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Structure elucidation of highly condensed stilbenoids: chiroptical properties and absolute configuration

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ABSTRACT

We investigated the potential roles of the skeleton-based comparative study of electronic circular dichroism (ECD) spectra for an application of absolute configuration (AC) determination of oligostilbenoids (OS). This approach was ultimately achieved followed by the isolation and elucidation of relative configuration (RC) of upunaphenol Q (**1**) (new compound) and vateriaphenol A (**2**), namely two octamers are dimeric tetramers of resveratrol (Res). The common building blocks (BB) provide further insight into how smaller OS are apparently conserved during downstream metabolites, as well as providing additional impetus to resolve AC of highly condensed stilbenoids (HCS). They also underline the importance of studies on determination of AC of common BB in the chemical library and to provide chiroptical properties.

1. Introduction

OS are regioselectively biosynthesized by phenoxy radical coupling, producing several specific skeletons with condensed heterocyclic and bicyclo ring systems.[1–3] They usually comprise asymmetric carbons in proportion to oligomerization degree, i.e., dimers and tetramers of Res in many cases have four and eight chiral atoms, respectively. However, the way plants control phenoxy radical coupling is enigmatic. About 200 OS of this type have been isolated from the Dipterocarpaceae family.[3] Dimers, trimers, and tetramers are more common in the family, and that goes for the other families such as Vitaceae.[2] The phytochemical documentations of further oligomerized OS (HCS) are pentamers,[4,5] hexamers,[6,7] heptamers,[6,8] and octamers,[9,10] however, they are less common. Since different OS are attributable to skeletal variations and the presence of stereoisomers with several asymmetric carbons, analysis of the stereostructures of OS presents interesting challenges. Dipterocarpaceaesous plants produce a number of OS analogues, which typically possess a common skeleton of specific AC as seen in 1,2-diaryldihydrobenzofuran of (−)-ε-viniferin.[1] This stereochemical homogeneity of OS infers that downstream biosynthetic product of (−)-ε-viniferin (trimer-octamer) may be elaborated with the same AC in 1,2-diaryldihydrobenzofuran skeleton. On the other hand, there are other types of OS from this plant family, such as uliginoside A and hemsleyanoside B in *Shorea uliginosa*.[11] The fact that they bear antipodal stereochemistry for two corresponding counterparts in each 1,2-diaryldihydro benzofuran demonstrates the need for multiple chemical, physical, and spectroscopic approaches to determine AC of OS. In Fig. 1, we have summarized some reported OS whose ACs were determined by different approaches, i.e., X-ray crystallographic analysis of their chemical derivatives using anomalous scattering of the bromine atom(s) ((−)-hopeaphenol[12] and shorealactone[13]), comparison of optical rotation and(or) circular dichroism ((+)- and (−)-ε-viniferin,[14] (+)-hopeaphenol,[15] uliginosides A,[11] cordifoloside A[16]), and modified Mosher's method (vaticahainol A).[17] Comparison of the experimental and theoretical ECD spectra (vaticahainol B),[17] application of the olefin cleavage strategy to a known compound to get ECDs of the newly separated products (uliginoside B,[11] laetevirenol D[18]), regioselective, and stereospecific transformations of a hypothetical biogenetic precursor (+)-ε-viniferin ((+)-ampelopsin A, (+)-vitisin A),[19,20] acid-catalyzed skeletal conversion to get monoalkyl ether of known derivative (shoreaketone),[21] and assignment based on the comparison of AC of D-β-glucopyranosyl group (hopeaside E)[22] were also conducted to achieve the AC determination. We also developed the novel approach on AC determination, which is conducted by comparison of experimental and theoretical electronic circular dichroic spectra of the dehydroxylated derivative ((−)-pauciflorol B).[23]

However, the ACs of most OS are left undetermined, because OS in typical cases are neither crystalline nor secondary alcohols so

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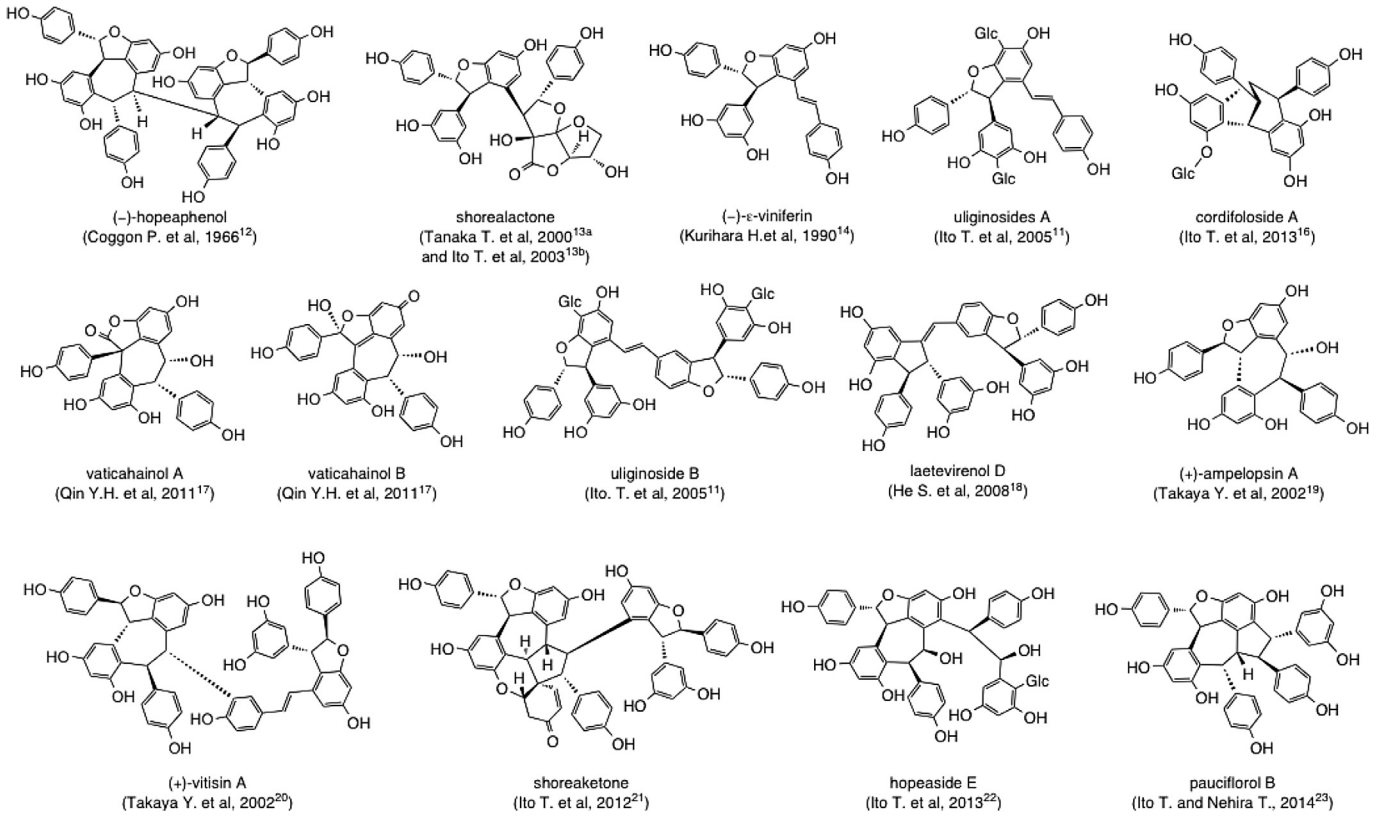

Fig. 1. Absolute configuration of resveratrol oligomers.

that they are unsuitable for general methodologies such as X-ray crystallography, modified Mosher's method, or CD exciton chirality method. Therefore the application of a comparative study using an ECD database produced from a reliable chemical library is potentially a general method for determining the AC of OS. The CD method hitherto undertaken to Res oligomers are limited to several specific skeletons of trans oriented 1,2-diaryldihydrobenzofuran,[11] 2,3-diaryldihydro-1*H*-indene,[18] and dibenzobicyclo[3.2.1]octadiene chromophore.[16] In the current study, ECD-aided empirical method was conducted in order to determine the ACs of three Res oligomers, upunaphenol Q (**1**: octamer),[10] vateriaphenol A (**2**: octamer),[9] and (−)-vaticanol B (**3**: tetramer).[24] The method includes comparison of ECD spectra with the help of our chemical library originated from *Vateria indica*[9] and *Vatica pauciflora*[25] ((−)-hopeaphenol (**4**: tetramer), (−)-pauciflorol B (**5**: trimer),[23] (−)-ampelopsin A (**6**: dimer), and (2*R*,3*R*)-3-(3,5-dihydroxy phenyl)-6-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-4-carbaldehyde (**7**)),[11] where additive and differential data were also utilized. This paper describes the scope of the ECD application on the elucidation of the ACs of some OS, as well as the MS and NMR aided structural elucidation of **1** and **2**.

2. Results and discussion

2.1. Isolation and structural elucidation of upunaphenol Q (1)[10]

Upuna borneensis Sym. was cultivated at Bogor Botanical Garden, Bogor, Indonesia, and the leaves were collected in May 2000. An acetone extract (115 g) was subjected to reversed-phase column chromatography (CC) on Chromatorex DMS and further purification by Sephadex LH-20 CC, reversed-phase CC by Sep-Pak C_{18} cartridge, and preparative HPLC, leading to the isolation of **1** (10.2 mg).

Upunaphenol Q (**1**) was obtained as a pale yellow amorphous solid. The molecular formula was established as $C_{112}H_{84}O_{18}$ from the HRESIMS data [*m*/*z* 1811.5291 $[M-H]^-$; 1811.5280 calcd for $C_{112}H_{83}O_{18}$]. The structure is composed of two tetrameric Res, which include Res A–D (**1A**) [(Res A: ring A_1–C-7a–C-8a–ring A_2)] and Res E–H (**1B**). Analysis of the ^1H and ^{13}C NMR signals (Table 1) supported by double quantum filtered correlation spectroscopy (DQF-COSY), heteronuclear multiple quantum coherence (HMQC) spectra, and heteronuclear multiple bond correlation (HMBC) spectra (Fig. 2) confirmed the partial structures (**1A** and **1B**) and the connection (C-12b–C-7e). The ambiguity of ^1H and ^{13}C NMR signals under certain conditions required optimized NMR measurements. At room temperature, many proton signals due to hydroxy groups were obscurely observed, while at lower temperatures they turned to clear signals, and hence, we performed detailed NMR spectral analyses at −10 °C.

The NMR data indicated that the presence of eight 4-hydroxyphenyl groups (A_1–H_1), three 3,5-dihydroxyphenyl groups (D_2, F_2, and H_2), three 3,5-dioxygenated-1,2-disubstituted benzene rings (A_2, C_2, and G_2), a 3,5-dioxygenated-1,2,6-trisubstituted benzene ring (E_2), four mutually coupled aliphatic methine sequences [CH(7a)–CH(8a), CH(7d)–CH(8d), CH(7f)–CH(8f), and CH(7h)–CH(8h)], and two sets of four aliphatic methine sequences [CH(7b)–CH(8b)–CH(7c)–CH(8c) and CH(7e)–CH(8e)–CH(7g)–CH(8g)]. The remaining six quaternary aromatic carbons in the ^{13}C NMR spectrum (C-9b–C-14b) were assigned to those of a 3,5-dioxygenated fully substituted benzene ring (B_2). Among the methine signals, four protons (H-7a, H-7d, H-7f, and H-7h) were correlated to the oxygen-substituted carbons [δ_C 88.0 (C-7a), 95.2 (C-7d), 92.7 (C-7f), and 94.1 (C-7h)] in the HMQC spectrum. The connection of the partial structures in **1A** was established by the HMBC correlations observed between H-7a/C-2a(6a), H-8a/C-14a, H-8a/C-11b, H-7b/C-11a, H-7b/C-2b(6b), H-7b/C-9b, H-7c/C-2c(6c), H-8c/C-13b, H-8c/C-14c, H-7d/C-2d(6d), H-8d/C-11c, H-8d/C-10d, and H-7d/C-11c, which deduced the 12 C–C bonds and