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An Enantioselective Synthesis of the Epoxyquinol (+)-Isoepiepoformin

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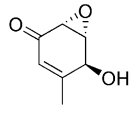
The epoxyquinol natural product (+)-isoepiepoformin (**1**) has been synthesized for the first time and in an unambiguous fashion by using the scalemic *cis*-1,2-dihydrocatechol **2** as starting material. The spectroscopic data derived from the synthetic sample of compound **1** match those reported in the literature for the natural product and thereby confirm the structure assigned to the latter.

Introduction

In 1986 Jarvis and Yatawara reported that, under certain conditions, cultures of the fungus *Myrothecium roridum* CL-514 (ATCC 20605) produced a new antibiotic to which they assigned the epoxyquinol-type structure **1** and which they named isoepiepoformin.[1] Their structural assignment was based on ^{1}H and ^{13}C NMR analyses, while the absolute stereochemistry of the compound was established by CD spectroscopy. Isoepiepoformin differs from the related epoxyquinol natural products epoformin and epiepoformin in that the methyl group is located on the β- rather than the α-carbon atom of the enone moiety. Despite this unusual structural feature and the demonstrated antibacterial effects exerted by compound **1**, it has not been the subject of any synthetic studies.



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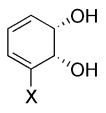

2 (X = Cl, Br or I)

Recently we reported[2,3] the ready preparation of a series of enantiomerically pure epoxyquinol synthons from *cis*-1,2-dihydrocatechols of the general form **2** (X = Cl, Br or I) – the latter compounds being available in large quantity and enantiomerically pure form through the whole-cell biotransformation of the corresponding halobenzene.[4] The acquisition of these synthons enabled us to develop highly abbreviated total syntheses of (–)-bromoxone, (–)-bromoxone acetate, (–)-epiepoformin, (–)-harveynone, (+)-panepophenanthrin, (+)-hexacyclinol and (–)-tricholomenyn A, all of which incorporate a substituent on the α-carbon atom of the enone moiety or a derived substructure.[5] Accordingly, we were interested in determining if our synthetic protocols could be modified so as to allow for the preparation of isoepiepoformin (**1**). The outcome of our successful studies of this matter is detailed here.

Results and Discussion

The reaction sequence used to establish the first total synthesis of isoepiepoformin (**1**) is shown in Scheme 1, and this began with the ready conversion of the iodobenzene-derived *cis*-1,2-dihydrocatechol **2** (X = I) into the corresponding *p*-methoxyphenyl (PMP) acetal **3** (97%). This acetal was obtained exclusively in the illustrated epimeric form, presumably because the reaction leading to it operates under kinetic control.[6] In keeping with our recently reported studies on its bromo analogue,[7] when a *tert*-butyl methyl ether (TBME) solution of compound **3** was treated at –78 °C with 6.5 mol-equiv. of DIBAl-H, then a ca. 2.5:1 mixture (as determined by ^{1}H NMR analysis) of the expected *p*-methoxybenzyl (PMB) ethers **4** and **5** was obtained. The structures of these chromatographically inseparable products follow from a single-crystal X-ray analysis (vide infra) of a derivative of ether **4**, the preferential generation of which presumably derives from selective coordination of DIBAl-H to the acetal oxygen atom of substrate **3** that is remote from the sterically demanding iodine atom. As a result of such coordination, the O-1–C-2 bond within compound **3** is cleaved preferentially. Several attempts to improve the selectivity of this reductive cleavage process, including those involving an examination of variations in reaction solvent and temperature as well as the nature of the reducing agent, failed. Treatment of the 2.5:1 mixture of monoethers **4** and **5** with *N*-bromosuccinimide (NBS) in wet THF under conditions used in our earlier studies[2,3]

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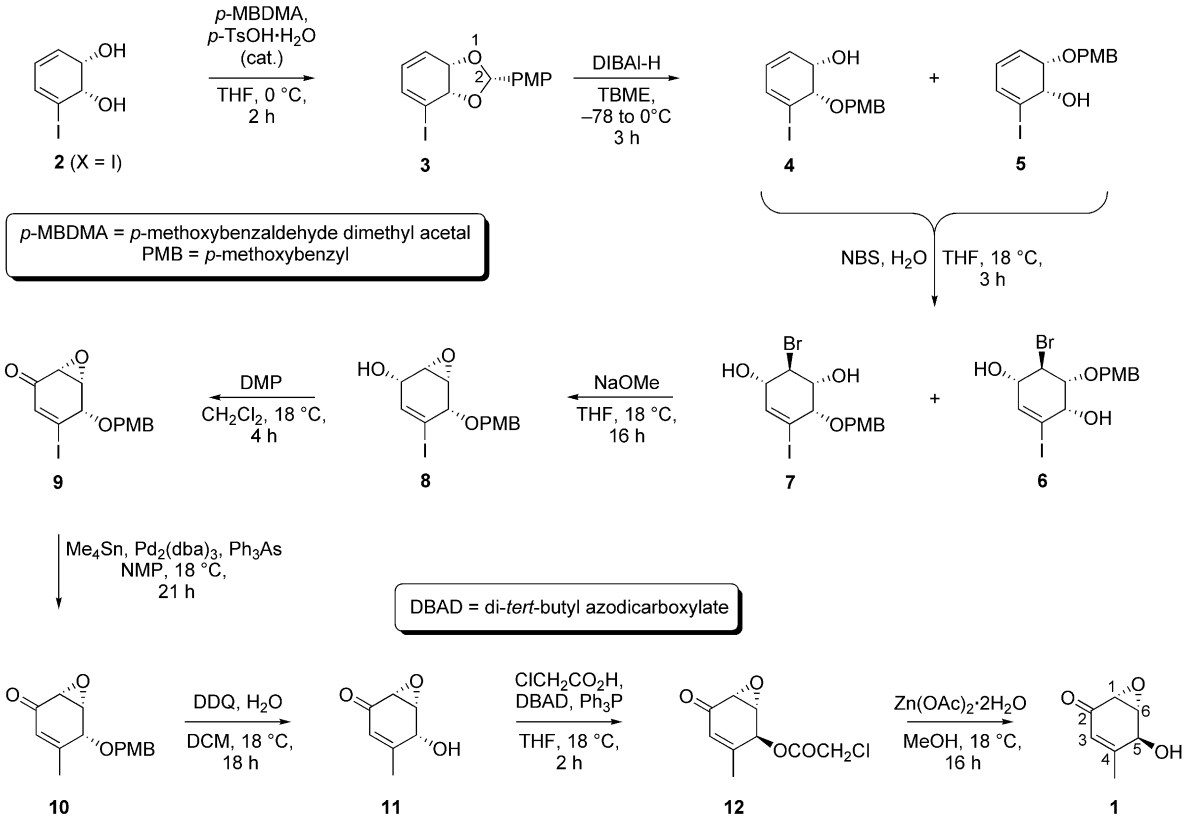

Scheme 1.

presumably generated both of the expected bromohydrins **6** and **7** (37% yield of a >2.5:1 mixture), but only the latter product was readily isolated from the reaction mixture in pure form. In keeping with earlier observations,[2,3] reaction of compound **7** with freshly prepared sodium methoxide in THF at ambient temperatures gave epoxide **8**, which was obtained as a white, crystalline solid in 99% yield. The selectivity of this epoxide-forming step is attributed to the more favorable orientation of the non-allylic hydroxy group (over its allylic counterpart) for participation in the required internal nucleophilic displacement reaction.

With the pivotal epoxide **8** in hand, the closing stages of the total synthesis of (+)-isoepiepoformin (**1**) could be undertaken. Thus, reaction of this compound with the Dess–Martin periodinane[8] (DMP) proceeded smoothly to give the crystalline β-iodo enone **9** (92%), the structure of which was secured through a single-crystal X-ray analysis that also served to confirm the structures of all of its precursors. The derived ORTEP is shown in Figure 1, while additional details of this analysis are provided in the Supporting Information. Subjection of compound **9** to a Stille cross-coupling with tetramethyltin and in the presence of $Pd_2(dba)_3/Ph_3As$ mixtures as catalyst precursors[2,3] resulted in formation of the crucial β-methylated enone **10**. This was obtained in 63% yield after purification by flash chromatography. Several attempts, including those involving variations in catalyst and solvent, were made to improve the outcome of this cross-coupling reaction, but all were without useful effect. Nevertheless, sufficient quantities of compound **10** could be accumulated so as to allow for the completion of the synthesis. To this end, the PMB residue within compound **10** was cleaved by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and the structure of the alcohol **11** thus obtained (in 48% yield) was confirmed by single-crystal X-ray analysis (see Supporting Information for details). Subjection of compound **11** to a Mitsunobu reaction by using chloroacetic acid as nucleophile[2] then gave the chloroacetate derivative **12** of target **1** in 73% yield. Finally, treatment of a methanolic solution of ester **12** with zinc(II) acetate dihydrate at 18 °C afforded target **1**, which was obtained as a light-yellow oil in 66% yield.

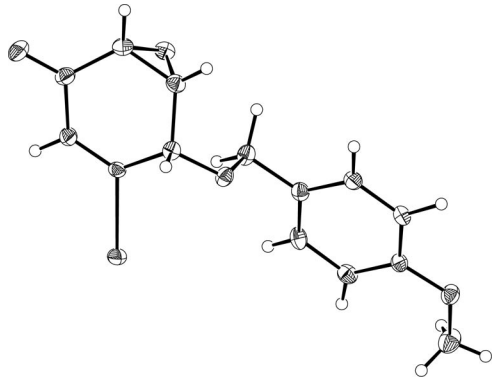

Figure 1. ORTEP derived from the single-crystal X-ray analysis of compound **9**. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

Table 1. Comparison of the ^{13}C and ^{1}H NMR spectroscopic data ($CDCl_3$; δ [ppm]) recorded on naturally and synthetically derived samples of (+)-isoepiepoformin (**1**).

^{13}C		^{1}H	
Natural **1** (100 MHz)	Synthetic **1** (125 MHz)	Natural **1** (400 MHz)[a]	Synthetic **1** (500 MHz)[b]
193.3	193.8 (C, C-2)	5.75 (m, 1 H)	5.77 (br. s, 1 H, H-3)
156.0	156.6 (C, C-4)	4.43 (dd, J = 1.3 and 0.7 Hz, 1 H)[c]	4.46 (d, J = 8.8 Hz, 1 H, H-5)
124.1	123.8 (CH, C-3)	3.75 (dd, J = 3.3 and 1.3 Hz, 1 H)	3.80 (dd, J = 3.4, 1.0 Hz, 1 H, H-1)
66.6	66.5 (CH, C-5)	3.38 (ddd, J = 3.3, 3.0 and 0.7 Hz, 1 H)	3.40 (m, 1 H, H-6)
56.9	56.9 (CH, C-6)	2.03 (d, J = 1.3 Hz, 3 H)	2.06 (d, J = 1.5 Hz, 3 H, CH_3)
52.2	52.2 (CH, C-1)	–	2.99 (d, J = 8.8 Hz, 1 H, OH)[d]
21.4	21.5 (CH_3)		

[a] Data derived from ref.[1] The field strengths of the spectrometers used in acquiring the cited ^{1}H and ^{13}C NMR spectra are ambiguous and could have been generated by using a machine operating at 200 MHz (for ^{1}H spectra). [b] Data derived from present work. [c] After H/D exchange. [d] This signal disappears upon treatment of the sample with D_2O.

The ^{13}C and ^{1}H NMR spectroscopic data derived from the synthetic sample of compound **1** are in complete accord with the assigned structure and, with one minor exception (vide infra), match those reported[1] for the natural product (Table 1). The only apparent discrepancy between the two data sets is seen in the resonances of H-5. In the natural product this appears as a doublet of doublets at δ = 4.43 ppm with J = 1.3 and 0.7 Hz, whereas in the synthetic material it appears at δ = 4.46 ppm as a doublet with J = 8.8 Hz. This difference arises because the former signal was recorded after an H/D exchange experiment had been carried out, whereas the latter was recorded without the analogous exchange process having taken place. As a result, in the spectrum of the synthetic material a significant three-bond coupling is observed between H-5 and the hydroxy group proton. This coupling obscures the other smaller ones that are reported for the natural product.

The specific rotation of the synthetic material {$[\alpha]_D$ = +430.2 (c = 0.6, $CHCl_3$)} proved to be more than ten times larger than that recorded[1] for naturally derived (+)-isoepiepoformin (**1**) {$[\alpha]_D$ = +36.4 (c = 0.5, $CHCl_3$)}. Given that the natural product (+)-epiepoformin, the α-methylated congener of compound **1**, is reported[9] to have a specific rotation of $[\alpha]_D$ = +310 (c = 0.46, ethanol), it is conceivable that the reported value for the (+)-isoepiepoformin may have been miscalculated and is, in fact, +364 or thereabouts. That being so, then the structure originally assigned to (+)-isoepiepoformin seems to be supported by the present study.

The antibacterial effects of compound **1** and certain of its precursors will be reported in due course.

Conclusions

The first total synthesis of (+)-isoepiepoformin (**1**) has been achieved, thereby confirming the structure assigned to this natural product. More broadly speaking, this work highlights the continued utility of microbially derived and enantiomerically pure *cis*-1,2-dihydrocatechols as starting materials in chemical synthesis.[2–4]

CCDC-774424 (for **9**) and -774425 (for **11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, ^{1}H NMR, ^{13}C NMR, IR spectroscopic together with mass spectrometric data for compounds **1**, **3**–**5** and **7**–**12**, as well as single-crystal X-ray analyses data for compounds **9** and **11** and an ORTEP of compound **11**.

Acknowledgments

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