Synthetic studies towards trichodimerol and related vertinoid polyketides

Emmanuel N. Pitsinos,[a] Veroniki P. Vidali,[a,b] and Elias A. Couladouros*[a,b]

[a] *Laboratory of Organic and Bio-Organic Chemistry, Inst. of Physical Chemistry, NCSR*
"DEMOKRITOS", P.O. Box 60228, GR-153 10 Ag. Paraskevi, Greece
[b] *Chemistry Laboratories, Agricultural University of Athens, Iera Odos 75, Athens 118 55,*
Greece
E-mail: ecoula@chem.demokritos.gr

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

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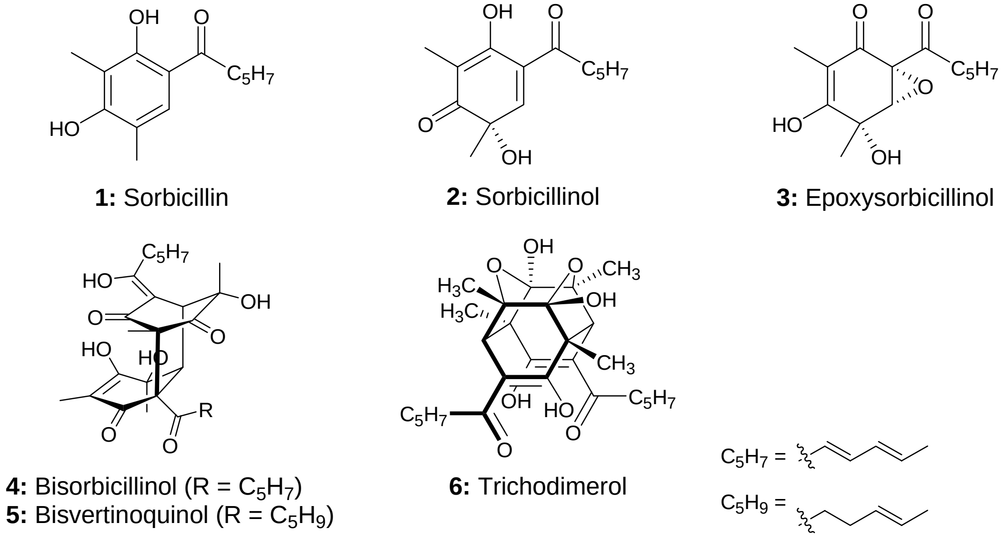
Introduction

Sorbicillin (**1**) is a known mold metabolite first isolated over fifty years ago from clinical penicillin.[1] 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**),[2] bisorbicillinol (**4**),[3] bisvertinoquinol (**5**)[4,5] and trichodimerol (**6**)[6,7] (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.[8] Furthermore, dimerization through a Diels-Alder reaction could lead to bisorbicillinol or bisvertinoquinol while oxidation would lead to epoxysorbicillinol.



1: Sorbicillin

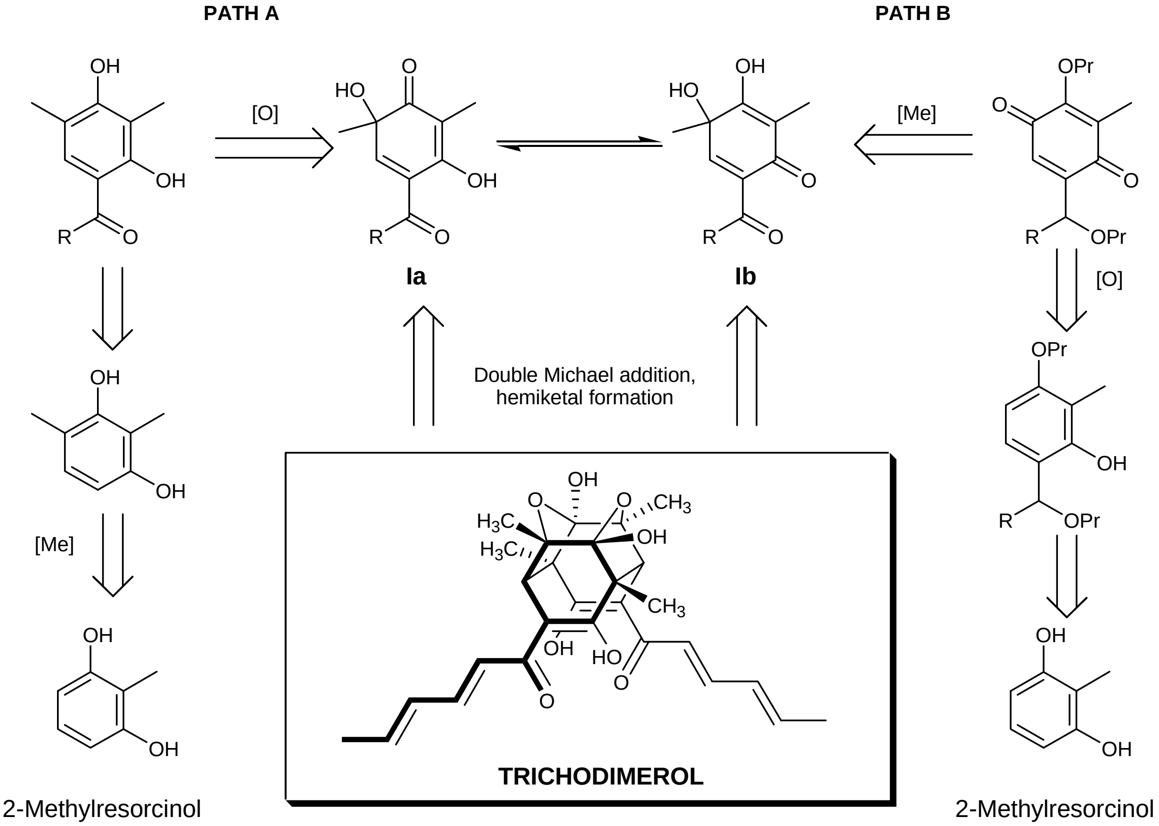
2: Sorbicillinol

3: Epoxysorbicillinol

4: Bisorbicillinol (R = C_5H_7)
5: Bisvertinoquinol (R = C_5H_9)

6: Trichodimerol

Figure 1. Some naturally occurring vertinoid polyketides.



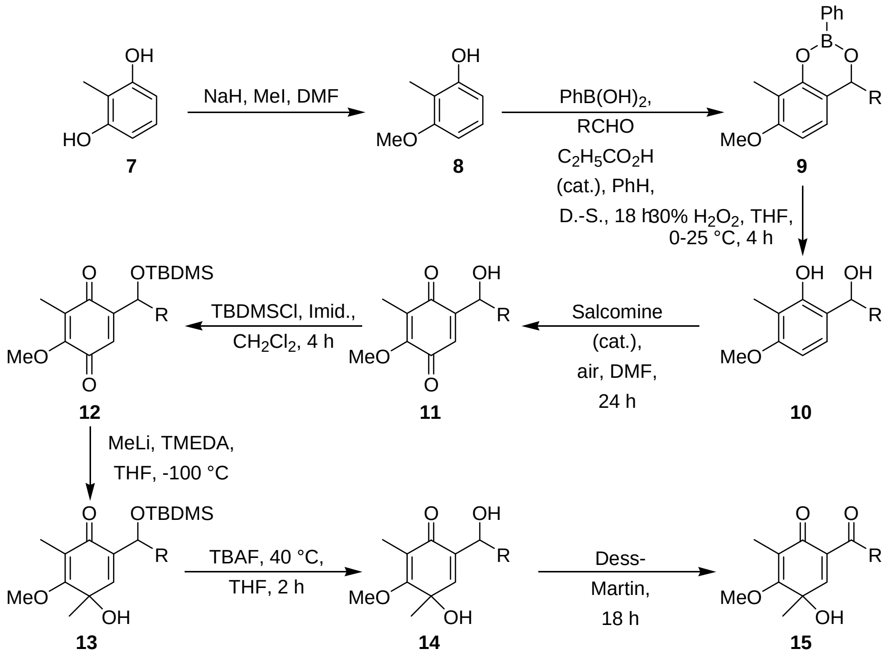
Scheme 1. Synthetic strategies towards trichodimerol. Pr = protective group.

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.[9] 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.[10]

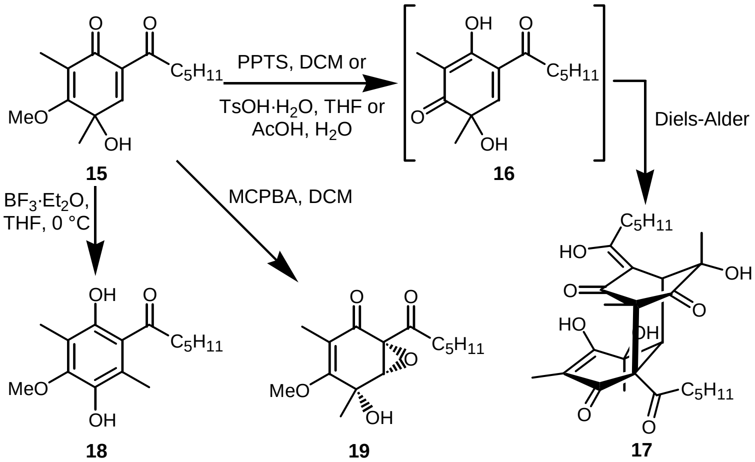
Results and Discussion

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**.[11] Since octahydrotrichodimerol is much more stable than trichodimerol[7] and in order to facilitate our exploratory synthetic studies we opted to utilize hexanal (R = C_5H_{11}) and not sorbic aldehyde (R = C_5H_7) 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 = C_5H_{11}).

Regio-selective 1,2-addition of methyl lithium to the more electrophilic carbonyl in the presence of tetramethylethylenediamine (TMEDA)[12] produced quinol **13** as a 7:1 mixture of diastereomers. Deprotection followed by oxidation with Dess-Martin periodinane furnished tetrahydromethylsorbicillinol (**15**).



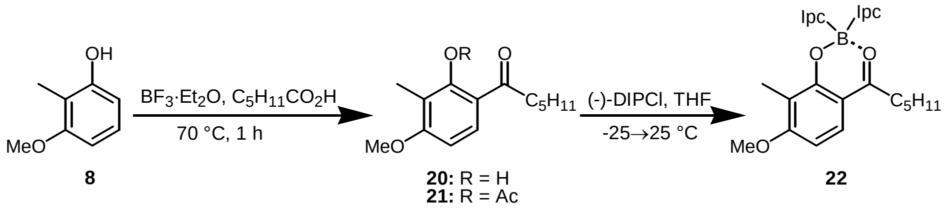
Scheme 3. Transformations of quinol **15**.

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 unsuccesful. By contrast, treatment of quinol **15** with $BF_3 \cdot Et_2O$ 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 $BF_3 \cdot Et_2O$[13] gave in good yield ketone **20**.

However, attempted asymmetric reduction using Brown's methodology[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 unsuccesful were attempts to reduce enantioselectively the acetate **21**.



Scheme 4. Attempted enantioselective preparation of key intermediate **10**.

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 indermediate **10**.

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

9. White low melting solid; ^1H NMR (360 MHz, $CDCl_3$): δ = 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); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 157.7, 147.5, 134.4, 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; ^1H NMR (360 MHz, $CDCl_3$): δ = 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); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 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; ^1H NMR (360 MHz, $CDCl_3$): δ = 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); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 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); ^1H NMR (360 MHz, CD_3OD): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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

1. Cram, D. J. *J. Am. Chem. Soc.* **1948**, *70*, 4240.
2. Sperry, S.; Samuels, G. J.; Crews, P. *J. Org. Chem.* **1998**, *63*, 10011.
3. Abe, N.; Murata, T.; Hirota, A. *Biosci., Biotechnol., Biochem.* **1998**, *62*, 661.
4. Trifonov, L. S.; Bieri, J. H.; Prewo, R.; Dreiding, A. S.; Hoesch, L.; Rast, D. M. *Tetrahedron* **1983**, *39*, 4243.
5. Trifonov, L. S.; Hilpert, H.; Floersheim, P.; Dreiding, A. S.; Rast, D. M.; Skrivanova, R.; Hoesch, L. *Tetrahedron* **1986**, *42*, 3157.
6. Warr, G. A.; Veitch, J. A.; Walsh, A. W.; Hesler, G. A.; Pirnik, D. M.; Leet, J. E.; Lin, P.-F. M.; Medina, I. A.; McBrien, K. D.; Forenza, S.; Clark, J. M.; Lam, K. S. *J. Antibiot.* **1996**, *49*, 234.
7. Andrade, R.; Ayer, W. A.; Mebe, P. P. *Can. J. Chem.***1992**, *70*, 2526.
8. Hagiwara, H.; Yamada, Y.; Sakai, H.; Suzuki, T.; Ando, M. *Tetrahedron* **1998**, *54*, 10999.
9. Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3555.
10. For other related synthetic efforts see: Pettus, L.H.; Van de Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2001**, *3*, 905 and references cited therein.
11. Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, 365.
12. Liotta, D.; Saindane, M.; Barnum, C. *J. Org. Chem.* **1981**, *46*, 3369.
13. Wahala, K.; Hase, T. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3005.
14. Ramachandran, P. V.; Gong, B.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 2141.