Synthetic studies towards trichodimerol and related vertinoid polyketides

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Dedicated with appreciation to professor Gerasimos J. Karabatsos on the occasion of his 70th birthdate

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Abstract
An alternative synthetic route towards trichodimerol, bisorbicillinol and epoxysorbicillinol employing a suitable para-quinol as a common versatile key synthetic intermediate was investigated. The validity of this approach for the preparation of bisorbicillinol and epoxysorbicillinol derivatives was demonstrated. However, attempts to obtain trichodimerol-related derivatives or to render this approach enantioselective were unsuccessful.

Keywords: Epoxysorbicillinol, quinones, quinoles, asymmetric reduction

Introduction
Sorbicillin (1) is a known mold metabolite first isolated over fifty years ago from clinical penicillin. More recently, a number of biosynthetically related natural products with diverse biological activities were isolated from various terrestrial and marine fungi. Although it has not been observed in the fermentation broth, sorbicillinol (2) is the postulated common biosynthetic intermediate which upon further oxidation or dimerization leads to epoxysorbicillinol (3), bisorbicillinol (4), bisvertinoquinol (5) and trichodimerol (6) (Figure 1).

Intrigued by the novel structures of these natural products and their postulated biosynthesis we embarked in a research aiming at their synthesis. We postulated that quinol I (Scheme 1) could serve as a versatile common key intermediate for this family of natural products. Thus, trichodimerol could arise from dimerization of quinol I through hemiketal formation and double
Michael addition. Furthermore, dimerization through a Diels-Alder reaction could lead to bisorubicillinol or bisvertinoquinol while oxidation would lead to epoxysorbicillinol.

![Chemical structures](image)

**Figure 1.** Some naturally occurring vertinoid polyketides.

![Synthetic pathways](image)

**Scheme 1.** Synthetic strategies towards trichodimerol. Pr = protective group.
Following path A, quinol Ia could be derived from oxidation of sorbicillin, prepared from 2-methyl-resorcinol as described in the literature. Indeed this approach was successful and led to the total synthesis of bisorbicillinol and trichodimerol. Alternatively, the tautomeric quinol Ib (Scheme 1; Path B) could be prepared by regio-selective methylation of a suitably substituted p-benzoquinone originating from the same starting material. Although this is longer synthetic route than the previous one, it is anticipated to be easier to evolve to an enantioselective approach.

We report herein our preliminary results from the latter approach.

Results and Discussion

Monomethylation of 2-methylresorcinol (7; Scheme 2) followed by ortho-selective hydroxyalkylation with a suitable aldehyde in the presence of benzeneboronic acid furnished benzodioxaborin 9. Since octahydrotrichodimerol is much more stable than trichodimerol and in order to facilitate our exploratory synthetic studies we opted to utilize hexanal (R = C₅H₁₁) and not sorbic aldehyde (R = C₅H₇) at this stage. Deprotection of dioxaborin 9 by oxidation with hydrogen peroxide in tetrahydrofuran furnished the sensitive saligenol derivative 10. Air oxidation in the presence of catalytic amount of N,N'-bis(salicylidene)ethylenediamine cobalt (II) (salcomine) in dimethylformamide followed by protection of the secondary hydroxyl group as a tert-butyldimethylsilyl ether yielded p-benzoquinone 12.

Scheme 2. Synthesis of tetrahydromethylsorbicillinol (R = C₅H₁₁).
Regio-selective 1,2-addition of methyl lithium to the more electrophilic carbonyl in the presence of tetramethylethylenediamine (TMEDA)\textsuperscript{12} produced quinol 13 as a 7:1 mixture of diastereomers. Deprotection followed by oxidation with Dess-Martin periodinane furnished tetrahydromethylsorbicillinol (15).

\begin{equation}
\text{MeO} \quad \text{C}_5\text{H}_{11} \quad \text{OH} \\
\text{OH} \quad \text{OH} \quad \text{O} \quad \text{O} \quad \text{C}_5\text{H}_{11} \quad \text{OH} \quad \text{OH} \quad \text{MeO} \quad \text{C}_5\text{H}_{11} \quad \text{OH} \quad \text{O} \quad \text{O} \quad \text{C}_5\text{H}_{11} \\
\text{BF}_3\cdot\text{Et}_2\text{O} \quad \text{THF, 0 °C} \\
\text{MCPBA, DCM} \\
\text{PPTS, DCM or} \\
\text{TsOH·H}_2\text{O, THF or AcOH, H}_2\text{O}
\end{equation}

\begin{equation}
\text{Diels-Alder}
\end{equation}

**Scheme 3.** Transformations of quinol 15.

Dimerization of quinol 15 could in principle be achieved upon treatment with either protic or Lewis acids. Protic aqueous acids are expected to first cleave the enol methyl ether to afford the corresponding free quinol. This could subsequently dimerize either through double Michael addition and hemiketal formation to octahydrotrichodimerol or through Diels-Alder cycloaddition to octahydrobisorbicillinol. On the other hand, non-aqueous protic acids or Lewis acids should favor initial hemiketal formation leading to double Michael addition products exclusively.

In practice, upon treatment of quinol 15 with para-toluenesulfonic acid monohydrate in tetrahydrofuran at ambient temperature it was cleanly converted to octahydrobisorbicillinol (17, Scheme 3). The progress of the reaction was monitored by TLC analysis and it clearly indicated the initial formation of an intermediate, presumably free quinol 16. However, all attempts to isolate this compound were unsuccessful. By contrast, treatment of quinol 15 with BF\textsubscript{3}·Et\textsubscript{2}O in dry tetrahydrofuran at 0 °C led to exclusive rearrangement through sigmatropic shift to hydroquinone 18 while use of PPTS in dry dichloromethane led to formation of octahydrobisorbicillinol as the major product. At least two more compounds were formed but their identification was hindered by the small amount obtained. On the other hand, oxidation of quinol 15 with m-chloroperbenzoic acid in dichloromethane at ambient temperature led, as planned, to methyl-octahydro-epoxysorbicillinol (19).

Finally, in order to render our approach enantioselective, we briefly explored the asymmetric preparation of key intermediate 10. Condensation of monomethylated 2-methyl-resorcinol (8, Scheme 4) with hexanoic acid in the presence of BF\textsubscript{3}·Et\textsubscript{2}O\textsuperscript{13} gave in good yield ketone 20.
However, attempted asymmetric reduction using Brown’s methodology\textsuperscript{14} failed to yield saligenol derivative 10. Although we observed formation of the initial reddish boron complex 22, it did not proceed to give the expected alcohol complex even after three days at ambient temperature. In fact complex 22 was stable enough to allow purification by silica gel chromatography. Treatment of this complex with tetrabutylammoniumborohydride at −90 °C led to essentially racemic alcohol 10. Equally unsuccessful were attempts to reduce enantioselectively the acetate 21.

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\begin{align*}
\text{Scheme 4. Attempted enantioselective preparation of key intermediate 10.}
\end{align*}
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In conclusion, we have demonstrated the feasibility of an alternative synthetic approach towards vertinoid polyketides and in particular towards bisorbicillinol and epoxysorbicillinol. We are currently pursuing the total synthesis of these natural products and are investigating alternative methods for the enantioselective preparation of key intermediate 10.

Selected physical properties of compounds 9, 11, 15, 17, 18 and 19

9. White low melting solid; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}): \(\delta = 8.03–7.99\) (m, 2 H), 7.51–7.37 (m, 3 H), 6.82 (d, \(J = 8.2\) Hz, 1 H), 6.58 (d, \(J = 8.2\) Hz, 1 H), 5.19 (dd, \(J = 6.9, 4.7\) Hz, 1 H), 3.85 (s, 3 H), 2.29 (s, 3 H), 1.89–1.77 (m, 2 H), 1.62–1.43 (m, 2 H), 1.40–1.25 (m, 4 H), 0.88 (t, \(J = 7.1\) Hz, 3 H); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}): \(\delta = 157.7, 147.5, 134.3, 131.3, 128.3, 127.7, 122.3, 118.9, 104.7, 72.9, 55.7, 39.8, 31.6, 24.2, 22.6, 14.0, 8.2\).

11. Orange oil; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}): \(\delta = 6.52\) (d, \(J = 1.1\) Hz, 1 H), 4.68 (bdd, \(J = 7.3, 4.3\) Hz, 1 H), 4.04 (s, 3 H), 3.12 (bs, 1 H), 1.95 (s, 3 H), 1.79–1.22 (m, 8 H), 0.90 (t, \(J = 6.5\) Hz, 3 H); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}): \(\delta = 188.5, 183.7, 129.5, 120.3, 115.8, 68.9, 60.8, 36.4, 31.4, 25.2, 22.4, 13.9, 8.5\).

15. Light yellow oil; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}): \(\delta = 6.99\) (s, 1 H), 4.00 (s, 3 H), 3.21 (bs, 1 H), 2.80 (m, 2 H), 1.85 (s, 3 H), 1.63–1.45 (m, 2 H), 1.52 (s, 3 H), 1.32–1.20 (m, 4 H), 0.84 (t, \(J = 7.1\) Hz, 3 H); \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}): \(\delta = 202.3, 185.5, 170.8, 150.1, 136.2, 117.5, 60.3, 61.4, 42.9, 31.2, 26.0, 23.4, 22.4, 13.8, 9.0\).

17. White solid; \(R_f = 0.1\) (silica gel, hexane:ethyl acetate 6:4); \textsuperscript{1}H NMR (360 MHz, CD\textsubscript{3}OD): \(\delta = 3.58\) (d, \(J = 2.2\) Hz, 1 H), 3.43 (d, \(J = 2.3\) Hz, 1 H), 2.79–2.66 (m, 1 H), 2.59–2.36 (m, 3 H), 1.63 (s, 3 H), 1.60–1.54 (m, 4 H), 1.52 (s, 3 H), 1.42–1.29 (m, 8 H), 1.23 (s, 3 H), 1.20 (s, 3 H), 0.99–0.90 (m, 6 H).
18. Yellow oil; $R_f = 0.5$ (silica gel, hexane:ethyl acetate 8:2); $^1$H NMR (360 MHz, CDCl$_3$): $\delta =$ 11.6 (s, 1 H), 5.48 (s, 1 H), 3.82 (s, 3 H), 2.89 (t, $J = 7.4$ Hz, 2 H), 2.43 (s, 3 H), 2.18 (s, 3 H), 1.78–1.65 (m, 2 H), 1.38–1.27 (m, 4 H), 0.90 (t, $J = 6.7$ Hz, 3 H); $^{13}$C NMR (90 MHz, CDCl$_3$): $\delta =$ 209.0, 150.1, 60.9, 44.2, 31.5, 25.0, 22.5, 15.3, 13.9, 9.2.

19. White solid; $R_f = 0.1$ (silica gel, hexane:ethyl acetate 8:2); $^1$H NMR (360 MHz, CDCl$_3$): $\delta =$ 4.01 (s, 3 H), 3.53 (s, 1 H), 2.62 (dd, $J = 7.1$, 2.2 Hz, 1 H), 2.61 (bs, 1 H), 2.58 (dd, $J = 6.7$, 1.5 Hz, 1 H), 1.82 (s, 3 H), 1.67–1.57 (m, 2 H), 1.55 (s, 3 H), 1.36–1.24 (m, 4 H), 0.88 (t, $J = 6.9$ Hz, 3 H).

References