Natural Product Synthesis

Catalytic Enantioselective Total Syntheses of Bisorbicillinolide, Bisorbicillinol, and Bisorbibutenolide**

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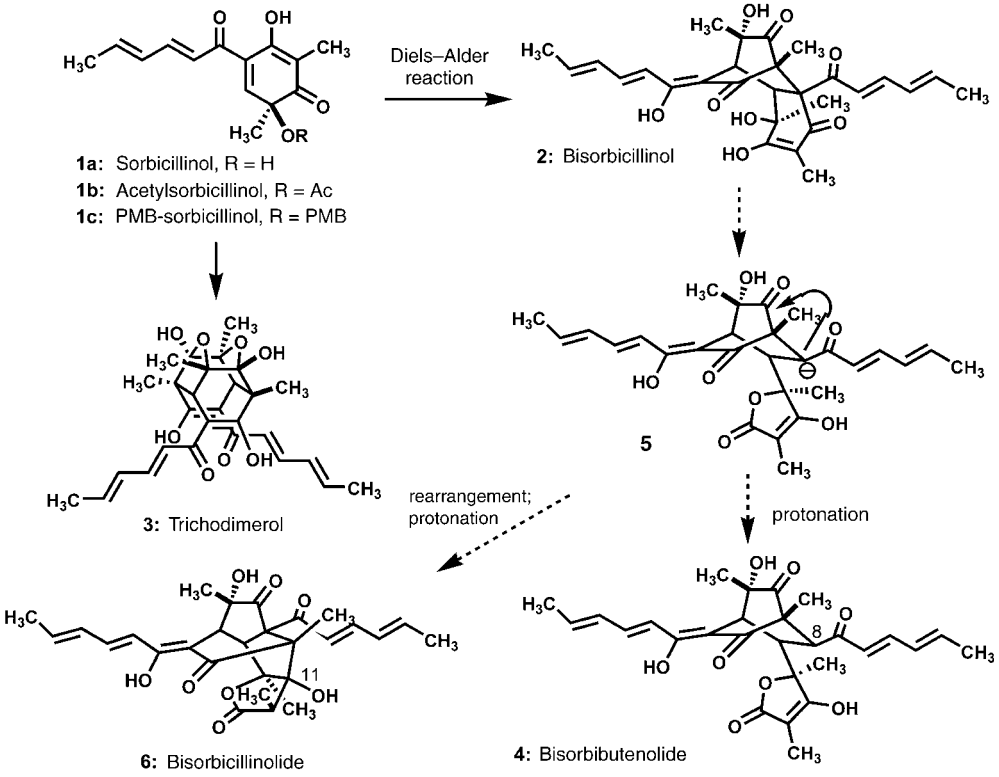
Dedicated to Professor Eric N. Jacobsen

The remarkable structural complexity and broad range of interesting biological activitiesis of bisorbicillinoids have made them attractive synthetic targets. Although structurally diverse, it was postulated that bisorbicillinoids were biosynthetically generated from a common intermediate, sorbicillinol (**1a**), through several fascinating and chemically distinct dimerizations of **1a** (Scheme 1).[1,2] This notion was confirmed in pioneering synthetic studies of bisorbicillinoids by the research groups of Corey and Nicolaou that culminated in the successful biomimetic total syntheses of bisorbicillinol (**2**) and trichodimerol (**3**) through a [4+2] dimerization and a Michael reaction/ketalization dimerization, respectively.[1,2] Furthermore, the Corey and Nicolaou groups showed that dimerization of optically active sorbicillinol (**1a**), prepared by hydrolysis of the optically active 6-acetylsorbicillinol (**1b**; obtained through preparative HPLC resolution of its racemic counterpart), led to the formation of **2** and **3** in the optically active form.[2a,d] Nicolaou et al. also demonstrated that bisorbicillinol (**2**) could be converted into bisorbibutenolide (**4**),[2c,d] thus supporting the proposal of Abe et al. that bisorbicillinol (**2**) is a biosynthetic precursor to other more structurally complex bisorbicillinoids.[3] Although Abe et al. postulated that intermediate **5**, which is formed during the conversion of **2** into **4**, could also give rise to bisorbicillinolide (**6**),[3b] the total synthesis of **6**, in either its racemic or optically active form, has not yet been reported.

These inspiring synthetic studies underscored the importance of developing a highly enantioselective synthesis of sorbicillinol derivatives (**1**). The presence of a single heteroatom-substituted quaternary stereocenter and densely packed sensitive functionalities apparently render this task highly challenging, as no enantioselective total synthesis of any member of the bisorbicillinoids has been reported.[4] Herein, we describe a catalytic, enantioselective, and flexible synthesis of sorbicillinol derivatives **1** and the enantioselective total syntheses of bisorbicillinolide (**6**), bisorbicillinol (**2**), and bisorbibutenolide (**4**).



Scheme 1. Selected bisorbicillinoids and the biosynthesis hypothesis.

Our synthetic plan, outlined in Scheme 2 featured a catalyst-controlled enantioselective construction of the het-

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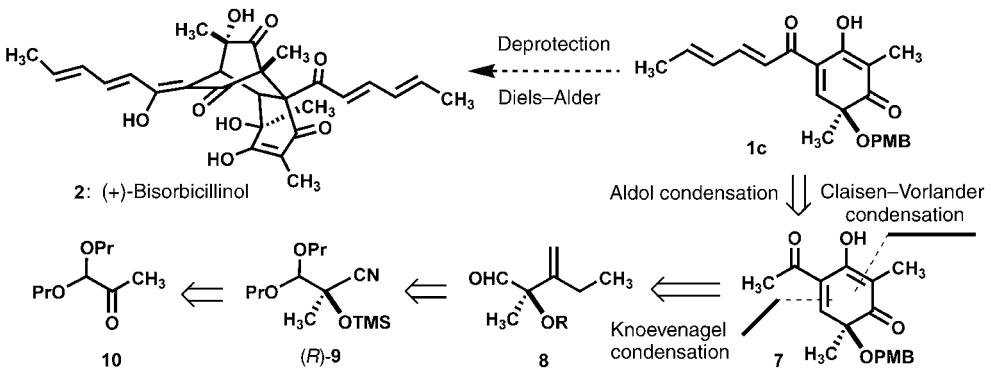
[**] This work was financially supported by the National Institutes of Health (GM-61591).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.20050480



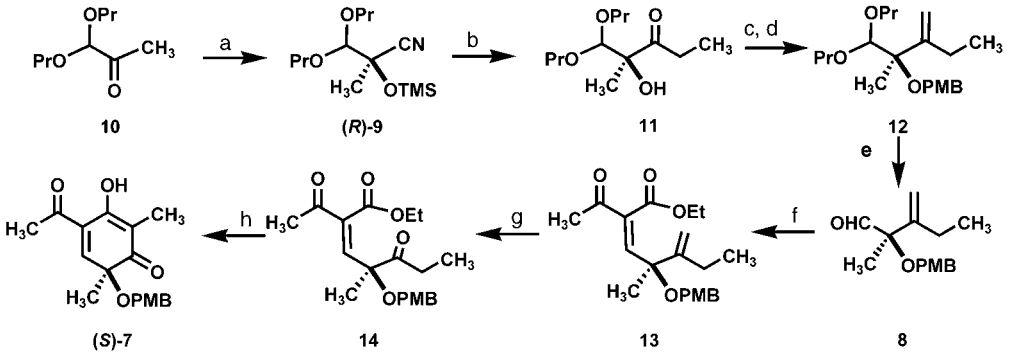
Scheme 2. Retrosynthetic analysis of bisorbicillinol (**2**). TMS = trimethylsilyl.

eroatom-substituted quaternary stereocenter in sorbicillinol derivative **1c**. Considering the sensitive nature of the dienone side chain,[5] we planned to introduce it at a later stage in our synthesis of **1c**. We envisaged that quinol **7** could be derived from aldehyde **8** through a Knoevenagel condensation and a subsequent Claisen–Vorländer condensation.[6] Aldehyde **8** could be prepared from cyanohydrin (*R*)-**9**, which was prepared in 92% *ee* and quantitative yield on a multigram scale by a modified cinchona alkaloid catalyzed enantioselective cyanosilylation of acetal ketone **10** (Scheme 3).[7]

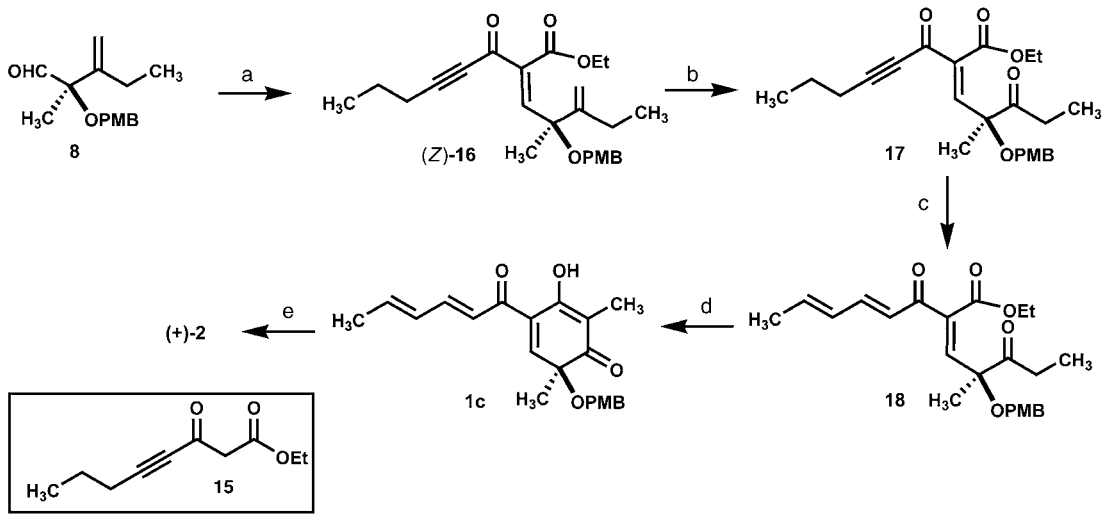
The addition of Grignard reagent EtMgBr to the optically active cyanohydrin **9** in THF/Et_2O proceeded smoothly to form α-hydroxy ketone **11** in nearly quantitative yield (Scheme 3).[8] After masking the ketone as a methylene group through a Wittig olefination,[9] the tertiary alcohol was protected as a *para*-methoxybenzyl (PMB) ether to furnish **12**.[10] The acetal group of **12** was readily hydrolyzed in excellent yield with aqueous HCl to provide aldehyde **8**, which was required for the critical Knoevenagel condensation. A modification of the procedure developed by Lehnert[11] was used for the $TiCl_4$-promoted Knoevenagel condensation of aldehyde **8** with ethyl acetoacetate, which proceeded to generate **13** as a 7:1 mixture of isomers (*Z*/*E*). The desired *Z* isomer was isolated in 85% yield. Ozonolysis in the presence of pyridine at −72 °C provided diketone ester **14** in 80% yield.[12] Gratifyingly, the Claisen–Vorländer condensation with NaOH in dry dimethyl sulfoxide (DMSO) furnished the PMB-protected chiral quinol **7** in 67% yield.

Having secured an eight-step enantioselective route for the construction of the chiral quinol ring, we turned our attention to the installation of the dienone side chain to form the PMB-protected sorbicillinol **1c**. Unfortunately, all attempts to accomplish this task through either an aldol condensation or a two-step sequence[5b] of allylation followed by dehydrogenation were unsuccessful because of the propensity of **7** to undergo decomposition under basic conditions. We then began to explore an alternative strategy involving the introduction of all the carbon atoms required for the construction of sorbicillinol derivatives **1** before the formation of the quinol ring. We envisaged using the readily accessible ynone ester **15**[13] instead of ethyl acetoacetate for the Knoevenagel condensation (Scheme 4) with subsequent isomerization of the alkynone to a dienone.

The Knoevenagel condensation of **15** with aldehyde **8** proceeded in the presence of *N*-methylmorpholine (NMM)[11b] with exceedingly high Z selectivity ($Z/E > 50:1$) to afford **16** in 93% yield. Following the ozonolysis of **16**, the isomerization of ynone **17** to dienone **18** was accomplished in 92% yield with a modified Trost–Lu protocol[14] utilizing palladium acetate and tri-*p*-tolylphosphine. The outcome of the Claisen–Vorländer cyclization of **18** depended critically on the base used for the generation of the enolate, as **18** readily underwent decomposition with either lithium diisopropylamide (LDA) or NaH, whereas no reaction occurred with lithium bis(trimethylsilyl)amide (LiHMDS) or sodium bis(trimethylsilyl)amide (NaHMDS). After numerous experi-



Scheme 3. Conditions: a) TMSCN, $(DHQ)_2AQN$ (2 mol%), $CHCl_3$, 100%, 92% *ee*; b) EtMgBr, Et_2O/THF (4:1), 98%; c) Ph_3PCH_3Br, $Et(Me)_2COK$, benzene, 82%; d) $PMBOC(=NH)CCl_3$, TfOH (cat.), Et_2O, 92% (based on the recovered starting material); e) 3 N HCl (aq), acetone, 90%; f) ethyl acetoacetate, $TiCl_4$, pyridine, THF, 85%; g) ozone, pyridine, CH_2Cl_2, 80%; h) NaOH, DMSO, 67%. $(DHQ)_2AQN$ = 1,4-bis(dihydroquinyl)anthraquinone, TfO = trifluoromethanesulfonate; PMB = *para*-methoxybenzyl.



Scheme 4. Conditions: a) **15**, $TiCl_4$, NMM, THF, 93%; b) ozone, pyridine, CH_2Cl_2, 99%; c) $Pd(OAc)_2$ (cat.), *p*-tol_3P, benzene, 92%; d) Ph_3COH, KH, THF, 90%; e) TFA, CH_2Cl_2, 54%. tol = tolyl.

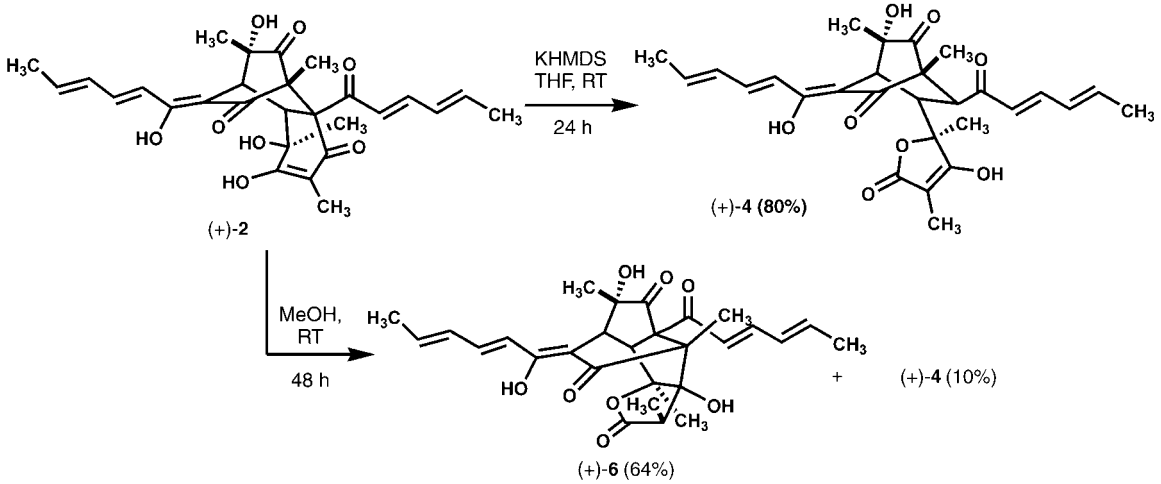
ments, we found that the cyclization proceeded cleanly with Ph_3COK to afford PMB-protected sorbicillinol **1c** in 90% yield. Treatment of **1c** with trifluoroacetic acid (TFA) at room temperature[15] accomplished the removal of the PMB group and the [4+2] dimerization of the resulting sorbicillinol **1a** in one pot to afford (+)-bisorbicillinol (**2**) in 54% yield after isolation. The conversion of (+)-**2** into (+)-**4** following the procedure reported by Nicolaou et al.[2c,d] allowed us to complete an 11-step enantioselective synthesis of **4** in 15% overall yield.[16,17]

In light of the proposal by Abe et al. that bisorbicillinol (**2**) is the possible biosynthetic precursor for bisorbicillinolide (**6**),[3b] we attempted the conversion of synthetic (+)-**2** into (+)-**6**. We were pleased to observe that (+)-**2**, on standing in methanol for 48 hours, rearranged to give (+)-**6** and (+)-**4** as a 4:1 mixture, which after isolation gave these compounds in 64% and 10% yield, respectively (Scheme 5). Thus, the first total synthesis of bisorbicillinolide (**6**) was completed.[16,17]

In conclusion, the first enantioselective total syntheses of bisorbicillinolide (**6**), bisorbicillinol (**2**), and bisorbibutenolide (**4**) have been accomplished in 10/11 steps and 12–19% overall yields by using a modified cinchona alkaloid catalyzed cyanosilylation as the stereochemistry-defining step.[18] Moreover, the rearrangement of **2** into **6** sheds light on the biosynthesis of **6**. Further exploration of the potential for modified cinchona alkaloid catalyzed enantioselective ketone cyanosilylations in target-oriented synthesis are now underway. These investigations are being carried out in the context of asymmetric total syntheses of other complex natural products and biosynthetically related analogues of chiral quinols **7** or sorbicillinol derivatives **1**.

Received: February 8, 2005
Published online: April 28, 2005

Keywords: bisorbicillinoids · natural products · rearrangement · sorbicillinol · total synthesis



Scheme 5. Total synthesis of bisorbicillinolide (**6**).

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[16] Synthetic (+)-**2**, (+)-**4**, and (+)-**6** were spectroscopically identical to reported natural products (see the Supporting Information for details). (+)-**2**: $[\alpha]_D = +181°$ ($c = 0.23$, MeOH) (Ref. [17a]: $+195.2°$ ($c = 0.5$, MeOH)); (+)-**6**: $[\alpha]_D = +310°$ ($c = 0.05$, MeOH) (Ref. [17b]: $+318°$ ($c = 0.1$, MeOH)); (+)-**4**: $[\alpha]_D = +128.6°$ ($c = 0.14$, MeOH) (Ref. [17b]: $+124.4°$ ($c = 0.5$, MeOH)).

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[18] The absolute configuration of cyanohydrin **9** has been determined to be *R*;[7] consequently, the current asymmetric syntheses with (*R*)-**9** as an intermediate provide direct experimental evidence confirming the previous assignment of the absolute configurations for (+)-**2**, (+)-**4**, and (+)-**6** based on their biosynthesis hypothesis (see the Supporting Information).

