Total Synthesis

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Biomimetic Synthesis of the Calcineurin Phosphatase Inhibitor Dibefurin**

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Abstract: *Dibefurin is a C_i-symmetric natural product that acts as an inhibitor of calcineurin phosphatase. A six-step synthesis of this compound is reported, which features an oxidative dimerization of the aromatic polyketide epicoccine as the key step. Dibefurin is proposed to be related to epicolactone, a complex yet racemic fungal metabolite that has recently been discovered. Attempts to access epicolactone from epicoccine and epicoccone B resulted in an unusual dimer that is formed through a hetero-Diels–Alder reaction of a para-quinone methide with an ortho-quinone.*

The oxidative coupling of phenolic compounds accounts for the formation of intriguing natural products that have inspired synthetic chemists for decades.[1,2] A particularly interesting mode of this reactivity is provided by pyrogallols. Oxidation of two adjacent phenolic hydroxyl groups in these molecules provides an *ortho*-quinone that is also a cyclic dienol. This combination of electrophilic and nucleophilic motifs, which are also able to undergo concerted cycloadditions, allows the effective formation of dimers, such as purpurogallin, through intricate cascade reactions (Figure 1 A).[3,4]

Pyrogallols are commonly found in plants as esters of the shikimic acid derivative gallic acid.[5] They also occur in fungi, where they are usually more highly substituted and are derived from polyketide pathways.[6] The endophytic fungus *Epicoccum* sp., for instance, is known to produce a variety of bioactive metabolites of this class, the best-known of which is flavipin (Figure 1 B).[7] Several heterocyclic derivatives of flavipin, such as epicoccine or epicoccone A and B,[8] as well as dimeric congeners, such as epicoccolides A and B or epicocconigrone A, have also been described.[9] Recently, Marsaioli and co-workers isolated epicolactone from *Epicoccum nigrum*, which dwells as an endophyte in sugarcane.[10]

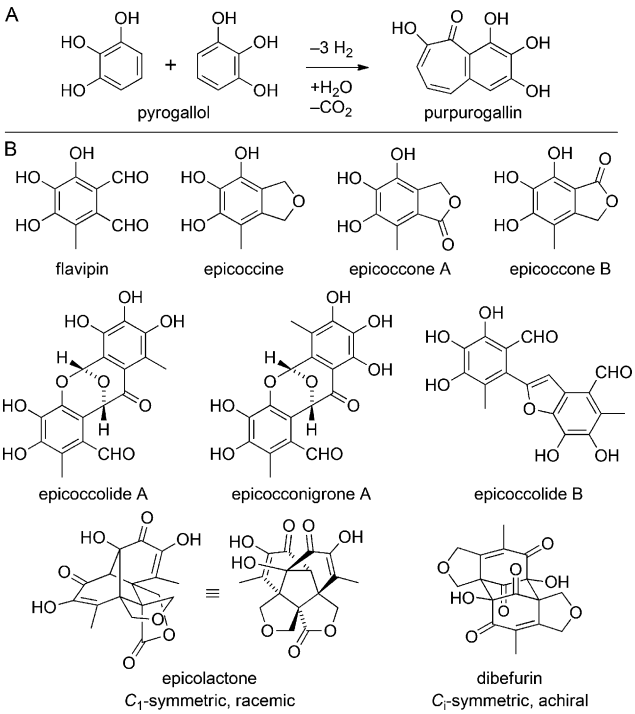

Figure 1. A) Pyrogallol and its oxidative dimerization to purpurogallin. B) Fungal pyrogallols and their dimers.

Laatsch and co-workers subsequently reported that this compound also occurs in an *Epicoccum* species associated with the cocoa tree.[9a] Epicolactone exhibits an unprecedented pentacyclic structure that contains five contiguous stereocenters, three of which are quaternary. Despite its high degree of stereochemical complexity, it was isolated as a racemate in both cases.

Dibefurin is an intriguing pentacyclic natural product that is achiral (Figure 1 B).[11] Although isolated from a different fungal source, it shows certain structural resemblance to the natural products isolated from *Epicoccum*. Bearing an inversion center, dibefurin belongs to the molecular point group C_i, which is rare amongst natural products.[12] By contrast, C_2 symmetry is frequently encountered in fungal metabolites, for instance in the phenolic dimers (+)-rugulosin[13] and (−)-trichodimerol.[2a,b,14]

Further increasing its attractiveness as a synthetic target, dibefurin shows remarkable biological activity.[11] It has been identified as an inhibitor of calcineurin, a phosphatase that is critically involved in the activation of T lymphocytes (IC_{50} = 44 μM).[15] As opposed to well-established immunosuppressants, such as cyclosporin A or FK-506, it does not exert its action through ternary immunophilin complexes,[16] but

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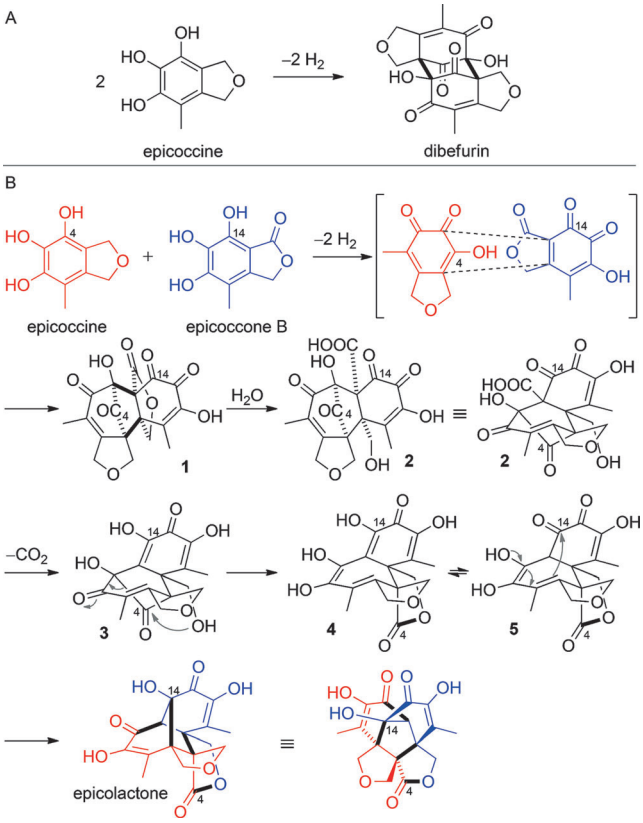
inhibits the enzyme directly. Despite the therapeutic potential and uncommon structure of dibefurin, its synthesis has not been reported to date and the details of its biosynthetic origin and chemical properties have not been published.

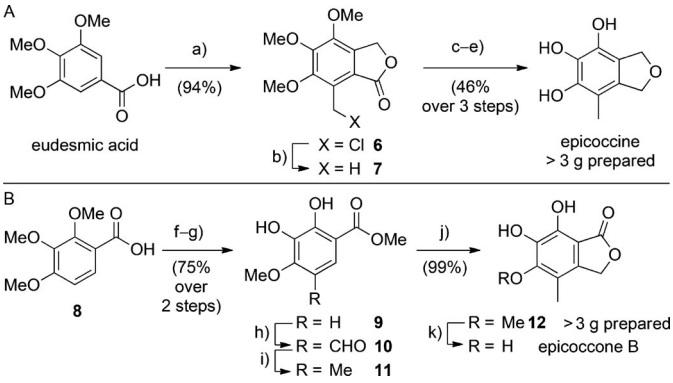
We propose that both dibefurin and epicolactone are biosynthesized from the pyrogallol epicoccine through oxidative dimerizations. Dibefurin could be formed by two-electron oxidation, followed by homodimerization (Scheme 1 A). Conversely, we hypothesize that epicolactone stems



Scheme 1. A) Proposed biosynthetic connection between epicoccine and dibefurin. B) Proposed biosynthesis of epicolactone.

from a non-enzymatic oxidative heterodimerization of epicoccine with epicoccone B (Scheme 1 B). In a step resembling the formation of purpurogallin, this would initially give a dimer of type **1**, which would then undergo lactone opening by water to give carboxylic acid **2**. An ensuing decarboxylation of the β-keto acid would yield tetracycle **3**. Nucleophilic attack by the primary hydroxy group on the bridging carbonyl (C4), followed by a retro-Dieckmann-type cleavage, would result in the formation of lactone **4**. Finally, vinylogous aldol addition to the C14-keto tautomer **5** would yield epicolactone.

To explore these biosynthetic connections, we devised a reliable synthesis of the electron-rich hexasubstituted benzene derivatives epicoccine and epicoccone B (Scheme 2). Eudesmic acid was converted into isobenzofuranone **6** under chloromethylation conditions in excellent yield.[17] Subsequent dechlorination afforded compound **7**. Two-step reduction of lactone **7** with DIBAL followed by

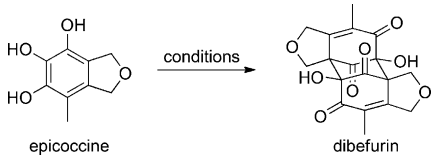


Scheme 2. A) Total synthesis of epicoccine. B) Total synthesis of epicoccone B. a) conc. HCl, formalin, 140 °C, 94 %; b) Zn, THF/ aq KH_2PO_4, 85 %; c) DIBAL, CH_2Cl_2, −60 °C; d) Et_3SiH, TFA, CH_2Cl_2, 0 °C to RT, 58 % over 2 steps; e) BBr_3, CH_2Cl_2, −78 °C to RT, 80 %; f) BCl_3, CH_2Cl_2, 0 °C to RT, 76 %; g) conc. H_2SO_4, MeOH, reflux, 98 %; h) TFA, hexamethylenetetramine, 80 °C, 94 %; i) 10 mol % Pd/C, H_2 (balloon), THF/4 M HCl, 92 %; j) $(HCHO)_n$, 40 % H_2SO_4, dioxane, 80 °C, 99 %; k) BBr_3, CH_2Cl_2, −78 °C to RT, 72 %; DIBAL = diisobutylaluminium hydride, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

TFA and triethylsilane, and subsequent global demethylation with boron tribromide smoothly furnished epicoccine. This sequence gave access to the natural product in multigram quantities. Epicoccone B was synthesized starting from 2,3,4-trimethoxybenzoic acid (**8**), which was selectively demethylated using boron trichloride[18] and esterified to afford methyl ester **9** (Scheme 2 B). Installation of the required methyl group was achieved by Duff formylation to give aldehyde **10**, followed by catalytic hydrogenation under strongly acidic conditions to furnish catechol **11**. Hydroxymethylation with paraformaldehyde yielded lactone **12**, which was converted into epicoccone B through carefully controlled demethylation.

With large amounts of epicoccine in hand, we turned our attention to its oxidative homodimerization (Table 1). Reactions of this type have been previously observed with simple and symmetric pyrogallol and phloroglucinol derivatives.[19] Exposing epicoccine to *ortho*-chloranil or DDQ failed to yield dibefurin (entries 1,2). However, the use of excess Frémy's salt afforded our target compound in modest yield (entry 3). Oxidants based on Mn^{IV}, Ag^{I}, Ag^{II}, Ce^{IV}, or iron trichloride either led to decomposition or gave trace amounts of dibefurin (entries 4–8). Gratifyingly, treatment of epicoccine with potassium ferricyanide under mildly basic conditions provided dibefurin in good yield (entry 9). Purification of the natural product posed a significant challenge owing to its insolubility in most solvents. Furthermore, the formation of a regioisomer of dibefurin, observed under all successful conditions (entries 3, 5, 9, 10), complicated isolation of the pure natural product (see the Supporting Information). However, we were able to obtain pure dibefurin in 49 % yield after repeated trituration with THF. We also tested the reactivity of epicoccine with oxygen as the terminal oxidant (entry 10). Whereas dibefurin was formed in negligible amounts in the presence of catalytic Cu^{II}, Zn^{II}, or Mn^{II}

Table 1: Selection of tested conditions for the oxidative dimerization of epicoccine to dibefurin (for the complete table, see the Supporting Information).



epicoccine dibefurin

Entry	Oxidant	Additive (equiv)	Yield by ^{1}H NMR [%][a]	Yield[b] [%]
1	*o*-chloranil	–	decomp.	–
2	DDQ	–	–	–
3	Frémy's salt	–	42	25
4	MnO_2	–	decomp.	–
5	Ag_2O	–	30	n.d.[c]
6	AgO	aq HNO_3	decomp.	–
7	CAN	–	decomp.	–
8	$FeCl_3 \cdot 6H_2O$	$NaHCO_3$ (2.0)	–	–
9	**$K_3[Fe(CN)_6]$**	**$NaHCO_3$ (2.0)**	**62**	**49**
10	O_2 (balloon)	$FeSO_4 \cdot 7H_2O$ (0.1)	31	23

[a] Internal standard: 1,3,5-trimethoxybenzene. [b] Yield of isolated product. [c] Purification procedure not applicable. *o*-Chloranil = 3,4,5,6-tetrachloro-1,2-benzoquinone, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, Frémy's salt = potassium nitrosodisulfonate, CAN = ceric ammonium nitrate.

metal salts, exposure of epicoccine to catalytic amounts of Fe^{II} in an aqueous solution under oxygen atmosphere gave dibefurin in 23% yield (31% based on ^{1}H NMR). These results suggest that dibefurin could be formed spontaneously from epicoccine, that is, without enzymatic catalysis under fermentation conditions.

The spectra of synthetic dibefurin were in full agreement with those reported in the literature.[11] Structural confirmation by single-crystal X-ray analysis provided interesting insights into the supramolecular chemistry of the natural product (Figure 2). In the solid state, dibefurin forms linear

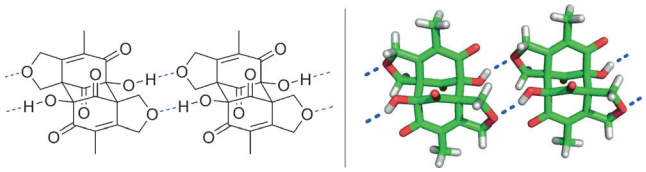
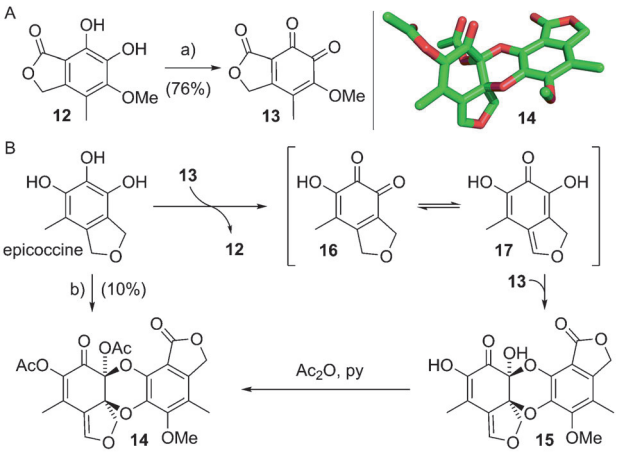


Figure 2. The hydrogen-bonding network of dibefurin in the solid state.[20]

rods held together by strong hydrogen-bonding interactions. Each molecule serves as a two-fold hydrogen-bond donor and acceptor. The rods assemble through hydrophobic interactions to form extended sheets, which stack in the crystal. This arrangement accounts for the insolubility of dibefurin in most organic solvents and its low solubility in aqueous solution.

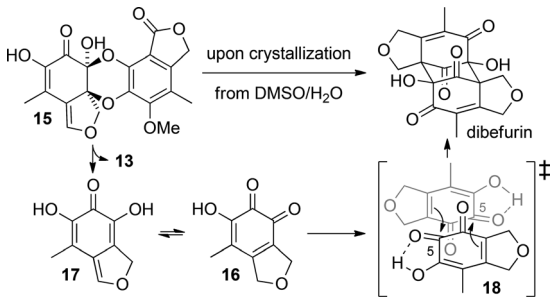
Having identified efficient conditions for the synthesis of dibefurin, we next explored oxidative heterodimerizations en route to epicolactone. Exposure of epicoccine and epicoccone B to various oxidants led to the exclusive formation of dibefurin and re-isolation of unreacted epicoccone B. In order to effect the desired heterodimerization, we therefore used oxidized versions of epicoccone B as dimerization partners. Since the isolation of epicoccone B *ortho*-quinone was not successful, we turned to selectively protected analogues. To this end, epicoccone B methyl ether **12** was exposed to *ortho*-chloranil, which gave *ortho*-quinone **13** in good yield (Scheme 3A). The reaction of epicoccine with **13** gave a labile heterodimer, the diacetate of which (**14**) afforded crystals suitable for X-ray analysis (Scheme 3B).[21] Thus, the initial heterodimer was pentacyclic dihydrobenzodioxine **15**.



Scheme 3. A) Oxidation of lactone **12**. B) Dimerization of epicoccine and *ortho*-quinone **13**. H atoms are omitted for clarity in the X-ray structure of **14**.[20] a) *o*-Chloranil, Et_2O, 76%; b) **13** (2 equiv), dioxane, RT; Ac_2O, py, CH_2Cl_2, 10% over 2 steps; Ac_2O = acetic anhydride, py = pyridine.

Mechanistically, we interpret the formation of **15** as follows: After initial oxidation of epicoccine by *ortho*-quinone **13**, the resultant *ortho*-quinone **16** undergoes tautomerization to the *para*-quinone methide **17**.[22] Quinone methide **17** then engages in a Diels–Alder reaction with the second equivalent of *ortho*-quinone **13** to afford the intriguing heterodimer **15**. To the best of our knowledge, **15** constitutes the first Diels–Alder heterodimer involving two different pyrogallols.[23] Whereas *ortho*-quinones are known heterodienes, oxidative dimerizations of pyrogallols through [4+2]-cycloadditions are rare and none of these appear to involve quinone methides as the dienophile.[24] The formation of other regioisomers in the hetero-Diels–Alder reaction that decompose upon aqueous workup or under the acetylation conditions cannot be ruled out.

Interestingly, attempts to purify dihydrobenzodioxine **15** by recrystallization resulted in the formation of dibefurin (Scheme 4). Decomposition of **15** through retro-hetero-Diels–Alder reaction presumably yielded *para*-quinone methide **17**, which was again in equilibrium with its *ortho*-quinone tautomer **16** (Scheme 4). This could undergo dimerization via transition state **18**. According to this proposal, the carbonyl groups at C5 are electrophilically activated by an



Scheme 4. Formation of dibefurin through retro-Diels–Alder reaction and dimerization of the resultant hydroxy *ortho*-quinone **16**.

intramolecular hydrogen bond while simultaneously acting as a base to increase the nucleophilicity of the adjacent dienol. This would result in a potentially concerted double aldol addition to generate the pentacyclic framework of dibefurin in a single step. Whether the direct oxidative dimerization of epicoccine to dibefurin (Table 1) proceeds via transition state **18** or involves radical intermediates remains to be determined.

In conclusion, we have achieved the first total synthesis of the C_i-symmetric calcineurin phosphatase inhibitor dibefurin through oxidative dimerization of epicoccine in six steps. Investigation of the oxidative heterodimerization of epicoccine and epicoccone B yielded a novel hetero-Diels–Alder product, which, despite its instability, may well be isolated from cultures of the fungus *Epicoccum* sp. in the future. Our studies on the biomimetic synthesis of epicolactone along our biosynthetic hypothesis are ongoing and will be reported in due course.

Experimental Section

Epicoccine (50 mg, 0.27 mmol) was suspended in MeCN (2.0 mL) and cooled to 0 °C. A solution of $K_3[Fe(CN)_6]$ (181 mg, 0.550 mmol, 2.0 equiv) and $NaHCO_3$ (46 mg, 0.55 mmol, 2.0 equiv) in H_2O (4.0 mL) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C and the precipitate was separated by centrifugation (4000 rpm, 15 min, 10 °C). The aqueous phase was decanted, crude dibefurin triturated with THF (1 mL), and the suspension centrifuged (11 000 rpm, 5 min). The trituration was repeated twice to afford dibefurin as a colorless solid. The combined THF phases were concentrated under reduced pressure and the remaining solid was again triturated according to the above procedure to afford a second batch of dibefurin as a colorless solid (combined yield: 24 mg, 49 %).

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[1] For reviews: a) T. Wezeman, K.-S. Masters, S. Bräse, *Angew. Chem. Int. Ed.* **2014**, *53*, 4524 – 4526; *Angew. Chem.* **2014**, *126*, 4612 – 4614; b) S. P. Roche, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068 – 4093; *Angew. Chem.* **2011**, *123*, 4154 – 4179; c) L. F. Silva, Jr., B. Olofsson, *Nat. Prod. Rep.* **2011**, *28*, 1722 – 1754; d) L. Pouységu, T. Sylla, T. Garnier, L. B. Rojas, J. Charris, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 5908 – 5917.

[2] For selected syntheses involving oxidation of phenolic compounds: a) K. C. Nicolaou, K. B. Simonsen, G. Vassilikogiannakis, P. S. Baran, V. P. Vidali, E. N. Pitsinos, E. A. Couladouros, *Angew. Chem. Int. Ed.* **1999**, *38*, 3555 – 3559; *Angew. Chem.* **1999**, *111*, 3762 – 3766; b) K. C. Nicolaou, G. Vassilikogiannakis, K. B. Simonsen, P. S. Baran, Y.-L. Zhong, V. P. Vidali, E. N. Pitsinos, E. A. Couladouros, *J. Am. Chem. Soc.* **2000**, *122*, 3071 – 3079; c) C. Li, E. Lobkovsky, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2000**, *122*, 10484 – 10485; d) C. Li, R. P. Johnson, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2003**, *125*, 5095 – 5106; e) C. Qi, H. Cong, K. J. Cahill, P. Müller, R. P. Johnson, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2013**, *52*, 8345 – 8348; *Angew. Chem.* **2013**, *125*, 8503 – 8506; f) S. A. Snyder, F. Kontes, *J. Am. Chem. Soc.* **2009**, *131*, 1745 – 1752; g) S. A. Snyder, T. C. Sherwood, A. G. Ross, *Angew. Chem. Int. Ed.* **2010**, *49*, 5146 – 5150; *Angew. Chem.* **2010**, *122*, 5272 – 5276; h) A. Bérubé, I. Drutu, J. L. Wood, *Org. Lett.* **2006**, *8*, 5421 – 5424; i) L. Pouységu, S. Chassaing, D. Dejugnac, A.-M. Lamidey, K. Miqueu, J.-M. Sotiropoulos, S. Quideau, *Angew. Chem. Int. Ed.* **2008**, *47*, 3552 – 3555; *Angew. Chem.* **2008**, *120*, 3608 – 3611; j) J. Gagnepain, F. Castet, S. Quideau, *Angew. Chem. Int. Ed.* **2007**, *46*, 1533 – 1535; *Angew. Chem.* **2007**, *119*, 1555 – 1557; k) Q. Yang, J. T. Njardarson, C. Draghici, F. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 8648 – 8651; *Angew. Chem.* **2013**, *125*, 8810 – 8813; l) S. Akai, K. Kakiguchi, Y. Nakamura, I. Kuriwaki, T. Dohi, S. Harada, O. Kubo, N. Morita, Y. Kita, *Angew. Chem. Int. Ed.* **2007**, *46*, 7458 – 7461; *Angew. Chem.* **2007**, *119*, 7602 – 7605.

[3] For a review on tropolones, including benzotropolones: R. Bentley, *Nat. Prod. Rep.* **2008**, *25*, 118 – 138.

[4] For studies on purpurogallin: J. Salfeld, *Angew. Chem.* **1957**, *69*, 723 – 724; L. Horner, S. Göwecke, W. Dürckheimer, *Chem. Ber.* **1961**, *94*, 1276 – 1291; W. Dürckheimer, E. F. Paulus, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 224 – 225; *Angew. Chem.* **1985**, *97*, 219 – 220.

[5] P. M. Dewick, *Medicinal Natural Products*, *3rd ed.*, Wiley, Chichester, **2009**, Chap. 3 – 4.

[6] a) C. Hertweck, *Angew. Chem. Int. Ed.* **2009**, *48*, 4688 – 4716; *Angew. Chem.* **2009**, *121*, 4782 – 4811; b) R. B. Herbert, *The Biosynthesis of Secondary Metabolites*, *2nd ed.*, Chapman&Hall, London, **1989**, Chap. 3.

[7] P. C. Bamford, G. L. F. Norris, G. Ward, *Trans. Br. Mycol. Soc.* **1961**, *44*, 354 – 356.

[8] a) Y. Ishikawa, T. Ito, K. H. Lee, *J. Jpn. Oil Chem. Soc.* **1996**, *45*, 1321 – 1326; b) A. Abdel-Lateff, K. M. Fisch, A. D. Wright, G. M. König, *Planta Med.* **2003**, *69*, 831 – 834; c) H. V. K. Wangun, K. Ishida, C. Hertweck, *Eur. J. Org. Chem.* **2008**, 3781 – 3784.

[9] a) F. M. Talontsi, B. Dittrich, A. Schüffler, H. Sun, H. Laatsch, *Eur. J. Org. Chem.* **2013**, 3174 – 3180; b) M. El Amrani, D. Lai, A. Debbab, A. H. Aly, K. Siems, C. Seidel, M. Schnekenburger, A. Gaigneaux, M. Diederich, D. Feger, W. Lin, P. Proksch, *J. Nat. Prod.* **2014**, *77*, 49 – 56.

[10] F. D. da Silva Araújo, L. C. de Lima Fávaro, W. L. Araújo, F. L. de Oliveira, R. Aparicio, A. J. Marsaioli, *Eur. J. Org. Chem.* **2012**, 5225 – 5230.

[11] a) G. M. Brill, U. Premachandran, J. P. Karwowski, R. Henry, D. K. Cwik, L. M. Traphagen, P. E. Humphrey, M. Jackson, J. J. Clement, N. S. Burres, S. Kadam, R. H. Chen, J. B. McAlpine, *J. Antibiot.* **1996**, *49*, 124 – 128; b) Dibefurin was isolated from a fungus of phylum Basidiomycota; *Epicoccum* belongs to the phylum Ascomycota (personal communication with Dr. George S. Sheppard, AbbVie).

[12] Other C_i-symmetric natural products are truxillic acid derivatives: a) M. Krauze-Baranowska, *Acta Pol. Pharm.* **2002**, *59*, 403 – 410; b) A. Sergeiko, V. V. Poroikov, L. O. Hanuš, V. M.

Dembitsky, *Open Med. Chem. J.* **2008**, *2*, 26 – 37; c) K. L. Dhar, S. Shah, A. Prabhakar, R. L. Sharma, *Fitoterapia* **1995**, *66*, 390 – 392; d) R. B. Filho, M. P. de Souza, M. E. O. Mattos, *Phytochemistry* **1981**, *20*, 345 – 346; e) A. I. Hamed, I. Springuel, N. A. El-Emary, H. Mitome, Y. Yamada, *Phytochemistry* **1997**, *45*, 1257 – 1261.

[13] For isolation of rugulosin: a) J. C. Bouhet, P. P. Van Chuong, F. Toma, M. Kirszenbaum, P. Fromageot, *J. Agric. Food Chem.* **1976**, *24*, 964 – 972; for synthesis of rugulosin, see: b) K. C. Nicolaou, Y. H. Lim, C. D. Papageorgiou, J. L. Piper, *Angew. Chem. Int. Ed.* **2005**, *44*, 7917 – 7921; *Angew. Chem.* **2005**, *117*, 8131 – 8135; c) D.-M. Yang, U. Sankawa, Y. Ebizuka, S. Shibata, *Tetrahedron* **1976**, *32*, 333 – 335.

[14] For isolation of trichodimerol: a) R. Andrade, W. A. Ayer, P. P. Mebe, *Can. J. Chem.* **1992**, *70*, 2526 – 2535; for synthesis of trichodimerol, see references [2a,b], as well as: b) D. Barnes-Seeman, E. J. Corey, *Org. Lett.* **1999**, *1*, 1503 – 1504.

[15] F. Rusnak, P. Mertz, *Physiol. Rev.* **2000**, *80*, 1483 – 1521.

[16] K. A. Jørgensen, P. B. Koefoed-Nielsen, N. Karamperis, *Scand. J. Immunol.* **2003**, *57*, 93 – 98.

[17] F. E. King, T. J. King, *J. Chem. Soc.* **1942**, 726 – 727.

[18] A. Yanagisawa, M. Taga, T. Atsumi, K. Nishimura, K. Ando, T. Taguchi, H. Tsumuki, I. Chujo, S. Mohri, *Org. Process Res. Dev.* **2011**, *15*, 376 – 381.

[19] a) H. Erdtman, G. Moussa, M. Nilsson, *Acta Chem. Scand.* **1969**, *23*, 2515 – 2518; b) H.-J. Teuber, M. Dietrich, *Chem. Ber.* **1967**, *100*, 2908 – 2917.

[20] CCDC 1022042 (dibefurin) and CCDC 1022044 (**14**) 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.

[21] Two equivalents of **13** were employed, one for sacrificial oxidation and the other for the desired dimerization.

[22] Related tautomerizations of quinones to quinone methides have been described: a) A. Takuwa, H. Iwamoto, O. Soga, K. Maruyama, *J. Chem. Soc. Perkin Trans. 1* **1986**, 1627 – 1631; b) A. I. Poddel′sky, A. V. Piskunov, N. O. Druzhkov, G. K. Fukin, V. K. Cherkasov, G. A. Abakumov, *Z. Anorg. Allg. Chem.* **2009**, *635*, 2563 – 2571; c) J. T. Lowe, J. S. Panek, *Org. Lett.* **2008**, *10*, 3813 – 3816; d) J.-P. Lumb, D. Trauner, *J. Am. Chem. Soc.* **2005**, *127*, 2870 – 2871; e) J.-P. Lumb, D. Trauner, *Org. Lett.* **2005**, *7*, 5865 – 5868; f) J.-P. Lumb, K. C. Choong, D. Trauner, *J. Am. Chem. Soc.* **2008**, *130*, 9230 – 9231; g) J.-P. Lumb, J. L. Krinsky, D. Trauner, *Org. Lett.* **2010**, *12*, 5162 – 5165; h) V. Sofiyev, J.-P. Lumb, M. Volgraf, D. Trauner, *Chem. Eur. J.* **2012**, *18*, 4999 – 5005.

[23] A homodimerization of a sterically encumbered pyrogallol derivative through Diels – Alder cycloaddition of the respective *ortho*-quinones has been reported: V. V. Tkachev, S. M. Aldoshin, G. V. Shilov, V. N. Komissarov, Y. A. Sayapin, M. S. Korobov, G. S. Borodkin, V. I. Minkin, *Russ. Chem. Bull. Int. Ed.* **2007**, *56*, 276 – 280.

[24] Intriguingly, a small number of diterpenoid and triterpenoid natural products are formed by hetero-Diels–Alder dimerization after oxidation of their catechol moiety: a) O. Shirota, H. Morita, K. Takeya, H. Itokawa, *Tetrahedron* **1995**, *51*, 1107 – 1120; b) A. G. González, N. L. Alvarenga, A. Estévez-Braun, A. G. Ravelo, I. L. Bazzocchi, L. Moujir, *Tetrahedron* **1996**, *52*, 9597 – 9608; c) A. G. González, N. L. Alvarenga, I. L. Bazzocchi, A. G. Ravelo, L. Moujir, *J. Nat. Prod.* **1999**, *62*, 1185 – 1187; d) N. E. Jacobsen, E. M. K. Wijeratne, J. Corsino, M. Furlan, V. D. S. Bolzani, A. A. L. Gunatilaka, *Bioorg. Med. Chem.* **2008**, *16*, 1884 – 1889; e) Y. Aoyagi, Y. Takahashi, Y. Satake, H. Fukaya, K. Takeya, R. Aiyama, T. Matsuzaki, S. Hashimoto, T. Shiina, T. Kurihara, *Tetrahedron Lett.* **2005**, *46*, 7885 – 7887.

