and substituents. This encapsulation based only on a hydrophobically shielded, hydrophilic solvating microenvironment represents a different principle in comparison to the topological entrapment observed for some dendrimer-based structures.[2] From light scattering measurements it was tentatively concluded that the solvating species are present in a unimolecular form in organic solvents, thus, representing "inverted unimolecular micelles". Since there appears to be no measurable release of encapsulated guests, the term "micelle" is slightly misleading; we favor the term "molecular nanocapsules". Release of the encapsulated dyes is achieved by means of cleaving the ester bond, thus, removing the hydrophobic molecular shield of the nanocapsules.

Molecular nanocapsules and their corresponding host/guest compounds offer an attractive potential for use in a wide variety of applications ranging from controlled drug release, solubilization of inorganic compounds in organic media, dispersion of polar dyes in hydrophobic polymers, preparation of inorganic/organic hybrid nanoparticles, to the design of microreactors and catalysts.[17]

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[16] In a typical experiment the respective aqueous dye solution (4 mL) was manually shaken for some seconds with 0.01 wt% solution (4 mL) of the partially esterified polyglycerol in chloroform. After phase separation (two experiments after 3 h and 24 h), an aliquot of the organic layer (2 mL) was transfered into a UV/Vis cuvette and its absorption spectrum measured. No difference between the 3 h and 24 h measurements was observed. The solutions remained unchanged for several months.
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Biomimetic Explorations Towards the Bisorbicillinoids: Total Synthesis of Bisorbicillinol, Bisorbibutenolide, and Trichodimerol**

K. C. Nicolaou*, Klaus B. Simonsen, Georgios Vassilikogiannakis, Phil S. Baran, Veroniki P. Vidali, Emmanuel N. Pitsinos, and Elias A. Couladouros

Dedicated to Professor Gerasimos J. Karabatsos on the occasion of his 67th birthday

The bisorbicillinoids[1] are a growing family of novel natural products with interesting and diverse biological activities. Included within this class are bisorbicillinol (**1**),[2] bisorbibutenolide (**2**),[3] trichodimerol (**4**),[4] bisorbicillinolide (**5**),[3] and

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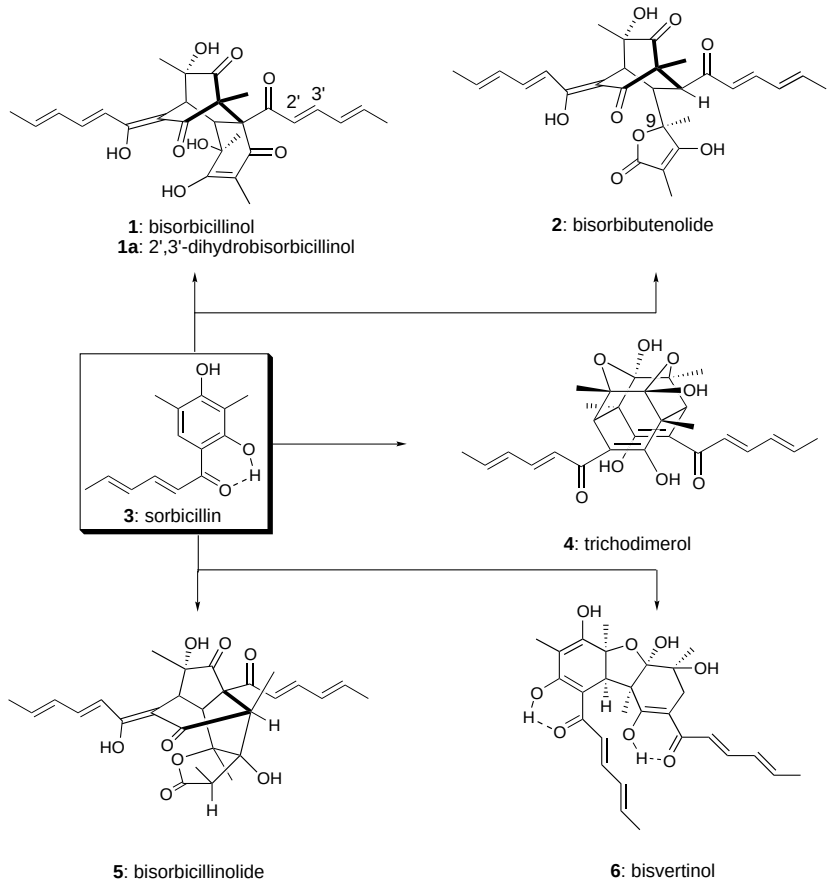

Figure 1. Structures of selected bisorbicillinoids and their postulated biosynthetic precursor sorbicillin (**3**).

bisvertinol (**6**),[5] all of which are thought to be biosynthetically derived from sorbicillin (**3**), itself a naturally occurring substance (Figure 1).[6]

Isolated from various species of fungi, bisorbicillinol (**1**), bisorbibutenolide (**2**), and bisorbicillinolide (**5**) exhibit antioxidant properties,[2, 3] while an oxidized form of bisvertinol (**6**) represents the first inhibitor of β-6-glucan biosynthesis, and is, therefore, considered as a potential antifungal agent.[5b] Trichodimerol (**4**), on the other hand, originally isolated from the genus *Trichoderma*, showed inhibitory activity against lipopolysaccharide-induced production of tumor necrosis factor α (TNF-α) in human monocytes and, consequently, is considered to be a potential lead for the treatment of septic shock.[4b] The novel and complex molecular architectures of these molecules coupled with their intriguing biological properties and unusual biosynthetic pathways prompted us to initiate a program directed towards their biomimetic total synthesis. Here we report the total syntheses of three members of this class of natural products, namely, bisorbicillinol (**1**), bisorbibutenolide (**2**) and trichodimerol (**4**).

The unifying feature of these structurally connected dodecaketides resides in the mechanistically related proposals regarding their biosynthetic origin from sorbicillin (**3**; Figures 1 and 2). Thus, the first member of this family, bisvertinoquinol (**1a**), reported by Dreiding et al. in 1983, was postulated to arise from a Diels–Alder reaction between two different quinols derived from **3** and 2′,3′-dihydrosorbicillin by enantioselective oxidation.[7] A similar hypothesis was advanced by Abe et al. to explain the biosynthesis of the newly isolated bisorbicillinol (**1**) (Figure 1).[2] The same group also proposed the biosynthesis of the soon thereafter isolated bisorbibutenolide (**2**) and bisorbicillinolide (**5**) by anionic rearrangement of **1**.[3a] We have recently proposed a possible biosynthetic pathway for trichodimerol (**4**) involving a two-step Michael addition–ketalization sequence from an oxidized form of **3**.[1] We now suggest that the bisvertinols (e.g. **6**), representing the largest group of the bisorbicillinoids, are biosynthesized by a similar mechanism involving a Michael addition followed by ketalization and finally reduction (see Figure 2).[8]

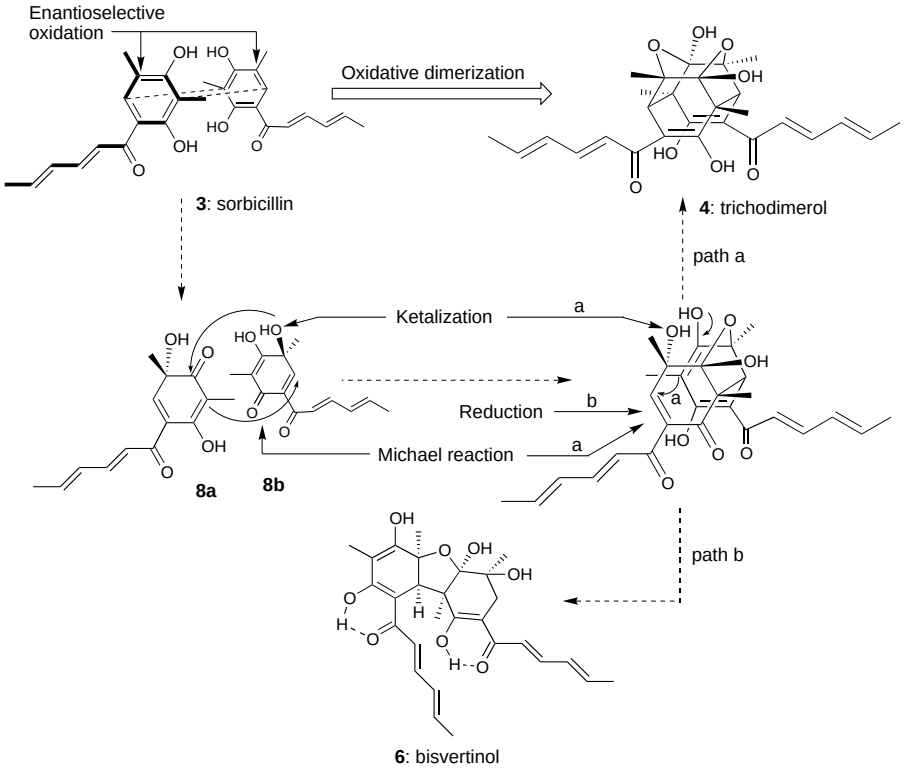

Figure 2. Proposed biosynthetic pathways from sorbicillin (**3**) to trichodimerol (**4**) and bisvertinol (**6**).

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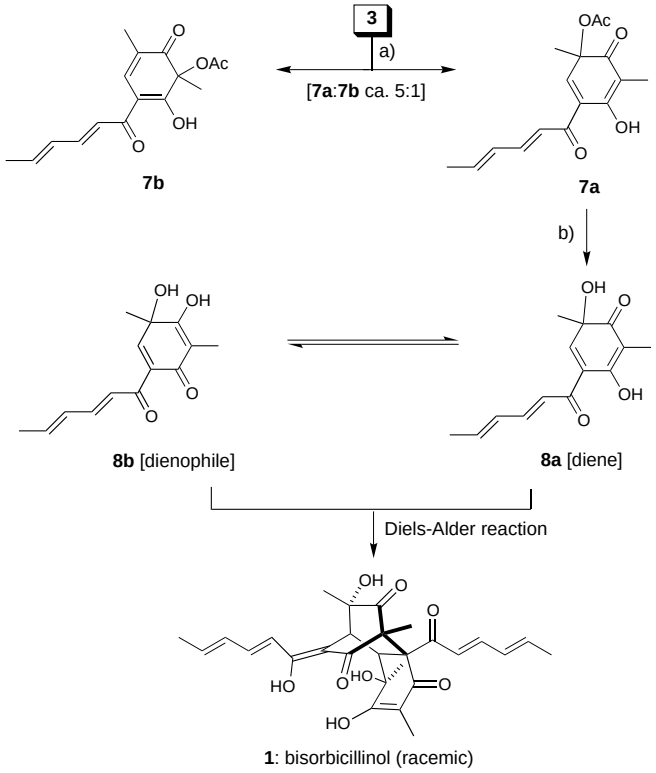
Inspired by biosynthetic considerations, we began our synthetic studies towards the bisorbicillinoids with sorbicillin (**3**) and had acetate **7a** (Scheme 1) as the first objective. Thus, **3**, obtained by the boron trifluoride catalyzed acylation of 2,4-dimethylresorcinol[9] with sorbic acid,[10] was subjected to



Scheme 1. Biomimetic total synthesis of bisorbicillinol (**1**) from sorbicillin (**3**). a) $Pb(OAc)_4$ (1.2 equiv), AcOH, 25 °C, 2 h, 40 % **7a** and 10 % **7b**; b) KOH (10 equiv), THF/H_2O (9/1), 0 °C, 2 h; then 1N aq. HCl, 40 %; or THF/conc. HCl (9/1), 25 °C, 2 h, 43 %.

oxidation with lead tetraacetate in acetic acid to afford the desired α-hydroxydienone **7a** as the major product together with its regioisomer **7b** (ca. 5:1 ratio, Scheme 1). Flash column chromatography (silica, dichloromethane/acetone 9/1) followed by recrystallization furnished **7a** in 40 % yield (Table 1).

When acetate **7a** was treated with solid KOH (10 equiv) in THF/H_2O (9/1; 0.05 M) at 0 °C for 1 h followed by quenching with 1N aq. HCl, the Diels–Alder adduct bisorbicillinol (**1**) was isolated in 40 % yield. The spectral properties of synthetic **1** were identical to those reported by Abe et al.[2, 11] Generating four stereogenic centers, two of which are quaternary, this reaction proceeds with remarkable regio- and diastereocontrol (*endo* selectivity).[12]

It is postulated that the first stages of this sequence (**7a** → **1**) involve deacetylation followed by scrambling of the resulting dianion to a mixture of diquinolates (derived from **8a** and **8b**, Scheme 1). Acidification of the reaction mixture presumably results in the formation of quinols **8a** and **8b**, which readily combine in a Diels–Alder reaction to generate **1**. A similar dimerization was observed by Barton et al. when they generated *ortho*-quinols by allowing phenols to react with

Table 1. Selected physical properties of compounds **7a**, **12**, and **13**.

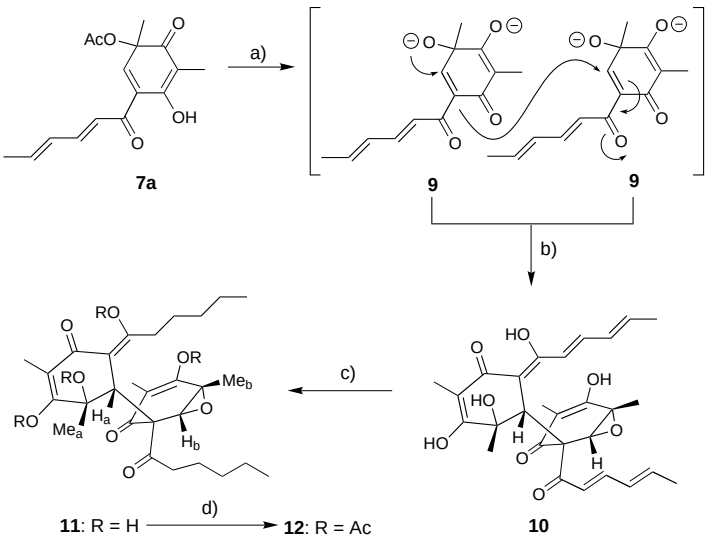
7a: $R_f = 0.41$ (silica gel, dichloromethane/acetone 9/1); m.p. 149–150 °C (diethyl ether/*n*-hexane); IR (film): $\tilde{\nu}_{max} = 2930, 1737, 1650, 1644, 1612, 1555, 1215, 1245, 1070, 1018\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 11.90$ (s, 1H), 7.46 (dd, $J = 14.8, 10.8$ Hz, 1H), 7.25 (s, 1H), 6.66 (d, $J = 14.8$ Hz, 1H), 6.38 (m, 1H), 6.31 (m, 1H), 2.15 (s, 3H), 1.93 (d, $J = 6.6$ Hz, 3H), 1.86 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 195.4, 193.7, 170.4, 162.9, 152.3, 148.7, 145.3, 130.5, 125.9, 120.6, 112.1, 78.6, 24.5, 21.0, 19.6, 7.6$; HR-MS (MALDI): calcd for $C_{16}H_{18}O_5Na$ $[M + Na^+]$: 313.1052, found: 313.1055

12: $R_f = 0.40$ (silica gel, ethyl acetate/hexane 2/3); IR (film): $\tilde{\nu}_{max} = 2931, 1769, 1710, 1671, 1370, 1242, 1185, 1071\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta = 5.90$ (s, 1H), 4.08 (s, 1H), 3.51 (ddd, $J = 13.8, 10.0, 5.5$ Hz, 1H), 2.87 (dt, $J = 19.3, 7.3$ Hz, 1H), 2.63 (ddd, $J = 13.7, 10.1, 5.5$ Hz, 1H), 2.19 (dt, $J = 19.3, 7.3$ Hz, 1H), 1.96 (s, 3H), 1.92–1.86 (m, 1H), 1.86 (s, 3H), 1.78 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H), 1.68–1.61 (m, 1H), 1.59 (s, 3H), 1.58–1.52 (m, 2H), 1.50 (s, 3H), 1.41–1.34 (m, 2H), 1.33–1.26 (m, 2H), 1.25–1.16 (m, 2H), 1.15–1.07 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H), 0.81 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 205.2, 194.5, 184.9, 168.6, 167.7, 166.2, 165.4, 163.4, 157.8, 157.7, 127.3, 127.0, 119.7, 82.7, 79.6, 79.2, 71.5, 59.7, 44.0, 33.0, 32.0, 31.2, 27.7, 25.4, 23.4, 23.0, 22.9, 22.9, 21.6, 20.7, 20.0, 19.9, 14.3, 14.1, 10.7, 10.6$; HR-MS (MALDI): calcd for $C_{36}H_{48}O_{12}Na$ $[M + Na^+]$: 695.3038, found: 695.3013

13: $R_f = 0.38$ (silica gel, dichloromethane/methanol 19/1); IR (film): $\tilde{\nu}_{max} = 2933, 1790, 1619, 1558, 1415, 1349, 1224, 1095, 948\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 16.95$ (s, 1H), 7.48 (dd, $J = 14.5, 10.9$ Hz, 1H), 6.19–6.11 (m, 1H), 5.74 (d, $J = 14.4$ Hz, 1H), 5.72–5.64 (m, 1H), 2.77 (dd, $J = 12.2, 8.3$ Hz, 1H), 2.08 (dd, $J = 17.5, 8.3$ Hz, 1H), 2.05 (s, 3H), 1.90 (dd, $J = 17.5, 12.2$ Hz, 1H), 1.53 (d, $J = 7.0$ Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 189.9, 175.2, 168.7, 163.9, 140.2, 137.7, 131.1, 119.4, 110.9, 101.7, 84.0, 41.5, 36.4, 23.9, 18.6, 7.8$; HR-MS (MALDI): calcd for $C_{16}H_{18}O_5Na$ $[M + Na^+]$: 313.1052, found: 313.1063

diphenylseleninic acid anhydride.[13] The proposed pathway from **7a** to **1** was supported by NMR studies. Thus, when the above experiment was carried out in an NMR tube using $[D_8]$THF and D_2O, the ^1H NMR signals of the rapidly formed deep orange solution revealed the presence of two distinct quinolates and the absence of **1** until acidification, whereupon the resonances corresponding to **1** appeared. These observations suggested the possibility of converting **7a** into **1** directly by acid hydrolysis of the acetate group. Indeed this was proven to be the case, whereby treatment of **7a** with concentrated HCl in THF produced **1** in 43 % yield. Again a ^1H NMR experiment proved the fleeting nature of quinols **8a** and **8b**, while it nicely allowed the monitoring of the appearance of **1** at the expense of **7a** during the course of two hours.

Interestingly, when the saponification of **7a** was carried out with KOH (10 equiv) in a minimum amount of THF/H_2O (10/1), a different product was formed, together with only a small amount of the previously obtained **1** (Scheme 2). Although the major product according to thin-layer chromatography (TLC, ca. 65 % crude yield), the new compound proved labile on silica gel and could only be isolated in pure form by flash column or preparative thin layer chromatography, and the yield was much lower. The physical properties of the new compound were suggestive of the dimeric structure **10**. Further support for this structure was obtained by hydrogenation of the side chains (H_2, 10 % Pd/C, EtOAc, 81 %) and acetylation of the resulting compound (**11**; Ac_2O, 4-DMAP, 80 %) to furnish tetraacetate **12**, whose structure was fully established by ^1H, ^{13}C, $^1H-^1H$ COSY, HMQC, and



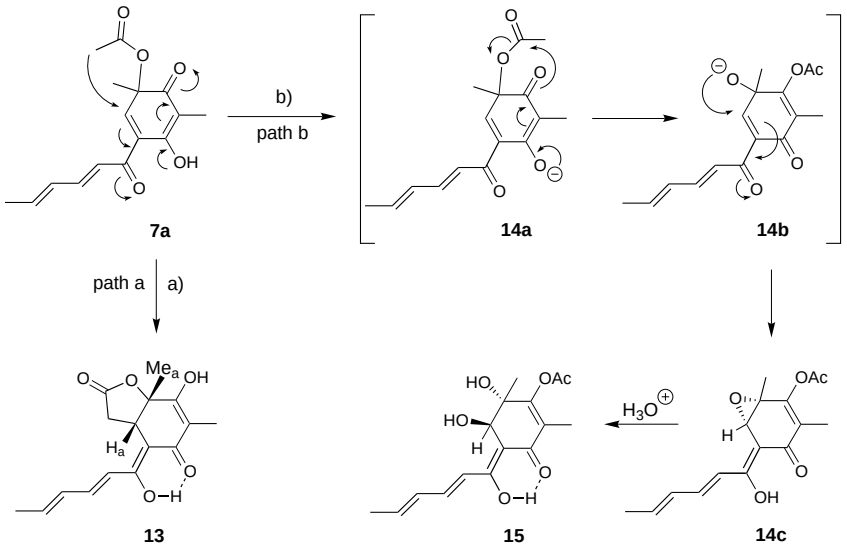
Scheme 2. Synthesis of sorbicillin dimer **10** from acetate **7a**. a) KOH (10 equiv), THF/H_2O (10/1), 0 °C, 2 h; b) 1N aq. HCl, 65% (crude yield); c) H_2, 10% Pd/C, EtOAc, 25 °C, 2 h, 81%; d) Ac_2O (10 equiv), 4-DMAP (0.1 equiv), EtOAc, 25 °C, 2 h, 80%. nOes observed for **12**: Me_a/H_a (4.5%), H_a/H_b (3.9%), and H_b/Me_b (3.0%). 4-DMAP = 4-(dimethylamino)pyridine.

HMBC NMR spectroscopic techniques. Particularly useful in defining the configuration of **12** were the nOes observed, in a 1D nOe experiment, for the following protons: Me_a/H_a (4.5%); H_a/H_b (3.9%); H_b/Me_b (3.0%). A mechanistic rationale for the formation of **10** from **7a** is presented in Scheme 2. Thus, it is reasoned that the initially formed dianion **9** rearranges by an intramolecular Michael reaction to an epoxy dianion (not shown), which attacks a second molecule of **9** in an intermolecular Michael reaction, generating in the process a quaternary center; the observed product **10** is formed upon acidification.

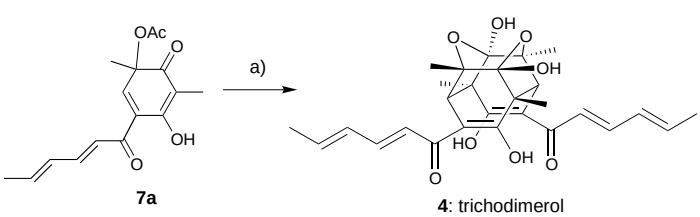
In another series of experiments, we attempted to force acetate **7a** into entering pathways that may lead to other bisorbicillinoids. Thus, while reaction of **7a** with LiHMDS at $-78 \rightarrow 25$ °C produced only the orange lithium enolate, treatment of **7a** with excess KHMDS (3.0 equiv) in anhydrous THF at -78 °C produced first a red solution and subsequently, upon acidification, the yellow γ-lactone **13** (60% yield, Scheme 3). When the same reaction was performed with 0.9 equiv of KHMDS at -78 °C, a yellow solution (presumably of the enolate anion) was initially formed, and after stirring at 25 °C for 12 h followed by aqueous workup, the yellow and rather labile *trans*-diol **15** was isolated. Mechanistically, these events can be rationalized by assuming enolate-induced cascade reactions. Thus, for the formation of **13**, acetate **7a** is required to undergo rearrangement of its quinol moiety to form its acetate enolate before collapsing, by an intramolecular Michael addition, on its enone system (Scheme 3, path a). With less than one equivalent of base, **7a** follows a different pathway (path b) initiated by the formation of its quinolate **14a**. Thus, rearrangement of quinolate **14a** followed by acetate migration leads to alkoxy anion **14b**, which undergoes an intramolecular Michael addition to the enone system to form epoxide **14c**. Stereoselective epoxide opening by a molecule of water furnishes diol **15**.[14]

The prospect of generating trichodimerol (**4**) from acetate **7a** was finally realized when we altered the method of quenching the corresponding monomeric diquinolate (Scheme 4). Thus, treatment of **7a** with $CsOH \cdot H_2O$ for 7 h followed by addition of powdered $NaH_2PO_4 \cdot H_2O$ and stirring at 25 °C for 12 h furnished **4**, which was isolated in 16% yield after column chromatography together with **3** (12%) and **1** (22%). Synthetic **4** (racemic) exhibited identical spectroscopic properties to that reported by Ayer et al.[4a, 15] The very slow neutralization of this reaction is crucial for the extraordinary dimerization of acetate **7a**.[16]

Finally, the hypothesis put forward by Abe et al.[3] for the biosynthesis of bisorbibutenolide (**2**) and bisorbicillinolide (**5**) from bissorbicillinol (**1**) was investigated. Indeed, when a solution of **1** in THF was treated with one equivalent of KHMDS at ambient temperature, a more polar compound was formed (80% yield) whose structure was established to be that of bisorbibutenolide (**2**) by spectroscopic means and



Scheme 3. Transformations of acetate **7a**. a) KHMDS (3.0 equiv), THF, -78 °C, 2 h, 60%; b) KHMDS (0.9 equiv), THF, $-78 \rightarrow 25$ °C, 2 h: then 25 °C, 12 h, 35%. nOes observed for **13**: Me_a/H_a (1.8%). KHMDS = potassium salt of 1,1,1,3,3,3-hexamethyldisilazane.



Scheme 4. Biomimetic total synthesis of trichodimerol (**4**) from acetate **7a**. a) $CsOH \cdot H_2O$ (10 equiv), MeOH, 25 °C, 7 h; then $NaH_2PO_4 \cdot H_2O$, 25 °C, 12 h, 16% **4**, 12% sorbicillin (**3**) and 22% bisorbicillinol (**1**).

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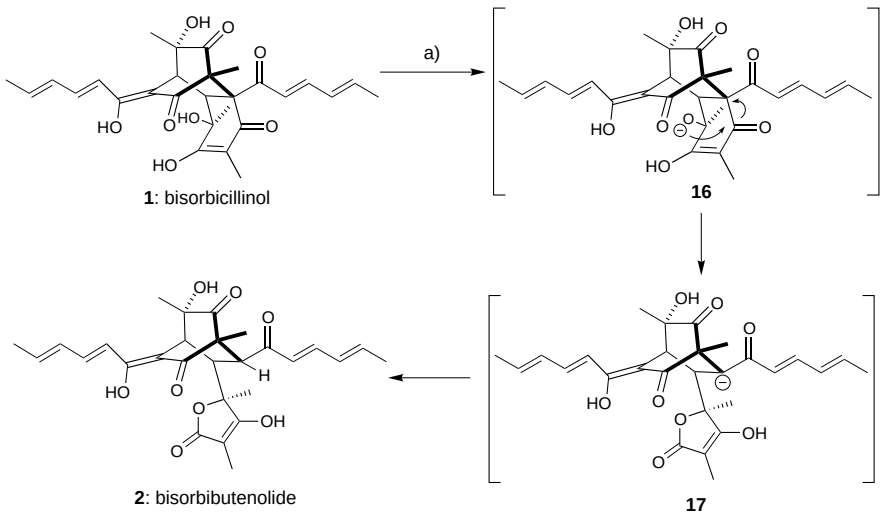

Scheme 5. Biomimetic synthesis of bisorbibutenolide (**2**) from bisorbicillinol (**1**). a) KHMDS (1.1 equiv), THF, 25 °C, 24 h; then 1N aq. HCl, 80 %.

comparison of its ^{1}H and ^{13}C NMR spectra with those of the naturally occurring compound (Scheme 5).[11] Interestingly, bisorbicillinolide (**5**) was not observed in this reaction.

The findings described herein—including the total synthesis of bisobicillinol (**1**), bisorbibutenolide (**2**), and trichodimerol (**4**)—shine light on the chemistry of the bisorbicillinoids and confirm a number of hypothetical proposals regarding their biosynthesis. Furthermore, the novel synthetic pathways elucidated during this study add to the repertoire of cascade reactions as an enabling technology for complex molecule construction, while the unusual molecular frameworks produced enrich our pool of advanced synthetic intermediates and building blocks.

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[8] A previous proposal regarding the biosynthesis of bisvertinol (**6**) from sorbicillin postulates a different pathway, in which an initial epoxidation of sorbicillin followed by reduction and then dimerization and ketalization is believed to be involved.[7]

[9] W. Baker, H. F. Bondy, J. F. W. McOmie, H. R. Tunnicliff, *J. Chem. Soc.* **1949**, 2834 – 2835.

[10] J. F. W. McOmie, M. S. Tute, *J. Chem. Soc.* **1958**, 3226 – 3227. This method was found to be superior on larger scale to the procedure described by the Sartori group; see F. Bigi, G. Casiraghi, G. Casnati, S. Marchesi, G. Sartori, C. Vignali, *Tetrahedron* **1984**, *40*, 4081 – 4084.

[11] We thank Dr. N. Abe of the University of Shizuoka for kindly providing us with the ^{1}H and ^{13}C NMR spectra of bisorbicillinol (**1**) and bisorbibutenolide (**2**).

[12] The acetate **7a** did not give any Diels – Alder product **1** when heated in benzene or in AcOH for several hours.

[13] a) D. H. R. Barton, P. D. Magnus, M. N. Rosenfeld, *J. Chem. Soc. Chem. Commun.* **1975**, 301 – 301; b) D. H. R. Barton, P. D. Magnus, J. C. Quinney, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1610 – 1614; see also: E. Adler, K. Holmberg, *Acta. Chem. Scand. Ser. B* **1974**, *28*, 465 – 472.

[14] Attempts to induce **7a** to react under Lewis acid catalysis conditions were also made. Interestingly, when **7a** was exposed to TBSOTf or TMSOTf, **3** was the major product formed together with small amounts of **1**. TBS = *tert*-butyldimethylsilyl, Tf = trifluormethanesulfonyl, TMS = trimethylsilyl.

[15] Trichodimerol (**4**) was unavailable to us for direct comparison.

[16] For the first synthesis of enantiomerically pure trichodimerol by dimerization of resolved acetate **7a**, see D. Barnes-Seeman, E. J. Corey, *Org. Lett.* **1999**, *1*, 1503 – 1504.

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