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SYNTHESES OF ANTIOXIDANT FLAVONOID DERIVATIVES

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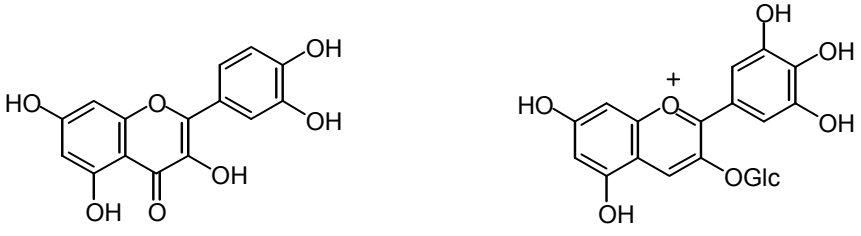
To celebrate the 85th birthday of Professor Albert Eschenmoser

Abstract – Quercetin-caffeic acid and quercetin-curcumin conjugates have been synthesized as potent antioxidants to prevent age-related macular degeneration. Thus, the widely disributed plant antioxidant quercetin was linked to other plant antioxidants, caffeic acid and curucumin, to enhance its antioxidative properties.

Flavonoids (Figure 1), plant secondary metabolites are also called polyphenols due to the presence of multiple phenolic hydroxyls. The flavonols, represented by quercetin **1**, are the most abundant flavonoid, and are present in fruits and vegetables either as aglycones or as glycosides. With respect to the their bioregulatory functions, activities such as antibiotic, antiviral, antiallergic, antimutagenic and antihypertensive are known.[1,2] Most of these activities are due to the antioxidative properties of the multiple phenolic functions.[3-5] The anthocyanins, glycosides of anthocyanidins, are primarily responsible for various colors of flowers and fruits, are renown for their effect against ocular fatigue diseases and age-related macular degeneration (AMD).



quercetin anthocyanin

Figure 1. Flavanoids: quercetin and an anthocyanin

In AMD, fluorescent granules accumulate in the macular region or visual focal region due to natural aging. No efficient remedy is known and in worst cases lead to blindness. So far it has been elucidated that with aging, A2E[6a] (Figure 2) biosynthesized within the eye from two molecules of vitamin A and phosphatidylethanolamine[6b] accumulates in the retinal pigment epithelium cell and is oxidized to an unprecedented nonaoxirane[7-9]; the electrophilic oxiranes react with protein and nucleic acid amino groups leading to their destruction.

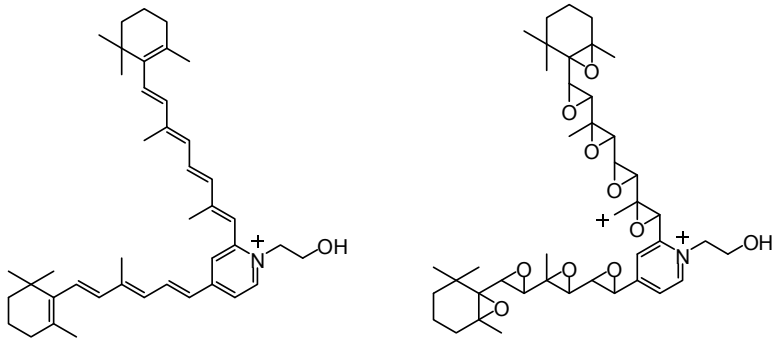


Figure 2. A2E and A2E nonaoxirane

We have shown that anthocyanins in bilberry are effective in preventing the photooxidation of A2E.[10] However, due to the presence of the cationoid oxygen in anthocyanins (Figure 1), they are unstable, difficult to isolate in large quantities and to modify chemically. We thus investigated the antioxidative properties of quercetin and its glycoside, renown potent antioxidants. This showed that they exhibited potent activity against A2E photooxidation (unpublished). We therefore targeted the preparation of antioxidants that are more potent than known flavonoids. The syntheses of these antioxidants are reported.

Our plan was to synthesize modified flavonoid derivatives carrying additional functional groups that would further increase the antioxidant activity of the natural flavonoid. We thus designed quercetin derivatives connected to other natural products, e.g., the antioxidants caffeic acid and curcumin I, linked via an appropriate linker (Figure 2).

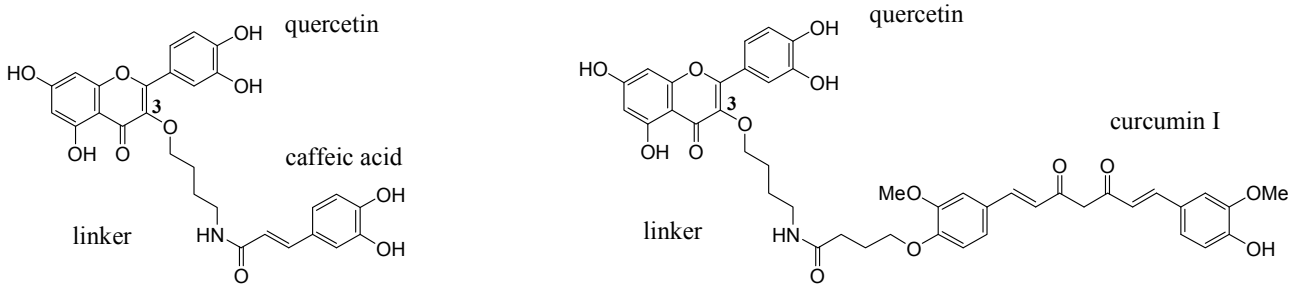
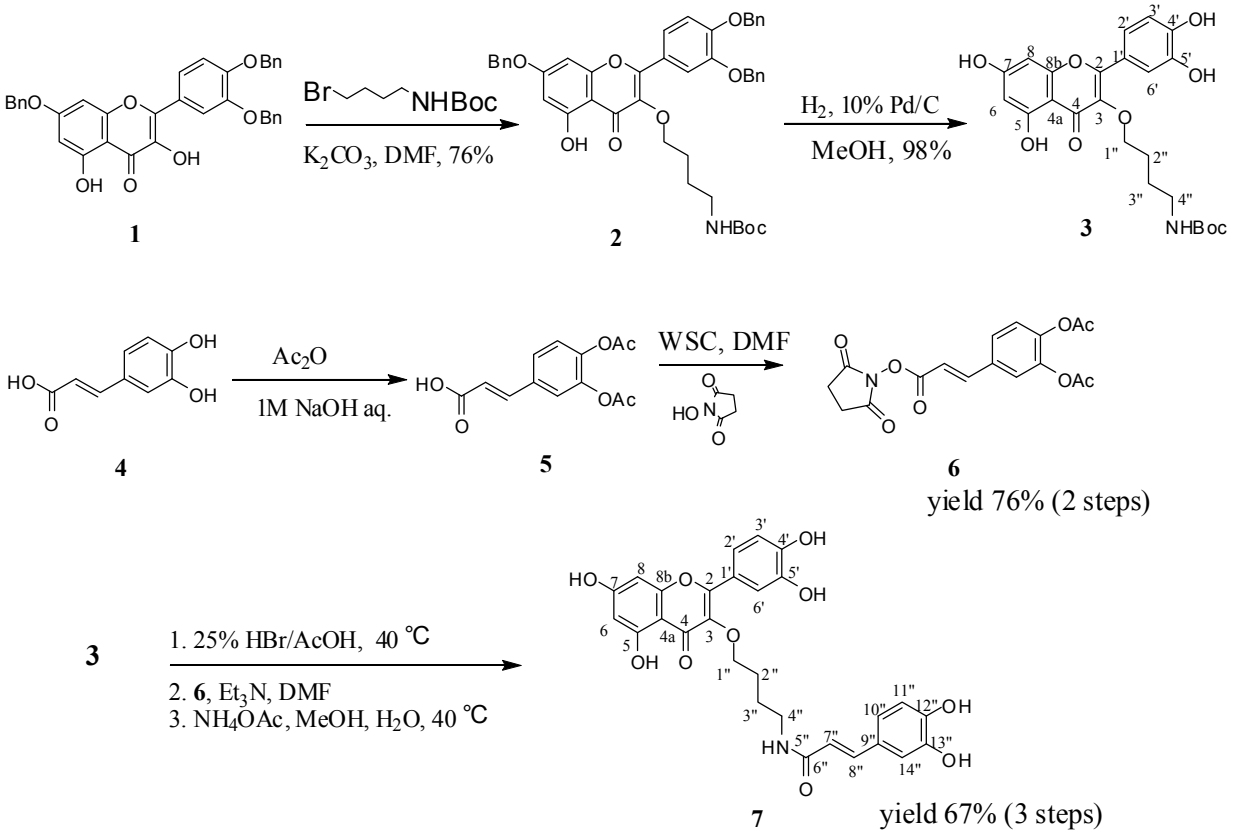


Figure 3. Potent antioxidants

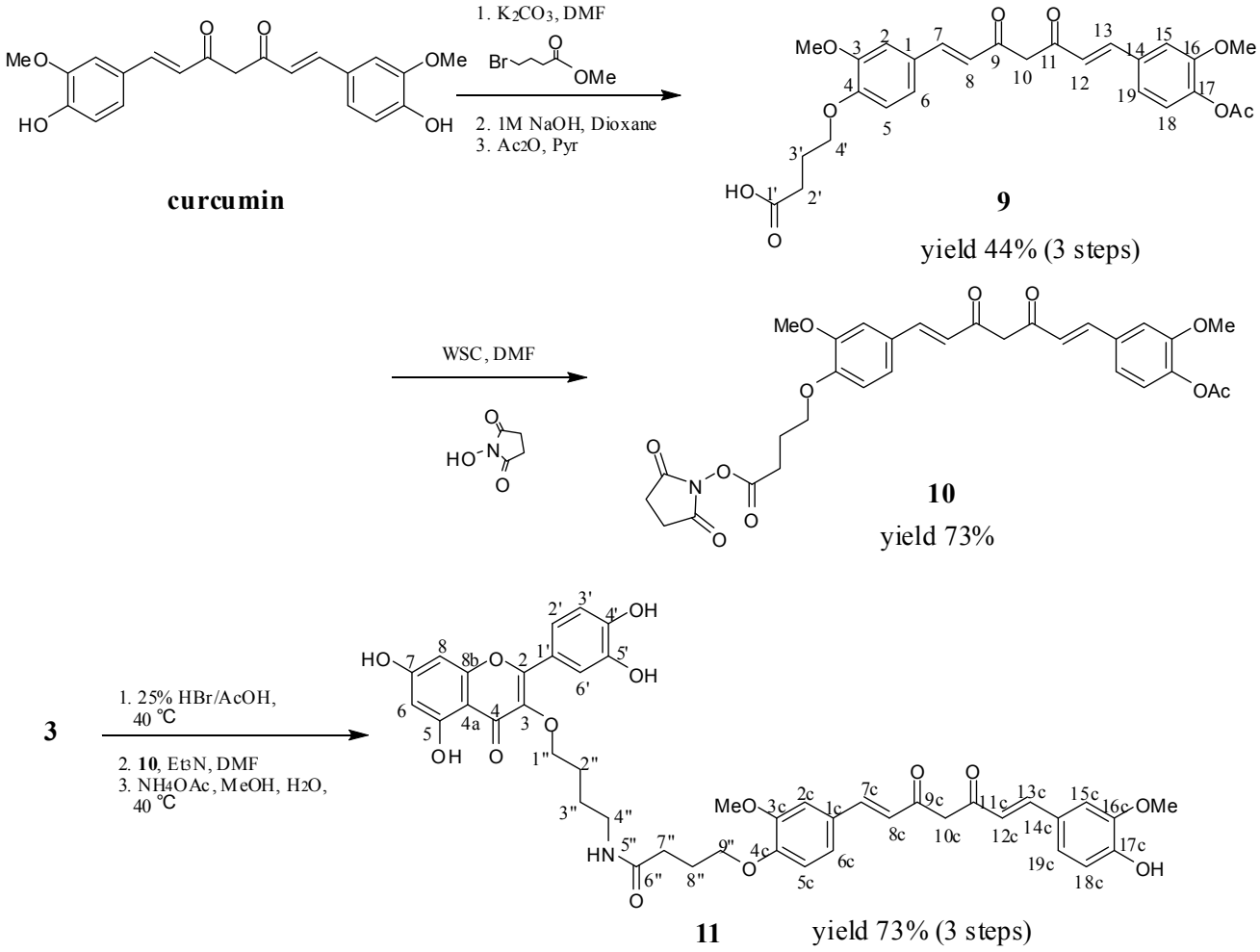
Caffeic acid is a component of the polyphenolic chlorogenic acid, while curcumin is the yellow pigment of the popular Indian curry spice turmeric that exhibits radical scavenging ability.[11,12] We expected such condensation products to enhance both the chemical stability as well as antioxidative activities.

Scheme 1 summarizes the synthesis ofthe quercetin-caffeic acid conjugate **7**. The linker was attached to the quercetin 3-OH, since it was considered that attachment at this position would only exert a small effect on the antioxidant capability. Quercetin with the protected phenolic hydroxyl was prepared from rutin, the glycoside of quercetin.[13] Benzylquercetin **1** was derivatized to aminoquercetin **2** and then to **3**, in 74% overall yield from **1**. The carboxyl group of caffeic acid **4** was converted to activated ester **6** to form the amide bond with aminoquercetin **3**, in 76% overall for the two steps. Finally, coupling of activated-ester **6** and quercetin derivative **3** followed by hydrolysis of the acetyl-group[14] yielded the new flavonid **7**, 67% overall yield for the three steps.



Scheme 1. The synthesis of Quercetin-caffeic acid conjugate

Scheme 2 summarizes the synthesis of quercetin-curcumin I conjugate **11**. The phenolic hydroxyl in curcumin I **8** is elongated to the linker attached **9** in 44% overall yield in three steps. The terminal carboxyl is then converted to activated ester **10**. Coupling of **10** with quercetin derivative **3** followed by hydrolysis of the acetate with ammonium acetate[14] afforded the flavonoid **11**. Finally, coupling of activated-ester **10**and quercetin derivative **3** followed by hydrolysis of the acetyl group gave the new flavonid **11**.



Scheme 2 The synthesis of Quercetin-curcumin conjugate

We have thus achieved the syntheses of new type of antioxidants, quercetin/caffeic acid derivative **7** and quercetin/curcumin derivative **11** from natural flavonoids via an appropriate linker. In addition, this synthetic approach via linker can be applied to similar types of flavonoid derivatives. We plan to compare the antioxidant properties of the quercetin derivatives with other known antioxidants. The study of the antioxidant activity of the mentioned compounds against A2E photooxidation is under study.

ACKNOWLEDGEMENTS

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