.70 (d, *J* = 2.3 Hz, 1H), 5.81 (m, 1H), 5.15–5.02 (complex m, 2H), 4.30 (m, 2H), 3.82 (dd, *J* = 5.9 and 11.3 Hz, 1H), 2.42 (m, 1H), 2.23 (m, 1H), 1.58 (s, 3H), 1.39 (s, 3H), 0.88 (s, 9H) and 0.06 (s, 6H).

(11) During the course of this work, Ley et al. reported⁴ⁱ a related approach to (+)-aspicilin.

(12) The phosphonoacetate **10** was prepared from commercially available alcohol **a** according to the sequence shown below. The key step involved enantioselective nucleophilic methylation of aldehyde **b** using procedures described by Knochel et al. (*Tetrahedron Lett.* **1994**, *35*, 4539).



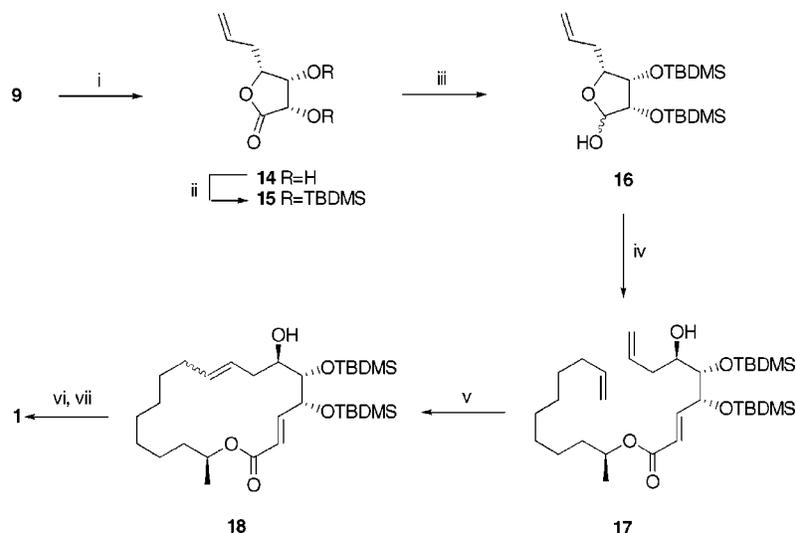
Reagents and conditions: (i) oxalyl chloride (1.2 molar equiv), DMSO (2.6 molar equiv), CH_2Cl_2 , -78 °C, 4 h, then Et_3N (2.6 molar equiv), -78 to -10 °C, 0.66 h; (ii) $\text{Ti}(\text{OPr}^i)_4$ (0.6 molar equiv), (1*R*-*trans*)-*N,N*-(cyclo-

(6) For an excellent and up-to-date review on the production and synthetic utility of enzymatically derived *cis*-1,2-dihydrocatechols, see: Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta* **1999**, *32*, 35.

(7) Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc.* **1994**, *116*, 5099.

(8) All new compounds had spectroscopic data [IR, UV (where appropriate), NMR, mass spectrum] consistent with those of the assigned structure. Satisfactory combustion and/or high-resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

(9) Unless stated otherwise, specific rotations were recorded in chloroform at 22 °C.

Scheme 2^a

^a Reagents and conditions: (i) HCl (2 M solution in MeOH), 0 °C, 3 h; (ii) TBDMS-Cl (2.5 molar equiv), imidazole (3 molar equiv), DMF, 18 °C, 12 h; (iii) DIBAL-H (1.5 molar equiv of a 1 M solution in hexane), hexane, -78 °C, 0.16 h; (iv) compound **10** (1.5 molar equiv), NaH (1.5 molar equiv), THF, 0 °C, 0.5 h, then compound **16** (1.0 molar equiv), 0 °C, 0.5 h; (v) (PCy₃)₂Cl₂Ru=CHPh (20 mol %), CH₂Cl₂, 18 °C, 14 h; (vi) H₂ (1 atm), 5% Pd on BaSO₄ (catalyst), ethyl acetate, 18 °C, 0.4 h; (vii) HCl (2 M solution in MeOH), 0 °C, 3 h.

manner the desired ring-closing metathesis (RCM)¹⁴ substrate, viz. α,β -unsaturated ester **11**¹⁵ {91%, [α]_D +34 (*c* 0.5)}, was obtained. However, reaction of a dilute solution of compound **11** in dichloromethane with 10 mol % of Grubbs' catalyst¹⁶ failed to give the target compound **12**. Rather, the alternate, and undesired, RCM product cyclohexene **13** {81%, [α]_D -72 (*c* 1.3)} was observed.

We reasoned that selective formation of alkene **13** occurs because the conformationally rigid acetonide protecting group within compound **11** facilitates simultaneous interaction of the double bonds of the carboxylic acid residue with Grubbs' catalyst and, therefore, metathesis of these olefinic moieties. On this basis we sought to replace the acetonide protecting group within the metathesis substrate by two independent hydroxy-protecting groups. However, all attempts to effect

hexane-1,2-diylbis(trifluoromethanesulfonamide) (0.04 molar equiv), toluene, 40 °C, 0.33 h, then Me₂Zn (2.2 molar equiv of a 2 M solution in toluene) and **b**, -78 °C, warm to -25 °C over 4 h; (iii) trimethyl phosphonoacetate (3.0 molar equiv), DMAP (0.3 molar equiv), toluene, 111 °C, 14 h.

(13) A comparison of the optical rotations of our samples of compounds **c**¹² and **10** with those determined (S. Hatakeyama, personal communication to M. G. Banwell) for their enantiomerically pure counterparts suggests that the phosphonate ester obtained by the present route to be of ca. 88% ee.

(14) For a useful point-of-entry to the current literature on RCM processes, see: Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.

(15) The reaction of the sodium salt of compound **10** with aldehyde **3** delivers only the illustrated diastereoisomeric form **11** of the coupling product despite the fact that the former substrate is obtained in only 88% ee.¹³ We attribute the selectivity associated with this Wadsworth-Emmons reaction to the operation of Horeau's amplification of chirality principle (see Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515). Thus, when a stoichiometric excess of compound **10** is employed in this bimolecular process, there is, throughout the course of the reaction, a kinetic selection for condensation of the enantiomerically pure aldehyde **3** with the more abundant enantiomeric form of the sodium salt of phosphonoacetate **10**.

(16) Purchased from Strem Chemicals, Inc.

acid-catalyzed hydrolysis of the offending acetonide unit within compound **11** resulted in complex mixtures of products, perhaps because of the presence of the rather acid-sensitive acrylate moiety. To circumvent these problems, appropriate protecting group manipulations were carried out on a less-advanced intermediate (Scheme 2). Thus, treatment of ester **9** with methanolic HCl effected global deprotection and concomitant lactonization to give compound **14** {91%, mp 111–113 °C, [α]_D +42 (*c* 0.9, MeOH)} which was reprotected as the corresponding bis-TBDMS ether **15** {95%, mp 67–69 °C, [α]_D +3 (*c* 1.3)}. Reduction of the last compound with DIBAL-H then afforded the corresponding lactol **16** (obtained as predominantly one anomer). Subjection of the latter compound to a Wadsworth-Emmons reaction with phosphonoacetate **10** then gave the RCM substrate **17** { $[\alpha]_D +12$ (*c* 1.1)} in 80% overall yield from lactone **15**. Gratifyingly, exposure of compound **17** to Grubbs' catalyst under high-dilution conditions afforded the desired product **18** (70%) as a ca. 3:1 mixture of *E*- and *Z*-isomers. This material was immediately hydrogenated in the presence of the Rosenmund catalyst and the bis-TBDMS ether of (+)-aspicilin {mp 78–81 °C, [α]_D +19 (*c* 0.8, MeOH)} was thereby obtained in 92% yield.

Smooth deprotection of this last compound was achieved with methanolic HCl to provide the target natural product (**1**) {76%, mp 152–154 °C, [α]_D +39 (*c* 1.10)} which was identical, in all respects, with an authentic sample.¹⁸

(17) The reaction of the sodium salt of compound **10** with lactol **16** delivers only the illustrated diastereoisomeric form **17** of the coupling product despite the fact that the former substrate is obtained in 88% ee.¹³ Once again, this outcome is attributed to the operation of Horeau's amplification of chirality principle.¹⁵

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(18) For a comprehensive listing of the physical and spectroscopic properties of (+)-aspicilin, see: Huneck, S.; Yoshimura, I. *Identification of Lichen Substances*; Springer-Verlag: Berlin, 1996; p 137.

Supporting Information Available: Experimental procedures and full characterization of compounds **1** (synthetic material), **6–11**, **13–15**, **17**, and (+)-aspicilin bis-TBDMS ether; experimental procedures together with ^1H and ^{13}C NMR spectral data for compound **3**; experimental procedure and ^1H NMR spectral data for compound **16**; experimental procedure for compound **18**; ^1H and ^{13}C NMR spectra for synthetic (+)-aspicilin; ^1H NMR spectrum for natural (+)-aspicilin. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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