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Total Syntheses of Hopeanol and Hopeahainol A Empowered by a Chiral Brønsted acid-Induced Pinacol Rearrangement**

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hopeanol; hopeahainol A; resveratrol; cascade reaction; total synthesis

Although the stilbene resveratrol is simple in terms of its size and functional group array, it possesses high chemical reactivity, a property that enables its conversion into hundreds of architecturally diverse bioactive oligomeric natural products.^[1–3] Among recent dimeric isolates, hopeanol and hopeahainol A (**1** and **2**, Scheme 1) are two of the most intriguing given their constrained, partially dearomatized bicyclic cores and potent activity in antitumor and acetyl-cholinesterase inhibition assays.^[4] Indeed, these molecules have already been the subject of synthetic interest, with reports by Nicolaou, Chen, and co-workers describing racemic and enantioselective syntheses of **1** and **2** in 15 linear steps.^[5] Their route featured several cascade-based bond constructions^[6] and the discovery that hopeahainol A (**2**) could be converted into hopeanol (**1**) upon treatment with base, an idea counter to the original biosynthetic proposal.^[4b] In this communication, we describe a distinct approach for the total synthesis of these natural products empowered by a unique, reagent-driven pinacol rearrangement and substrate-specific oxidation chemistry. Significantly, it has potential for scaleability as well as biogenetic implications.

Our retrosynthetic analysis is shown in the lower portion of Scheme 1, wherein our key disconnections were focused on rapidly constructing the 7-membered ring and attendant quaternary carbon (C-7b) found in both natural products as best noted by a redrawing of **1** and **2**. Critical insights came following a change in the oxidation state of **2** to that of **3**, in that we anticipated that its all carbon-based quaternary center (C-7b) could potentially arise from diol **5** through a pinacol rearrangement.^[7] Although such events often possess modest selectivity due to ambiguity in the site of carbocation formation and/or migrating group, we hoped that the specific patterning of **5** could avoid such issues. And, assuming that such a rearrangement could proceed with any stereoisomeric variant of **5**, then issues of diastereocontrol would not be a relevant concern since all isomers of **3** should be able to be funneled to racemic **2** through oxidation chemistry. Issues in diastereocontrol occurred several times in the Nicolaou/Chen approach to this same ring system,^[5] eroding overall efficiency and material throughput since such flexibility was not part of their design.

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Additionally, we felt the complete route should be concise if the materials needed for this key rearrangement step could arise from ketone **6**, variants of which we synthesized previously through acid-induced cyclizations of alcohol **7**.^[8] These materials have already enabled controlled syntheses of nearly 20 dimeric and higher-order natural products within the resveratrol class through several distinct, cascade-based constructions of diverse C–C and C–O bonds.^[8,9] Finally, the route had two additional appealing elements. First, it is redox economic.^[10] Second, it might possess biogenetic relevance given the structures of other 7-membered ring natural products. For example, if reactive compounds **8–10** were precursors^[11] for natural products **11–14**^[12] via proton cyclizations, then the same starting materials could lead to the C-7b quaternary carbon of **1** and **2** by initial oxidation (to generate **5** or a related congener) followed by acid treatment as likely needed to initiate pinacol rearrangement.^[13]

We began our efforts by synthesizing diols of type **5**. As shown in Scheme 2, that goal was accomplished through a unique protocol starting from ketone **15** (prepared in 5 steps from commercial resveratrol in 48% overall yield, see Supporting Information),^[14] a methyl ether protected version of **6** (cf. Scheme 1) redrawn with three-dimensional structure.^[15] Following Corey–Chaykovsky epoxidation,^[16] which afforded **16** with complete relative stereocontrol, subsequent dissolution in CH₂Cl₂ and stirring with AcOH at 25 °C generated what we believe to be acetate-opened epoxide and/or an intermediate diol with inverted chirality at the C-7b position;^[17] subsequent exposure to Dess–Martin periodinane, followed by Grignard attack, afforded separable diols **19** and **20** in a 1:1.3 ratio.^[18] Critically, the two ring-based chiral centers were formed with complete relative stereocontrol, an outcome that can be rationalized via the steric bulk of the remote aryl ring within **17**^[19] and one that proved essential to the success of the later sequence (*vide infra*). Worth noting is that other routes towards pinacol-type precursors were attempted, largely by trying to add nucleophiles to the ketone in **15**. However, none provided the expected materials with the exception of the Tebbe reagent; in this case, the resultant methylene could not be functionalized further.

Nevertheless, with **19** and **20** in hand, explorations into the critical pinacol rearrangement could begin. Pleasingly, many protic and Lewis acids (such as *p*-TsOH, PPTS, and TMSOTf) could generate the desired quaternary carbon of **22** and **23**, though there were some (such as benzoic acid) that did not. However, those that worked did so in low to moderate yield and modest diastereocontrol, a critical issue since only **22** proved competent in later chemistry. Several side-products were also observed in varying amounts, the most significant and consistent of which was epoxide **24**, a material whose structure was confirmed by X-ray analysis and which could not be converted into a pinacol rearranged product under any conditions.^[20] A small subset of these initial results are collated within Table 1 in entries 1–3. However, the most important and consistent observation in all experiments was that diol diastereomer **19** transformed into **22** quickly and with high diastereoselectivity (typically >10:1), while **20** reacted much more slowly, provided more side-products, and required increased reaction temperatures for any conversion (leading to **22** and **23**).^[21]

As such, the goal for optimization became finding an acid source with a suitable *pK_a* capable not only of rearranging **19** smoothly, but also improving the throughput of **20**. Our first significant advance based on this analysis occurred when a mixture of both **19** and **20** was stirred with 1.0 equivalents of (*R*)-BINOL•HPO₄^[22] in CHCl₃ at 100 °C under microwave irradiation for 1 h. These conditions led to pinacol-rearranged products **22** and **23** in 63% yield and 3.9:1 diastereocontrol in favor of **22** (Table 1, entry 4) alongside varying amounts of epoxide **24** (~10–15%).^[23] Other solvents and conditions with this promoter afforded decreased selectivity and/or yield (entries 7–9) for **22**. Interestingly, while use of the opposite enantiomer of promoter [(*S*)-BINOL•HPO₄] under these conditions

afforded nearly identical results, its racemic form provided inferior stereoselection (entries 5 and 6).^[24] The same phenomenon was also observed when decreased quantities of phosphoric acid were used, though these cases afforded improved diastereoselectivity (4.5:1) at the price of yield (entries 10–12). It was also observed when the promoter size was changed to that of VAPOL•HPO₄ (**21**, entries 13–15).^[25] In these cases, high diastereoselection (>18:1) and similar throughput efficiency (56% yield of **22** and **23**; trace **24**) was achieved when a single enantiomer was used. At present, it is too preliminary to provide a rationale for these unexpected outcomes between the use of racemic or single enantiomer forms of these promoters other than to state that it is a reproducible result over several runs. We do note, however, that this effect may be specific to materials of the BINOL and VAPOL scaffolds in that both chiral and racemic CSA gave nearly identical results (entries 16–18).^[26] Current work is directed at understanding the parameters of this event more fully, especially determining whether chiral acids have value in other pinacol rearrangements where incongruities exist in diastereomer reactivity and stereoselection. What we can state is that, to the best of our knowledge, this event constitutes the first use of a chiral Brønsted acid for this rearrangement in a total synthesis.

With this key quaternary carbon forged with good efficiency, our next goal was to effect the remaining oxidations needed to access the natural products. These steps had to install the missing ketone located at C-8a, convert the hindered aldehyde into a carboxylic acid, and generate the C–C bond leading to the dearomatized *p*-quinone ring essential to hopeanol (**1**). After an exhaustive screen of oxidants [including DDQ, hypervalent iodine, and Pd(OAc)₂/H₂O₂],^[27] we discovered that the Jones reagent could uniquely accomplish two of these tasks when it was added to an acetone solution of **22** (Scheme 3) at 0 °C and stirred for 30 min. This step leading to **26** proceeded in 27% overall yield, with only the drawn diastereomer of **22** reacting productively.^[28] Equally intriguing, this event appears to proceed via the initial formation of **25**, as a trace amount of this material was obtained when insufficient Jones reagent was available to drive the reaction to completion; this material (i.e. **25**) was quickly converted into **26** following re-exposure to the Jones reagent. Surprisingly, the aldehyde within **22** was not oxidized in this step; thus, a different oxidant (NaOCl) proved necessary. Then, following treatment with TMSCHN₂, protected hopeanol (**27**) was obtained in 75% yield (4.3% overall from **15**). Despite much effort, however, this material could not be deprotected,^[29] including use of the Nicolaou/Chen conditions.^[5]

As such, efforts were made to deprotect the phenolic methyl ethers earlier in the sequence, such as at the stage of aldehyde **26** and intermediate **22**. Unfortunately, in both cases (as well as many others not explicitly described here), these attempts consistently led to rearrangement reactions and/or decomposition, one of which is denoted in the Supporting Information section. Pleasingly, when carboxylic acid **28** was treated with BBr₃ in CH₂Cl₂, methyl ether cleavage was attended by lactone formation to afford **29**; a small amount of decarboxylated material was also observed. Although all attempts at oxidizing this material directly to **1** or **2** failed, its benzyl ether analog could be oxidized with CAN to afford the structure of hopeahainol A in 65–89% yield depending on the scale. No other oxidant succeeded. Finally, deprotection with BCl₃ then delivered the natural product (**2**) in 75% yield, a portion of which was converted to hopeanol (**1**) following the exact conditions developed by Nicolaou, Chen, and co-workers.^[5] In total, the route to hopeahainol A (**2**) is 14 steps long, and as one reflection of its overall efficiency (4.0% overall from **15**), we have prepared over 60 mg of it along with 180 mg of its protected precursor to date.

In conclusion, we have accomplished an efficient total synthesis of both hopeanol (**1**) and hopeahainol (**2**) from our key precursor for the controlled preparation of the resveratrol family (i.e. **7**) through a pathway that traces both of these structures to a more common manifold within this fascinating oligomer family. Critical steps involved a pinacol

rearrangement empowered by a chiral phosphoric acid and multi-stage, substrate specific oxidation processes. Current efforts are directed towards developing asymmetric syntheses of these materials and probing their chemical biology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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13. If this proposal is accurate, it would mean that these dimers result from the reorganization of bonds within a dimeric framework rather than a union of resveratrol monomers as originally proposed (Ref. 4).
14. This route is shorter than our previously published procedures (Ref. 8) due to a change in commercial starting material. See SI for full details.
15. The drawn orientation of **15** is based on a crystal structure of a closely related compound (see SI) indicating the *pseudo*-axial orientation of the pendant aryl ring on the 7-membered ring as well as the positioning of the ketone relative to the neighboring aryl substituents.
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17. The intermediate acetate was never observed and likely hydrolyzes on work-up; in practice, the AcOH reaction and oxidation were performed as a single step without intervening chromatography.
18. Extensive efforts to characterize **19** and **20** via crystallization failed; the current assignment is based on nOe experiments as noted in the SI.
19. As evidence for the existence of **17**, the pendant aryl ring could form a disubstituted quinone methide in some yield (see SI).
20. This outcome suggests that semi-pinacol processes from **24** are not operative.
21. The basis for the differential diastereoselectivity of **19** and **20** in the pinacol rearrangement is not obvious based on simple molecular models, though it is clear based on experimental observation that diol **19** has a lower energy barrier for the conversion.
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Scheme 1.

Structures of hopeanol (**1**) and hopeahainol A (**2**) and retrosynthetic analysis based on a pinacol rearrangement and site-specific oxidations inspired by a potential biogenesis from **8–10**.

Scheme 2.

Synthesis and pinacol rearrangement of **19** and **20**. a) Me_3SI (10 equiv), *n*-BuLi (8.0 equiv), THF, 0 °C, 1 h; d) AcOH , CH_2Cl_2 , 25 °C, 30 min; b) Dess-Martin periodinane (1.2 equiv), 25 °C, 1 h, 45% over two steps; c) 4-OMePhMgBr (5.0 equiv), THF, 0 25 °C, 1.5 h, 87%, ~1.3:1 of **20**:**19**; d) (R)-**21** (1.0 equiv), CHCl_3 , μwave , 100 °C, 1 h, 56% **22**:**23** as a >18:1 mix of diastereomers.

Scheme 3.

Completion of hopeanol (**1**) and hopeahainol A (**2**). a) Jones reagent (20 equiv), acetone, 0 °C, 30 min, 27%; b) resorcinol (15 equiv), NaH₂PO₄•H₂O (10 equiv), NaClO₂ (5 equiv), THF/*t*-BuOH/H₂O (1/1/2), 25 °C, 3 d, 70%; c) TMSCHN₂ (5 equiv), THF/MeOH (4/1), 0 °C, 15 min, 98%; d) resorcinol (15 equiv), NaH₂PO₄•H₂O (10 equiv), NaClO₂ (5 equiv), THF/*t*-BuOH/H₂O (1/1/2), 25 °C, 3 d; e) BBr₃ (18 equiv), CH₂Cl₂, -78 °C, 3 h; f) BnBr (20 equiv), K₂CO₃ (20 equiv), *n*-Bu₄NI (1.0 equiv), acetone, 25 °C, 12 h, 29% over 3 steps; g) CAN (8.0 equiv), DMSO, 25 °C, 12 h, 65–89%; h) BCl₃ (12 equiv), CH₂Cl₂, -78 °C, 15 min, 75%; i) NaOMe (1.2 equiv), MeOH, 25 °C, 4 d, 69%. CAN = ceric ammonium nitrate.

Table 1

Exploration of the key pinacol cyclization step.

Entry	Acid	Equivalents	Solvent	Temperature [°C]	Time [h]	Yield [%]	d.r.
1	<i>p</i> -TsOH	5.0	toluene	25	24	40–60 ^[a]	2.5:1 ^[a]
2	PPTS	3.0	toluene	100	1	39	3.3:1
3	H ₃ PO ₄	3.0	THF	25	24	38	5.5:1
3	H ₃ PO ₄	3.0	THF	25	24	38	5.5:1
4	(<i>R</i>)-BINOL•HPO ₄	1.0	CHCl ₃	100 ^[b]	1	63	3.9:1
5	(<i>S</i>)-BINOL•HPO ₄	1.0	CHCl ₃	100 ^[b]	1	62	3.9:1
6	rac-BINOL•HPO ₄	1.0	CHCl ₃	100 ^[b]	1	55	3.0:1
7	(<i>R</i>)-BINOL•HPO ₄	1.0	CHCl ₃	25	24	32	>10:1
8	(<i>R</i>)-BINOL•HPO ₄	1.0	DMSO	25	24	33	1.8:1
9	(<i>R</i>)-BINOL•HPO ₄	1.0	CHCl ₃ /MeOH (5:1)	25	24	41	5.0:1
10	(<i>R</i>)-BINOL•HPO ₄	0.7	CHCl ₃	100 ^[b]	1	55	4.5:1
11	(<i>S</i>)-BINOL•HPO ₄	0.7	CHCl ₃	100 ^[b]	1	54	4.6:1
12	rac-BINOL•HPO ₄	0.7	CHCl ₃	100 ^[b]	1	50	3.1:1
13	(<i>R</i>)- 21	1.0	CHCl ₃	100 ^[b]	1	56	18.4:1
14	(<i>S</i>)- 21	1.0	CHCl ₃	100 ^[b]	1	56	18.9:1
15	rac- 21	1.0	CHCl ₃	100 ^[b]	1	59	13.6:1
16	(<i>R</i>)-CSA	2.0	CHCl ₃	50	2	54	4.0:1
17	(<i>S</i>)-CSA	2.0	CHCl ₃	50	2	56	4.1:1
18	rac-CSA	2.0	CHCl ₃	50	2	53	4.0:1

^[a] Both yield and d.r. proved highly variable between runs; d.r. as high as 4:1 for **22:23** were observed, but 2.5:1 was more common, especially on scale;

/b/ under microwave irradiation.

PPTS = pyridinium *p*-toluenesulfonate, CSA = camphorsulfonic acid.

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