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Communication

Total Synthesis

Total Synthesis of the Resveratrol Oligomers (±)-Ampelopsin B and (±)-ε-Viniferin

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Abstract: The total synthesis of the resveratrol dimers (±)-ampelopsin B and (±)-ε-viniferin is reported. Highlights of the approach include the use of cyclopropylmethyl groups to protect aromatic alcohols. This group allows an acid promoted three-step, one-pot deprotection–epimerization–cyclization of an advanced intermediate to give (±)-ampelopsin B. An important advantage with our strategy is the possibility of synthesizing analogs to these natural products to further study the chemistry and biology of resveratrol oligomers.

Introduction

We recently discovered that (–)-hopeaphenol (**1**), a tetramer of resveratrol (**2**) (Figure 1) isolated from the stem bark of *Hopea hainanensis*, inhibits the type III secretion system[1] (T3SS) in *Yersinia pseudotuberculosis* and *Pseudomonas aeruginosa*.[2] The conserved[3] T3SS is critical for these pathogens to cause disease and therefore constitutes an attractive target for the development of new antibacterials.[4] While large amounts of (–)-hopeaphenol can be obtained from natural sources,[5] structure–activity relationships cannot be elucidated since structural isomers are not readily available. We became intrigued by the three-dimensional structure of *trans* dihydrobenzofurans and decided to investigate whether the entire hopeaphenol structure is required, or if it can be reduced to a resveratrol dimer such as ampelopsin B (**4**) (Figure 1). The scientific community's interest in the chemistry and biology of polyphenols is increasing[6] and the total syntheses of several related natural products have been reported.[7] This includes the biomimetic synthesis of ampelopsin B via ε-viniferin (**3**) by an oxidative dimerization of resveratrol[8] followed by a final cyclization. However, a flexible and divergent synthetic strategy that allows alterations to the substitution pattern of, for example, ampelopsin B does not exist.

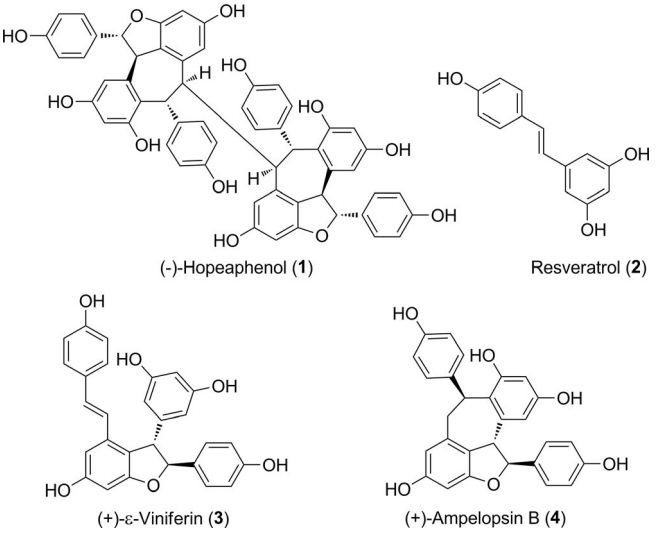
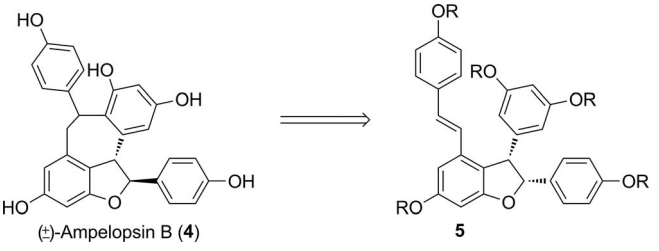


Figure 1. The structures of (–)-hopeaphenol (**1**), a tetramer of resveratrol (**2**), and (+)-ε-viniferin (**3**) and (+)-ampelopsin B (**4**), both dimers of resveratrol.

We hypothesized that if a suitable protecting group could be found it should be possible to obtain ampelopsin B (**4**) in a three-step, one-pot deprotection–epimerization–cyclization of compound **5** (Scheme 1). A model experiment was first executed to investigate whether the epimerization of C2 was feasi-



Scheme 1. The envisioned three-step, one-pot formation of ampelopsin B (**4**) from compound **5**.

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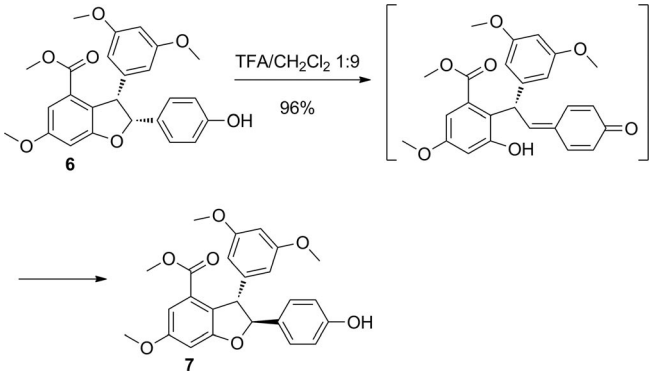
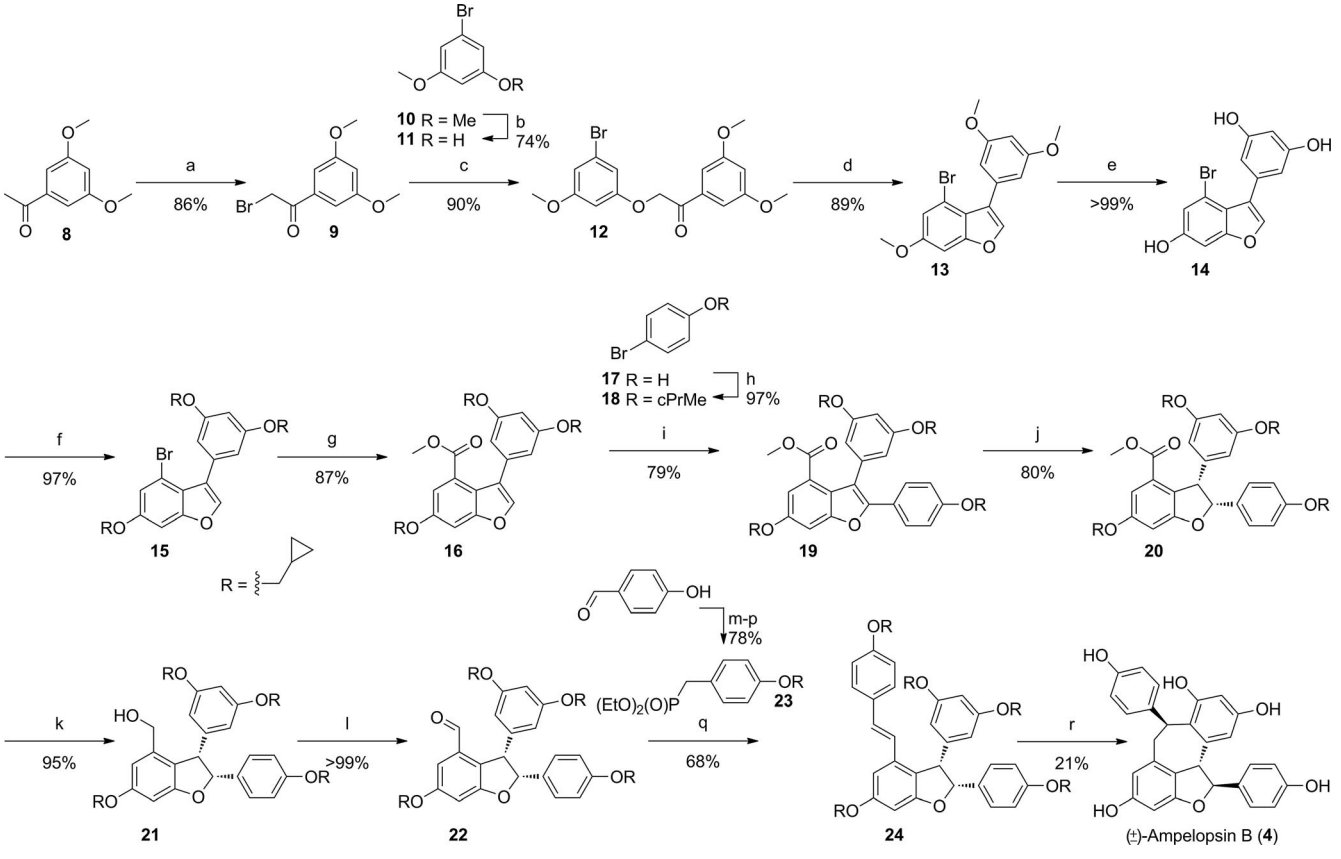
ble. After investigating several options[9] *cis*-dihydrobenzofuran **6** was prepared[10] in five steps using methods inspired by Kim's synthesis of pentamethylated viniferifuran.[11] By treating compound **6** with the moderately strong acid trifluoroacetic acid (TFA) in CH_2Cl_2, *trans* epimer **7** was obtained in excellent yields (Scheme 2). The next step was to investigate if a one-step deprotection–cyclization could be realized on protected ε-viniferin. Pentamethylated ε-viniferin was first prepared by methylating ε-viniferin (**3**) obtained through dimerization of resveratrol (**2**).[8] However, despite our best efforts we did not manage to find conditions for this reaction with phenols protected as methyl ethers. Most well established techniques for ether cleavage were investigated but none could remove the methyl groups and cyclize to produce ampelopsin B in acceptable yields.



Scheme 2. The key step in the synthesis of pentamethylated (±)-ε-viniferin.

Results and Discussion

Hence, we realized that a different protecting group was needed and theorized that cyclopropylmethyl groups (cPrMe) should be suitable since they are reported as being relatively easy to remove under acidic conditions using, for example, HCl (aq) in methanol.[12] Synthesis of the cPrMe-protected compound **24** commenced according to Scheme 3. Unfortunately, benzofuran **16** (Scheme 3) could not be prepared directly as the cPrMe protecting groups were incompatible with the benzofuran-forming conditions.[13] Also, we failed to deprotect the methylated analog of **16** since it proved prone to cyclization (see the Supporting Information).[14] Thus, the ester functionality had to be installed after the protecting group switch.



Scheme 3. Preparation of intermediate **24** and synthesis of (±)-ampelopsin B (**4**). Reagents and conditions: (a) $CuBr_2$, EtOAc/$CHCl_3$ (1:1), reflux, 23 h; (b) BBr_3, CH_2Cl_2, 0–20 °C, 23 h; (c) K_2CO_3, acetone, reflux, 2 h; (d) $Bi(OTf)_3$, CH_2Cl_2, reflux, 22 h; (e) BBr_3, CH_2Cl_2, –78–20 °C, 18 h; (f) (bromomethyl)cyclopropane, K_2CO_3, acetone, reflux, 22 h; (g) $Pd(OAc)_2$, K_2CO_3, $Mo(CO)_6$, MeOH, dppf, DMF, 120 °C, 15 h; (h) 4-bromophenol, (bromomethyl)cyclopropane, K_2CO_3, acetone, reflux, 24 h; (i) $Pd(OAc)_2$, tricyclohexylphosphonium tetrafluoroborate, K_2CO_3, pivalic acid, DMA, 100 °C, 20 h; (j) Pd/C 10 %, H_2, EtOAc/MeOH (1:9), 20 °C, 3 d; (k) DIBAL, CH_2Cl_2, –78 °C, 1 h; (l) DMP, CH_2Cl_2, 20 °C, 90 min; (m) 4-hydroxybenzaldehyde, (bromomethyl)cyclopropane, K_2CO_3, acetone, reflux, 24 h; (n) $NaBH_4$, MeOH, 20 °C, 1 h; (o) $SOCl_2$, Et_2O, 20 °C, 2 h; (p) $P(OEt)_3$, 130 °C, 22 h; (q) KO*t*Bu, THF, –78 °C, 16 h; (r) 12 M HCl (aq), THF, 80 °C, 1 h. All chiral compounds are racemic mixtures. dppf = 1,1′-bis(diphenylphosphino)ferrocene; DMA = dimethylacetamide; DMP = Dess–Martin periodinane.

Starting from ketone **8** (Scheme 3), which was brominated using $CuBr_2$,[10] and aryl bromide **11**, which was obtained by mono-deprotection of **10** by using BBr_3, compound **12** was formed and consecutively cyclized to benzofuran **13** using $Bi(OTf)_3$. The methyl groups could then be removed by using BBr_3 and replaced with cPrMe groups to form **15**.

After screening a range of conditions (see the Supporting Information) the methyl ester could be installed by using a $Pd(OAc)_2$/dppf catalyzed carbonylation with $Mo(CO)_6$ as the CO source to give **16**.[15,16]

This was followed by a direct arylation at C2 by using $Pd(OAc)_2$ and $P(Cy)_3{\cdot}HBF_4$ to obtain compound **19**.[13,17] The furan ring in **19** was then reduced by catalytic transfer hydrogenation to form the racemic dihydrobenzofuran **20** in excellent yield considering that this transformation typically is difficult and there are only a handful reports in which 2,3-disubstituted benzofurans are hydrogenated.[18] The methyl ester in **20** was first reduced to alcohol **21** with DIBAL and then reoxidized to aldehyde **22** by using Dess–Martin periodinane.[19] The final benzene ring was then connected by using a Horner–Wadsworth–Emmons[20] reaction to form cPrMe-protected "*cis*-viniferin" **24**. Ampelopsin B (**4**) could then be obtained by treating compound **24** with 12 M HCl in THF. This is, to the best of our knowledge, the first total synthesis of ampelopsin B that does not involve a dimerization of resveratrol (**2**). Ampelopsin B (**4**) was obtained in 5 % overall yield over 12 steps in the longest linear sequence and the synthesis concludes with a noteworthy three-step, one-pot deprotection–cyclization–epimerization that proceeds in 21 % yield.

We hypothesized that it should be possible to identify conditions that would provide a delicate balance where deprotection and epimerization is achieved but the cyclization, which presumably proceeds via a quinone intermediate, does not take place. Despite rigorous screening we never managed to find conditions where ε-viniferin (**3**) could be isolated from the final multistep reaction. It became apparent that the cyclization to form ampelopsin B (**4**) took place at milder conditions than what was required to remove the cPrMe protecting groups. Alternative paths to reach ε-viniferin were thus investigated and it was decided to replace cPrMe with acetyl groups in a second protecting group switch. Upon treating **20** with HCl (aq) a one pot deprotection–epimerization could be achieved to form compound **25** (Scheme 4).[21,22] Reprotection of **25** led to an observed change in coupling constant between the protons at C2 and C3 from 8.0 to 4.8 Hz proving the reversed stereochemistry at C2 (Figure 2).

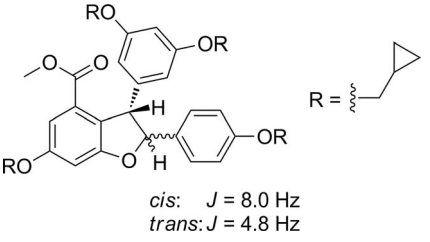
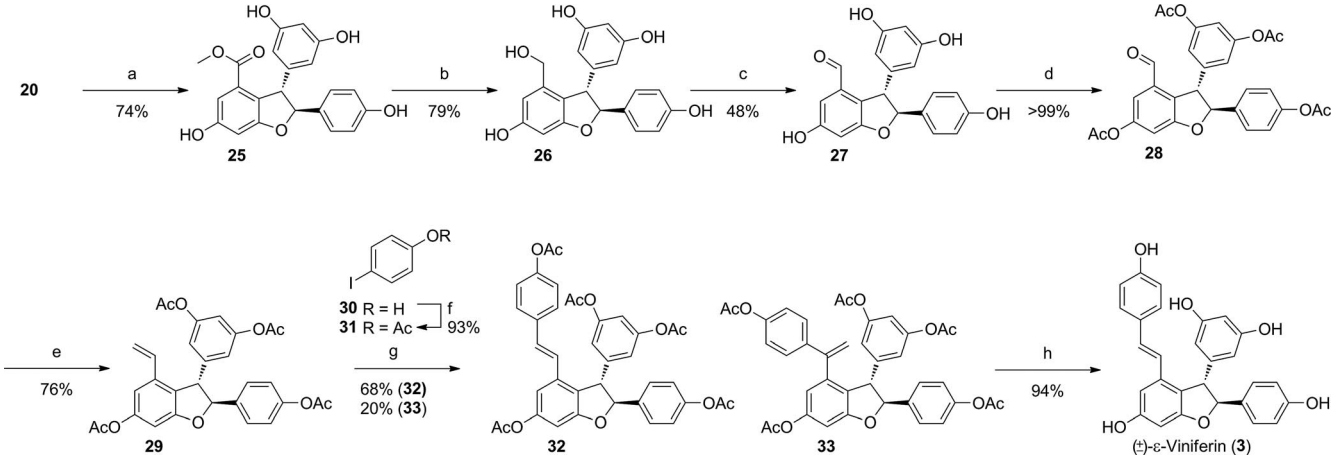


Figure 2. The ^1H–^1H coupling constant (*J*) is 8.0 and 4.8 Hz for the *cis*- and *trans*-epimer of **20**, respectively.

The methyl ester in **25** was subsequently reduced by using $LiAlH_4$ to form alcohol **26** and then reoxidized with PDC to form aldehyde **27**, which was acetyl protected by using Ac_2O and TEA to form **28** [compound **26** has previously been reported[7] as an uncharacterized *cis*/*trans* (1:10) mixture]. Subsequent attempts to transform **28** to **32** in one step by using Horner–Wadsworth–Emmons conditions failed. A single carbon atom was instead added by using standard Wittig[23] conditions to form olefin **29**. Compound **32** could then be prepared by using a Heck coupling.[24] After screening a range of reaction conditions (see the Supporting Information) it was found that $Pd(OAc)_2$, $P(tBu)_3{\cdot}HBF_4$, and TEA in MeCN produced full conversion within three hours at 120 °C. Unfortunately, compound **32** and regioisomer **33** were formed in a 78:22 ratio that we were unable to improve. The two regioisomers were inseparable by column chromatography on silica gel but could be easily separated by preparative thin-layer chromatography. Removal of the



Scheme 4. Synthesis of (±)-ε-viniferin from **20**. Reagents and conditions: (a) 12 M HCl, CH_2Cl_2, MeOH, 100 °C, 1 h; (b) $LiAlH_4$, –78–20 °C, 5 d; (c) PDC, THF, 20 °C, 17 h; (d) Ac_2O, TEA, THF, 20 °C, 17 h; (e) methyltriphenylphosphonium bromide, K_2CO_3, THF, reflux, 20 h; (f) 4-iodophenol, Ac_2O, pyrdine, 20 °C, 18 h; (g) tri-*tert*-butylphosphonium tetrafluoroborate, $Pd(OAc)_2$, TEA, MeCN, 120 °C, 3 h; (h) KOH, MeOH, 0 °C, 70 min. All chiral compounds are racemic mixtures. PDC = pyridinium dichromate; TEA = triethylamine.

acetyl protecting groups by using KOH proceeded smoothly and produced (±)-ε-viniferin (**3**) in 5 % overall yield over 15 steps in the longest linear sequence starting from **8**.

Conclusions

In conclusion, a successful strategy for the total synthesis of ampelopsin B (**4**) and ε-viniferin (**3**) is reported. Through this approach the two natural products were prepared in 12 and 15 steps, respectively, starting with commercially available 3,3-dimethoxyacetophenone. An important benefit of our approach vs. the previously reported dimerization of resveratrol is that specific alterations to the substitution patterns are possible. In addition we explore the unconventional cPrMe group for protection of phenols and our data suggest that this group, due to its greater acid sensitivity compared with methyl groups, should have potential for wider application in the synthesis of polyphenolic compounds. We are currently in the process of synthesizing a library of analogs to these two natural products to establish structure–activity relationships and identify potent inhibitors of bacterial pathogens.

Acknowledgments

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Keywords: Protecting groups · Cyclopropylmethyl · Polyphenols · Total synthesis · Natural products

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