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Concise Synthesis of Bicyclic Pyridinol Antioxidants

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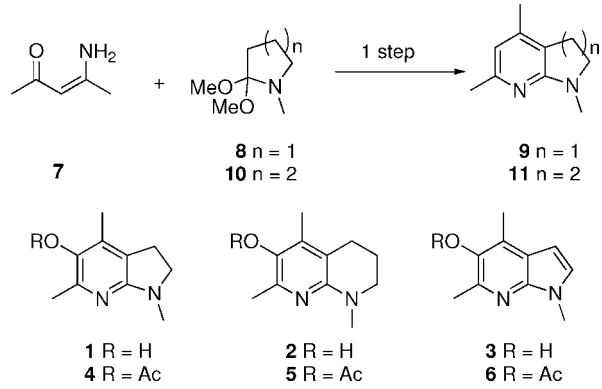
ABSTRACT



The recently reported bicyclic pyridinols 1 and 2 are highly effective antioxidants exhibiting 88- and 28-fold greater potency, respectively, than α-tocopherol when assayed for their ability to suppress the autoxidation of methyl linoleate. Described herein is a short, economical, and scalable strategy for the synthesis of this novel group of antioxidants, as well as analogues 3−6. Key reactions involved the cyclocondensation reaction of lactam acetals with enaminone 7 and selective functionalizaton of the heterocyclic systems.

The importance of antioxidants in human health has been attracting increasing attention as accumulating evidence has demonstrated that reactive oxygen species and other free radicals are implicated in a variety of biological phenomena, including aging, mutation, carcinogenesis, and other diseases.[1,2] α-Tocopherol (α-TOH), a form of vitamin E, is perhaps the best known natural antioxidant. By transferring its phenolic H atom to propagating lipid radicals, it quenches lipid peroxidation.[3] The development of synthetic radical-scavenging antioxidants with activity superior to α-TOH is an ongoing aim of many studies.

6-Amino-3-pyridinols have been synthesized and demonstrated to be very efficient antioxidants. In particular, the bicyclic pyridinols **1** and **2** (Figure 1) displayed 88- and 28-fold larger inhibition rate constants, respectively, than α-TOH in quenching the oxidation of methyl linoleate in benzene solution.[4,5] However, reported syntheses of the bicyclic pyridinols having annulated five-membered or six-membered rings required 11 and 6 steps, respectively, and proceeded in moderate yields. The key step in the reported annulation process consists of an intramolecular inverse electron demand Diels−Alder reaction in diphenyl ether at reflux.[4,5] From a synthetic point of view, the synthesis of azaindole and dihydropyrrolopyridine systems presents a unique challenge.[6,7] A frequently employed strategy for azaindole synthesis starts with a substituted pyridine and appends a pyrrole ring. However, the electron-deficient nature of the pyridine ring limits the application of this method for indole formation.[8] Another

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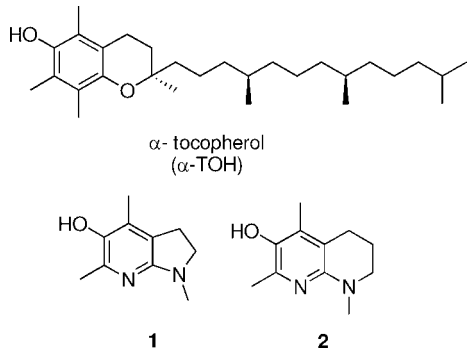
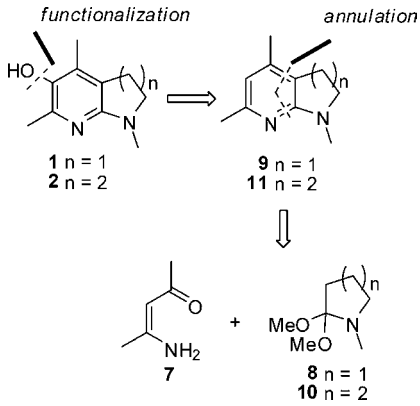


Figure 1. Structures of α-tocopherol and tocopherol-like antioxidants **1** and **2**.

strategy applied to the preparation of azaindoles is through a coupling reaction followed by intramolecular cyclization.[9,10] The dihydropyrrolopyridine structure is usually generated from the azaindole by Pd-catalyzed hydrogenation which typically proceeds sluggishly.[11]

In the context of research projects ongoing in our laboratory, we sought to develop a concise, practical, and economical route to this novel group of antioxidants, which might also be amenable to the facile preparation of structural analogues. A pyridine structure with a fused five- or six-membered ring was constructed in one step by the cyclocondensation of lactam/amide acetals with enaminone **7**. The bicyclic structures so obtained were then easily functionalized to afford several desired analogues.

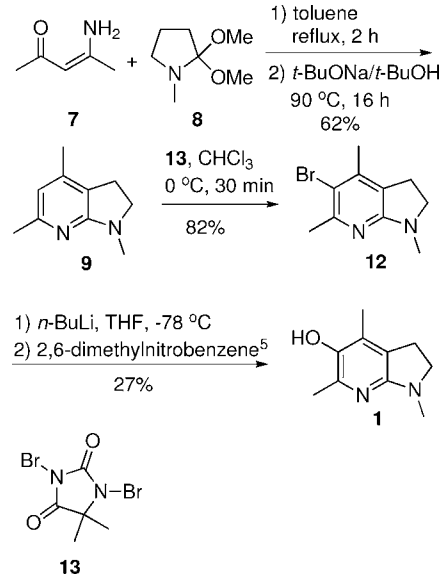
Scheme 1. Retrosynthetic Analyses of Pyridinols **1** and **2**



A retrosynthetic analysis, shown in Scheme 1, suggested that pyridinols **1** and **2** could be prepared from 1,4,6-trimethylpyrrolo[2,3-*b*]pyridine (**9**) or 1,5,7-trimethylpiperidinyl[2,3-*b*]pyridine (**11**) by functional group transformations. The formation of **9** and **11** was envisioned by a cyclocondensation reaction of enaminone **7**[12] with lactam acetals **8** and **10**,[13] respectively.

The synthesis of **1** is shown in Scheme 2; the formation of the dihydropyrrolopyridine (azaindoline) intermediate constitutes the key step. Accordingly, 1,4,6-trimethyl-2,3-

Scheme 2. Synthesis of Pyridinol **1**



dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (**9**) was prepared in 62% yield by treatment of enaminone **7** with lactam acetal **8** in *t*-BuOH/*t*-BuONa at 90 °C.[14] The bromination of **9** was first attempted using NBS as the bromination reagent in concentrated H_2SO_4/TFA.[15] However, the bromination conditions proved to be too harsh, affording dibrominated byproduct as well as the desired monobrominated product. Since these were difficult to separate, another method was sought. 1,3-Dibromo-5,5-dimethylhydantoin (**13**) was chosen for the selective bromination of **9**.[16] The reaction was carried out at 0 °C in chloroform and afforded **12** in 82% yield; no dibrominated byproduct was observed. In the final step, the hydroxylation of **12** to afford pyridinol **1** could be achieved as reported previously, albeit only in modest yield.[5]

The low yield of the final step prompted us to consider other strategies for the conversion of bromide **12** to the corresponding pyridinol **1**. The hydroxylation of aryl halides in high yields has been reported by Buchwald et al. by using KOH in the presence of a Pd catalyst.[17] This approach was attempted using compound **12** (Scheme 3). Due to the instability of **1** toward air oxidation, we also

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(14) This reaction was reported previously, although **9** was obtained in only low yield (24%) by treatment of **7** with **8** at 120–130 °C. See: Jotwani, P.; Singh, J.; Anand, N. *Indian J. Chem.* **1988**, *27B*, 166.
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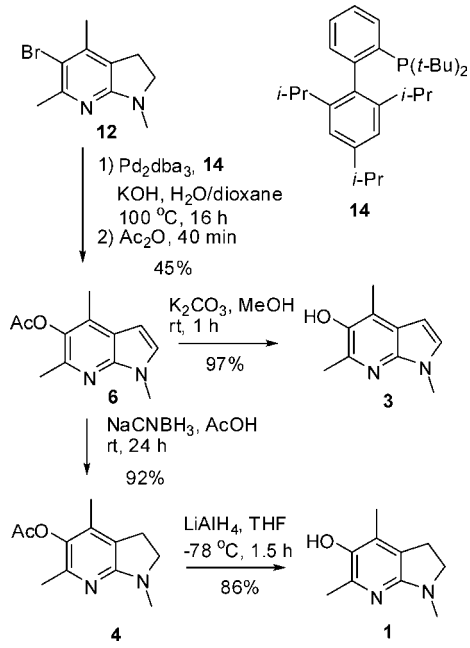
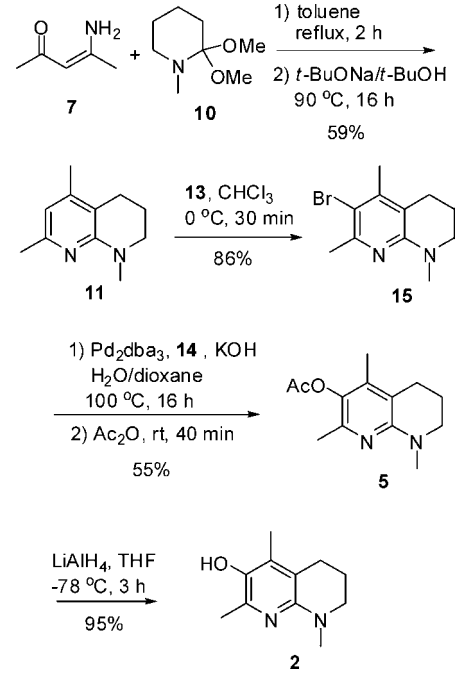
Scheme 3. Synthesis of **1** and the Corresponding Analogues Using an Alternative Route



attempted to convert this compound to its acetate ester **4** following the in situ formation of **1**. This strategy would also permit easy scale-up and storage of the intermediates prior to conversion to the unstable pyridinol. At first, **12** was treated with KOH in 1:1 H_2O-1,4-dioxane in the presence of Pd_2dba_3 and ligand **14** at 100 °C, followed by the addition of Ac_2O. Unexpectedly, we obtained 7-azaindole **6** in 45% yield, rather than 7-azaindoline **4**. Presumably, **4** was quickly oxidized to **6** under Pd-catalyzed hydroxylation conditions in spite of efforts to maintain an inert atmosphere. Although **6** was obtained unexpectedly, we reasoned that its corresponding pyridinol **3** might also prove to be an interesting antioxidant. Accordingly, pyridinol **3** was prepared from **6** by hydrolysis with K_2CO_3 in methanol in 97% yield. The desired 7-azaindoline **4** was prepared readily from azaindole **6** by reduction. The reduction of azaindole has been achieved in low yield previously by Pd-catalyzed hydrogenation.[11] Since $NaCNBH_3$ in acetic acid media has recently been reported to effect the facile reduction of indole to the corresponding indoline,[18] we applied this method in our azaindole system. Compound **4** was obtained in 92% yield. For deacetylation to provide **1**, we employed $LiAH_4$ in THF to remove the acetyl group reductively rather than by hydrolysis, so that this reaction could be carried out at low temperature to facilitate isolation of the final product. The synthesis of **1** was thus achieved in 5 steps and 18.1% overall yield, as compared to the previous reported route which required 11 total steps and provided **1** in 5.8% yield.[5] Further, the new route proceeds through a stable *O*-acetate derivative that can be stored conveniently.

Pyridinol **2**, having a fused six-membered ring, was synthesized using a similar strategy (Scheme 4). The cyclocondensation of **7** with **10** afforded **11** in 59% yield. Bromide **15** was prepared from **11** in 86% yield. Hydroxylation of **15**, followed by acetylation of the nascent OH group, afforded **5** in 55% yield. Finally, pyridinol **2** was obtained by treatment with $LiAH_4$ in 95% yield. This method provided **2** in 26.5% overall yield (four total steps), while **2** was obtained previously in 3.3% overall yield over six steps.

Scheme 4. Synthesis of Pyridinols with Fused Six-Membered Rings



In summary, we have developed an efficient strategy for the synthesis of bicyclic pyridinols. To overcome their instability, the corresponding acetate esters were prepared. Two 7-azaindole analogues were also prepared by this procedure and are expected to have interesting properties as novel antioxidants. The biological evaluation of these and related antioxidants is in progress in our laboratory.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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