Marquette University
e-Publications@Marquette

School of Dentistry Faculty Research and Publications | Dentistry, School of

7-17-2020

Rare A-Type, Spiro-Type, and Highly Oligomeric Proanthocyanidins from *Pinus massoniana*

Bin Zhou
University of Illinois at Chicago

Yvette Alania
Marquette University

Mariana C. Reis
University of Illinois at Chicago

James McAlpine
University of Illinois at Chicago

Ana K. Bedran-Russo
Marquette University, ana.bedran-russo@marquette.edu

See next page for additional authors

Follow this and additional works at: https://epublications.marquette.edu/dentistry_fac

 Part of the Dentistry Commons

Recommended Citation

Zhou, Bin; Alania, Yvette; Reis, Mariana C.; McAlpine, James; Bedran-Russo, Ana K.; Pauli, Guido F.; and Chen, Shao-Nong, "Rare A-Type, Spiro-Type, and Highly Oligomeric Proanthocyanidins from *Pinus massoniana*" (2020). *School of Dentistry Faculty Research and Publications*. 383.
https://epublications.marquette.edu/dentistry_fac/383

Authors

Bin Zhou, Yvette Alania, Mariana C. Reis, James McAlpine, Ana K. Bedran-Russo, Guido F. Pauli, and Shao-Nong Chen

This article is available at e-Publications@Marquette: https://epublications.marquette.edu/dentistry_fac/383

Marquette University

e-Publications@Marquette

Dentistry Faculty Research and Publications/College of Dentistry

***This paper is NOT THE PUBLISHED VERSION*.**
Access the published version via the link in the citation below.

Organic Letters, Vol. 22, No. 14 (July 8, 2020): 5304-5308. DOI. This article is © American Chemical Society and permission has been granted for this version to appear in e-Publications@Marquette. American Chemical Society does not grant permission for this article to be further copied/distributed or hosted elsewhere without express permission from American Chemical Society.

Rare A-Type, Spiro-Type, and Highly Oligomeric Proanthocyanidins from Pinus massoniana

Bin Zhou
Department of Pharmaceutical Sciences (PSCI), College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois
Yvette Alania
Department of Restorative Dentistry, College of Dentistry, University of Illinois at Chicago, Chicago, Illinois
Department of General Dental Sciences, School of Dentistry, Marquette University, Milwaukee, Wisconsin
Mariana C. Reis
Department of Restorative Dentistry, College of Dentistry, University of Illinois at Chicago, Chicago, Illinois
Department of General Dental Sciences, School of Dentistry, Marquette University, Milwaukee, Wisconsin
James B. McAlpine

Department of Pharmaceutical Sciences (PSCI), College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612, United States
Program for Collaborative Research in the Pharmaceutical Sciences (PCRPS), College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois

Ana K. Bedran-Russo

Department of Restorative Dentistry, College of Dentistry, University of Illinois at Chicago, Chicago, Illinois
Department of General Dental Sciences, School of Dentistry, Marquette University, Milwaukee, Wisconsin
Program for Collaborative Research in the Pharmaceutical Sciences (PCRPS), College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois

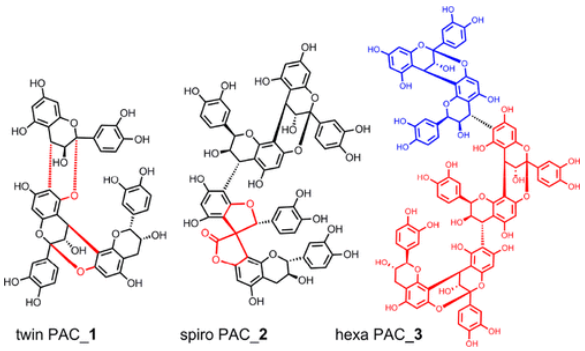
Guido F. Pauli

Department of Pharmaceutical Sciences (PSCI), College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois
Program for Collaborative Research in the Pharmaceutical Sciences (PCRPS), College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois

Shao-Nong Chen

Department of Pharmaceutical Sciences (PSCI), College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois
Program for Collaborative Research in the Pharmaceutical Sciences (PCRPS), College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois

Abstract



An investigation of the dental bioactive proanthocyanidin (PAC) oligomer fractions led to three structurally distinct new PACs (**1**–**3**) from pine bark. Pinutwindoublin (**1**) is the first reported trimer with double A-type interflavanyl linkages (2α→O→5,4α→6 and 2α→O→7,4α→8). Pinuspirotetrin (**2**) represents the first reported PAC tetramer with a heterodimeric framework consisting of one spiro-type and one A-type dimer. Pinumassohexin (**3**) was elucidated as a mixed A + B-type hexamer that consists of a peanut-derived tetramer, peanut procyanidin E, and an A-type dimer (**5**). Compound **3** increased the modulus of elasticity of dentin by an impressive 4.3 times at a concentration of 0.65%.

The bark of the pine species *Pinus massoniana* is a rich source of proanthocyanidins (PACs), a phylogenetically ancient group of polyphenols that occur ubiquitously in vascular plants. Accordingly,

PACs inevitably impact human life via nutrition and medicine. Representing a group of vast structural diversity, PACs exhibit a broad spectrum of bioactivities.(1−7) Specific to pine bark, a series of tri- and tetrameric PACs has the demonstrated capability of enhancing the biomechanical properties of dentin and instilling resistance to proteolytic dentin degradation.(6,7) Continuing these interdisciplinary efforts at the interface of natural products chemistry and dentistry, the exploration of structurally unique compounds from bioactive PAC oligomer fractions has led to three structurally distinctive new PACs (**1**–**3**) (Figure 1).

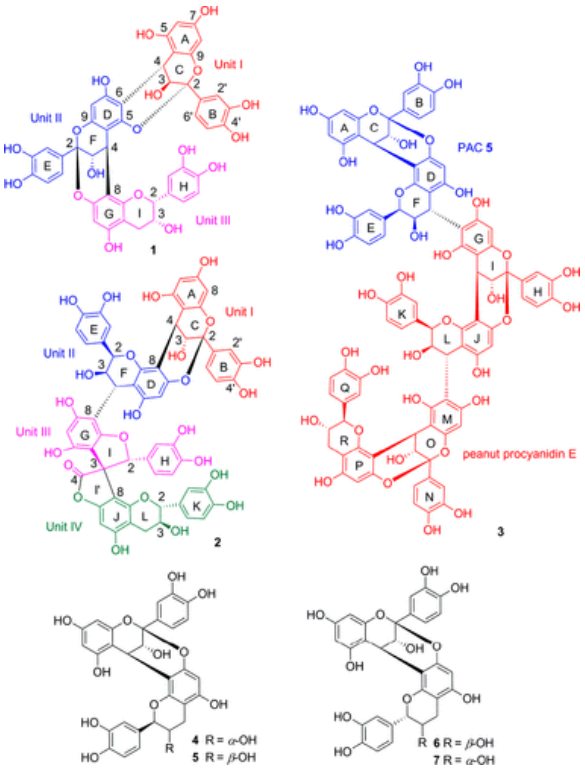


Figure 1. Novel structures of **1**–**3** with color-coded constituent catechin monomers compared with the known dimers, **4**–**7**.

Pinutwindoublin (**1**) is the first A-type-only trimer linked with (2α→O→5,4α→6) and (2α→O→7,4α→8) bonds. This unprecedented linkage combination is a plausible reason for the observed atropisomeric line-broadening in its nuclear magnetic resonance (NMR) spectra, which otherwise is atypical of A-type PACs. Pinuspirotetrin (**2**) represents the first PAC with a heterodimeric framework consisting of a spiro-type dimer connected with an A-type dimer. Also characterized in underivatized form and exhibiting dentin bioactivity, pinumassohexin (**3**) was elucidated as a hexameric PAC with mixed A + B-type interflavanyl linkages (IFLs), assembled from the known tetramer, peanut procyanidin E,(8) and the dimer, epicatechin–(2β→O→7,4β→8)–epicatechin (**5**),(8,9) via a 4β→6 bond. The structure elucidation of **1**–**3** utilized 1D/2D NMR, electric circular dichroism (ECD), and ^{13}C NMR γ-gauche effects as well as phloroglucinolysis, a recently established toolbox for absolute configurational assignments in PACs.(8)

The molecular formula $C_{45}H_{34}O_{18}$ of **1** was determined using the ^{13}C NMR carbon counts and the (+)-HRMS (high-resolution mass spectrometry) (electrospray ionization (ESI)) ion at *m/z* 863.1823 $[M + H]^+$. Two pairs of characteristic AX resonances at δ_H 3.87 and 4.26 (both d, J = 4.0 Hz) as well as δ_H 4.22 and 4.87 (both d, J = 4.3 Hz) revealed the presence of two doubly linked interflavanyl bonds and, in

connection with the molecular formula, indicated the 2A-type trimeric nature of **1**. The NMR data (Table S1) showed the characteristic ^{1}H AMX patterns of the three 1,3,4-trisubstituted aromatic B-, E-, and H-rings. Additionally, a small *J* coupling (<1 Hz) between H-2 and H-3 suggested the terminal unit to be 2,3-*cis*-configured (*ent*)-epicatechin. The IFLs were elucidated via HMBC (heteronuclear multiple bond correlation) and NOESY (nuclear Overhauser enhancement spectroscopy) data (Figure S1): The presence of 2→O→7/4→8 linkages between units II and III was assigned by the HMBC cross-peaks from both II-H-4 (δ_H 4.87) and III-H-2 (δ_H 4.96) to III-C-9 (δ_C 152.4). The NOESY correlations from II-H-8 to II-H-2′ and II-H-6′ and from I-H-2′ to II-H-4 and III-H-2 indicated that 2→O→5/4→6 bonds connected units I and II. This established the 2D structure of **1**.

The absolute configuration of **1** was gleaned from ECD and NOESY data (Figure S1). Because of a high-amplitude negative Cotton effect (CE) in the diagnostic region 220–240 nm (Figure 2A), the C-4 aryl functionalities in both units II and III were determined to be α-configured.(10−12) The absolute configurations of C-4 in units I and II were thus assigned as S and R, respectively. (Note the change in Cahn–Ingold–Prelog priorities due to different connections causing different stereodescriptors for spatially identical configurations at both C-4.)(12) Taking into account the 2,4-*cis* configuration in A-type PACs,(13) units I/II and II/III had to be doubly connected via (2α→O→5,4α→6) and (2α→O→7,4α→8) IFLs, respectively. A NOESY correlation between II-H-3 and III-H-6 indicated a 3,4-*trans* configuration in the F-ring, and thus II-C-3 was S-configured.(11) A comparison of the tendency of ECD curves of **1** in the diagnostic region 280–300 nm with those of proanthocyanidin A2 (**5**)(8) and proanthocyanidin A5 (**7**)(8) revealed that **1** is closely mirror-symmetric to **7** (Figure 2B). Thus the partial structures of units II and III in **1** were assigned to be enantiomeric to those in **7**. This was consistent with the R-configuration of III-C-2 deduced from the negative CE at 280–300 nm(10,11) and the NOESY correlation of II-H-4 and III-H-6′ (Figures S7, S7-1, and S7-2). Finally, I-H-3 had to be *β*-oriented based on NOESY correlations between I-H-3 and both III-H-2 and III-H-6′. Accordingly, **1** was assigned as *ent*-epicatechin–(2α→O→5,4α→6)–*ent*-epicatechin–(2α→O→7,4α→8)–epicatechin.

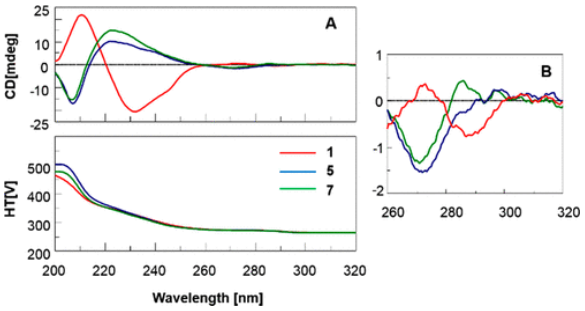


Figure 2. (A) Full ECD spectra of **1**, **5**, and **7** with (B) expansions for the diagnostic range 260–320 nm.

This renders **1** the first reported double A-type trimer with an unusual combination of (2α→O→5,4α→6) and (2α→O→7,4α→8) IFLs. Restricted rotation along the C-4 aryl (sp^3–sp^2) carbon–carbon bond is otherwise only typical for B-type PACs, thereby giving rise to atropisomerism and often severe NMR line broadening at ambient temperature. In contrast, A-type PACs, with two IFLs, generally do not exhibit atropisomerism due to the rigidity of the double linkage.(6,14,15) Improving the ^{1}H NMR lineshapes of **1** required acquisition at low temperature (255 K; Figure 3). The unexpected dynamic peak broadening of **1** despite its two double linkages indicated that the combination of

(2α→O→5,4α→6) and (2α→O→7,4α→8) IFLs poses sufficient steric hindrance for restricted rotation between rings B and H to generate observable atropisomers, thus leading to NMR line broadening.

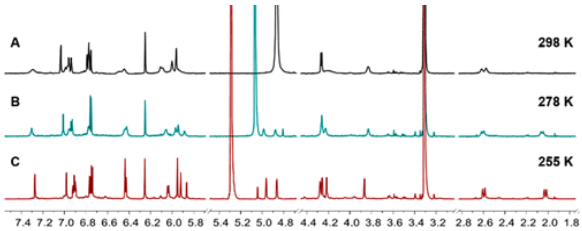


Figure 3. ^{1}H NMR spectra of **1** acquired in CD_3OD under the following conditions: (A) 298 K at 400 MHz, NS = 64; (B) 278 K at 800 MHz, NS = 64; and (C) 255 K at 800 MHz, NS = 128.

PAC tetramer **2** exhibited a molecular ion at *m/z* 1149.2291 $[M + H]^+$ in the (+)-HRMS (Supporting Information), corresponding to a molecular formula $C_{60}H_{44}O_{24}$, as supported by the ^{13}C NMR data. A lower temperature (255 K) was applied during the 1D and 2D NMR experiments to overcome line broadening due to atropisomerism (Figure S10).(6,14,16) An analysis of the ^{1}H NMR spectrum showed four AMX spin systems, corresponding to four 1,3,4-trisubstituted aromatic rings (B/E/H/K). Three singlets at δ_H 5.90, 5.96, and 6.16 as well as two meta-coupled doublets at δ_H 6.02 and 6.03 (J = 2.3 Hz) showed the presence of aromatic rings J, G, D, and A and further confirmed the tetrameric nature of **2**. Two sequential spin systems (δ_H 3.70 and 4.44, both d, J = 3.5 Hz; and δ_H 5.30, 3.95, and 4.47, each brs), which were assigned by the COSY data (Figure 4A), indicated the presence of one double (A-type) and one single (B-type) IFL of **2**. Units II and IV were identified as (*ent*)-epicatechin and (*ent*)-catechin, respectively, based on the $J_{2,3}$ values of ~0 and 6.3 Hz.

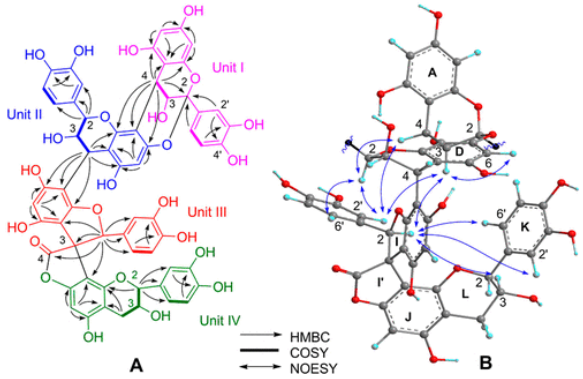


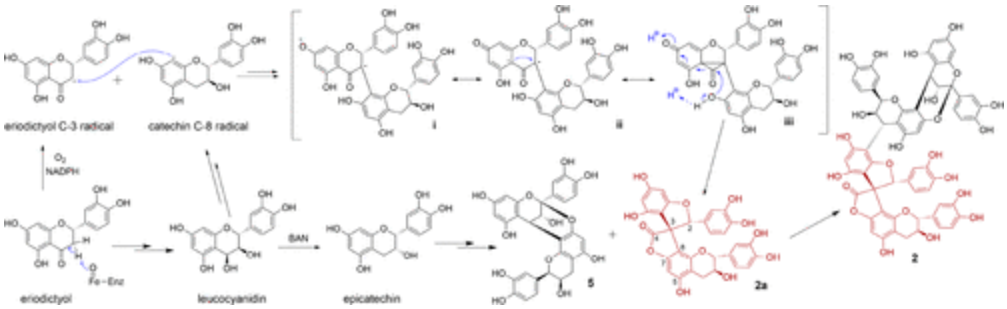
Figure 4. (A) Selected COSY (bold bond) and HMBC and (B) NOESY correlations in **2**.

Unusual features involved an oxygenated methine (δ_H 5.81, s, and δ_C 88.2) that showed HMBC correlations with the carbonyl carbon at δ_C 177.0 assigned to a γ-lactone unit and a spiro carbon resonating at δ_C 61.4. Both are characteristic of a spiro-biflavanoid similar to larixinol.(17,18) Linkages between the four units were further elucidated by HMBC and NOESY data (Figure 4). Units I and II were recognized as being connected by double (2→O→7/4→8) IFLs based on the I-H-4/II-H-2 NOESY correlation as well as the diagnostic upfield shift of II-C-8 (δ_C 106.3).(7,19) The presence of a 4→8 linkage between units II and III was deduced from the cross-peaks between II-H-2 and both III-H-2′ and III-H-6′ in the NOESY spectrum. The spiro-biflavanoid arrangement of units III and IV was corroborated by the HMBC correlations from III-H-2 to III-C-3, III-C-4, III-C-10, III-C-2′, III-C-6′, and IV-C-8; from IV-H-2

to IV-C-9; and from IV-H-6 to IV-C-5 and IV-C-7. Thus the 2D structure of **2** had to be the first tetrameric spiro-PAC, consisting of one A-type and one spiro-type dimeric unit. An analysis of its ECD spectrum showed a high-amplitude positive Cotton effect in the region 220–240 nm (Figure S2), characteristic of β-substituted flavan-3-ol moieties,(10−12) confirming the absolute configuration of the spiro center III-C-3 as being S.(18) The absolute configurations of the C-4 centers in both units I and II were thus assigned as R-configured. I-C-2 was S-configured based on the inherent 2,4-*cis* configuration in A-type PACs.(13) A NOESY correlation between I-H-3 and II-H-6 indicated H-3 and H-4 in the C-ring to be trans, and thus I-C-3 was R-configured.(11) The upfield shift of II-C-2 (δ_C 78.7) suggested a 2,4-*trans* configuration in the F-ring based on the γ-gauche effect.(20,21) Unit II was therefore epicatechin (2*R*, 3*R*), which was confirmed by the NOESY correlations between II-H-2/III-H-2′ and III-H-6′. NOESY correlations from III-H-2 to IV-H-3, IV-H-2′, and IV-H-6′ assigned III-C-2 as R-configured, which determined the terminal unit IV to be catechin (2*R*, 3*S*) (Figures S15, S15-1, and S15-2). In conclusion, the structure of pinuspirotetrin (**2**), was assigned unambiguously, as shown.

The molecular formula $C_{90}H_{68}O_{36}$ gleaned from (+)-HRMS (ESI) and ^{13}C NMR carbon counts identified **3** as a hexamer with 3A + 2B IFLs. The close resemblance of the ^{1}H and ^{13}C NMR resonances of units II/IV and III/V as well as their congruence with reported data of the major tetramer from peanuts, peanut procyanidin E,(8) suggested this tetramer plus an additional A-type dimer as building blocks of **3**. Its ^{1}H NMR spectrum revealed three AX-type doublet pairs (δ_H 4.13 and 4.47, J = 3.4 Hz; δ_H 4.17 and 4.38, J = 3.6 Hz; and δ_H 4.12 and 4.23, J = 3.6 Hz), which corroborated the presence of three doubly linked A-type motifs. Similarly, two B-type single-bond linkages were assigned by the observed two sets of three coupled methines resonating as broad singlets at δ_H 5.27, 4.04, and 4.74 as well as δ_H 5.42, 3.89, and 4.78. All three A-type IFLs were assigned as 2β→O→7/4β→8 via NOESY correlations (Figure S22) from H-4 (rings C, I, and O) to H-2 (rings F, L, and R) (Figures S22-1 and S22-2) as well as a strongly positive Cotton effect in the region 220–240 nm (Figure S2). The 3-OH functional groups in rings C, I, and O had to be trans-oriented relative to H-4 based on the NOESY correlations from H-3 (rings C, I, and O) to H-6 (rings D, J, and P). The two 4β→6 linkages were deduced from the chemical shifts of C-6 (δ_C 110.5 in the G-ring and δ_C 111.0 in the M-ring) and ECD evidence. Units II and IV were both elucidated as epicatechin by the singlet signals of II-H-2 and IV-H-2 and the upfield shifted C-2 (δ_C 78.7 in F-ring and δ_C 79.9 in the L-ring) to the corresponding carbon in proanthocyanidin A1 (**4**) (δ_C 81.6).(8) Phloroglucinolysis(8) confirmed the absolute stereochemical assignments. An analysis of the reaction products used a combination of chiral-phase high-performance liquid chromatography (HPLC) and MS (Figure S24) to verify that **4** and **5** are the basic components of **3**. Collectively, this assigned the structure of pinumassohexin (**3**) unambiguously as [PAC **5**]–(4β→6)–[PAC **5**]–(4β→6)–[PAC **4**].

Pinuspirotetrin (**2**) represents the first heterodimeric framework in any PAC, consisting of a spiro-type dimer (**2a**) and an A-type dimer (**5**). Scheme 1 shows a plausible biosynthetic pathway for **2**,(22,23) which rationalizes the spiro dimer **2a** as resulting from intermediates (i→ii→**2a**) via oxidative flavanone–flavonol conversion.(23)



Scheme 1. Proposed Biosynthetic Pathway for the Formation of the Spiro Element in PAC Tetramer **2**

Whereas all isolates stemmed from a bioactive fraction, only **3** could be evaluated for dentin bioactivity due to limited yields. In the same concentration (0.65%), hexamer **3** increased the modulus of elasticity of dentin by a remarkable 4.3 times, a value between those of A-type dimers (**4**–**7**) and those of the most highly potent trimer and tetramers. This further supports the overall hypothesis that medium-size (*n* = 3 and 4) PACs elicit the highest increase in the key mechanical properties of dentin. These enhancements to dentin have promising therapeutic applications for the development of novel dental biomaterials. A comprehensive structure and bioactivity relationship of PACs will be reported in due course. Whereas the structural novelties of **1** and **2** and the unusual size and complexity of **3** did not infer bioactivity in the dentin bioassays, they contribute valuable structure–activity relationship (SAR) information and expand the 3D chemical diversity space of oligomeric PACs.

Acknowledgments

This research was supported by grants R01 DE021040 and R56DE021040 from the NIDCR/NIH. We thank Drs. Joseph Ray, David Lankin, and Benjamin Ramirez at the University of Illinois at Chicago for NMR discussions and support. The construction of the UIC Center for Structural Biology (CSB) facility and the 800 MHz NMR instrument purchase were generously funded by NIGMS/NIH grant P41 GM068944 awarded to Dr. Peter Gettins (PI).

References

1 Li, W. G.; Zhang, X. Y.; Wu, Y. J.; Tian, X. *Acta Pharmacol. Sin.* **2001**, *22*, 1117– 1120

2 Anderson, R. A.; Broadhurst, C. L.; Polansky, M. M.; Schmidt, W. F.; Khan, A.; Flanagan, V. P.; Schoene, N. W.; Graves, D. J. *J. Agric. Food Chem.* **2004**, *52*, 65– 70, DOI: 10.1021/jf034916b

3 Mandel, S.; Youdim, M. B. H. *Free Radical Biol. Med.* **2004**, *37*, 304– 317, DOI: 10.1016/j.freeradbiomed.2004.04.012

4 Kim, Y. J.; Park, H. J.; Yoon, S. H.; Kim, M. J.; Leem, K. H.; Chung, J. H.; Kim, H. K. *World J. Gastroenterol.* **2005**, *11*, 4674– 4678, DOI: 10.3748/wjg.v11.i30.4674

5 Skerget, M.; Kotnik, P.; Hadolin, M.; Hras, H. R.; Simonic, M.; Knez, Z. *Food Chem.* **2005**, *89*, 191– 198, DOI: 10.1016/j.foodchem.2004.02.025

6 Nam, J. W.; Phansalkar, R. S.; Lankin, D. C.; Bisson, J.; McAlpine, J. B.; Leme, A. A.; Vidal, C. M. P.; Ramirez, B.; Niemitz, M.; Bedran-Russo, A.; Chen, S. N.; Pauli, G. F. *J. Org. Chem.* **2015**, *80*, 7495– 7507, DOI: 10.1021/acs.joc.5b01082

7 Nam, J. W.; Phansalkar, R. S.; Lankin, D. C.; McAlpine, J. B.; Leme-Kraus, A. A.; Vidal, C. M. P.; Gan, L. S.; Bedran-Russo, A.; Chen, S. N.; Pauli, G. F. *J. Org. Chem.* **2017**, *82*, 1316– 1329, DOI: 10.1021/acs.joc.6b02161

8 Zhou, B.; Alania, Y.; Reis, M.; Phansalkar, R. S.; Nam, J.-W.; McAlpine, J. B.; Chen, S.-N.; Bedran-Russo, A. K.; Pauli, G. F. *J. Org. Chem.* **2020**, *85*, 8462– 8479, DOI: 10.1021/acs.joc.0c00783
9 Jacques, D.; Haslam, E.; Bedford, G. R.; Greatbanks, D. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2663– 2671, DOI: 10.1039/p19740002663
10 Botha, J. J.; Young, D. A.; Ferreira, D.; Roux, D. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1213– 1219, DOI: 10.1039/p19810001213
11 Kolodziej, H.; Sakar, M. K.; Burger, J. F.; Engelshowe, R.; Ferreira, D. *Phytochemistry* **1991**, *30*, 2041– 2047, DOI: 10.1016/0031-9422(91)85064-7
12 Slade, D.; Ferreira, D.; Marais, J. P. *Phytochemistry* **2005**, *66*, 2177– 2215, DOI: 10.1016/j.phytochem.2005.02.002
13 Bilia, A.; Morelli, I.; Hamburger, M.; Hostetmann, K. *Phytochemistry* **1996**, *43*, 887– 892, DOI: 10.1016/0031-9422(96)00291-9
14 Fletcher, A. C.; Porter, L. J.; Haslam, E.; Gupta, R. K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1628– 1637, DOI: 10.1039/p19770001628
15 Dudek, M. K.; Glinski, V. B.; Davey, M. H.; Sliva, D.; Kazmierski, S.; Glinski, J. A. *J. Nat. Prod.* **2017**, *80*, 415– 426, DOI: 10.1021/acs.jnatprod.6b00946
16 Killday, K. B.; Davey, M. H.; Glinski, J. A.; Duan, P. G.; Veluri, R.; Proni, G.; Daugherty, F. J.; Tempesta, M. S. *J. Nat. Prod.* **2011**, *74*, 1833– 1841, DOI: 10.1021/np1007944
17 Shen, Z. B.; Falshaw, C. P.; Haslam, E.; Begley, M. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1135– 1137, DOI: 10.1039/c39850001135
18 Wada, S.; Hitomi, T.; Tanaka, R. *Helv. Chim. Acta* **2009**, *92*, 1610– 1620, DOI: 10.1002/hlca.200900032
19 Lou, H. X.; Yamazaki, Y.; Sasaki, T.; Uchida, M.; Tanaka, H.; Oka, S. *Phytochemistry* **1999**, *51*, 297– 308, DOI: 10.1016/S0031-9422(98)00736-5
20 Cai, Y.; Evans, F. J.; Roberts, M. F.; Phillipson, J. D.; Zenk, M. H.; Gleba, Y. Y. *Phytochemistry* **1991**, *30*, 2033– 2040, DOI: 10.1016/0031-9422(91)85063-6
21 Lokman Khan, M.; Haslam, E.; Williamson, M. P. *Magn. Reson. Chem.* **1997**, *35*, 854– 858, DOI: 10.1002/(SICI)1097-458X(199712)35:12<854::AID-OMR184>3.0.CO;2-N
22 Xie, D. Y.; Sharma, S. B.; Paiva, N. L.; Ferreira, D.; Dixon, R. A. *Science* **2003**, *299*, 396– 399, DOI: 10.1126/science.1078540
23 Shen, Z.; Haslam, E.; Falshaw, C. P.; Begley, M. J. *Phytochemistry* **1986**, *25*, 2629– 2635, DOI: 10.1016/S0031-9422(00)84524-0
24 Zhou, B.; Alania, Y.; Reis, M.; McAlpine, J.; Bedran-Russo, A.; Pauli, G.; Chen, S. N. Rare A-Type, New Spiro-Type, and Highly Oligomeric Proanthocyanidins from *Pinus massoniana*. *Chemrxiv* **2020**, DOI: 10.26434/chemrxiv.12168168