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On the Synthesis and Chiroptical Properties of the Tri- and Tetragalloylquinic Acids

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Summary. A synthesis of the potential pharmaceutical agents 3,4,5-trigalloylquinic acid and 1,3,4,5-tetragalloylquinic acid is described. It involves three steps starting from commercially available quinic acid and provides overall yields of about 15%. The acylation of benzyl or 4-nitrobenzyl quinate with tribenzylgalloyl chloride is the key step. It leads selectively to the triacyl product in the case of benzyl quinate and can be either stopped at the triacyl stage or driven to the tetraacyl derivative in the case of the 4-nitrobenzyl quinate. From the chiroptical properties of the two compounds their stereochemistry was derived by means of the benzoate rule.

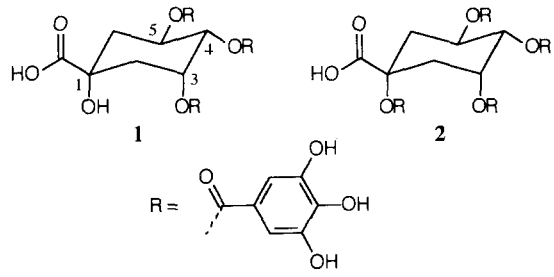
Keywords. 3,4,5-Trigalloylquinic acid; 1,3,4,5-Tetragalloylquinic acid; Synthesis; Configuration; Conformation; Circular dichroism

Zu Synthese und chiroptischen Eigenschaften der Tri- und Tetragalloylchinasäuren

Zusammenfassung. Eine Synthese von 3,4,5-Trigalloylchinasäure und 1,3,4,5-Tetragalloylchinasäure, die potentielle Pharmaka darstellen, wird beschrieben. Sie umfaßt drei Stufen, welche ausgehend von kommerziell erhältlicher Chinasäure Gesamtausbeuten um 15% ergeben. Die entscheidende Stufe dabei ist die Acylierung von Benzyl- oder 4-Nitrobenzylchinat mit Tribenzylgalloylchlorid. Sie führt im Falle des Benzylchinats selektiv zum Triacylprodukt und kann im Fall des 4-Nitrobenzylchinats entweder auf der Stufe des Triacylderivates abgebrochen oder bis zum Tetraacylprodukt durchgezogen werden. Aus den chiroptischen Eigenschaften der beiden Verbindungen wurde ihre Stereochemie abgeleitet.

Introduction

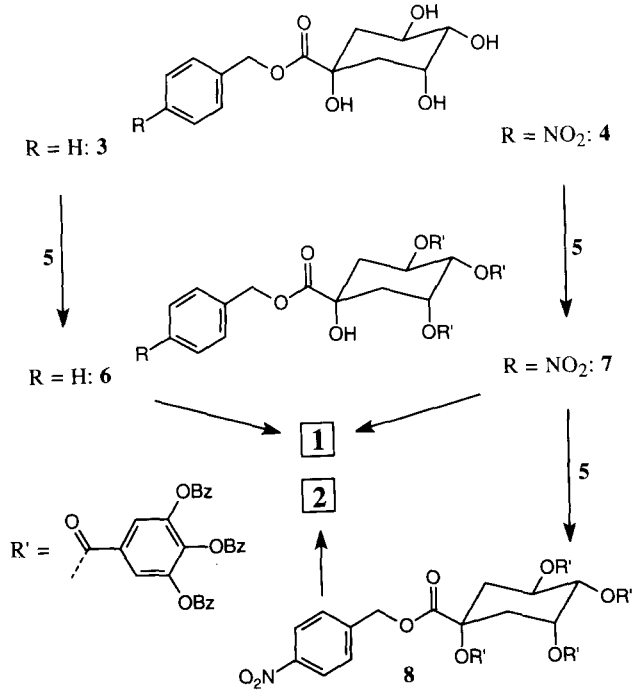
3,4,5-Trigalloylquinic acid (**1**) and 1,3,4,5-tetragalloylquinic acid (**2**) are natural products contained in the tannic acid fractions of certain plants. Whereas **1** is mainly present in Turkish and Chinese galls, **2** is found in Tara tannin and in extracts from *Galphimia glauca* [1–3]. It has been found that **1** is a weak human immunodeficiency virus reverse transcriptase inhibitor [1] and **2** is an antihistaminic principle [3]. These highly interesting physiological properties prompted a search for an efficient synthesis of these two compounds, which will be described in this report.



Results and Discussion

Synthesis

The trigalloylquinic acid **1** has been prepared involving six steps and providing a rather low overall yield [4] with questionable purity. There has been also a report on the synthesis of the tetragalloylquinic acid **2** [4]. However, we and others [5] were unable to reproduce this synthesis which involves heating of the reaction mixture for rather inconvenient 25 days in one of the steps. Thus, it was found that on proceeding along the reported procedure [4] the product isolated according to this recipe did not contain galloylquinic acids. However, from the reaction mixture the desired compound **2** could be isolated in trace amounts after tedious chromatography.



To prepare **1** and **2**, the most convenient starting material obviously was the commercially available quinic acid. To introduce three to four ester groups into a hydroxyacid which themselves bear phenolic groups, mandated a balanced protecting group strategy. It was found that the acid function of quinic acid had

to be protected in order to allow the acylation of its hydroxy groups. It was most conveniently protected as a benzyl (**3**) or a 4-nitrobenzyl (**4**) derivative. The corresponding esterification of quinic acid was achieved using benzyl or 4-nitrobenzyl chloride in dimethylformamide as the solvent and triethyl amine as the base. Having in mind the hydrogenolytic deprotection reaction for these benzyl esters, benzyl groups were also chosen to protect the phenolic groups of the activated galloyl derivative. Hence, tribenzylgalloyl chloride (**5**) was used as the acylating reagent.

From the broad variety of acylation conditions tried, using **5** as the reagent to acylate **3** or **4** in the presence of 4-dimethylaminopyridine in dry pyridine as the solvent at 60 °C provided the best results. Interestingly enough, it turned out that the acylation reaction was regioselective in the case of the benzyl ester **3** which exclusively yielded the triacylation product **6**. In the case of the nitrobenzyl ester **4** the triacylated derivative **7** was produced upon reaction times in the order of two days and the tetraacylated derivative **8** was produced only upon prolonged reaction times of about five days and a large excess of reagents. This behavior is thought to be due to a sterically hindered and hydrogen bridge deactivated 1-hydroxy group in **3** and **4**. It should be mentioned that the 4-nitrobenzyl derivatives displayed an advantage over the benzyl derivatives. They could be easily spotted in chromatographic separations due to their faintly yellow color.

Hydrogenolysis of **6**, **7** and **8** with palladium on charcoal as the catalyst and ethyl acetate as the solvent yielded the respective desired products **1** and **2** in almost quantitative yields. The overall yields for **1** and **2** based on the commercially available quinic acid for the three steps were 25% and 11%, respectively. The ^{1}H and ^{13}C NMR spectroscopic properties of these compounds were in accordance with their constitutions and agreed with data of **1** and **2** isolated from natural sources [1, 3]. Moreover, these products proved to be of $\geq 99\%$ purity as judged from HPLC. Accordingly, an efficient and convenient synthesis for these interesting natural products is now available.

Chiroptical Properties and Stereochemistry of **1** *and* **2**

In addition to the intrinsic interest in their chiroptical properties, which to our knowledge have not yet been recorded, the tri- and tetragalloyl derivatives **1** and **2** provided interesting examples to apply *Nakanishi's* benzoate rule [6] in order to elucidate their preferred conformations in solution. An inspection of the CD spectra of **1** and **2** (Figs. 1 and 2) clearly revealed bisignate couplets in the benzoate L_a transition region between 250 and 300 nm.

For the tribenzoate **1** two conformers (**a** and **b**, $Y = H$, $R =$ galloyl, see Scheme 1) are possible in principle. The pairwise interactions (3↔4, 3↔5, 4↔5) in the **a** conformer are of negative chirality and resembled closely the situation observed for α-methyl-*D*-mannoside 2,3,4-tri-*p*-chlorobenzoate [6a]. Hence, this conformer should exhibit a marked negative exciton couplet. In the **b** conformer, the 3↔4 pairwise interaction exhibits positive chirality, the 3↔5 one negative chirality, and due to an *antiperiplanar* arrangement the 4↔5 interaction will be negligible. Hence, the **b** conformer should exhibit only marginal exciton chirality. Accordingly, the experimental result shown in Fig. 1 allowed an unequivocal assignment of

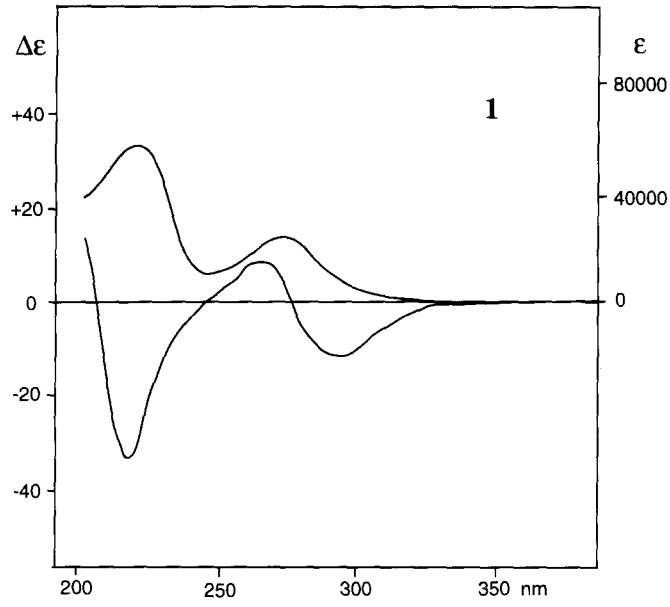
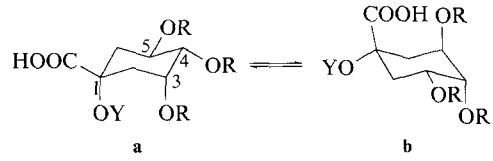


Fig. 1. UV and CD spectra of **1** in water



Scheme 1

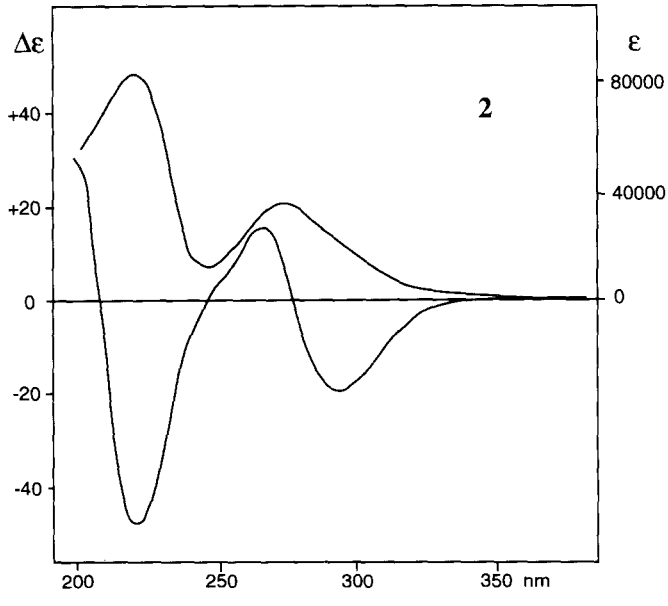


Fig. 2. UV and CD spectra of **2** in water

conformer **a** to **1**. This result is in accordance to the conformational situation of quinic acid as found in the crystal by means of an X-ray crystallographical study [7].

For the tetrabenzoate **2**, the conformational situation (**a** and **b**, Y = R = galloyl, see Scheme 1) is similar to the one discussed for **1**. The additional interactions between the 1-galloyl residue and the three benzoates in positions 3, 4, and 5 should be less important due to the larger distance between the interacting moities and due to nearly *planar* sub arrangements. Accordingly, the experimental data of Fig. 2 also pointed to the preponderance of the **a** conformer present for **2**. This result is in accordance with the X-ray data on quinic acid [7] and with a recent force field study of **2** [3].

Experimental

Melting points were measured on a Kofler hot stage microscope (Reichert, Vienna). ^{1}H and ^{13}C NMR spectra were recorded by means of Bruker AC-200 and WM-360 spectrometers. IR and UV spectra were obtained on Biorad-FT-IR-45 and Hitachi U-3210 instruments. The CD data of **1** and **2** were recorded by means of a Jobin-Yvon Mark VI instrument with water as the solvent and a path length of 1 cm. The optical rotation was measured with a Perkin Elmer 254 photoelectric polarimeter. For the HPLC analysis of **1** and **2**, a Hypersil ODS (RP-18) column (250 × 4 mm, 5 μm) with 5% water in acetonitrile as the mobile phase was used. The acid chloride **5** was prepared according to Ref. [8] starting from methyl-tri-O-benzyl gallate [9].

3,4,5-Tri-O-galloylquinic acid (**1**; $C_{28}H_{24}O_{18}$)

132 mg **6** (0.085 mmol), or alternatively the equivalent of **7**, were dissolved in 40 ml ethyl acetate and hydrogenolyzed over 30 mg Pd/C (10%) at ambient temperature at normal pressure for 12 h. After filtration, the solvent and the toluene formed were distilled off in high vacuum. The residue was dissolved in water, washed with chloroform, and extracted with ethyl acetate. After evaporation of the solvent, 55 mg **1** (100%) were obtained as a white crystalline material of m.p. 210 °C (dec). Its purity according to HPLC was ⩾99%. ^{1}H NMR (CD_3OD, 360 MHz, δ): 2.27 (m, 2H, H-2 or H-6), 2.49 (m, 2H, H-6, or H-2), 5.46 (dd, 1H, J = 7.7 and 3.1 Hz, H-4), 5.73 (m, 1H, H-5), 5.79 (m, 1H, H-3), 6.99 (s, 2H, $H_{galloyl}$), 7.02 (s, 2H, $H_{galloyl}$), 7.09 (s, 2H, $H_{galloyl}$) ppm; ^{13}C NMR (CD_3OD, 50 MHz, δ): 36.62 (C-6), 38.42 (C-2), 70.45 (C-3), 70.18 (C-5), 72.50 (C-4), 74.65 (C-1), 110.04, 110.33, 110.34, 110.51 (C_{ar}-2, 6), 120.87, 120.87, 121.05 (C_{ar}-1), 139.95, 140.08, 140.15 (C_{ar}-4), 146.41, 146.46, 146.49 (C_{ar}-3,5), 167.29, 167.33, 167.68 (COO), 177.29 (COO) ppm; IR (KBr): ν = 3367 (OH), 2925, 2855 (CH), 1704 (C=O), 1614, 1539, 1452, 1372, 1320, 1214, 1122, 1096, 1033, 856, 765 cm^{-1}; UV (acetonitrile): λ_{max} = 271 (10130), 216 (25160) nm (ε); UV (water): λ_{max} = 274 (21100), 213 (51820) nm (ε); CD (water): λ_{max} = 288 (−12.5), 262 (+7.3), 214 (−32.9) nm ($\Delta\varepsilon$); $[\alpha]_D$ = −133° (c = 0.15, water, d = 1 dm, 20 °C).

1,3,4,5-Tetra-O-galloylquinic acid (**2**; $C_{35}H_{28}O_{22}$)

45 mg **8** (0.022 mmol) were dissolved in 15 ml ethyl acetate and hydrogenated over 9 mg Pd/C (10%) at ambient temperature at normal pressure for 24 h. Every 6 h, an additional amount of 6 mg catalyst was added. After filtration, the solvent and the toluene formed were distilled off in high vacuum. The residue was dissolved in water, washed with chloroform, and evaporated. Thereby, 16 mg **1** (90%) were obtained as a white crystalline solid of m.p. 215 °C (dec; 208–214 °C (Ref. [3])). Its purity according to HPLC was ⩾99%. ^{1}H NMR (CD_3OD, 360 MHz, δ): 2.38 (m, 1H, H-6), 2.81 (m, 2H, H-2, 6), 2.95 (m, 1H, H-2), 5.55 (dd, 1H, J = 8.3 and 3.5 Hz, H-4), 5.83 (m, 1H, H-3), 5.92 (m, 1H, H-5), 6.89 (s, 2H, $H_{galloyl}$), 6.97 (s, 2H, $H_{galloyl}$), 7.02 (s, 2H, $H_{galloyl}$), 7.06 (s, 2H, $H_{galloyl}$) ppm; ^{13}C NMR

(CD_3OD, 50 MHz, δ): 33.05 (C-6), 37.99 (C-2), 69.10 (C-3), 70.29 (C-5), 72.59 (C-4), 80.58 (C-1), 110.29, 110.39 (C_{ar}-2,6), 120.68, 120.71, 120.63, 120.10 (C_{ar}-1), 139.721, 140.00, 140.09, 140.14 (C_{ar}-4), 146.11, 146.29, 146.40 (C_{ar}-3,5), 167.23, 167.46, 167.63, 174.06 (COO), 174.06 (COO) ppm; IR (KBr): $\nu = 3400$ (OH), 1706 (C=O), 1616, 1540, 1453, 1356, 1223, 1097, 1034, 989, 868, 764 cm^{-1}; UV (acetonitrile): $\lambda_{max} = 271$ (14870), 216 (35150) nm (ε); UV (water): $\lambda_{max} = 273$ (37900), 212 (85970) nm (ε); CD (water): $\lambda_{max} = 290 (-19.8), 264 (+16.3), 217 (-51.8)$ nm ($\Delta\varepsilon$); $[a]_D = -138°$ ($c = 0.16$, water, $d = 1$ dm, 20 °C).

Benzyl-quinate (**3**; $C_{14}H_{18}O_5$)

To 2.0 g quinic acid (98%, Aldrich; 10.4 mmol) dispersed in 30 ml dry dimethylformamide, 1.155 g triethylamine (11.4 mmol) were added. After the acid had dissolved, 1.843 g freshly distilled benzyl chloride were added and the mixture was refulxed for 8 h. The reaction mixture was evaporated on a rotatory evaporator, the residue triturated with acetone, and the solvent distilled off. The residue was dissolved in water, extracted with chloroform, and the water phase was saturated with NaCl and extracted with ethyl acetate (3×150 ml). The organic phase was dried over Na_2SO_4 and evaporated. After drying in high vacuum, 1.7 g (58%) of **3** were obtained; m.p.: 66–69 °C. ^{1}H NMR (*DMSO*-d_6, 200 MHz, δ): 1.89 (m, 4H, H-2,6), 3.30 (m, 1H, H-4), 3.75 (m, 1H, H-5), 3.88 (m, 1H, H-3), 4.51 (d, 1H, $J = 6.34$ Hz, OH-4), 4.52 (d, 1H, $J = 3.64$ Hz, OH-5), 4.62 (d, 1H, $J = 4.26$ Hz, OH-3), 5.05 (d, 1H, $J = 14.4$ Hz, CH_2), 5.05 (d, 1H, $J = 14.4$ Hz, CH_2), 5.51 (s, 1H, OH-1), 7.32 (m, 5 H, H_{ar}) ppm; ^{13}C NMR (CD_3OD, 50 MHz, δ): 38.17 (C-6), 41.99 (C-2), 68.00 (COO-CH_2), 67.98 (C-3), 71.43 (C-5), 76.57 (C-4), 76.81 (C-1), 129.13, 129.27, 129.53 (C_{ar}-2,3,4,5,6), 137.19 (C_{ar}-1), 175.17 (COO) ppm; IR (KBr): $\nu = 3367$ (OH), 2932 (CH), 1736 (C=O), 1636, 1453, 1262, 1224, 1123, 1079, 973, 913, 746, 698, 616 cm^{-1}; UV (acetonitrile): $\lambda_{max} = 207$ (7780), 192 (26910) nm (ε).

4-Nitrobenzyl-quinate (**4**; $C_{14}H_{17}O_7N$)

Prepared according to the procedure given above for **3**, yield 30%; m.p.: 107–109 °C. ^{1}H NMR (*DMSO*-d_6, 200 MHz, δ): 1.85 (m, 4H, H-2, -6), 3.33 (m, 1H, H-4), 3.77 (m, 1H, H-5), 3.90 (m, 1H, H-3), 4.52 (d, 1H, $J = 6.27$ Hz, OH-4), 4.55 (d, 1H, $J = 4.04$ Hz, OH-5), 5.21 (d, 1H, $J = 6.9$ Hz, CH_2), 5.21 (d, 1H, $J = 6.9$ Hz, CH_2), 5.58 (s, 1H, OH-1), 7.65 (d, 2*H*, $J = 8.67$ Hz, H_{ar}), 8.22 ppm (d, 2H, $J = 8.67$ Hz, H_{ar}) ppm; ^{13}C NMR (CD_3OD, 50 MHz, δ): 38.16 (C-6), 41.66 (C-2), 66.45 (COO–CH_2), 68.15 (C-3), 71.10 (C-5), 76.25 (C-4), 76.64 (C-1), 124.55 (C-2′,6′), 129.45 (C-3′,5′), 144.78 (C-1′), 148.87 (C-4′), 175.84 (COO) ppm; IR (KBr): $\nu = 3434$, 3286 (OH), 3083, 2923, 2867 (CH), 1742, 1727 (C=O), 1609, 1598, 1442, 1243, 1204, 1125, 1073, 736, 611 cm^{-1}; UV (acetonitrile): $\lambda_{max} = 199$ (12510), 213 (6880), 268 (10627) nm (ε).

Benzyl-3,4,5-tris-O-tri-O-benzylgalloyl-quinate (**6**; $C_{98}H_{84}O_{18}$)

16 mg **3** (0.057 mmol), 520 mg **5** (1.134 mmol), and 42 mg 4-dimethyl-aminopyridine (0.34 mmol) were dissolved in 20 ml dry pyridine and stirred for 48 h at 60 °C. The solvent was evaporated and the residue triturated with ethyl acetate, filtered, and the organic phase was washed to neutrality with 1 *N* HCl and water. After drying and evaporation, the residue was chromatographed over silica using $CHCl_3$:CH_3OH = 100:1 as eluent. Yield: 38 mg (43%) of a glassy material with no defined melting behavior. ^{1}H NMR ($CDCl_3$, 200 MHz, δ): 2.40 (m, 4H, H-2, -6), 4.72, 4.94, 4.96, 5.04, 5.08, 5.11, 5.17 (s, 18H, $-OCH_2-$Ph), 5.21 (s, 2H, $-COOCH_2-$Ph), 5.54 (dd, 1H, $J = 9.62$ and 3.26 Hz, H-4), 5.86 (m. 1H, H-3), 5.98 (m, 1H, H-5), 7.22 (m, 56 H, H_{ar}), 7.50 ppm (s, 2H, H_{ar}) ppm; ^{13}C NMR (CD_3OD, 50 MHz, δ): 36.09, 39.06, 68.15, 68.42, 69.37, 72.86, 74.03, 70.65, 70.74, 70.96, 74.86, 74.90, 74.96, ($6 \times OCH_2-$Ph), 108.74, 108.98 ($C_{galloyl}$-2,6), 124.08, 124.47, 124.76 ($C_{galloyl}$-1), 127.28–128.75 (C_{phenyl}-2,3,4,5,6), 134.5 (C_{phenyl}-1), 136.13, 136.32, 136.39, 136.52, 137.24, 137.26 (C_{phenyl}-1), 142.48, 142.55 ($C_{galloyl}$-4), 152.29, 152.42 ($C_{galloyl}$-3,5), 165.12, 165.19, 165.21 ($3 \times$ COO), 174.05 (COO) ppm; IR (KBr): $\nu = 3468$ (OH), 3045, 3031, 2944, 2870 (CH), 1716 (C=O), 1588, 1500, 1454, 1428, 1374,

1335, 1206, 1114, 1077, 969, 859, 751, 734, 695 cm^{-1}; UV (acetonitrile): $\lambda_{max} = 269$ (30020), 212 (125790) nm (ε).

4-Nitrobenzyl-3,4,5-tris-O-tri-O-benzylgalloyl-quinate (**7**; $C_{98}H_{83}O_{20}N$)

15.7 mg **4** (0.07 mml), 264 mg **5** (0.58 mmol), and 70 mg 4-dimethylaminopyridine (0.576 mmol) were dissolved in 20 ml dry pyridine and the mixture was stirred for 53 h at 60 °C. The solvent was evaporated and the residue triturated with ethyl acetate, filtered, and the organic phase was washed with 1 *N* HCl and water. After drying, the solvent was evaporated and the residue chromatographed over silica using $CHCl_3$:CH_3OH = 100:1 as eluent. Yield: 60 mg (70%) of a glassy material with no defined melting behavior. ^1H NMR ($CDCl_3$, 200 MHz, δ): 2.3 (m, 4H, H-2,6), 4.65, 4.87, 4.90, 4.95, 4.97, 4.98 (ss, 18 H, $-OCH_2-Ph$); 5.17 (s, 2H, $-COOCH_2$), 5.50 (dd, 1H, $J = 9.64$ and 3.11 Hz, H-4), 5.80 (m, 1H, H-3), 5.88 (m, 1H, H-5), 7.20 (m, 54 H, H_{arom}), 8.15 (d, 2H, $J = 8.63$ Hz, H_{arom}) ppm; IR (KBr): $\nu = 3422$ (OH), 3090, 3095, 2929, 2870 (CH), 1719 (C=O), 1588, 1522, 1500, 1454, 1429, 1372, 1337, 1219, 1111, 982, 854, 747, 737, 696 cm^{-1}; UV (acetonitrile): $\lambda_{max} = 269$ (32500), 208 (124600) 193 (240000) nm (ε).

4-Nitrobenzyl-1,3,4,5-tetrakis-O-tri-O-benzylgalloyl-quinate (**8**; $C_{126}H_{98}O_{24}N$)

22 mg **4** (0.067 mmol), 494 mg **5** (1.075 mmol), and 132 mg 4-dimethyl-aminopyridine 1.09 mmol) were dissolved in 15 ml dry pyridine and stirred for 5 days at 60 °C. The solvent was evaporated, the residue dissolved in ethyl acetate, washed with 1 *N* HCl and water, dried with Na_2SO_4, and evaporated. The residue was chromatographed over silica using $CHCl_3$:CH_3OH = 100:2 as eluent. Yield: 57 mg (42%) of a glassy material with no defined melting behavior. ^1H NMR ($CDCl_3$, 200 MHz, δ): 2.8 (m, 2H, H-2,6), 4.52, 4.66, 4.70, 4.81, 4.86, 4.98, 5.01 (s, 24H, OCH_2-Ph), 5.19 (s, 2H, $COOCH_2$), 5.59 (dd, 1H, $J = 9.7$ and 3.2 Hz, H-4), 5.91 (m, H-3), 6.11 (m, H-5), 7.20 (m, 70 H, H_{ar}), 8.05 (d, 2H, $J = 8$ Hz, H_{ar}) ppm; ^{13}C NMR (CD_3OD, 50 MHz, δ): 33.48, 36.41, 66.10, 67.54, 69.57, 70.43, 70.58, 70.79, 70.95 (4 OCH_2), 72.27, 74.68, 74.84, 74.95, 75.03 (4 OCH_2), 79.59, 108.34, 108.66, 108.93, 123.66, 123.72, 123.85, 123.94, 124.02, 126.99–128.39, 135.94, 136.06, 136.15, 136.27, 137.14, 137.51, 137.48, 141.82, 142.67, 142.83, 143.13, 147.65, 152.28, 152.33, 152.46, 164.92, 164.98, 165.03, 165.26, 169.70 (5 COO) ppm; IR (KBr): $\nu = 3031$, 2982, 2868 (CH), 1720 (C=O), 1588, 1523, 1500, 1454, 1429, 1373, 1210, 1114, 1079, 970, 854, 735, 695(cm^{-1}; UV (acetonitrile): $\lambda_{max} = 269$ (34570), 217 (12458), 191 (22150) nm (ε).

Acknowledgments

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