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OLIGOMERIC FLAVANOIDS. PART 15[a]. BASE–CATALYZED PYRAN REARRANGEMENTS OF PROCYANIDIN B–2, AND EVIDENCE FOR THE OXIDATIVE TRANSFORMATION OF B– TO A–TYPE PROCYANIDINS

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Abstract —— Procyanidin B–2 3 is subject to facile C–ring isomerizations in 0.1M $NaHCO_3$ solution to form a novel series of 3,4,9,10–tetrahydro–2*H*,8*H*–pyrano[2,3–*h*]chromenes 7, 9, and 10. The low percentage conversion of B– to A–type procyanidin 2 is rationalized in terms of an initial oxidative removal of hydride ion at C–2 (C–ring).

Proanthocyanidin A–2 1 [(–)-epicatechin(4β → 8, 2β → *O* → 7)-(–)epicatechin] was first isolated by Mayer *et al.* from the seed of *Aesculus hippocastanum*[1]. The structure was deduced by Haslam and his co-workers *via* spectroscopic and chemical evidence[2] and has, more recently, been unequivocally established by X–ray crystallography[3]. A variety of proanthocyanidins possessing the doubly-linked unit of type 1 has since been reported[2,4–10]. Owing to the close structural relationship between proanthocyanidin A–2 1 and procyanidin B–2 3, Porter[11] has proposed a biosynthetic pathway for the conversion of B– to A-type procyanidins which involves an enzyme mediated hydroxylation at C–2 (C–ring) of 3. Despite the considerable progress in the semi–synthetic approach towards condensed tannins over the last decade similar efforts for the A-type procyanidins are limited to a fortuitous reference[9] to the oxidative conversion of procyanidin B–1 to proanthocyanidin A–1, but with no experimental details. Our recent investigations of the base-catalyzed pyran rearrangements of profisetinidins[12,13] and procyanidin B–3[14] which emphasizes the involvement of 7–OH(D) and C–2(C) (*cf.* structure 3), in conjunction with the industrial interest[15,16] in the base-simulated reactions of procyanidins, prompted application of a similar protocol to procyanidin B–2 3.

Owing to the lability of the interflavanyl bond in procyanidins at alkaline pH[14,17], the conditions previously[12–14] employed were adjusted for procyanidin B–2. Thus, treatment of (4β,8)-bis-(–)-

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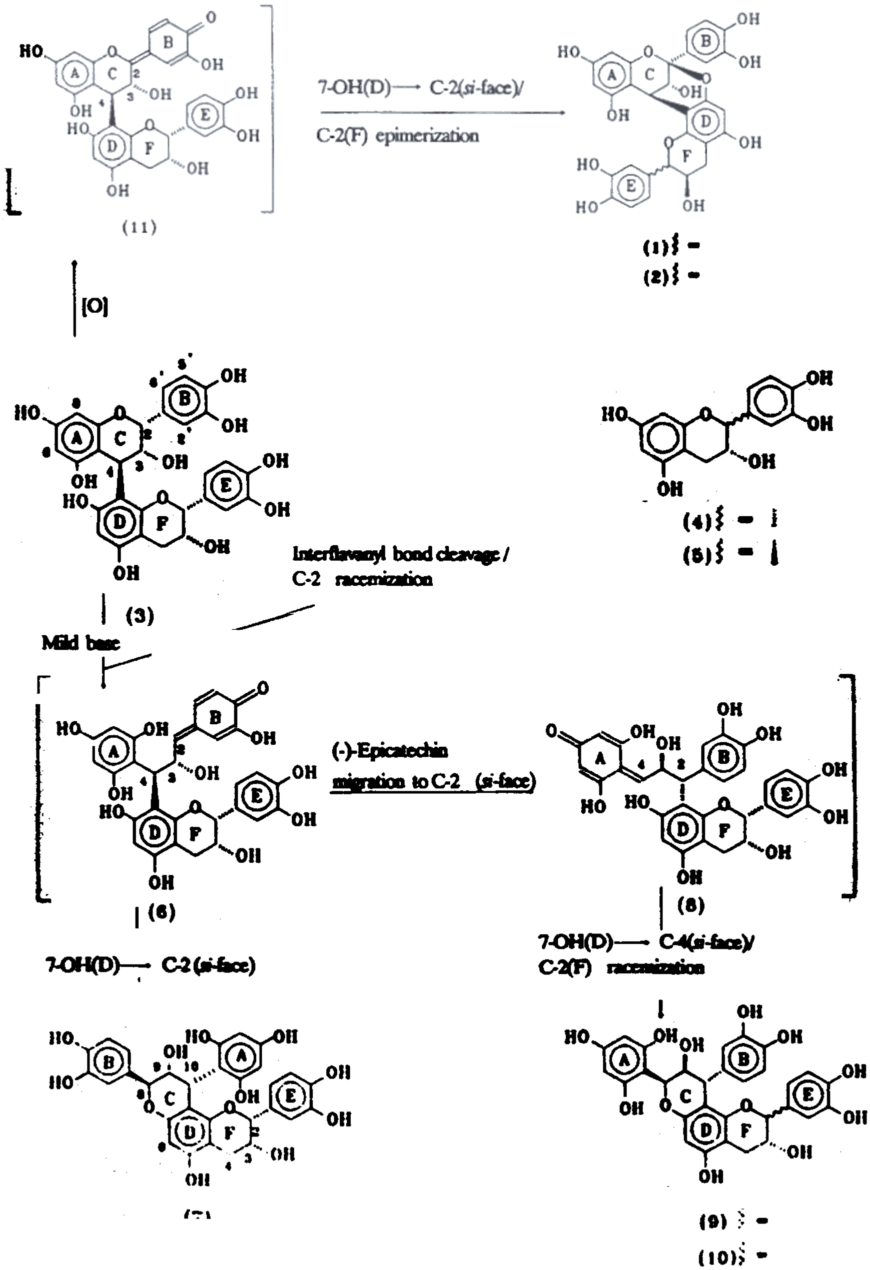

Scheme : Proposed routes to the formation of phlobatannins 7, 9, 10, and the C-2(F) epimer 2 (A-4) of procyanidin A-2 epicatechin 3 with 0.1M $NaHCO_3$ (pH 8.15) for 6.5 h at 40°C under nitrogen containing traces of oxygen, gave complete conversion into a mixture consisting of oligomeric procyanidins (*ca.* 70%) and five mobile fractions following chromatography on Sephadex LH–20 in ethanol. The latter fractions afforded a mixture (47:53 by ¹H NMR analysis) of (–)-epicatechin 4 and (–)-catechin 5 ($J_{2,3}$ *ca.* 1.0 and 8.0 Hz respectively), and four pure compounds with modified C-rings (Scheme). These comprised the functionalized 8,9-*cis*-9,10-*trans*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano[2,3–*h*]chromene 9 as the major product, its C–2(F) epimer 10, the 8,9-*trans*-9,10-*cis* analogue 7, and the C–2(F) epimer 2 of proanthocyanidin A–2 1. The relative ease of purification of these phenols contrasts with those derived from the profisetinidins[12,13] where the additional chromatographic stages offered by successive methylation and acetylation were a prerequisite for compound purity.

The ¹H NMR spectra of the tetrahydropyrano[2,3–*h*]chromenes 7, 9, and 10 are conspiciously free of the effects of dynamic rotational isomerism[18] at ambient temperatures hence indicating their pyran rearranged nature[12]. ¹H NMR coupling constants (Table) of the heterocyclic proton resonances ($J_{2,3}$ *ca.* 1.0 Hz for 7 and 9, $J_{2,3}$ 8.5 Hz for 10; $J_{8,9}$ 7.5, $J_{9,10}$ 5.0 Hz for 7; $J_{8,9}$ *ca.* 1.0 Hz for 9 and 10, $J_{9,10}$ 2.5 and 2.0 Hz for 9 and 10 respectively) are in accordance[12] with 2,3-*cis*-8,9-*trans*-9,10-*cis* relative configuration for 7, 2,3-*cis*-8,9-*cis*-9,10-*trans* for 9, and 2,3-*trans*-8,9-*cis*-9,10-*trans* for 10.

Table ¹H NMR peaks of the tetrahydropyrano[2,3–*h*]chromenes 7, 9, and 10, and the A-type procyanidin 2 in $(CD_3)_2CO$ (23°C) at 300 MHz. Splitting patterns and J-values (Hz) are given in parentheses.

Ring	Proton	7	9	10	2
A	3/5 or 6/8	5.98(br.s)	5.90(d,2.0) 5.98(d,2.0)	5.94(d,2.0) 6.01(d,2.0)	6.08(d,2.5) 6.10(d,2.5)
B	2	6.86(d,2.0)	6.65(d,2.0)	6.63(d,2.0)	7.17(d,2.0)
	5	6.74(d,8.0)	6.70(d,8.0)	6.68(d,8.0)	6.81(d,8.0)
	6	6.67(dd,2.0,8.0)	6.46(dd,2.0,8.0)	6.47(dd,2.0,8.0)	7.03(dd,2.0,8.0)
	8	4.99(d,7.5)	5.65(br.s,*ca*.1.0)	5.59(br.s,*ca*.1.0)	3-H: 4.16(d,3.5)
	9	4.21(dd,5.0,7.5)	4.30(dd,1.0,2.5)	4.15(dd,1.0,2.0)	4-H: 4.29(d,3.5)
	10	4.73(d,5.0)	4.22(d,2.5)	4.19(d,2.0)	
D	6	6.06(s)	6.00(s)	5.86(s)	5.97(s)
E	2	6.57(d,2.0)	6.66(d,2.0)	6.85(d,2.0)	6.83(d,2.0)
	5	6.58(d,8.0)	6.77(d,8.0)	6.76(d,8.0)	6.73(d,8.0)
	6	6.17(dd,2.0,8.0)	6.12(dd,2.0,8.0)	6.69(dd,2.0,8.0)	6.67(dd,2.0,8.0)
F	2	4.76(br.s,*ca*.1.0)	4.69(br.s,*ca*.1.0)	4.53(d,8.5)	4.56(d,7.5)
	3	4.07(m)	4.12(m)	3.97(m)	3.95(m)
	4_{ax}	2.70(dd,3.0,17.0)	2.69(dd,2.5,17.0)	2.49(dd,8.0,16.0)	2.54(dd,8.0,17.0)
	4_{eq}	2.81(dd,4.5,17.0)	2.85(dd,5.0,17.0)	2.83(dd,5.5,16.0)	2.89(dd,5.5,17.0)

In contrast to the analogous pyran rearranged products from the base-catalyzed conversion of procyanidin

B–3[14] which were characterized as octamethyl ether diacetates thus facilitating demonstration of a 'liberated' phloroglucinol A-ring by ^{1}H nuclear Overhauser effect (n.O.e.) difference spectroscopy, a different approach had to be adopted towards the structural elucidation of free phenols 7, 9, and 10. The ^{1}H NMR spin systems in all three analogues were differentiated and fully analyzed by extensive spin-decoupling experiments using the benzylic 2–, 8–, and 10–H resonances as reference signals. A weak but structurally significant n.O.e. association (0.9, 1.9% resp.)[b] of the broadened two-proton singlet (δ5.98) of the A-ring with 2– and 6–H(E) (δ6.57, 6.17 resp.) not only confirmed the tetrahydropyrano[2,3–*h*]chromene arrangement for analogue 7 but also established the location of the phloroglucinol moiety at C–10. It furthermore indicated a *cis*-relationship[13] of the aryl substituents at C–2 and –10. When taken in conjunction with the known α-orientation of the E–ring of the (–)-epicatechin DEF unit, this also indicated an α-orientation for the phloroglucinol A-ring. A strong negative Cotton effect (CE) at 237 nm in the CD spectrum confirmed the 10α-aryl substituent by application of the aromatic quadrant rule[19]. These CD and ^{1}H NMR (Table) features collectively facilitated definition of the absolute configuration of 7 as 2*R*,3*R*:8*S*,9*R*,10*R*.

The spin-decoupling experiments on analogues 9 and 10 also established a benzylic connection of 2–H(F) (δ4.69, 4.53 for 9 and 10 resp.) and 10–H(C) (δ4.22, 4.19 for 9 and 10 resp.) with the 2– and 6-protons of the respective pyrocatechol E– and B-rings. Besides the n.O.e. effect of 8–H(C) (δ5.65, 5.59 for 9 and 10 resp.) with 2– and 6–H (3.5, 3.8 and 3.9, 4.3% for 9 and 10 resp.) of a pyrocatechol moiety in both 9 and 10, reminiscent of these structural types with a 3,4-disubstituted aryl group at C–10[12], the former proton did not exhibit additional long-range coupling thus reflecting the presence of an *ortho*-disubstituted phenyl residue at C–10. These observations hence implied an 'interchange' of the phloroglucinol A– and pyrocatechol B-rings in analogues 9 and 10 relative to the positions of these rings in the tetrahydropyrano-[2,3–*h*]chromene 7[c]. The chemical shifts of 8– and 10–H(C) and thus unambiguous proof for such an A–/B–ring interchange in 9 were confirmed by 2D-heteronuclear correlation of these protons with, respectively, C–8 and 10– (δ69.04, 45.33 resp.). This experiment also facilitated assignment of the chemical shifts of all H-bearing carbons (*cf.* Experimental). Confirmation of both the *cis*-relationship between the C–2 and –10 pyrocatechol E– and B-rings, both α-orientated (*vide supra*), and the tetrahydropyrano[2,3–*h*]-chromene arrangement of 9 was again furnished by the n.O.e. associations of both 5– and 6–H(B) (δ6.70, 6.46 resp.) with 6–H(E) (δ6.12) (0.7, 1.1% resp.). A high-amplitude negative CE at 238 nm in the CD spectrum confirmed the 10α-aryl substituent hence facilitating, in conjunction with ^{1}H NMR coupling constants of C-ring protons, definition of 2*R*,3*R*:8*S*,9*S*,10*R* absolute configuration for 9. Although insufficient sample quantities precluded similar confirmation of the chemical shifts of 8– and 10–H(C) in 10, the very similar shifts of the C–ring protons in 9 and 10 (Table) were taken as sufficient proof of a [2,3–*h*]arrangement for 10. These small chemical shift differences may be attributed to the β-orientated E-ring in the latter compound. The conspicuous absence of n.O.e. associations between the protons of the pyro-

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[b]Approximated value owing to signal overlap

[c]Compare refs. 12–14 for similar phenomena occurring during base–catalyzed conversions of profisetinidins and procyanidin B–3

catechol B– and E-rings in 10 presumably indicated a *trans*-relationship of these rings and hence a 10α B-ring. The CD spectrum, however, exhibited an intense positive CE at 239 nm which apparently reflected a 10β B-ring. Such a contradiction was commonly encountered for profisetinidin related analogues[12,13] with 2,10-*trans* aryl groups and had been explained by significant contributions of A-conformers[20,21] (F-ring) reversing the sign of the low-wavelength CE. We thus favour the 2*S*,3*R*:8*S*,9*S*,10*R* absolute configuration depicted for analogue 10. The inversion of the absolute configuration at C–9 in 9 and 10 relative to that at C–3 in the biflavanoid precursor 3 is explained later.

The ^{1}H NMR spectrum (Table) of the remaining analogue 2 displayed in the heterocyclic proton region an AB-system [δ4.16 (3–H), 4.29 (4–H), $J_{3,4}$ 3.5 Hz] characteristic[2] of the C-ring protons of A-type procyanidins. Confirmation of the chemical shift of 3–H was obtained by its pronounced n.O.e. association with both 2– and 6–H (B; 3.9, 4.3% resp.). Epimerization[23] at 2–C(F) under the mild basic conditions and hence conversion of the (–)-epicatechin DEF unit in precursor 3 to a (–)-catechin moiety in 2 was evident from the coupling constant ($J_{2,3}$ 7.5 Hz) of 2– and 3–H(F). A high-amplitude positive CE at 234 nm in the CD spectrum confirmed the β-orientation at C–4 and, combined with ^{1}H NMR data and known absolute configuration of procyanidin B–2 3, subsequently also the configuration as is depicted in 2. Analogue 2 therefore represents the C–2(F) epimer of procyanidin A–2 which was previously isolated by Nishioka *et al.*[9] and designated proanthocyanidin A–4.

Under the mild basic conditions procyanidin B–2 3 is presumably transformed to an intermediate B-ring quinone-methide[22] 6[d] which then serves as common precursor to the novel tetrahydropyrano[2,3–*h*]-chromenes 7, 9, and 10. Analogue 7 originates *via* stereospecific pyran recyclization[12–14] involving 7–OH(D) and the *si*-face at C–2 in quinone-methide 6. Migration of the (–)-epicatechin moiety, assisted by the strongly electron-releasing phloroglucinol unit at C–4, to the *si*-face at C–2 in 6 and subsequent recyclization *via* 7–OH(D) and the *si*-face at C–4 in quinone-methide 8[d] may feasably rationalize the genesis of the tetrahydropyrano[2,3–*h*]chromene with its 'interchanged' phloroglucinol A– and pyrocatechol B-rings. Inversion of configuration[21] at the equivalent of C–3(C) in procyanidin B–2 3 associated with the observed ring interchange is substantiated by CD data (*vide supra*). The susceptibility of the E-ring in *eg*. 3, 6, and 8 to quinone-methide formation at alkaline pH[12–14,22] presumably also initiates epimerization at C–2(F) and hence formation of the (–)-catechin DEF unit in the ring-interchanged tetrahydropyrano[2,3–*h*]-chromene 10. Generation of the (–)-epicatechin/(–)-catechin mixture 4 and 5 is attributable to a similar phenomenon following cleavage of the base-labile[17] interflavanyl bond in procyanidin B–2. A putative A-ring quinone-methide[14,17] resulting from such a bond rupture may also induce the formation of the condensed analogues of unknown constitution *via* uncontrolled condensation with procyanidin B–2.

Formation of the A–/B–ring interchanged analogues 9 and 10, arising *via* the exclusive 1,3-migration of the (–)-epicatechin moiety in quinone-methide 6, contrasts with results for procyanidin B–3[14] where pre-

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[d]Quinone–methides 6 and 8 are postulated and have not been isolated

ferential migration of the phloroglucinol A-ring at 4–C in an analogous quinone-methide was observed. Such an exclusivity in the shift of the (–)-epicatechin unit with its reduced migratory aptitude compared to that of the phloroglucinol moiety at C–4 for quinone-methide 6, is presumably attributable to steric factors. The *cis*-coplanarity of the *β*-orientated sp^3-orbital adjoining C–4 and C–8(D) and the electron-deficient *p*-orbital at the *si*-face of C–2 should provide the additional driving force for the 1,3-migration of the (–)-epicatechin unit in 6.

The transformation of procyanidin B–2 3 into the C–2(F) epimer 2 of procyanidin A–2 1 presumably involves the oxidative removal of hydride ion at C–2(C) as the initial step. The nature of the oxidizing species is, however, not clear. Although the trace amounts of oxygen may effect the transformation 3 → 11, it seems more reasonable to suggest that the prevailing conditions induce oxidation of the *o*–dihydroxy functionality of the pyrocatechol B– or E-rings to an *o*-quinone[23] which subsequently serves as oxidant for the conversion 3 → 11. Experiments aimed at verifying the latter proposal *via* selective protection of the 3'-OH groups of the pyrocatechol rings of 3 and related procyanidins are presently being investigated. These results will be discussed in an impending publication. The results presented here nevertheless provide unequivocal chemical evidence in favour of the *β*-orientated doubly-linked unit of procyanidin A–2 1 and of its C–2(F) epimer 2. The apparently exclusive formation of procyanidin A–4 2 is explicable in terms of formation of an E–ring quinone-methide of either 3 or 11 and subsequent recyclization to the thermodynamically more stable 2,3-*trans* relative configuration.

Under these extremely mild conditions we could not find evidence of rearrangements of procyanidin B–2 to catechinic acid-type products[24,25] reputed for either decreasing its reactivity towards aldehydes or enhancing acidity[24,26,27]. Our results, when considered in conjunction with similar observations for procyanidin B–3[14], hence indicate that with the proper selection of conditions, extraction of conifer barks[15,16] at alkaline pH may be performed without the adverse effects which have hitherto hampered the successful application of such an approach towards the economically important procyanidins. The 'liberated' phloroglucinol-type A-rings in tetrahydropyrano[2,3–*h*]chromenes 7, 9, and 10 should, indeed, lead to increased reactivity towards aldehydes compared to that of procyanidin B–2 3.

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker AM–300 spectrometer, for $(CD_3)_2CO$ solutions (D_2O exchange) with Me_4Si as internal standard. Mass spectral data were obtained with a Kratos MS80 instrument, and CD data in MeOH on a Jasco J–20 spectropolarimeter. TLC was performed on precoated Merck plastic sheets (DC-Plastikfolien Kieselgel 60 PF_{254}, 0.25 mm) and compounds were located by H_2SO_4–HCHO (40:1 v/v) spray reagent. CC was done on Sephadex LH–20 in EtOH at a flow rate of 0.5 $cm^3 min^{-1}$. Evaporations were done under reduced pressure at *ca.* 60°C in a rotary evaporator.

Base–catalyzed Conversion of (4β,8)–Bis–(–)–epicatechin 3. —— Procyanidin B–2[28] 3 (500 mg) was dissolved in 0.1M $NaHCO_3$ (200 cm^3) and the mixture was stirred for 6.5 h at 40°C under nitrogen containing traces of oxygen. The mixture was chilled with crushed ice, acidified (0.1M HCl) to pH 6, and extracted with EtOAc (8x200 cm^3). Drying (Na_2SO_4) of the extract followed by evaporation of the solvent afforded a brown, amorphous solid (330 mg). This was subjected to CC (2.5x90 cm column; 15 cm^3/tube; first 400 cm^3 of eluant discarded) to give the following fractions: 1(tubes 56–66, 32 mg), 2(114–132, 17 mg), 3(146–150, 6 mg), 4(160–180, 29 mg), 5(211–240, 15 mg), and 6(245–280), 63 mg).

Fraction 1 consisted of a (–)epicatechin/(–)catechin mixture (47:53) and fraction 6 consisted of high-molecular-mass analogues of procyanidin B–2. Owing to its complexity this mixture was not further investigated.

Fraction 2 afforded the C–2(F) epimer 2 (A–4) of procyanidin A–2 as a white solid (Found: M^+, 576.1260. $C_{30}H_{24}O_{12}$ requires M, 576.1268); ^1H NMR data (Table); CD $[\Theta]_{297}$ 0, $[\Theta]_{278}$ 1.0×10^4, $[\Theta]_{255}$ 0, $[\Theta]_{234}$ 6.9×10^4, and $[\Theta]_{200}$ 1.9×10^4.

Fraction 3 gave (2R,3R:8S,9R,10R)-3,5,9-*trihydroxy*-2,8-bis-(3,4-*dihydroxyphenyl*)-10-(2,4,6-*trihydroxyphenyl*)-2,3-cis-8,9-trans-9,10-cis-3,4,9,10-*tetrahydro*-2H,8H-*pyrano*[2,3–*h*]*chromene* 7 as a white solid (Found: M^+, 578.1418. $C_{30}H_{26}O_{12}$ requires M, 578.1424); ^1H NMR data (Table); CD $[\Theta]_{320}$ 0, $[\Theta]_{276}$ -5.3×10^4, $[\Theta]_{252}$ -1.4×10^4, $[\Theta]_{237}$ -8.9×10^4, and $[\Theta]_{226}$ 0.

Fraction 4 afforded (2R,3R:8S,9S,10R)-3,5,9-*trihydroxy*-2,10-bis-(3,4-*dihydroxyphenyl*)-8-(2,4,6-*trihydroxyphenyl*)-2,3-cis-8,9-cis-9,10-trans-3,4,9,10-*tetrahydro*-2H,8H-*pyrano*[2,3–*h*]*chromene* 9 as a white solid (Found: M^+ 578.1431. $C_{30}H_{26}O_{12}$ requires M, 578.1424); ^1H NMR data (Table); δ_C [$(CD_3)_2CO$; 23°C, 75.4 MHz) 96.07, 94.92 (C–3 + –5, A–ring), 116.27 (C–2, B)[e], 115.95 (C–5, B), 120.24 (C–6, B), 69.04 (C–8, C), 73.99 (C–9, C), 45.33 (C–10, C), 97.55 (C–6, D), 113.14 (C–2, E)[e], 116.05 (C–5, E), 118.28 (C–6, E), 79.31 (C–2, F), 66.79 (C–3, F), and 29.03 (C–4, F); CD $[\Theta]_{319}$ 0, $[\Theta]_{277}$ 2.6×10^4, $[\Theta]_{246}$ 0, $[\Theta]_{238}$ -7.6×10^4, and $[\Theta]_{224}$ 0.

Fraction 5 consisted of (2S,3R:8S,9S,10R)-3,5,9-*trihydroxy*-2,10-bis-(3,4-*dihydroxyphenyl*)-8-(2,4,6-*trihydroxyphenyl*)-2,3-trans-8,9-cis-9,10-trans-3,4,9,10-*tetrahydro*-2H,8H-*pyrano*[2,3–*h*]*chromene* 10 as a white solid (Found: M^+, 578.1429. $C_{30}H_{26}O_{12}$ requires M, 578.1424); ^1H NMR data (Table); CD $[\Theta]_{302}$ 0, $[\Theta]_{270}$ -1.2×10^4, $[\Theta]_{257}$ 0, $[\Theta]_{239}$ 5.6×10^4, and $[\Theta]_{202}$ 0.

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[e]Assignments may be interchanged

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