ORGANIC LETTERS

2009
Vol. 11, No. 19
4290−4293

Chemoenzymatic Access to Versatile Epoxyquinol Synthons

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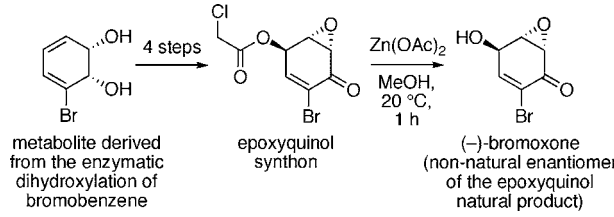
Received July 21, 2009

ABSTRACT



The enantiomerically pure and readily available metabolites 10−12 have been converted over four simple steps into the epoxyquinol derivatives 22−24, respectively. Compounds 23 and 24 or their immediate precursors have been exploited in efficient total syntheses of (−)-bromoxone (*ent*-1), (−)-epiepoformin (*ent*-2), (−)-harveynone (4), (+)-panepophenanthrin (6), and (+)-hexacyclinol (9).

(+)-Bromoxone (**1**), (+)-epiepoformin (**2**), (+)-epiepoxydon (**3**), and (−)-harveynone (**4**) are well-known and representative members of a significant and growing class of epoxyquinol-based natural products (Figure 1).[1] Compound **1** and its *O*-acetyl derivative were both isolated from a marine acorn worm, and the latter displays antitumor properties.[2] On the other hand, congeners **2** and **3** were extracted from the culture broth of an unidentified fungus residing on a diseased crepe myrtle leaf and shown to inhibit the germination of lettuce seeds.[3] (−)-Harveynone [**4**, aka (−)-PT toxin], which possesses the opposite absolute configuration, was first isolated from the mold *Curvularia harveyi* and shown, at that time, to inhibit spindle formation in sea urchin eggs.[4] This property is shared by *ent*-**4**, a phytotoxic metabolite of the tea gray blight fungus *Psetalotiopsis theae*.[5] Dienone **5**

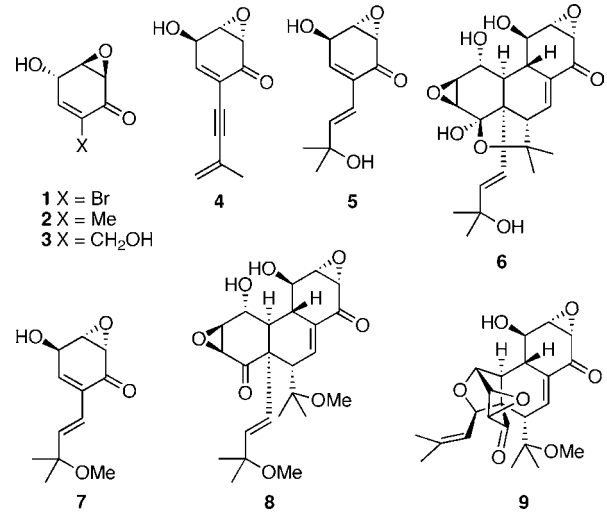


Figure 1. Structures of compounds **1**−**9**.

has been proposed[6] as the biosynthetic precursor to the epoxyquinol dimer (+)-panepophenanthrin (**6**), a compound isolated from the culture broth of the mushroom *Panus rudis* IF08994 and shown to act as an inhibitor of the ubiquitin-

(1) For a very useful introduction to this class of compound, see: (a) Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857. For a discussion of certain related compounds, see: (b) Thebtaranonth, C.; Thebtaranonth, Y. *Acc. Chem. Res.* **1986**, *19*, 84.

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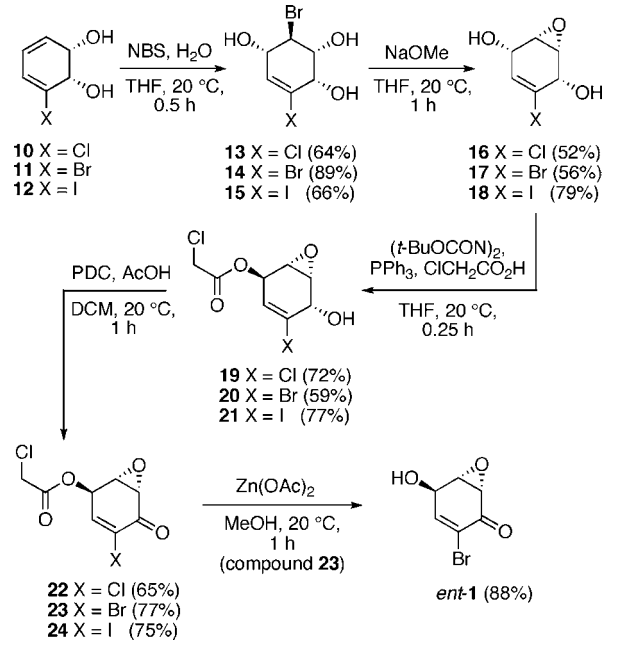
10.1021/ol9016657 CCC: $40.75
Published on Web 09/10/2009

activating enzyme E1.[7] The conversion **5** → **6** proceeds readily at room temperature through an unusual *exo*-[4 + 2] Diels−Alder cycloaddition reaction that is followed by a lactol-forming process within the initial cycloadduct.[6] The related epoxyquinol monomer **7** has been synthesized recently and shown to undergo an analogous dimerization process to give prehexacyclinol (**8**).[8] In the absence of the lactol-forming pathway, this last compound engages in an acid-catalyzed intramolecular S_N' reaction to give (+)-hexacyclinol (**9**), an antiproliferative agent originally isolated from the fungal strain *Panus rudis* HK1 0254 by Gräfe and co-workers.[9,10] Since compound **9** also displays moderate inhibitory activity against *Plasmodium falciparum* (IC_{50} 2.49 μg/mL)[9] it may serve as a lead for the development of new antimalarial agents.

The densely functionalized cyclohexene frameworks associated with the epoxyquinol natural products together with their diverse range of biological properties has prompted a great deal of effort to establish economical syntheses.[1,11−16] Much of this effort has relied upon the acquisition of protected forms of bromoxone or its iodo analogue which are then subjected to Heck, Sonogashira, Suzuki, or Stille reactions with the relevant cross-coupling partner.[17] The required haloxone derivative is often generated from benzoquinone or protected forms thereof[18] while enzymatically mediated desymmetrization or resolution processes[19] have been used to obtain the required substrates in enantiomerically pure form. As a consequence, somewhat lengthy reaction sequences can be involved. Accordingly, we now report on the facile and chemoenzymatic generation of several versatile epoxyquinol synthons from the *cis*-1,2-dihydrocatechols **10**−**12**, compounds that are readily obtained in large quantity and enantiomerically pure form via the enzymatic dihydroxylation of the corresponding halobenzene.[20] The value of these synthons is highlighted through their application to abbreviated total syntheses of (−)-bromoxone (*ent*-**1**), (+)-epiepoformin (*ent*-**2**), (−)-harveynone (**4**), (+)-panepophenanthrin (**6**), and (+)-hexacyclinol (**9**).

The key steps associated with the generation of the epoxyquinol synthons from the starting materials **10**−**12** are shown in Scheme 1. Thus, treatment of each of these halodienes with *N*-bromosuccinimide and water in THF at

Scheme 1



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(12) Syntheses of epiepoformin: (a) Kamikubo, T.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 1685 [(+)-**2**]. (b) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Chem.—Eur. J.* **2000**, *6*, 3991 [(+)-**2**]. (c) Shimizu, H.; Okamura, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2001**, *42*, 8649 [(+)-**2**]. (d) See ref 11d [(+)-**2**]. (e) Carreño, M. C.; Merino, E.; Ribagorda, M.; Somoza, Á.; Urbano, A. *Chem.—Eur. J.* **2007**, *13*, 1064 [(+)-**2**].

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(15) Syntheses of panepophenanthrin: (a) See ref 6a and 6c [(±)-**6** and (+)-**6**, respectively. (b) See ref 6b [(+)-**6**]. (c) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett.* **2004**, *45*, 1985 [(+)-**6**]. (d) See ref 13d [(−)-**6**]. (e) Matsuzawa, M.; Kakeya, H.; Yamaguchi, J.; Shoji, M.; Onose, R.; Osada, H.; Hayashi, Y. *Chem. Asian J.* **2006**, *1*, 845 [(+)-**6**].

(16) Syntheses of hexacyclinol: (a) See ref 8 [(+)-**9**]. (b) Mehta, G.; Roy, S. *Tetrahedron Lett.* **2008**, *49*, 1458 [(+)-**9**].

(17) See refs 12b, 14a,b, 15a,b,e, and 16a,b for examples of the use of these types of cross-coupling processes.

(18) See refs 11a−c, 12a,e, 13b,d, 14a,b, 15c and 16b for examples of this type of approach.

(19) See refs 11b−d, 12a, 13b,d, 14b, 15a,c, and 16b for examples of this type of approach.

(20) Compounds **10**−**12** can be obtained from Questor, Queen's University of Belfast, Northern Ireland. Questor Centre Contact Page: http://questor.qub.ac.uk/newsite/contact.htm (accessed July 21, 2009). 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. *Aldrichim. 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.; Vögtle, 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.

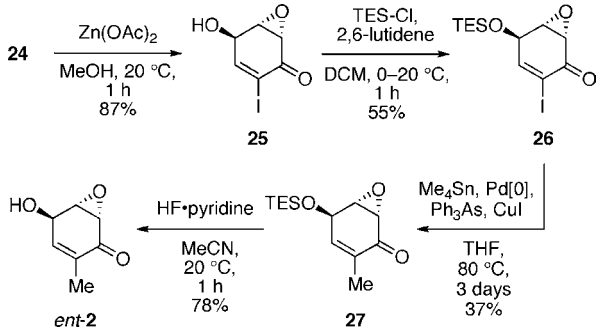
20 °C resulted in the selective formation of the corresponding bromohydrins **13** (64%), **14** (89%), and **15** (66%), respectively. Independent reaction of each of these with freshly prepared sodium methoxide then gave, in a selective manner, the corresponding cyclohexene oxides **16** (52%), **17** (56%), and **18** (79%), respectively, the structures of which follow from single-crystal X-ray analyses.[21] The two hydroxyl groups in each of these product diols are sufficiently differentiated by the presence of the halogen such that the one remote from chlorine, bromine, or iodine can be selectively engaged in a Mitsunobu reaction with chloroacetic acid,[22] thus generating the monoacetates **19** (72%), **20** (59%), or **21** (77%) from the relevant precursor. Oxidation of the remaining hydroxy group within each of these Mitsunobu products using pyridinium dichromate in the presence of a small amount of acetic acid[23] then provided the corresponding α-haloenone **22** (65%), **23** (77%), or **24** (75%). Treatment of the α-bromoenone **23** with zinc acetate in methanol[24] at 20 °C for 1 h gave (−)-bromoxone (*ent*-**1**) in 88% yield. The specific rotation of this material {$[\alpha]_D$ −187.1 (*c* 1.75, acetone)} was of similar magnitude but opposite sign to that reported[11e] for (+)-bromoxone {$[\alpha]_D$ +205.7 (*c* 0.32, acetone)}. The remaining spectral data derived from this material were identical, in all respects, with those reported[11] in the literature for its optical antipode. Since the enantiomer of compound **11** is also available,[25] the work reported herein also constitutes a formal total synthesis of (+)-bromoxone.

Initial attempts to exploit the iodinated epoxyquinol derivative **24** in a synthesis of (−)-epiepoformin (*ent*-**2**) were thwarted when the former compound failed to engage in a Stille cross-coupling reaction with tetramethylstannane. However, in keeping with observations made by Maycock et al.,[12b] when the α-chloracetyl group associated with compound **24** was removed (Scheme 2), using zinc acetate in methanol, and the resulting alcohol **25** (87%) was reprotected, under standard conditions, as the corresponding triethylsilyl (TES) ether **26** (55%) then a successful cross-coupling reaction with Me_4Sn followed, thus giving the required methylated enone **27** albeit in only 37% yield. Removal of the TES group within compound **27** was readily achieved using HF/pyridine and thereby providing (−)-epiepoformin (*ent*-**2**) as a colorless oil in 78% yield. Once again, the specific rotation of this material {$[\alpha]_D$ −311.0 (*c* 0.27, ethanol)} was of similar magnitude but of opposite sign to that reported[12a] for (+)-epiepoformin {$[\alpha]_D$ +316.04 (*c* 0.37, ethanol)}. The remaining spectral data derived from this material were identical, in all respects, with those reported[12] in the literature for its optical antipode. Thus far, we have been unable to adapt this approach to the synthesis (−)-epiepoxydon (*ent*-**3**) because none of (tri-*n*-butylstannyl)methanol,[26] triethyl[(tri-*n*-butylstannyl)methoxy]silane,[27] or (tri-*n*-butylstannyl)methyl 2-chloroacetate[27] could be engaged in the relevant Stille cross-coupling reaction with iodoenone **26**.

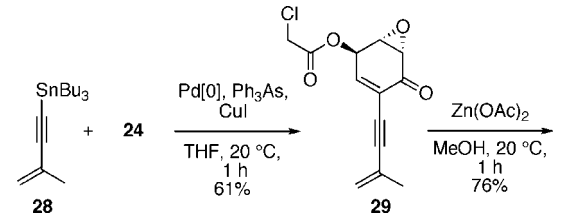
In contrast to the situation just described, the α-chloroacetoxy protecting group associated with synthon **24** proved to be an appropriate one for the synthesis of (−)-harveynone (**4**) (Scheme 3). Thus, Stille cross-coupling of iodoenone **24** with alkynyl stannane **28**,[14a] prepared from 2-methylbut-1-en-3-yne under conditions described by López,[28] gave the required dienyne **29** in 61% yield, and upon treatment of this last compound with zinc acetate in methanol at 20 °C the target epoxyquinol **4**, $[\alpha]_D$ −204.9 (*c* 0.89, methanol) {lit.[14d] $[\alpha]_D$ +206.6 (*c* 0.38, methanol)]} was realized as a clear, colorless oil, in 76% yield.

As shown in Scheme 4, the adaptation of the above-mentioned protocols to the synthesis of (+)-panepophenanthrin (**6**) proved straightforward. The stannylated coupling partner, **31**,[29] required for the preparation of the relevant epoxyquinol monomer was readily generated, in 94% yield, by Pd[0]-catalyzed hydrostannylation of the commercially available propargyl alcohol **30** with tri-*n*-butyltin hydride.

Scheme 2



Scheme 3



(21) Details of these analyses are presented in the Supporting Information.

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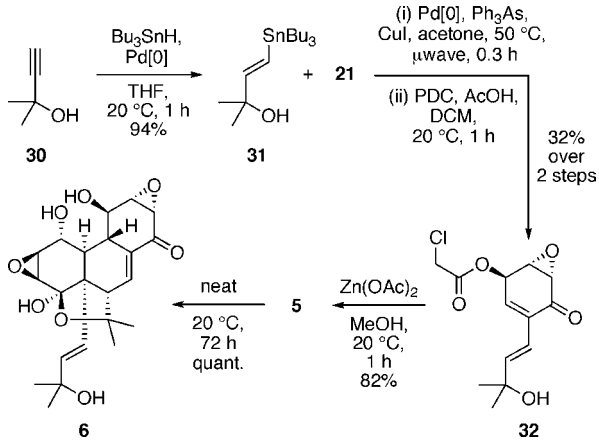
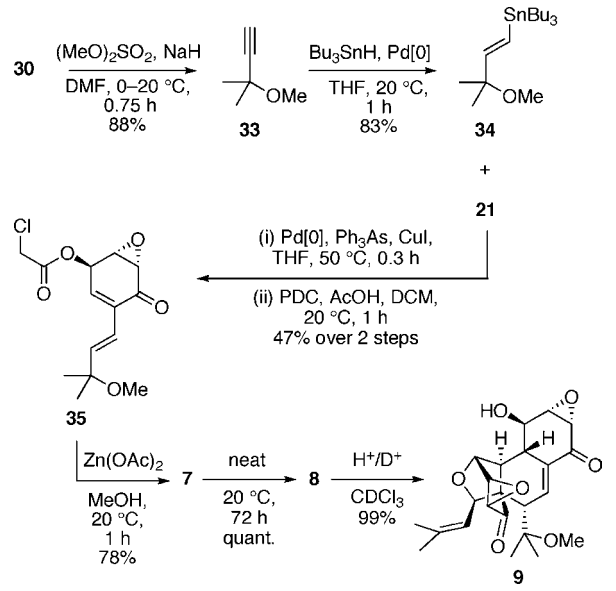
Scheme 4



Scheme 5



Stille cross-coupling of the compound **31** with the iodinated cyclohexene **21** proceeded smoothly under the conditions used previously for the conversion **24** + **28** → **29**, and the resulting alcohol was immediately oxidized with PDC in the presence of acetic acid to give enone **32** (32% yield over the two steps). Treatment of the last compound with zinc acetate in methanol at 20 °C for 1 h then gave the targeted epoxyquinol monomer **5** in 82% yield. While compound **5** could be subjected to full spectroscopic characterization, it displayed a propensity to undergo dimerization to give (+)-panepophenanthrin (**6**). Thus, on standing at ca. 20 °C for 72 h neat samples of compound **5** were converted into the dimer **6**, $[\alpha]_D$ +144 (*c* 0.5, methanol) {lit.[15a] $[\alpha]_D$ +146 (*c* 1, methanol)]} which was obtained as a crystalline solid, mp 140−144 °C (lit.[15a] mp 145−148 °C), in quantitative yield.

A strictly parallel sequence of reactions could be used to prepare (+)-hexacyclinol (**9**) (Scheme 5). Thus, the ether **33**,[30] obtained in 88% yield by *O*-methylation of alcohol **30**, was subjected to Pd[0]-catalyzed hydrostannylation using tri-*n*-butylstannane,[29] and the resulting alkenylstannane **34**[16a] (83%) was cross-coupled with iodocyclohexene **21**. The ensuing dienol was then oxidized, using PDC in the presence of acetic acid, to the enone **35** (47% over the two steps), which was, in turn, treated with zinc acetate in methanol to give the required epoxyquinol monomer **7**[16] (78%). In keeping with previous reports,[16] neat samples of compound **7** underwent essentially complete dimerization on standing at 20 °C for 72 h, thereby affording (+)-prehexacyclinol **8** in quantitative yield. During the course of characterizing samples of this last compound, as solutions in $CDCl_3$, it underwent ready (and presumably acid-catalyzed) conversion into (+)-hexacyclinol (**9**) which, under optimized conditions (see Supporting Information), was obtained in 99% yield as a white, crystalline solid, mp 176−178 °C (lit.[16b] mp 179−180 °C). The spectral data derived from this material were, once again, in complete agreement with those reported[9,16] in the literature.

The readily accessible and enantiomerically pure epoxyquinol synthons reported herein should be useful in the preparation of many other members of this class of natural product as well as in the generation of chemical libraries incorporating angular epoxyquinol scaffolds.[31] Work directed toward such ends is now underway in these laboratories, and results will be reported in due course.

Acknowledgment. We thank the Institute of Advanced Studies and the Australian Research Council for financial support.

Supporting Information Available: Full experimental procedures; ^1H and/or ^{13}C NMR spectra of compounds *ent*-**1**, *ent*-**2**, **4**−**9**, **13**−**27**, **29**, **32**, and **35**; data derived from the single-crystal X-ray analyses of compounds **16**−**18** (CCDC numbers 739393−739395, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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