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Sustainability from agricultural waste: chiral ligands from oligomeric proanthocyanidins via acid-mediated depolymerization

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ABSTRACT

Oligomeric proanthocyanidins (OPCs, Ar′ = 3,4-$(HO)_2(C_6H_3)$) are abundant natural products found in agricultural and forestry waste such as pine bark, grape seeds, and the peels of mangosteen. We have demonstrated that the OPCs can be converted into small molecule chiral ligands by using proper nucleophiles for acid depolymerization of the OPCs. The chiral ligands may have potential for sustainable asymmetric catalysis.

Environmentally benign and sustainable catalytic processes are a major theme of current chemical research in response to the demand for greener chemical processes with minimal energy consumption.[1] Full utilization of natural products in fine chemicals production is increasingly important because natural products are not only renewable and sustainable but also structurally diverse and complex. They would typically take many steps to be 'totally synthesized' from fossil fuel derived basic chemicals. Some shining examples are the privileged asymmetric catalysts such as cinchona alkaloids and tartaric acid derivatives, which are derived from natural products.[2] There are many more under-utilized natural products, particularly those from agricultural and forestry waste; oligomeric proanthocyanidins (OPCs) are oligomers of catechins/epicatechins. OPCs are abundant secondary metabolites in nature and are found in mangosteen peels (5% in dry matter), grape seeds (17%),[3] pine bark (5%),[4] cinnamon bark (8%),[5] sorghum bran (6%),[6] and in many other plants.[5] OPCs have diverse bioactivity and are potent radical scavengers, inhibitors of digestive enzymes,[7] and have antimicrobial activity.[8] With the large number of phenolic groups, OPCs are good metal chelators, yet their potential as ligands for transition metal catalysts has not been explored, presumably due to the various chelating sites and modes. In the hope of taking advantage of the rich source of OPCs as raw materials for fine chemical synthesis, presented herein are our results on converting OPCs into a wide range of chiral multidentate ligands through acid-mediated depolymerization and transformations.

It has been known for a long time that acid-mediated depolymerization of OPCs in the presence of carbon (phloroglucinol[9]) or thiol (benzylmercaptan[10]) nucleophiles leads to β-C-4 substituted epicatechin derivatives,[11] yet the utility of the resulting products was rarely investigated.

By selecting appropriate carbon nucleophiles, we were able to obtain a number of novel epicatechin derivatives by acid-mediated depolymerization of mangosteen OPCs (Scheme 1). These reagents are grouped into two main types: carbon and sulfur based nucleophiles. Depolymerization of OPCs in the presence of an unsubstituted pyrrole, a potent carbon nucleophile, yielded only a black mixture probably due to polymerization or unselective nucleophilic substitution on the α- or β-carbon substituted analogs, while 2,3-dimethylpyrazole and 3-ethyl-2,4-dimethylpyrrole successfully yielded **1** and **2**. The products were isolated conveniently by normal phase silica gel column chromatography. The HPLC chromatograms of the compounds all gave rise to one sharp peak indicating a single diastereomer for **1** and **2**, consistent with epicatechin derivatives. The stereochemistry of C4 was determined by comparing the ^{1}H NMR spectral pattern of C ring protons with known compounds.[12] Compounds **1** and **2** are rare examples of alkaloid-like flavonoid derivatives. Naturally, there are only three reported examples, that is, lotthanongine (a flavonoidal indole derivative),[13] ficine/isoficine,[14] and phyllospadine.[15] The bioactivity of these compounds has remained largely unexplored. Our method for preparing **1** and **2** is very mild and straightforward for large scale synthesis for further investigation. Regarding metal chelation, compounds **1** and **2** have two bidentate sites, one chiral (N, O) and the other achiral (catecholic unit on the B ring) and thus have potential as ligands to prepare bimetallic complexes. Alternatively, the catecholic unit on the B ring can be blocked selectively by reaction with methyl propiolate in the presence of dimethylaminopyridine (DMAP) as base in moderate yield. The resulting product **3** exists as two diastereomers as demonstrated by the two equally populated configurations of *CH–(CH_2) unit as revealed by two equal intensity doublet of doublets around 6.52–6.48 ppm.

Weaker carbon nucleophiles such as 3,5-dimethoxyphenol and 3,5-dimethoxyaniline led to depolymerization products **4** and **5** but in lower yields. Both **4** and **5** could be modified further by

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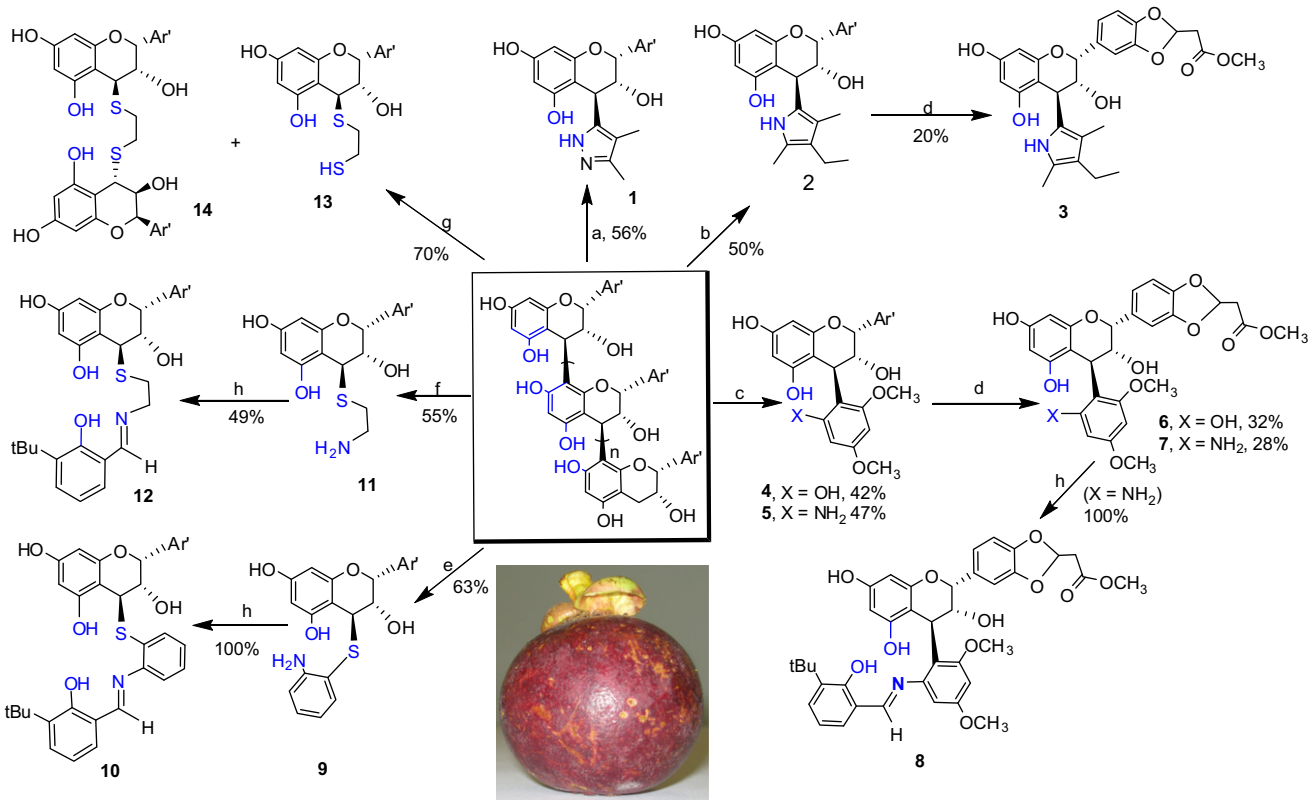
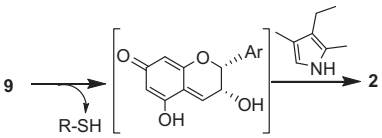


Scheme 1. From oligomeric proanthocyanidins (n = 2–50) in mangosteen peels (inset) to multidentate ligands, (Ar′ = 3,4-dihydroxyphenyl). Acid mediated depolymerization conditions are 0.22% HCl in CH_3OH, 45 °C, 2–8 h. (a) 2,3-Dimethylpyrazole; (b) 3-ethyl-2,4-dimethylpyrrole; (c) 3,5-dimethoxyphenol (for **4**), or 3,5-dimethoxyaniline (for **5**); (d) 4-(*N*,*N*-dimethylamino)pyridine, $HCCCOOCH_3$ CH_3CN, rt, 12 h; (e) *o*-thioaniline; (f) cysteamine; (g) 1,2-dithioethane; (h) 3-*tert*-butylsalicylaldehyde, CH_3OH, AcOH, 1 drop, rt. Percentage conversion was determined by HPLC.

protection of the catecholic units to give **6** and **7**. In addition, **7** was readily converted into tridentate Schiff base, **8**, in quantitative yield. The presence of a chiral tridentate pocket makes it a candidate for use in asymmetric catalysis in combination with transition metals.

Thiols are strong nucleophiles, and in fact, even highly odorous benzylmercaptan has been widely used for determination of the degree of polymerization of OPCs as the yield is almost quantitative. Herein, we prepared a number of new multidentate ligands using various thiols. The odorless *o*-thioaniline was found to be an excellent nucleophile in the depolymerization of OPCs as it gave **9** with high yield after a simple isolation. The multidentate Schiff base **10** was obtained after condensation with 3-*tert*-butylsalicylaldehyde. Although **9** and **10** are stable under acidic conditions, they readily eliminate thiol under weak basic solution (pH >8.5). The unobserved quinone methide intermediate can be trapped by other carbon nucleophiles such as 3-ethyl-2,4-dimethylpyrrole to give **2**, which is stable under the same conditions (Eq. 1). Hence, **9** is an alternative intermediate for the preparation of epicatechin derivatives.[16]



(1)

Less nucleophilic ArS^- may contribute to the high reactivity of **9** and **10** under basic conditions. The cysteamine derivative **11** and its Schiff base, **12**, are more stable for the elimination of the thiol under the same conditions; therefore, it might be a better ligand. By using 1,2-ethanedithiol as the nucleophile for depolymerization of OPCs, we were able to isolate mono and di-substituted products, **13** and **14**. The latter is particularly interesting as a tetradentate (O_2S_2) ligand with a C2 axis which is believed to be desirable in certain asymmetric reactions.[17]

In summary, we have demonstrated that mangosteen OPCs can be sustainable and renewable starting materials for a wide range of epicatechin derivatives. It is remarkable that their synthesis can be achieved in one or two steps without the need of protecting groups. Given the fact that there are plentiful resources for OPCs, large scale industrial applications would be feasible.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.123.

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