Biomimetic Total Synthesis of Bisorbicillinol, Bisorbibutenolide, Trichodimerol, and Designed Analogues of the Bisorbicillinoids

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Abstract: The bisorbicillinoids are a growing class of novel natural products endowed with unique biological activity and are associated with fascinating hypotheses for their biosynthesis. A full account of our biomimetic explorations toward the bisorbicillinoids including the total syntheses of bisorbicillinol (**1**), bisorbibutenolide (**2**), and trichodimerol (**4**) from sorbicillin (**3**) is disclosed. Utilizing the novel dimerization reactions discovered and fine-tuned en route to **1** and **4**, several analogues of these natural products have been synthesized. Furthermore, studies on the scope of these novel cycloaddition reactions and the isolation of a number of unexpected products along with proposed mechanisms for their formation are reported. These findings add to our knowledge of the largely unexplored chemistry of *o*-quinols and related aromatic systems.

Introduction

The dazzling mechanisms by which nature effortlessly knits together molecules often inspires biomimetic syntheses that not only lend credence to the proposed biosynthetic mechanisms but considerably advance synthetic organic chemistry. The bisorbicillinoids[1] (Figure 1) provide an exciting forum for explorations into such biosynthetic pathways and an opportunity to discover new chemistry through total synthesis.

Not surprisingly, this diverse class of structurally novel natural products, isolated from several species of fungi, is endowed with a broad range of biological activity. For instance, trichodimerol (**4**), isolated from three different sources (*Trichoderma longibrachiatum*,[2a] *Penicillium chrysogenun*,[2b] and *Trichoderma* sp. USF-2690[2c]), exhibits significant inhibitory activity against lipopolysaccharide-induced production of tumor necrosis factor α (TNF-α) in human monocytes and as such represents a new lead for a potential treatment of septic shock.[3] Bisvertinolone **7**,[4a] an oxidized form of bisvertinol (**6**),[4b] isolated from *Acremonium strictum*, is a novel antifungal agent which functions via inhibition of β-(1,6)-glucan biosynthesis.[4a] In addition, bisorbicillinol (**1**),[2c] bisorbibutenolide (**2**),[5] bisorbicillinolide (**5**),[5] and bisorbibetanone,[6] all isolated from the fermentation of *Trichoderma* sp. USF-2690, exhibit antioxidant properties.

Careful examination of these structurally related dodecaketides reveals that they could all potentially originate from the natural product sorbicillin (**3**, Figure 1).[7] The first member of this family, namely, 2′,3′-dihydrobisorbicillinol (**1a**), isolated by Dreiding et al. in 1983 from *Verticillium intertextum*, was postulated to arise from **3** and 2′,3′-dihydrosorbicillin after an enantioselective oxidation followed by [4 + 2] dimerization.[8] A similar mechanistic proposal was put forth by Abe et al. to explain the biosynthesis of the newly isolated bisorbicillinol (**1**, Figure 2).[5] The same group also advanced an elegant proposal for the biosynthesis of the soon thereafter isolated **2** and **5** via an anionic cascade rearrangement of **1** (Figure 2).[5] Sorbiquinol (**8**, Figure 1), isolated by Ayer and co-workers in 1996 from *T. longibrachiatum*, was postulated as the [4 + 2] adduct between the side-chain double bond of sorbicillin (dienophile) and the enantioselectively oxidized sorbicillin (diene).[9]

In 1999, we proposed a detailed mechanism for the formation of trichodimerol (**4**) from sorbicillin (**3**) by an oxidation−

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(1) The term bisorbicillinoids to describe all dimeric sorbicillin-derived natural products was recently introduced by us: Nicolaou, K. C.; Jautelat, R.; Vassilikogiannakis, G.; Baran, P. S.; Simonsen, K. B. *Chem. Eur. J.* **1999**, *5*, 3651−3665.

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(3) Mazzucco, C. E.; Warr, G. *J. Leukocyte Biol.* **1996**, *60*, 271−277.

(4) (a) Kontani, M.; Sakagami, Y.; Marumo, S. *Tetrahedron Lett.* **1994**, *35*, 2577−2580. (b) Trifonov, L. S.; Hilpert, H.; Floersheim, P.; Dreiding, A. S.; Rast, D. M.; Skrivanova, R.; Hoesch, L. *Tetrahedron* **1986**, *42*, 3157−3179.

(5) (a) Abe, N.; Murata, T.; Hirota, A. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2120−2126. (b) A second fungal metabolite very similar to bisorbibutenolide (**2**) differing only by the relative configuration at C9 was isolated in 1997 and named trichotetronine: Shirota, O.; Pathak, V.; Hossain, C. F.; Sekita, S.; Takatori, K.; Satake, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2961−2964.

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(8) (a) Trifonov, L. S.; Dreiding, A. S.; Hoesch, L.; Rast, D. M. *Helv. Chim. Acta* **1981**, *64*, 1843−1846. (b) Trifonov, L. S.; Bieri, J. H.; Prewo, R.; Dreiding, A. S.; Hoesch, L.; Rast, D. M. *Tetrahedron* **1983**, *39*, 4243−4256.

(9) Andrade, R.; Ayer, W. A.; Trifonov, L. S. *Can. J. Chem.* **1996**, *74*, 371−379.

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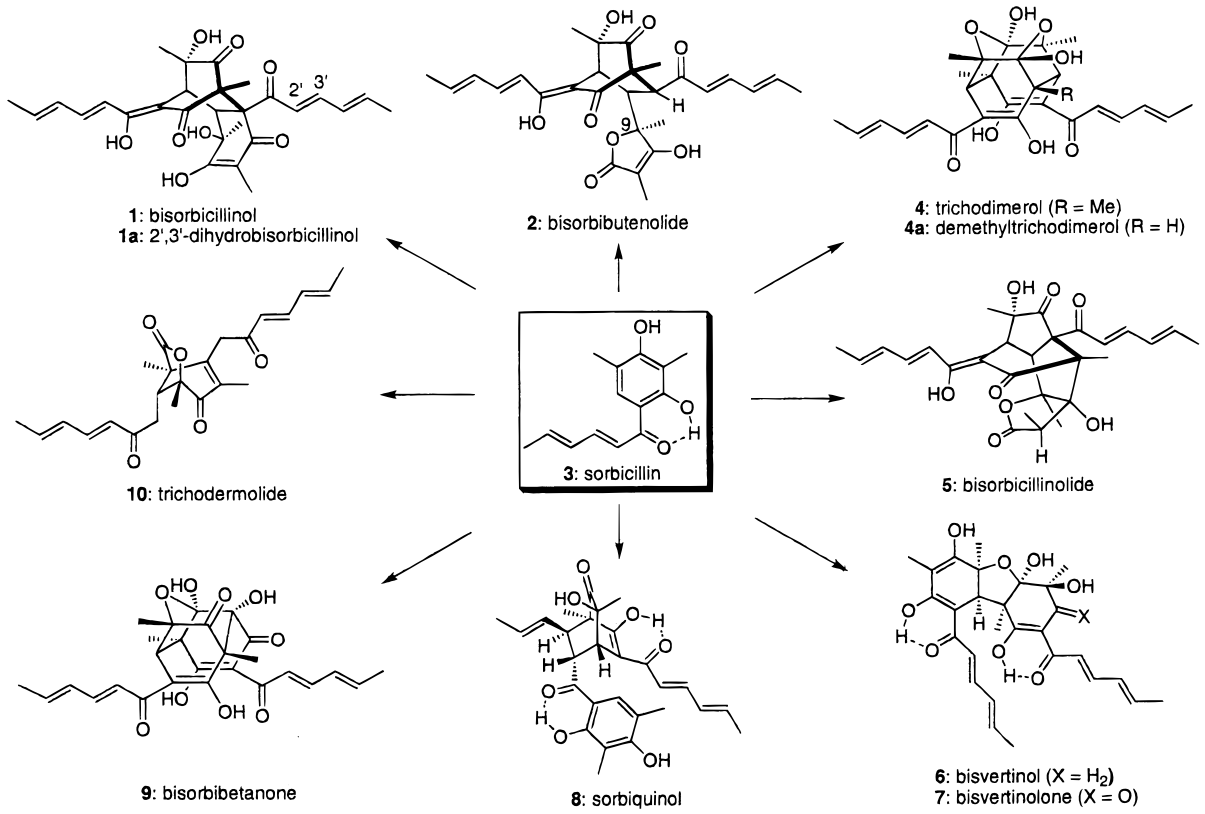


Figure 1. Structures of selected bisorbicillinoids and their postulated biosynthetic precursor, sorbicillin (**3**).

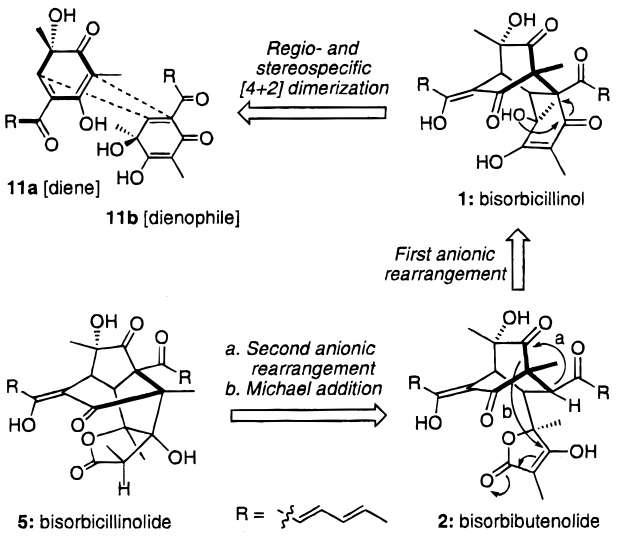


Figure 2. Proposed biosynthetic pathways for bisorbicillinol (**1**), bisorbibutenolide (**2**), and bisorbicillinolide (**5**).

Michael−ketalization cascade[1] and **6** from **3** by a related pathway (Figure 3).[10,11] The first synthesis of enantiomerically pure **4** from **3** by an oxidation−Michael−ketalization cascade was reported by Barnes-Seeman and Corey.[12]

The unusual combination of impressive molecular complexity, unique and diverse bioactivity, and intriguing biosynthetic avenues inspired us to embark on a program focusing on the

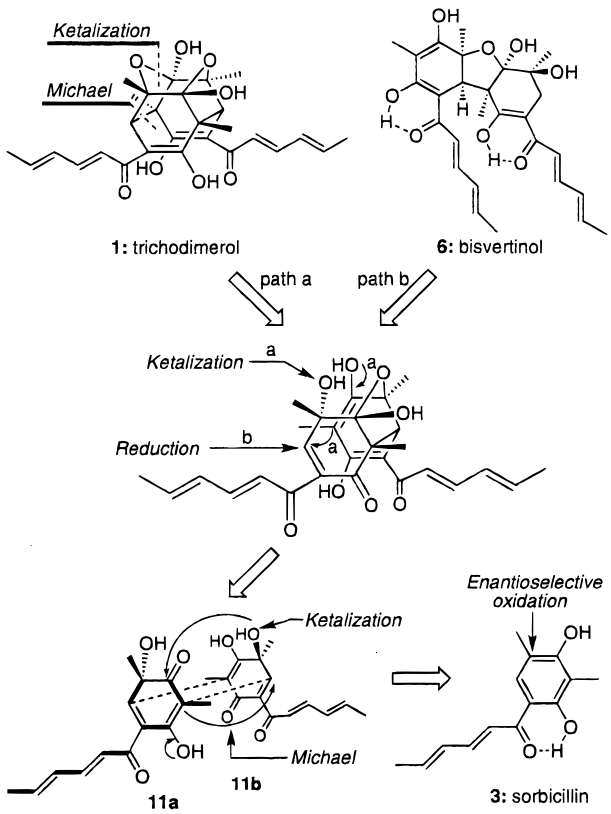


Figure 3. Proposed biosynthetic pathways from sorbicillin (**3**) to trichodimerol (**1**) and bisvertinol (**6**).

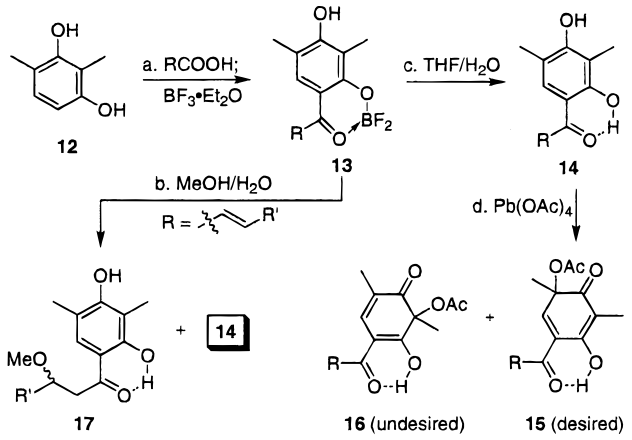
biomimetic total synthesis of the bisorbicillinoids. Herein, we present a full account of our biomimetic explorations into this class of natural products which culminated not only in the total synthesis of several members of this class, but also in the

(10) Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V.; Pitsinos, E. N.; Couladouros, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3555−3559.

(11) A previous proposal regarding the biosynthesis of **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: see ref 8.

(12) Barnes-Seeman, D.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1503−1504.

Scheme 1. Synthesis of Acetate **15** from 2,4-Dimethylresorcinol (**12**)[a]



[a]Conditions: (a) RCOOH (1 equiv), $BF_3{\cdot}Et_2O$, 120 °C, 1 h; (b) $MeOH/H_2O$ (1:1), 70 °C, 1 h; (c) THF/H_2O (1:1), 70 °C, 1 h; (d) $Pb(OAc)_4$ (1.05 equiv), $AcOH/CH_2Cl_2$ (1:1), 0 °C, 30 min.

biomimetic total syntheses of a variety of bisorbicillinoid analogues.[10]

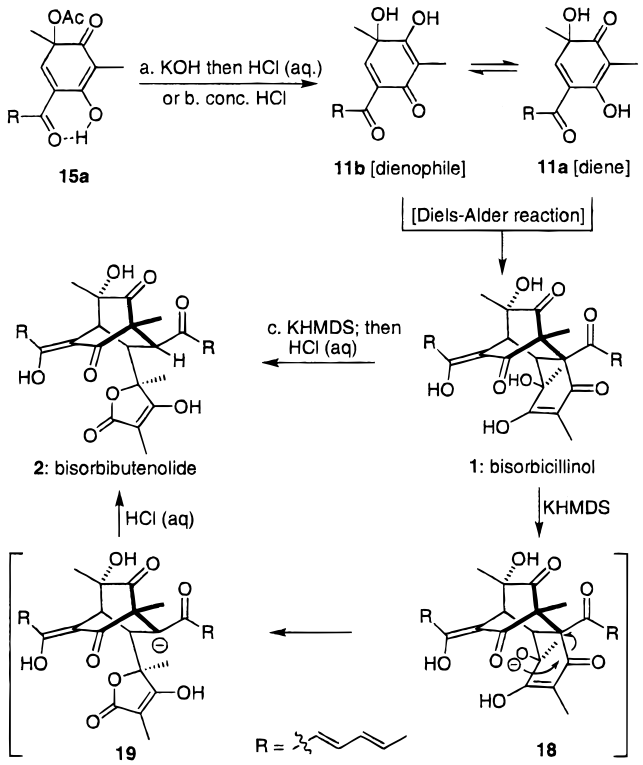
Results and Discussion

Our journey to the bisorbicillinoids commenced with the preparation of a suitably masked form of the expectedly fleeting quinol **11a/b** (Figures 2 and 3). To do this, we first required a reliable route to gram quantities of sorbicillin (**3**). Thus the procedure of McOmie et al.[13,14] was satisfactory for producing the boron complex **13** consistently; however, Michael addition of methanol occurred frequently when rupturing the boron complex ($MeOH/H_2O$, reflux) affording compounds of type **17** (see Scheme 1). We reasoned that methanol was present in the McOmie protocol solely for solubility purposes and, therefore, employed THF as a cosolvent, thereby eliminating this side reaction and providing practically pure **3** and analogues **14** after workup.

After considerable experimentation, it was found that the requisite α-acetoxy dienone **15a** ($R = C_5H_7$, Scheme 1) could be procured as the major regioisomer together with its regioisomer **16a** (**15a**:**16a** ~5:1) and in 40% isolated yield upon treatment with dry lead tetraacetate in degassed acetic acid (Scheme 1). Several methods for the direct ortho oxidation of phenols failed when applied to **3**, presumably due to the extreme reactivity of the *o*-quinol species. For instance, it was known from the work of Barton et al. that the dimerization of free *o*-quinols was instantaneous.[15]

With acetate **15a** in hand, the stage was set to explore the feasibility of a biomimetic approach to the bisorbicillinoids. To our delight, treatment of a 0.05 M solution of **15a** in THF/H_2O (9:1) with 10 equiv of solid KOH, followed by quenching with 1 N aqueous HCl led to the Diels−Alder adduct, bisorbicillinol (**1**) in 40% yield (Scheme 2). The spectral properties of synthetic **1** were identical in all respects to those reported by Abe et al.[2c,16] Using a chiral HPLC column, we were able to repeat the reaction

Scheme 2. Biomimetic Total Synthesis of Bisorbicillinol (**1**) and Bisorbibutenolide (**2**) from Acetate **15a**[a]



[a] Conditions: (a) KOH (10 equiv), THF/H_2O (9:1), 0 °C, 2 h; then 1 N HCl (aq), 40%; or (b) 12.1 N HCl, THF/H_2O (9:1), 25 °C, 2 h, 43%; (c) KHMDS (1.1 equiv), THF, 25 °C, 24 h; then 1 N HCl (aq), 80%.

using enantiomerically pure **15a** (*S* isomer). The optical rotation of synthetic **1** ($[\alpha]_D = +171.5°$, $c = 0.2$ in MeOH) was in good agreement with the literature ($[\alpha]_D = +195.2°$, $c = 0.5$ in MeOH).[2c] This remarkable Diels−Alder reaction proceeds with complete regio- and diastereocontrol (*endo* selectivity), generating four stereogenic centers, two of which are fully substituted. It is notable that the acetate **15a** did not give any Diels−Alder product when heated in benzene or in AcOH for several hours.

As supported by NMR studies (vide infra), the initial stages of this reaction involve deacetylation, thus revealing a diquinolate system (bis-deprotonated forms of **11a**/**b**) which rapidly scrambles to a mixture of diquinolates. Acidification of the reaction mixture undoubtedly leads to the formation of the fleeting quinols **11a/b**, which rapidly unite in a Diels−Alder reaction to generate bisorbicillinol (**1**; see Scheme 2).

Since it is impossible to monitor this transformation by thin-layer chromatography (TLC), we performed the reaction in deuterated media ($THF\text{-}d_8/D_2O$ 9:1) and observed the fate of acetate **15a** directly by ^1H NMR spectroscopy. Thus, upon addition of 10 equiv of KOH, the solution became characteristically deep orange and the resonances for acetate **15a** disappeared. As predicted, the ^1H NMR spectrum indicated the sole presence of two discrete quinolates (~3:2 ratio). The appearance of **1** occurred only after acidification of the reaction mixture (concentrated HCl). This observation led us to deduce that the free quinols would be necessary for most dimerization reactions of this type to occur rather than the corresponding quinolates. Therefore, a judicious choice of conditions for neutralization would likely have a profound impact on the nature

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(14) McOmie, J. F. W.; Tute, M. S. *J. Chem. Soc.* **1958**, 3226−3227. This method was found to be superior on larger scale to the procedure described by Sartori et al.: Bigi, F.; Casiraghi, G.; Casnati, G.; Marchesi, S.; Sartori, G.; Vignali, C. *Tetrahedron* **1984**, *40*, 4081−4084.

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(16) We thank Dr. N. Abe of the University of Shizouka for kindly providing us with the ^1H and ^{13}C NMR spectra of **1** and **2**.

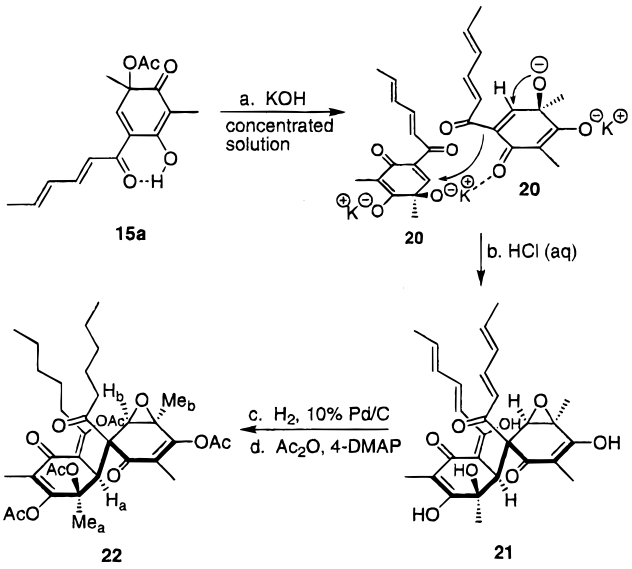
of the product formation (vide infra). As a corollary to this observation, it should then be plausible to *directly* produce **1** via acetate **15a** through simple acidic hydrolysis of the acetoxy function present in **15a** giving rise to the transitory quinols **11a/b**, and finally **1** itself. Indeed, treatment of **15a** with concentrated HCl in THF led to **1** in 43% isolated yield (Scheme 2). The ephemeral nature of quinols **11a/b** was once again reflected by an ^{1}H NMR experiment (THF-d_8/D_2O, concentrated HCl) that gradually showed the complete consumption of **15a** accompanied by proportionate formation of **1** over a 2-h period.

With **1** in hand, we were enticed to explore the hypothesis put forth by Abe et al. for the biosynthesis of bisorbibutenolide (**2**) and bisorbicillinolide (**5**) from **1** (see Figure 2 and Scheme 2).[5] The novel anionic rearrangement that converts **1** to **2** requires deprotonation of the tertiary alcohol leading to **18**, which must then engage the carbonyl group leading to rearranged anion **19** or proceed further to **5** (Figure 2 and Scheme 2). We reasoned that a potassium counterion might best function in this sequence due to its size and oxophilicity. In the event, subjection of **1** to *1.1 equiv* of KHMDS in THF led to exclusive formation of **2** in 80% isolated yield. It is notable that **1**, which contains four hydroxyl groups, required only 1 equiv of KHMDS to complete the transformation (**1** → **2**). Since **2** is an intermediate along the presumed anionic cascade pathway to **5** (Figure 2), several conditions commencing from either **1** or **2** to access **5** were evaluated. So far, however, while treatment of **1** with KHMDS led smoothly to **2**, NaHMDS, LiHMDS, and several other bases failed to convert **1** or **2** to **5**.

After completing syntheses of **1** and **2**, we set course towards other structurally challenging bisorbicillinoids. We reasoned that an increase in the concentration of the reaction that furnished **1** might also furnish **4** or **6** after acidification (Figure 3). Treatment of acetate **15a** with KOH in a minimum amount of solvent (THF/H_2O 10:1, 0.3 M) led to a major product along with a small amount of **1**. Although it appeared by TLC that the reaction had led to this new compound in high yield (~65% crude), it could only be isolated in a pure form by flash chromatography, resulting in a much lower isolated yield. The physical properties of the new compound were suggestive of the dimeric structure **21** (Scheme 3). Additional proof of structure was obtained after hydrogenation of the side chains (H_2, 10% Pd/C) and acetylation of the resulting compound (Ac_2O, 4-DMAP) to afford the stable tetraacetate **22**, whose structure was secured using ^{1}H, ^{13}C, ^{1}H−^{1}H COSY, ^{13}C APT, HMQC, and HMBC NMR spectroscopic techniques. Particularly striking is the fact that dimer **21** is formed as a single diastereomer, the configuration of which was defined 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 mechanism that accounts for the selective formation of the novel dimer **21** is illustrated in Scheme 3. Thus, it is reasoned that the initially formed dianion (**20**, Scheme 3) rearranges by an intramolecular Michael reaction to an epoxy dianion (not shown), which then engages another dianion in an intermolecular Michael reaction to stereoselectively generate a quaternary center. Since this is an intermolecular reaction between *quinolates*, a high concentration is necessary. We attribute the observed diastereospecificity (only one of four possible diastereomers) to a chelating effect which governs the attacking face of the incoming quinolate so as to minimize steric and charged interactions (Scheme 3).

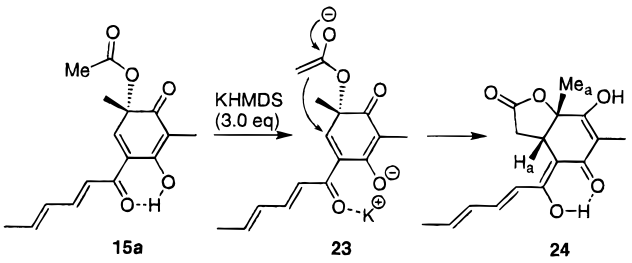
Another group of experiments attempting to convert acetate **15a** into other bisorbicillinoids led only to decomposition, recovery of starting material, or isolation of certain informative byproducts. For example (Scheme 4), treatment of **15a** with

Scheme 3. Synthesis of Sorbicillin Dimer **21** from Acetate **15a** and Its Transformation to the Corresponding Hydrogenated and Acetylated Dimer **22**[a]



[a]Conditions: (a) KOH (10 equiv), THF/H_2O (10:1), 0 °C, 2 h; then (b) 1 N HCl (aq) 65% (crude yield); (c) H_2, 10%, Pd/C, EtOAc, 25 °C, 2 h, 81%; (d) Ac_2O (10 equiv), 4-DMAP (0.2 equiv), EtOAc, 25 °C, 2 h, 80%. NOEs were observed for Me_a/H_a (4.5%), H_a/H_b (3.9%), and H_b/Me_b (3.0%) for **22**.

Scheme 4. Transformation of Acetate **15a** to the Cyclized Michael Product **24**[a]

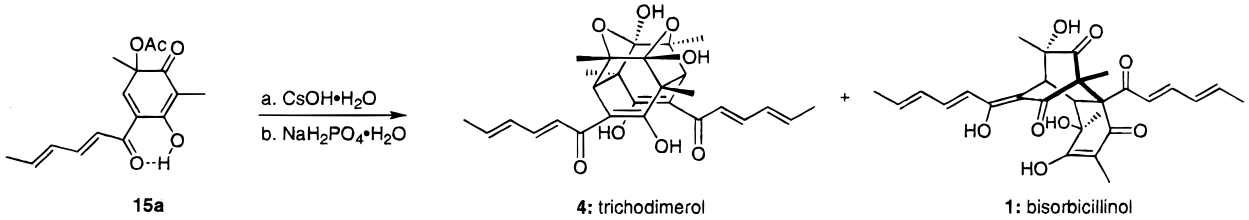


[a]Conditions: KHMDS (3.0 equiv), THF, −78 °C, 2 h, 60%; NOEs were observed for Me_a/H_a (1.8%).

excess KHMDS (3.0 equiv) in anhydrous THF at −78 °C produced first a red solution and, subsequently, upon acidification, the yellow γ-lactone **24** (60% yield). The use of LiHMDS led only to an orange lithium enolate with complete recovery of starting material upon acidification. Interestingly, treatment of **15a** with various Lewis acids (e.g., TBSOTf, TMSOTf) led only to the rearomatization and formation of **3** along with traces of **1**.

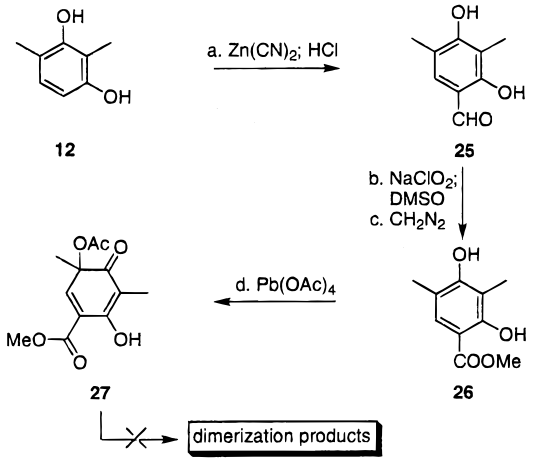
We then realized, as alluded to above, that the key to generating additional bisorbicillinoids resided in the workup protocol employed to quench the diquinolate (e.g., **20**, Scheme 3) derived from **15a**. We also feared that the presence of excess water (cosolvent) in the reaction would hinder the formation of certain bisorbicillinoids such as trichodimerol (**4**) due to expected ketalization difficulties. Extensive experimentation led us to identify the use of CsOH·H_2O/MeOH as a reliable method for the generation of the desired quinolate under protic conditions, but with only stoichiometric quantities of H_2O present. Varying the workup protocol of this reaction was a pivotal step in the biomimetic total synthesis of **4**. Thus, treatment of **15a** with CsOH·H_2O in MeOH for 7 h followed by neutralization with finely powdered NaH_2PO_4·H_2O and stirring at 25 °C for

Scheme 5. Novel Dimerization of the Acetate **15a**. Biomimetic Total Synthesis of Trichodimerol (**4**) and Bisorbicillinol (**1**)[a]



[a]Conditions: (a) $CsOH \cdot H_2O$ (10 equiv), MeOH, 25 °C, 7 h; then (b) $NaH_2PO_4 \cdot H_2O$, 25 °C, 12 h, 16% trichodimerol (**4**), 22% bisorbicillinol (**1**).

Scheme 6. Synthesis of Acetate **27** from 2,4-Dimethylresorcinol (**12**) and Failed Attempts To Produce Dimerization Products[a]



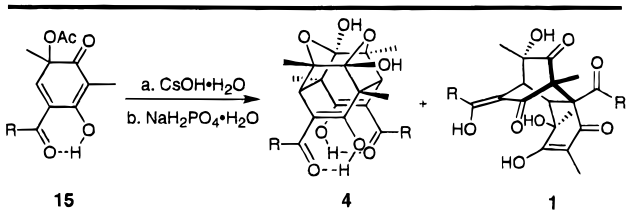
[a]Conditions: (a) $Zn(CN)_2$ (2.0 equiv), HCl (g), Et_2O, reflux, 1 h, 92%; (b) $NaClO_2$ (2.5 equiv), NaH_2PO_4 (2.5 equiv), DMSO/H_2O (1:1), 25 °C, 24 h, 69%; (c) CH_2N_2 (excess), C_6H_6/MeOH (1:2), 0 °C, 10 min, 78%; (d) $Pb(OAc)_4$ (1.05 equiv), AcOH/CH_2Cl_2 (1:1), 0 °C, 30 min, 55%.

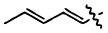
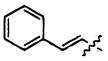
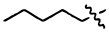
12 h furnished **4**, which was isolated in 16% yield after column chromatography together with **3** (12%) and **1** (22%, Scheme 5).

Synthetic **4** exhibited spectroscopic properties identical to that reported by Ayer et al., although **4** was unavailable to us for direct comparison.[2a] The very slow neutralization of this reaction is critical for the extraordinary biomimetic dimerization of **15a** to give **4** having no less than eight stereogenic centers, six of which are quaternary. The reaction could also be carried out with enantiomerically pure **15a** (vide supra) to provide optically active **4** ($[\alpha]_D = -375°$, $c = 0.1$ in MeOH for synthetic **4** and $[\alpha]_D = -376°$, $c = 0.26$ in MeOH for naturally occurring **4**)[2a] as first reported by Barnes-Seeman and Corey while these studies were still in progress.[12]

We immediately recognized the exciting potential of this reaction to furnish designed analogues of **1** and **4**. Therefore, we targeted the acetate **27** as a precursor to analogues of **1** and **4**, which would contain a versatile carbomethoxy group poised for further manipulations. Scheme 6 illustrates our successful synthesis of acetate **27**. Thus, 2,4-dimethylresorcinol (**12**) was formylated using the procedure of McOmie et al.[13] to afford aromatic aldehyde **25** in 92% yield. Conversion of aldehyde **25** to the corresponding carboxylic acid using $NaClO_2/NaH_2PO_4$ required the use of a DMSO cosolvent. After treatment of the resulting carboxylic acid with CH_2N_2 to provide methyl ester **26**, oxidation with $Pb(OAc)_4$ proceeded smoothly to afford acetate **27** in 55% yield. Despite our repeated attempts, however, we were unable to coax **27** into a biomimetic dimerization reaction. We rationalized that the reduced ability of the ester grouping to act as a Michael acceptor precluded dimerization and so we set our sights on modification of the side chain at the sorbicillin stage.

Table 1. [4 + 2] and [4 + 4] Dimerization of Acetates **15a**−**g** to Bisorbicillinol (**1**) and Trichodimerol (**4**) Analogues



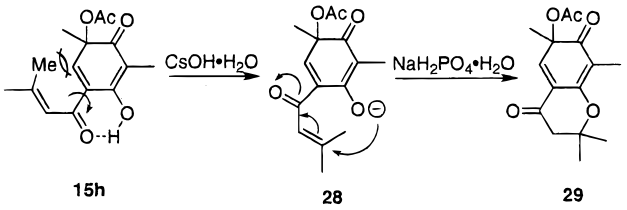
-R	Acetate	[4+4]-adduct (%)[a]	[4+2]-adduct (%)[a]
	**15a**	**4** (16)	**1** (22)
	**15b**	**4b** (16)[b]	-
	**15c**	**4c** (21)	-
-Me	**15d**	**4d** (17)	-
	**15e**	**4e** (5)	**1e** (39)
	**15f**	**4f** (13)	**1f** (35)
	**15g**	-	**1g** (55)

[a]Isolated yields. [b]Mixture of three geometrical isomers.

To probe the effect of differing side chains on the dimerization reaction, we synthesized (according to Scheme 1) an array of sorbicillin mimics which preserved the crucial ketone moiety. Table 1 illustrates the remarkable tolerance of the dimerization reaction to changes in the side chain size and electronic disposition. Conjugation throughout the side chain was found to be unnecessary as acetates **15d**−**f** led cleanly to the corresponding [4 + 4] products (**4d**−**f**, Table 1), and in the case of **15e**−**g** provided [4 + 2] products (**1e**−**g**, Table 1) as well. At this time, we are unable to contribute an explanation for the distribution of products (i.e., [4 + 4] vis-à-vis [4 + 2]) in this stunning biomimetic cascade dimerization.

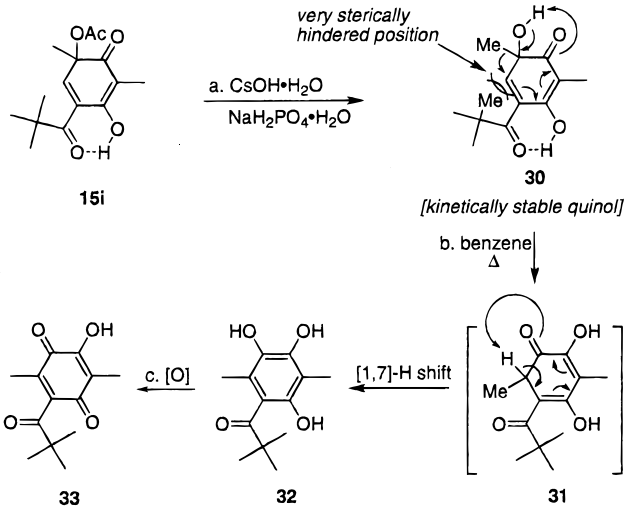
Although acetates **15b**,**c** succeeded in furnishing trichodimerol mimics **4b**,**c**, competing intra- and intermolecular Michael reactions frequently led to spurious byproducts. For example, in the case of acetate **15h** (Scheme 7), the dimerization reaction led exclusively to **29** rather than the desired [4 + 4] or [4 + 2] products. Scheme 7 depicts the unfavorable steric interaction in **15h** which is likely responsible for the efficient formation of **29** via an intramolecular Michael reaction. Utilizing the pure *E* acetate **15b** (Table 1), we observed formation of the desired [4 + 4] product as a mixture of three geometrical isomers

Scheme 7. Formation of the Intermolecular Michael Adduct **29** from Acetate **15h**[a]



[a]Conditions: $CsOH{\cdot}H_2O$ (10 equiv), MeOH, 25 °C, 7 h; then $NaH_2PO_4{\cdot}H_2O$, 25 °C, 12 h, 70%.

Scheme 8. Isolation of the Stable Quinol **30** and Its Thermal Rearrangement to Quinone **33**[a]



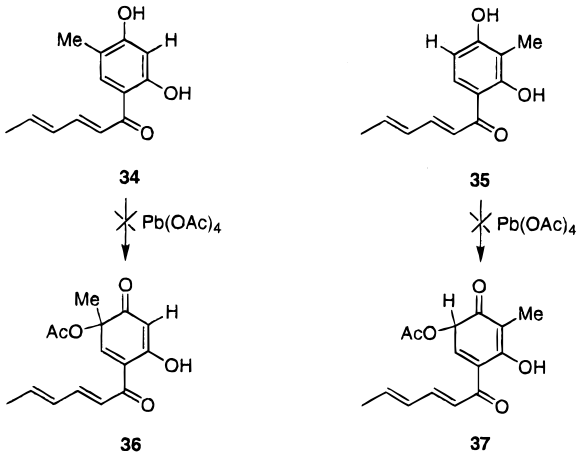
[a]Conditions: (a) $CsOH{\cdot}H_2O$ (10 equiv), MeOH, 25 °C, 7 h; then $NaH_2PO_4{\cdot}H_2O$, 25 °C, 12 h, 75%; (b) benzene, reflux, 12 h, 93%; (c) air, $CDCl_3$, 25 °C, 95%.

(because of the symmetry involved, only three isomers are theoretically possible) apparently due to isomerization processes of the final [4 + 4] product under the basic reaction conditions. In several instances in the unsaturated series (not shown), we also observed conjugate addition of MeOH to the side chain, leading to a multicomponent mixtures of products.

Not surprisingly, the *tert*-butyl acetate **15i** failed to dimerize due to extreme steric shielding (Scheme 8). However, the reaction led cleanly to the *free quinol* **30**, which was stable at room temperature. The formation of this stable quinol **30** gave us the rare opportunity to investigate the reactivity of this novel species when unable to dimerize. Thus, upon heating a solution of quinol **30** in benzene, we observed a quantitative conversion to the rearranged trihydroxybenzene **32**. A proposed mechanism for this unique transformation is given in Scheme 8. Furthermore, upon standing in $CDCl_3$ for several hours, a quantitative conversion of **32** to quinone **33** was observed.

Attempts to modify the central core of **1** and **4** by altering the presence of methyl groups in the acetate **15a** did not succeed. Although we were able to prepare the demethylsorbicillin compounds **34** and **35** by a route analogous to that depicted in Scheme 1, the ensuing oxidation with $Pb(OAc)_4$ resulted only in complete decomposition (Scheme 9). This difficulty is attributed to the ease with which re-aromatization must occur in the expected products along with other competing oxidatively destructive pathways. The isolation of demethyltrichodimerol (**4a**, Figure 1) from natural sources implies that an oxidized form of demethylsorbicillin **34** should be accessible, and thus, we are continuing to investigate this transformation (**34** → **36**, Scheme 9).

Scheme 9. Abortive at Attempts To Prepare Acetates **36** and **37** from Resorcinols **34** and **35**



Conclusion

Our explorations into the chemistry of the bisorbicillinoids have culminated in the total synthesis of several members of this class, designed analogues, and a wealth of new and interesting chemistry. In addition, several proposals regarding the biosynthesis of these compounds have been bolstered by experimental proof. The biomimetic synthesis of other bisorbicillinoids, development of a solid-phase variant of the key dimerization cascade, and biological evaluation of the novel bisorbicillinoid mimics reported herein are some of the directions pointed to by these findings.

Experimental Section

General Procedure for the Boron Trifluoride-Catalyzed Acylation of 2,4-Dimethylresorcinol with Carboxylic Acids. An equimolar solution of 2,4-dimethylresorcinol[13] (**12**, 500 mg, 3.7 mmol) and the appropriate carboxylic acid (3.7 mmol) in $BF_2{\cdot}Et_2O$ (5 mL, 0.74 M) was heated for 1−2 h at 120 °C under an argon atmosphere. The complete formation of the polar, yellow, stable BF -complex (Scheme 1) was observed by TLC. After cooling, the reaction mixture was quenched at 0 °C with H_2O (5 mL), followed by extraction with EtOAc (3 × 25 mL) and concentration under vacuum. The resulting material was refluxed for 30 min to 1 h in a THF/H_2O (1:1, 50 mL, 0.07 M), and the hydrolyzed compound was extracted with EtOAc (3 × 30 mL), dried ($MgSO_4$), and purified by flash column chromatography using a mixture of hexane/EtOAc (4:1) as eluent. The yield of the reaction ranges from 70 to 80%. When the hydrolysis of BF_2 complexes **13b** and **13h** were carried out in MeOH/H_2O (1:1), substantial amounts of the MeOH Michael adducts **17b** and **17h** were isolated (Scheme 1). The spectroscopic data for the desired acylated products **14b**−**i** are given as Supporting Information.

2-Demethylsorbicillin (34). The above-described experimental procedure was followed in this case, using 4-methylresorcinol instead of 2,4-dimethylresorcinol: orange semicrystalline solid; R_f 0.60 (silica gel, hexane/EtOAc 1:1); IR (film) ν_{max} (cm^{-1}) 3441 br w (OH), 1635 s (C═O), 1559 m, 1361 m, 1269 m, 1139 m, 998 m; ^1H NMR (600 MHz, $CDCl_3$) δ 13.39 (s, OH), 7.51 (s, 1 H), 7.45 (dd, J_1 = 14.2 Hz, J_2 = 10.9 Hz, 1 H), 6.94 (s, OH), 6.91 (d, J = 15.4 Hz, 1 H), 6.38 (s, 1 H), 6.33 (br d, J = 10.9 Hz, 1 H), 6.28 (m, 1 H), 2.18 (s, 3 H), 1.90 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.4, 164.4, 161.6, 144.9, 141.6, 131.9, 130.5, 121.5, 116.3, 113.8, 103.8, 18.9, 15.3; HRMS (MALDI) calcd for $C_{13}H_{14}O_3$ [M + H^+] 219.1021, found 219.1020.

6-Demethylsorbicillin (35). The above-described experimental procedure was followed in this case, using 2-methylresorcinol instead of 2,4-dimethylresorcinol: yellow crystals; R_f 0.60 (silica gel, hexane/EtOAc 1:1); mp 148−149 °C ($CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3171 br w (OH), 1615 s (C═O), 1564 m, 1487 m, 1366 m, 1266 s, 1219 m,

1110 m, 988 w, 780 w; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.35 (s, OH), 7.58 (d, J = 8.8 Hz, 1 H), 7.47 (dd, J_1 = 14.7 Hz, J_2 = 10.6 Hz, 1 H), 6.92 (d, J = 14.8 Hz, 1 H), 6.37 (d, J = 8.8 Hz, 1 H), 6.29 (m, 2 H), 5.37 (br s, OH), 2.14 (s, 3 H), 1.90 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 164.3, 160.2, 144.9, 141.6, 130.5, 128.7, 121.6, 113.9, 111.4, 106.9, 19.0, 7.8; HRMS (MALDI) calcd for $C_{13}H_{14}O_3$ [M + H$^+$] 219.1021, found 219.1018.

General Procedure for the Lead Tetraacetate Oxidation of 2,4-Dimethylresorcinols to the Corresponding α-Acetoxydienones. A solution of the appropriate acylated 2,4-dimethylresorcinol **14** (1.0 mmol) in AcOH/CH_2Cl_2 (1:1, 25 mL, 0.04 M) was stirred for 20 min with argon bubbling through the solution, and subsequently, lead tetraacetate (470 mg, 1.05 mmol, 1.05 eq) was added in one portion at 0 °C. After 30 min stirring at 0 °C, the reaction mixture was quenched with H_2O (25 mL), extracted with EtOAc (50 mL), washed with H_2O (4 × 50 mL), and dried ($MgSO_4$). The solvent was removed in vacuo, and the remaining traces of AcOH were pumped off under high vacuum. In most cases, the major byproduct was the undesired, less polar regioisomer (R_f 0.55−0.60, silica gel, hexane/EtOAc 1:1) (Scheme 1). The desired, more polar regioisomer (R_f 0.30−0.35, silica gel, hexane/EtOAc 1:1) was isolated by flash column chromatography using a mixture of hexane/EtOAc (1:1) as eluent. The spectroscopic data of the desired regioisomer **15a** and the undesired **16a** are given below, while the data for **15b**−**i** are given as Supporting Information.

2,6-Dimethyl-6-acetoxy-4-(2,4-hexadienoyl)-3-hydroxy-2,4-cyclohexadien-1-one (15a, desired acetate). Yellow crystals; R_f 0.35 (silica gel, hexane/EtOAc 1:1); mp 149−150 °C (ether/hexane 1:1); IR (film) ν_{max} (cm^{-1}) 2930 br w, 1737 m (C═O, acetate), 1650 s (C═O, enone), 1555 s, 1371 m, 1270 m, 1245 s, 1070 m, 1018 m, 768 m; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.90 (s, OH), 7.46 (dd, J_1 = 14.8 Hz, J_2 = 10.8 Hz, 1 H), 7.25 (s, 1 H), 6.66 (d, J = 14.8 Hz, 1 H), 6.38 (m, 1 H), 6.31 (m, 1 H), 2.15 (s, 3 H), 1.93 (d, J = 6.6 Hz, 3 H), 1.86 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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; HRMS (MALDI) calcd for $C_{16}H_{18}O_5Na$ [M + Na$^+$] 313.1052, found 313.1055. Separation of the two enantiomers of acetate **15a** was accomplished by semipreparative HPLC (Daicel Chiracel AD, hexane/*i*-PrOH/MeOH 80:15:5 containing 0.1% TFA, flow rate 5.5 mL/min, t_r = 15.3 min (*S* isomer) and t_r = 18.1 min (*R* isomer); (*S*)-**15a**: $[\alpha]_D$ = −580° (c = 0.1, MeOH). Reported $[\alpha]_D$ = −606° (c = 0.9, MeOH).[12] (*R*)-**15a**: $[\alpha]_D$ = +595 ° (c = 0.2, MeOH). Reported $[\alpha]_D$ = +615° (c = 1.0, MeOH).[12]

2,6-Dimethyl-6-acetoxy-4-(2,4-hexadienoyl)-5-hydroxy-2,4-cyclohexadien-1-one (16a, undesired acetate). Yellow oil; R_f 0.60 (silica gel, hexane/EtOAc 1:1); IR (film) ν_{max} (cm^{-1}) 1738 m (C═O, acetate), 1681 m (C═O, enone), 1606 s (C═O, enone), 1537 m, 1372 m, 1247 m, 997 w, 732 w; ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.75 (s, OH), 7.39 (dd, J_1 = 14.8 Hz, J_2 = 10.7 Hz, 1 H), 7.35 (d, allylic coupling J = 1.0 Hz, 1 H), 6.44 (d, J = 14.8 Hz, 1 H), 6.33 (dd, J_1 = 15.0 Hz, J_2 = 10.5 Hz, 1 H), 6.27 (m, 1 H), 2.16 (s, 3 H), 1.95 (d, allylic coupling, J = 1.0 Hz, 3 H), 1.91 (d, J = 6.6 Hz, 3 H), 1.52 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.3, 194.4, 173.5, 169.9, 144.0, 141.7, 136.1, 130.7, 124.6, 117.1, 105.4, 82.8, 23.3, 20.0, 19.0, 15.9; ESIMS ($C_{16}H_{18}O_5$): m/z (%) negative 289 ([M − H], 75).

Dimerization of Acetate 15a under Basic (KOH) Conditions. Bisorbicillinol (1). To a solution of acetate **15a** (29 mg, 0.1 mmol) in THF/H_2O (9:1, 2 mL, 0.05 M) was added KOH (56 mg, 1.0 mmol, 10 equiv) dissolved in a minimun amount of H_2O (one drop) at 0 °C. The reaction mixture turned orange immediately, indicating the formation of the corresponding diquinolate. After 1.5 h stirring at 0 °C, the reaction mixture was treated with 1 N HCl (2 mL) followed by extraction with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with H_2O (2 × 10 mL) and brine (10 mL) and dried ($MgSO_4$). Removal of the solvent followed by flash column chromatography (silica gel, CH_2Cl_2/acetone 5:1) gave the Diels−Alder adduct **1** (10 mg, 40%) as a pale yellow amorphous powder. The spectral properties of synthetic **1** were identical to those reported by Abe et al.:[2c] R_f 0.30 (silica gel, CH_2Cl_2/acetone 4:1); IR (film) ν_{max} (cm^{-1}) 3415 br w (OH), 1739 s (C═O), 1632 m, 1390 m, 1244 m, 1210 m, 1012 m; ^{1}H NMR (600 MHz, C_6D_6/CD_3OD 9:1) δ 7.37 (dd, J_1 = 15.0 Hz, J_2 = 11.0 Hz, 1 H), 7.34 (dd, J_1 = 14.9 Hz, J_2 = 11.0 Hz, 1 H), 6.74 (d, J = 14.8 Hz, 1 H), 6.40 (d, J = 15.0 Hz, 1 H), 6.00 (br t, J = 13.0 Hz, 1 H), 5.81 (br t, J = 11.8 Hz, 1 H), 5.72 (dq, J_1 = 14.8 Hz, J_2 = 6.7 Hz, 1 H), 5.64 (dq, J_1 = 14.1 Hz, J_2 = 7.0 Hz, 1 H), 3.94 (br s, 1 H), 3.77 (br s, 1 H), 2.01 (s, 3 H), 1.79 (s, 3 H), 1.47 (s, 3 H), 1.45 (d, J = 7.5 Hz, 3 H), 1.38 (d, J = 6.7 Hz, 3 H), 1.30 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6/CD_3OD 9:1) δ 208.5, 198.9, 197.2, 175.1, 170.4, 168.8, 146.2, 142.9, 142.3, 139.0, 131.5, 130.7, 124.9, 119.4, 111.5, 109.6, 74.7, 70.3, 68.7, 60.6, 48.4, 42.1, 33.0, 24.7, 18.6, 18.4, 10.5, 8.6; HRMS (MALDI) calcd for $C_{28}H_{32}O_8$ [M + H$^+$] 497.2175, found 497.2172. Repeating the reaction with enantiomerically pure (*S*)-**15a** gave (+)-(**1**); $[\alpha]_D$ = +171.5° (c = 0.2, MeOH). Reported $[\alpha]_D$ = +195.2° (c = 0.5, MeOH).[2c]

Formation of Dimer 21. When the above hydrolysis of acetate **15a** was carried out in a very concentrated solution of THF/H_2O (10:1, 0.3 M) a more polar dimer **21** was formed, together with a small amount of the previously obtained **1**. Dimer **21** was found to be labile on silica gel and could be isolated in pure form only in 10% yield, by fast flash column chromatography (silica gel, CH_2Cl_2/acetone 4:1): yellow amorphous powder; R_f 0.20 (silica gel, CH_2Cl_2/acetone 4:1); IR (film) ν_{max} (cm^{-1}) 3371 br w (OH), 1619 s, 1385 m, 1345 s, 1210 m, 1076 m; ^{1}H NMR (500 MHz, C_6D_6/CD_3OD 9:1) δ 7.38 (m, 2 H), 6.77 (d, J = 14.6 Hz, 1 H), 6.71 (d, J = 14.6 Hz, 1 H), 6.32 (dd, J_1 = 14.3 Hz, J_2 = 12.1 Hz, 1 H), 5.78 (dd, J_1 = 14.0 Hz, J_2 = 12.5 Hz, 1 H), 5.65 (m, 2 H), 4.94 (br s, 1 H), 4.50 (br s, 1 H), 2.03 (s, 3 H), 1.99 (s, 3 H), 1.46 (d, J = 5.9 Hz, 3 H), 1.38 (s, 3 H), 1.35 (d, J = 6.9 Hz, 3 H), 1.33 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6/CD_3OD 9:1) δ 197.9, 192.9, 170.8, 169.6 (br, 3 C), 146.4, 146.1, 142.9, 139.6, 139.4, 136.7, 132.3, 131.4, 125.7, 122.1, 120.6, 88.7, 82.0, 73.1, 59.3, 42.5, 26.0, 25.5, 18.9, 18.8, 8.7, 8.4; HRMS (MALDI) calcd for $C_{28}H_{32}O_8Na$ [M + Na$^+$] 519.1995, found 519.2003.

Hydrogenated Tetraacetate 22. The crude reaction mixture from the above reaction (85 mg, 0.17 mmol) was dissolved in EtOAc (5 mL) and 10% Pd/C (15 mol %) was added: the yellow reaction mixture was stirred under H_2 until the solution turned colorless (2 h). The solution was filtered through Celite and concentrated. Flash column chromatography (silica gel, CH_2Cl_2/acetone 4:1) gave 70 mg (81%) of the hydrogenated dimer as a clear oil, which was converted directly to the tetraacetate **22**. To a solution of the hydrogenated dimer (26 mg, 0.05 mmol) in EtOAc (2 mL, 0.025 M) were added Ac_2O (50 μL, 0.5 mmol, 10 equiv) and 4-DMAP (1 mg, 0.01 mmol, 0.2 equiv), and the reaction mixture was stirred for 2 h, concentrated, and purified by flash column chromatography (silica gel, hexane:EtOAc 2:1) to give tetraacetate **22** (28 mg, 80%) as a stable clear oil: R_f 0.25 (silica gel, hexane/EtOAc 2:1); IR (film) ν_{max} (cm^{-1}) 1769 s (C═O, acetate), 1710 s (C═O, enone), 1671 s (C═O, enone), 1370 m, 1242 m, 1185 m, 1071 m; ^{1}H NMR (500 MHz, C_6D_6) δ 5.90 (s, 1 H), 4.08 (s, 1 H), 3.51 (ddd, J_1 = 13.8 Hz, J_2 = 10.0 Hz, J_3 = 5.5 Hz, 1 H), 2.87 (dt, J_1 = 19.3 Hz, J_2 = 7.3 Hz, 1 H), 2.63 (ddd, J_1 = 13.7 Hz, J_2 = 10.1 Hz, J_3 = 5.5 Hz, 1 H), 2.19 (dt, J_1 = 19.3 Hz, J_2 = 7.3 Hz, 1 H), 1.96 (s, 3 H), 1.88 (m, 1 H), 1.86 (s, 3 H), 1.78 (s, 3 H), 1.73 (s, 3 H), 1.72 (s, 3 H), 1.69 (s, 3 H), 1.65 (m, 1 H), 1.59 (s, 3 H), 1.55 (m, 2 H), 1.50 (s, 3 H), 1.38 (m, 2 H), 1.30 (m, 2 H), 1.20 (m, 2 H), 1.11 (m, 2 H), 0.88 (t, J = 7.4 Hz, 3 H), 0.81 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 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 (2 CH_2), 21.6, 20.7, 20.0, 19.9, 14.3, 14.1, 10.7, 10.6; HRMS (MALDI) calcd for $C_{36}H_{48}O_{12}Na$ [M + Na$^+$] 695.3038, found 695.3013. Assignment of ^{1}H and ^{13}C signals were aided by ^{1}H−^{1}H COSY, ^{13}C APT, HMQC and HMBC experiments. NOE experiments (C_6D_6): irradiation of signal at δ 5.90 (H_b, Scheme 3) effects signals at δ 4.08 (3.9%, H_a) and 1.96 (3.0%, Me_b); irradiation of signal at δ 4.08 (H_a, Scheme 3) effects signals at δ 5.90 (3.8%, H_b) and 1.55 (4.5%, Me_a).

[4 + 2] Dimerization of Acetate 15a Under Acidic (HCl) Conditions. To a solution of acetate **15a** (29 mg, 0.1 mmol) in THF (2 mL, 0.05 M) was added concentrated HCl (12.1 N, 206 μL, 2.5 mmol, 25 equiv) followed by stirring for 2 h at 25 °C. The reaction mixture was diluted with EtOAc (5 mL), washed with H_2O (5 mL) and brine (5 mL), and dried with $MgSO_4$. Evaporation of the solvent followed by flash column chromatography (silica gel, CH_2Cl_2/acetone 5:1) furnished **1** (10.5 mg, 43%). The spectroscopic data of synthetic

1 were identical to those given above and in accordance to those reported by Abe et al.[2c]

Anionic Rearrangement of Bisorbicillinol (1) to Bisorbibutenolide (2). To a 0 °C cold solution of **1** (10 mg, 0.02 mmol) in dry THF (0.5 mL, 0.04 M) was added KHMDS (0.5 M solution in toluene, 44 μL, 0.022 mmol, 1.1 equiv), and the mixture turned orange. The reaction was allowed to warm to room temperature, and the mixture stirred for 24 h. Addition of 1 N HCl solution (1 mL) was followed by extraction with EtOAc (2 × 5 mL). The combined extracts were washed with brine (5 mL) and dried ($MgSO_4$), followed by flash column chromatography of the resulting residue (silica gel, CH_2Cl_2/acetone 4:1). The more polar natural product **2** was isolated as a pale yellow amorphous powder (8 mg, 80%). The spectral data of synthetic **2** were identical to those reported by Abe et al.:[5a] R_f 0.18 (silica gel, CH_2Cl_2/acetone 4:1); IR (film) ν_{max} (cm^{-1}) 3425 br w (OH), 1740 s (C═O), 1667 m, 1632 m, 1385 m, 1202 m; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, J_1 = 14.7 Hz, J_2 = 11.0 Hz, 1 H), 7.23 (dd, J_1 = 15.4 Hz, J_2 = 11.0 Hz, 1 H), 6.38 (dq, J_1 = 15.0 Hz, J_2 = 7.0 Hz, 1 H), 6.28 (m, 3 H), 6.14 (d, J = 15.0 Hz, 1 H), 6.10 (d, J = 14.6 Hz, 1 H), 3.37 (d, J = 6.2 Hz, 1 H), 3.33 (d, J = 2.2 Hz, 1 H), 3.19 (dd, J_1 = 6.2 Hz, J_2 = 2.2 Hz, 1 H), 1.92 (d, J = 7.8 Hz, 3 H), 1.90 (d, J = 7.7 Hz, 3 H), 1.55 (s, 3 H), 1.47 (s, 3 H), 1.27 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 202.6, 195.0, 175.4, 173.6, 169.8, 148.0, 145.6, 143.9, 141.0, 130.9, 130.1, 126.8, 117.7, 108.4, 98.5, 82.5, 74.9, 62.5, 51.3, 43.5, 42.3, 23.5, 23.1, 19.2, 19.0, 11.0, 6.2; HRMS (MALDI) calcd for $C_{28}H_{32}O_8Na$ [M + Na^+] 519.1995, found 519.2001.

Formation of Intramolecular Michael Adduct 24. To a −78 °C cold solution of acetate **15a** (9.5 mg, 0.03 mmol) in dry THF (1.0 mL, 0.03 M) was added dropwise KHMDS (0.5 M solution in toluene, 196 μL, 0.09 mmol, 3 equiv), and the mixture turned red. The reaction mixture was stirred for an additional 30 min and then it was quenched at −78 °C with 1 N HCl (2.0 mL). After being warmed to 25 °C, the mixture was extracted with CH_2Cl_2 (2 × 3 mL), washed with brine (5 mL), and dried ($MgSO_4$). The residue obtained after evaporation was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH 19:1) to give **24** (6 mg, 60%) as a yellow glass: R_f 0.38 (silica gel, CH_2Cl_2/MeOH 19:1); IR (film) ν_{max} (cm^{-1}) 1790 s (C═O, lactone), 1619 s (C═O, enone), 1558 m, 1415 m, 1349 m, 1224 m, 1095 m, 948 w; ^{1}H NMR (600 MHz, C_6D_6) δ 16.95 (s, OH), 7.48 (dd, J_1 = 14.5 Hz, J_2 = 10.9 Hz, 1 H), 6.15 (m, 1 H), 5.74 (d, J = 14.4 Hz, 1 H), 5.68 (m, 1 H), 2.77 (dd, J_1 = 12.2 Hz, J_2 = 8.3 Hz, 1 H), 2.08 (dd, J_1 = 17.5 Hz, J_2 = 8.3 Hz, 1 H), 2.05 (s, 3 H), 1.90 (dd, J_1 = 17.5 Hz, J_2 = 12.2 Hz, 1 H), 1.53 (d, J = 7.0 Hz, 3 H), 1.11 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 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; HRMS (MALDI) calcd for $C_{16}H_{18}O_5Na$ [M + Na^+] 313.1052, found 313.1063; NOE experiments (C_6D_6): irradiation of signal at δ 1.11(Me_a, Scheme 4) effects signal at δ 2.77 (1.8%, H_a).

6-Formyl-2,4-dimethylresorcinol (25). A vigorously stirred solution of 2,4-dimethylresorcinol (**12**, 3.94 g, 0.028 mol) and $Zn(CN)_2$ (6.8 g, 0.056 mol, 2.0 equiv) in dry ether (50 mL, 0.6 M) was charged with a rapid stream of HCl to allow gentle reflux. After 1 h the resulting aldimine hydrochloride precipitated out, and the solution was cooled to 25 °C. The ether was decanted off and the solid was washed with dry ether (2 × 20 mL). The resulting white solid was dissolved in H_2O (150 mL) and the solution was refluxed for 1 h, whereupon the product precipitated out. Ethanol (50 mL) was added, and the reaction mixture was heated to redissolve the crystals and finally cooled to 0 °C. The resulting crystals were filtered off, washed with cold H_2O/EtOH (1:1, 50 mL), and dried under vacuum over P_2O_5 to give **25** (4.40 g, 92%) as greenish crystals: R_f 0.45 (silica gel, CH_2Cl_2/MeOH 19:1); mp 178−179 °C (H_2O/EtOH 1:1); IR (film) ν_{max} (cm^{-1}) 3410 br w (OH), 1634 s (C═O), 1595 m, 1480 m, 1434 m, 1290 m, 1253 m, 1147 m, 951 w; ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.44 (s, OH), 9.71 (br s, OH), 9.65 (s, 1 H), 7.27 (s, 1 H), 2.11 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 195.1, 161.5, 159.5, 132.8, 117.0, 113.9, 110.4, 16.0, 8.0; ESIMS ($C_9H_{10}O_3$) m/z (%) negative 165 ([M − H], 100).

6-Carboxymethyl-2,4-dimethylresorcinol (26). To a solution of **25** (690 mg, 4.2 mmol) in DMSO (12 mL, 0.35 M) were added $NaClO_2$ (950 mg, 10.5 mmol, 2.5 equiv) in H_2O (12 mL) and NaH_2PO_4 (1.3 g, 10.5 mmol, 2.5 eq) in H_2O (3 mL). The slurry was stirred vigorously at ambient temperature for 24 h, at which time it was diluted with EtOAc (25 mL) and 1 N HCl (10 mL) was added. Extraction with EtOAc (3 × 25 mL) followed by drying with $MgSO_4$ and removal of the solvent under vacumn gave the crude carboxylic acid, which was directly dissolved in benzene/MeOH (1:2, 10 mL) and treated with excess CH_2N_2 (etheral solution) at 0 °C. After 10 min, the solvent was removed and the crude methyl ester was flash chromatographed (silica gel, hexane/EtOAc 5:1) to give pure **26** (440 mg, 54%) as off-white crystals: R_f 0.30 (silica gel, hexane/EtOAc 5:1); mp 136−138 °C ($CHCl_3$); IR (film) ν_{max} (cm^{-1}) 3435 br w (OH), 1646 (C═O, methyl ester) 1606 m, 1441 m, 1294 m, 1206 s, 1146 m, 1109 m, 1019 m, 786 m; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.05 (s, OH); 7.47 (s, 1 H), 5.17 (s OH), 3.89 (s, 3 H), 2.17 (s, 3 H), 2.13 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 159.8, 158.0, 128.5, 114.6, 110.0, 104.7, 51.9, 15.4, 7.7; HRMS (MALDI) calcd for $C_{10}H_{12}O_4$ [M + H^+] 197.0814, found 197.0807.

2,6-Dimethyl-6-acetoxy-4-carbomethoxy-3-hydroxy-2,4-cyclohexadien-1-one (27). The above-described general procedure for the lead tetraacetate oxidation of 2,4-dimethylresorcinols **14** to the corresponding α-acetoxydienones **15** was followed for the preparation of **27**: pale yellow glass; R_f 0.30 (silica gel, hexane/EtOAc 1:1); IR (film) ν_{max} (cm^{-1}) 1737 s (C═O, acetate), 1704 s (methyl ester), 1657 m (C═O, enone), 1441 m, 1372 m, 1241 s, 1104 w, 1020 w 732 w; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.68 (s, 1 H), 7.36 (s, 1 H), 3.90 s (3 H), 2.11 s (3 H), 1.95 s (3 H), 1.54 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.4, 182.5, 170.0, 160.1, 152.1, 118.5, 111.8, 78.0, 53.2, 23.8, 20.4, 7.3; ESIMS ($C_{12}H_{14}O_6$) m/z (%) negative 253 ([M − H], 100).

General Procedure for the Dimerization of the Acetates Using CsOH·H_2O as Base. To a solution of the appropriate acetate **15** (0.1 mmol) in MeOH (6 mL, 0.016 M) was added CsOH·H_2O (167 mg, 1.0 mmol, 10 equiv) at 25 °C, and the reaction mixture was stirred for 7 to 8 h. The resulting yellow-orange monomeric diquinolate was quenched with powdered NaH_2PO_4·H_2O (550 mg, 4.0 mmol, 40 equiv). After 12 h stirring at 25 °C, the remaining solid NaH_2PO_4·H_2O was removed by filtration and the reaction mixture was concentrated and then purified by careful gradient flash column chromatography (silica gel, hexane/EtOAc 1:1 → 1:2). The R_f value for the less polar [4 + 4] adducts ranged from 0.45 to 0.55, while for the more polar [4 + 2] adducts ranged from 0.30 to 0.40 (silica gel, hexane/EtOAc 1:2). The yields of these reactions are listed in Table 1. In the case of acetate **15h**, the intramolecular Michael adduct **29** (21 mg, 70%, Scheme 7) was isolated. The stable quinol **30** was isolated in high yield (22 mg, 75%) in the case of acetate **15i** (Scheme 8). Spectroscopic data for compounds **4b**−**f**, **1e**−**g**, **29**, and **30** are given as Supporting Information.

Trichodimerol (4). The spectral data of synthetic **4** were identical to those reported by Ayer et al.:[2a] pale yellow amorphous powder; R_f 0.55 (silica gel, hexane/EtOAc 1:2); IR (film) ν_{max} (cm^{-1}) 3430 br w (OH), 1610 s (C═O), 1610 m, 1405 m, 1285 m, 1148 s, 1000 m, 930 m; ^{1}H NMR (500 MHz, C_6D_6) δ 17.20 (s, 2 OH), 7.36 (dd, J_1 = 14.7 Hz, J_2 = 11.1 Hz, 2 H), 6.24 (d, J = 14.8 Hz, 2 H), 5.86 (dd, J_1 = 13.3 Hz, J_2 = 11.4 Hz, 2 H), 5.54 (dq, J_1 = 14.8 Hz, J_2 = 6.9 Hz, 2 H), 3.20 (br s, 2 OH), 3.10 (s, 2 H), 1.55 (s, 6 H), 1.43 (s, 6 H), 1.53 (dd, J_1 = 6.4 Hz, J_2 = 1.8 Hz, 6 H); ^{13}C NMR (125 MHz, C_6D_6) δ 197.9 (2 C), 175.9 (2 C), 143.6 (2 CH), 140.4 (2 CH), 130.9 (2 CH), 118.5 (2 CH), 104.0 (2 C), 102.8 (2 C), 78.7 (2 C), 58.8 (2 C), 57.5 (2 CH), 21.2 (2 CH_3), 19.0 (2 CH_3), 18.7 (2 CH_3); HRMS (MALDI) calcd for $C_{28}H_{32}O_8Na$ [M + Na^+] 519.1995, found 519.1999. Repeating the reaction with enantiomerically pure (*S*)-**15a** gave (−)-(**4**); $[\alpha]_D$ = −375° (c = 0.1, MeOH). Reported $[\alpha]_D$ = −376° (c = 0.3, MeOH).[2a]

3,6-Dimethyl-5-(trimethylacetyl)-1,2,4-trihydroxybenzene (32). Thermal Rearrangement of Quinol 30. A solution of quinol **30** (15 mg, 0.06 mmol) in dry benzene (5.0 mL, 0.01 M) was refluxed for 12 h. The solvent was removed by concentration, and the resulting residue was purified by flash column chromatography (silica gel, hexane/EtOAc 1:1) to give **32** (14 mg, 93%) as a yellow glass. Compound **32** was stored under argon to prevent its oxidation to **33**: R_f 0.40 (silica gel, hexane/EtOAc 1:1); IR (film) ν_{max} (cm^{-1}) 3413 br w (OH), 1666 s (C═O), 1631 m, 1462 m, 1391 m, 1361 m, 1285 s, 1129 m, 1075 m; ^{1}H NMR (500 MHz, C_6D_6) δ 5.71 (s, OH), 5.42 (s, OH), 4.58 (s, OH),

1.88 (s, 3 H), 1.78 (s, 3 H), 1.21 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.2, 145.1, 144.4, 137.1, 124.1, 118.9, 111.2, 45.1, 27.7 (3 CH_3), 13.6, 8.9; ESIMS ($C_{13}H_{18}O_4$) *m*/*z* (%) negative 235 ([M − 3 H], 100). This peak corresponds to the oxidized form **33**.

3,6-Dimethyl-5-(trimethylacetyl)-2-hydroxy-*p*-quinone (33). Air Oxidation of 32. Compound **32** (7 mg, 0.03 mmol) was completely oxidized to **33** upon standing in a NMR tube in either $CDCl_3$ (0.6 mL, 0.05 M, 4 h) or C_6D_6 (0.6 mL, 0.05 M, 24 h). Removal of the solvent followed by flash column chromatography (silica gel, hexane/EtOAc 2:1) gave **33** (6.5 mg, 95%) as a yellow semicrystalline solid: R_f 0.60 (silica gel, hexane/EtOAc 1:1); IR (film) ν_{max} (cm^{-1}) 3384 s (OH), 1702 s (C═O, enone), 1654 s (C═O), 1631 s, 1462 w, 1391 m, 1362 m, 1304 s, 1161 m, 1047 m; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.94 (s, 3 H), 1.93 (s, 3 H), 1.20 (s, 9 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.2, 186.5, 183.4, 151.3, 146.3, 135.0, 116.8, 44.5, 26.9 (3 CH_3), 12.9, 7.8; ESIMS ($C_{13}H_{16}O_4$) *m*/*z* (%) negative 235 ([M − H], 100).

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Supporting Information Available: Spectral data (R_f, mp, IR, ^{1}H NMR, ^{13}C NMR, HRMS) for **14b**−**i**, **15b**−**i**, **4b**−**f**, **1e**−**g**, **29**, and **30** (print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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