Tetrahedron 65 (2009) 7954–7962

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The reaction between phloroglucinol and *vic* polycarbonyl compounds: extension and mechanistic elucidation of Kim's synthesis for bipolarofacial bowl-shaped compounds

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ARTICLE INFO

Article history:
Received 26 March 2009
Received in revised form 16 June 2009
Accepted 23 July 2009
Available online 29 July 2009

Keywords:
Bowl-shaped compounds
Phloroglucinol
Ninhydrin
Hemiketals

ABSTRACT

Kim's serendipitous synthesis of a novel cavitand by the one-pot reaction between phloroglucinol and ninhydrin was revisited and extended. A much deeper cavitand was obtained by replacing ninhydrin with benzo[*f*]ninhydrin. Performing the reaction in a stepwise manner, employing both ninhydrin and benzo[*f*]ninhydrin, provided 'mixed bowls' of lower symmetry. Other cyclic polyketones, such as 1,2-indanedione and alloxan, form with phloroglucinol only partially closed structures. Crystallographic studies of the intermediate compounds in this reaction confirm Kim's postulate that the bowl formation involves hemiketal ring-openings and rearrangements.

1. Introduction

The design and synthesis of bowl-shaped molecular entities, and the probing of their structure and reactivity, have become an active area of organic chemistry research.[1] Such molecular containers are designed to exhibit for instance, besides aesthetics in chemistry, selective hosting of metal ions and enzyme mimicry. Of particular interest are structures that are characterized by two different faces, one hydrophobic and the other hydrophilic, due to their potential applications in a variety of areas of supramolecular chemistry.[2] In 2005, Kim and co-workers reported an easy and straight-forward synthesis of a novel bowl-shaped compound by the one-pot reaction between phloroglucinol (**1**) and ninhydrin (**2**, Scheme 1a). The reaction, which is carried out in acetic acid, provides the product in nearly quantitative yield.[3] Their molecular entity (**3**) is bipolarofacial, containing a hydrophobic cavity and a hydrophilic 'bottom' (Fig. 1a). The ease of formation of Kim's cavitand and its potential in supramolecular reactions drew our attention. We have noticed that compound **3** selectively binds and precipitates certain alkali metal salts. It also complexes Fe^{3+} and $PdCl_4^{2-}$ ions (to be reported in a forthcoming paper). Consequently, we tried to gradually modify the geometry of the cavity in **3** in an attempt to explore the correlation between its structure and reactivity, having in mind the possibility of tailoring the ligands toward specific metal ions. We studied the effectiveness of Kim's synthetic route for other vicinal polycarbonyl compounds, with the goal of producing similar molecular containers with e.g., deeper and less symmetrical cavities. We also carried out exhaustive acetylation on all six hydroxyl groups of **3** and elucidated some mechanistic aspects involved in the formation of this intriguing cavitand, with findings corroborating Kim's assumptions.

2. Results

Under even milder conditions (room temperature, 48 h), benzo[*f*]ninhydrin (**4**)[4] produced with **1** in a one-pot reaction, a tris-adduct (**5**), analogous to **3** (Scheme 1b). X-ray crystallography study showed **5** to have a 'vase-shaped' structure, with a hydrophobic cavity much deeper than that of **3** (Fig. 1b). The additional depth may play an important role in the ability to host target molecules.[5]

1,2-Indanedione (**6**), also produced with **1** a tris-adduct, which was found to be a mixture of isomeric 'incomplete bowls' (deduced from ^{1}H NMR and LC/MS). NMR and IR spectra suggest that in the main product, only two indanedione units form the side walls, but

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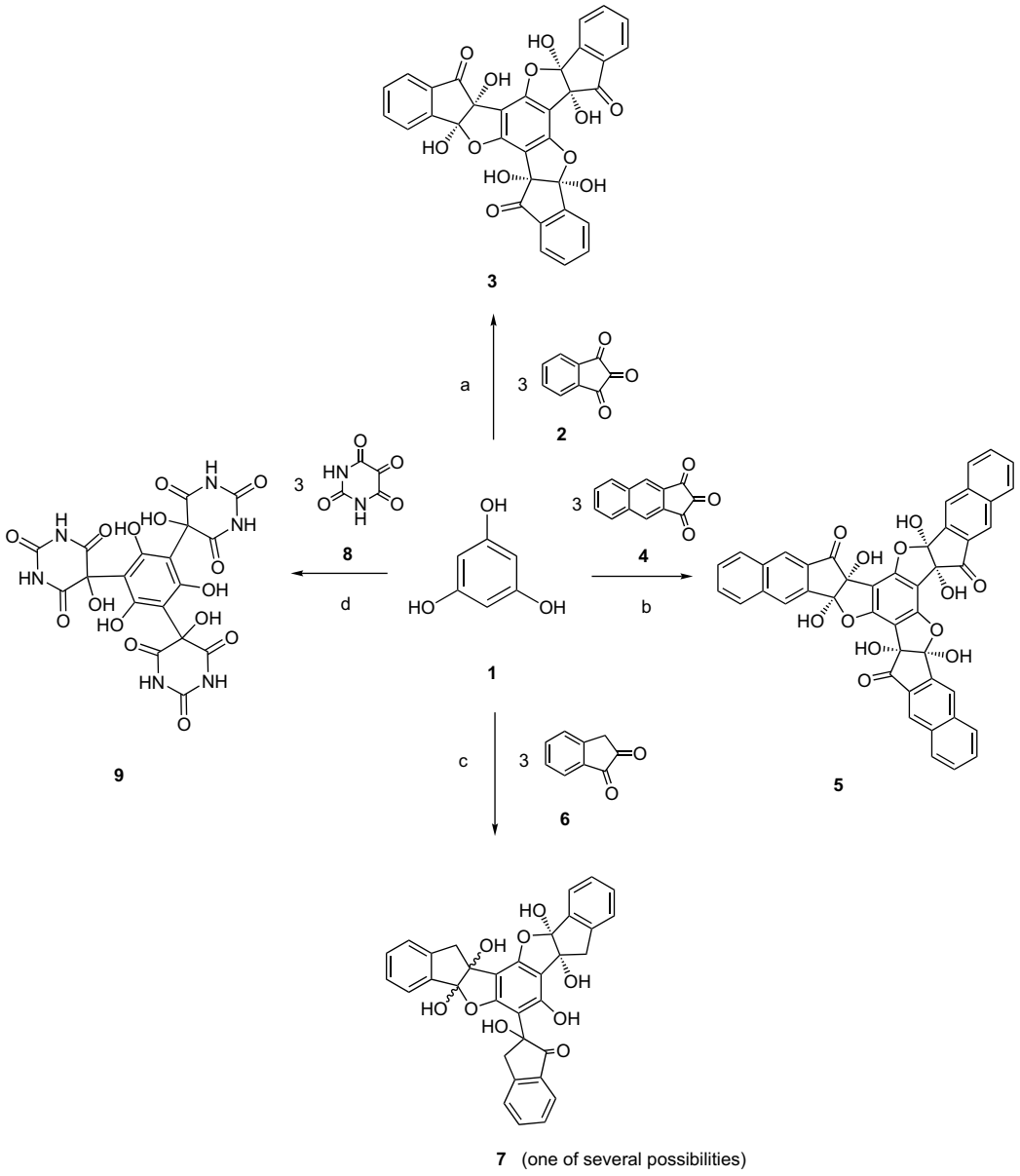
doi:10.1016/j.tet.2009.07.056



Scheme 1. The reaction between phloroglucinol and cyclic vicinal polyketones.

the third indanedione does not close to form the final hemiketal structure (**7**, Scheme 1c). Attempts to close the third ring by elevating the reaction temperature ended up with a dark, insoluble polymer. Alloxan (**8**), a six-membered ring vicinal tricarbonyl compound, which is not a 'true polyketone', reacted only half way. It formed a tris-adduct containing three alloxan units bound perpendicularly in a propeller-like shape to the aromatic positions of phloroglucinol (**9**, Scheme 1d). The final stage of ring closure, to form a bowl-shaped tris-hemiketal, was not accomplished under the reaction conditions. ^{1}H NMR corroborated this open structure and its spatial arrangement was established by X-ray crystallography (Fig. 2).

'Mixed bowls' containing ninhydrin and benzo[*f*]ninhydrin units in the same structure were prepared by carrying out the reaction in a stepwise manner. This route consists of preparing and isolating mono-adducts such as **10** or **11**, or bis-adducts (**12**, **13**) by reacting **1** with **2**[3] or with **4**, respectively, followed by addition of the other building block to form 'mixed bowls' **14** and **15** (Schemes 2 and 3, Fig. 1c and d).

Exhaustive acetylation of **3** with acetic anhydride, in the presence of $CuSO_4 \cdot 5H_2O$, a catalyst for acetylation of tertiary alcohols,[6] produced a mixture of hexaacetyl derivatives, from which we isolated not the expected 'bowl hexaacetate' (**16**, Scheme 4) but two rearranged, partially opened isomers (**17**, **18**, Fig. 3a and b).

3. Discussion

The ease of formation of bowl-shaped compounds by the reaction between phloroglucinol and ninhydrin or benzo[*f*]ninhydrin indicates that in acetic acid, the bowl is the most thermodynamically stable structure of all possible isomeric forms. We assume a solvent-dependent dynamic equilibrium between the various isomers, which include hemiketal ring-opening and rearrangement. Thus, while the bowl structure is the prevailing form in acetic acid, a mixture of isomeric forms prevails in DMSO solution, as can be deduced from the NMR spectra. The isomerization process can be easily followed by a color test with ethanolic

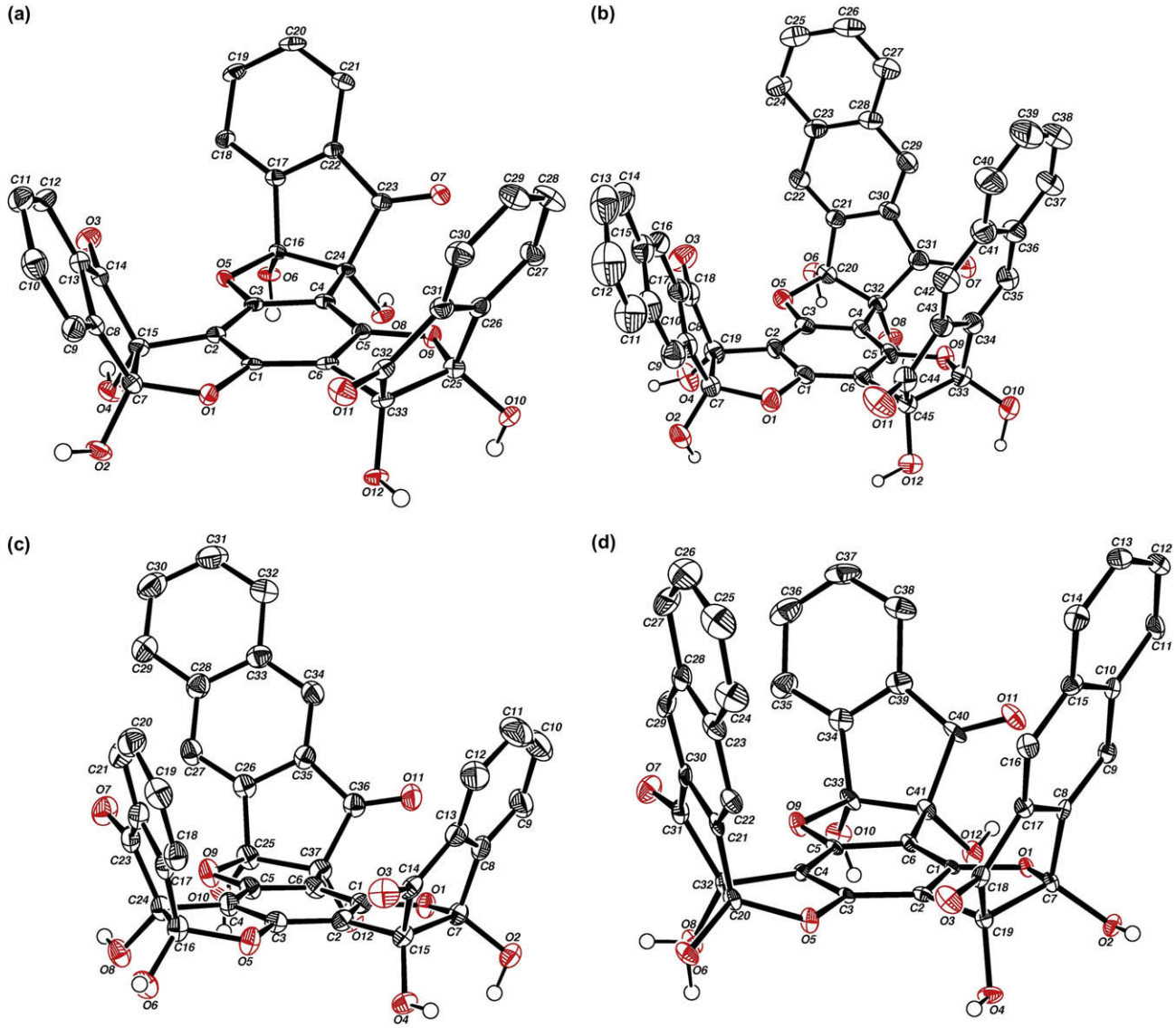


Figure 1. ORTEP drawing of: (a) ninhydrin bowl (**3**), (b) benzo[*f*]ninhydrin bowl (**5**), (c) mixed bowl 1 (**14**), and (d) mixed bowl 2 (**15**). The thermal ellipsoids are scaled to enclose 50% probability. Solvent molecules were hidden for clarity.

$Fe(NO_3)_3$. Isomerization of **3** must start with hemiketal ring-opening, releasing phenolic hydroxyl groups, which form a magenta-colored complex with Fe^{3+} ions. Indeed, all of the intermediates containing phenolic hydroxyls produce the magenta color with $Fe(NO_3)_3$.

As expected for cis-disubstituted five-membered rings, crystallographic studies have shown that even the mono-adducts between **1** and polyketones already demonstrate a considerable deviation from planarity and form gable-shaped structures with an angle of ca.110° between the polyketone and phloroglucinol planes (**10**, **11** Fig. 4a and b). While there is only one possible closed-ring mono-adduct, the addition of a second ninhydrin entity can produce several isomeric bis-adducts (Scheme 5). Only one of them (**12**) can produce the final bowl with a third ninhydrin molecule. Indeed, an NMR examination of the bulk product indicated several bis-adducts, of which we managed to isolate and characterize two. One had a 'cis–cis' conformation (**19**, Scheme 5, Fig. 5a), which cannot form the bowl structure directly and the other was the 'correct' 'cis–trans' isomer (**12**, Fig. 5b). With an additional equivalent of ninhydrin both were converted into bowl **3**.

Ring-opening of the 'cis–cis' form (**19**), followed by rearrangement, must occur to form the '*cis–trans*' bis-adduct **12**, which produces the bowl structure (Scheme 6). Hence, our findings confirm Kim's assumption that bowl formation might involve ring-opening and rearrangement of the initially formed bis-adduct.[3] Dynamic equilibrium between the closed and open forms of ninhydrin-hemiketal was recently reported.[7] Ring-opening and rearrangement also occurred in the acetylation reaction. $CuSO_4 \cdot 5H_2O$ is known also as a catalyst for de-ketalisation of ketals and hemiketals.[8] We therefore assume a preliminary ring-opening stage followed by rearrangement and exhaustive acetylation.

4. Conclusions

Kim's one-pot synthesis of a new bowl-shaped compound from phloroglucinol and ninhydrin was extended to the production of deeper and lower-symmetry cavitands. The formation of these compounds and their chemical reactions involve dynamic interconversion between cyclic and ring-opened isomeric hemiketals.

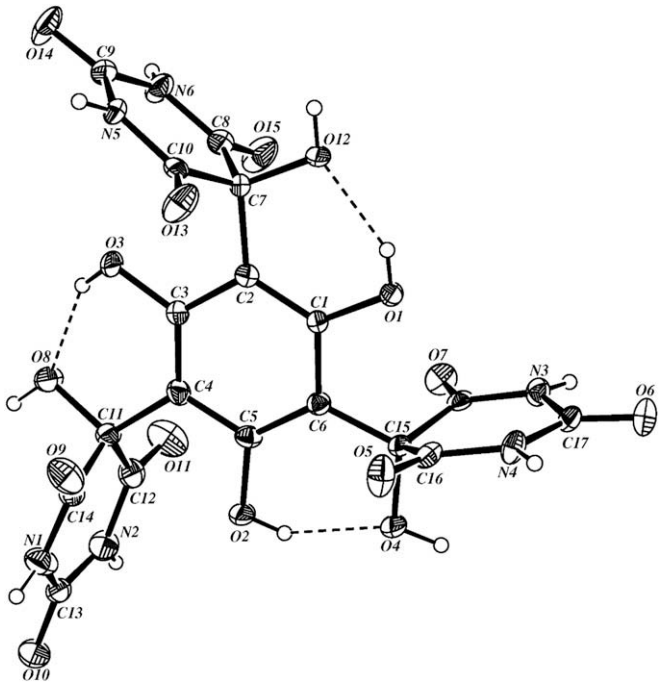


Figure 2. ORTEP drawing of alloxan 'tray' (**11**). The thermal ellipsoids are scaled to 50% probability. Solvent molecules were hidden for clarity.

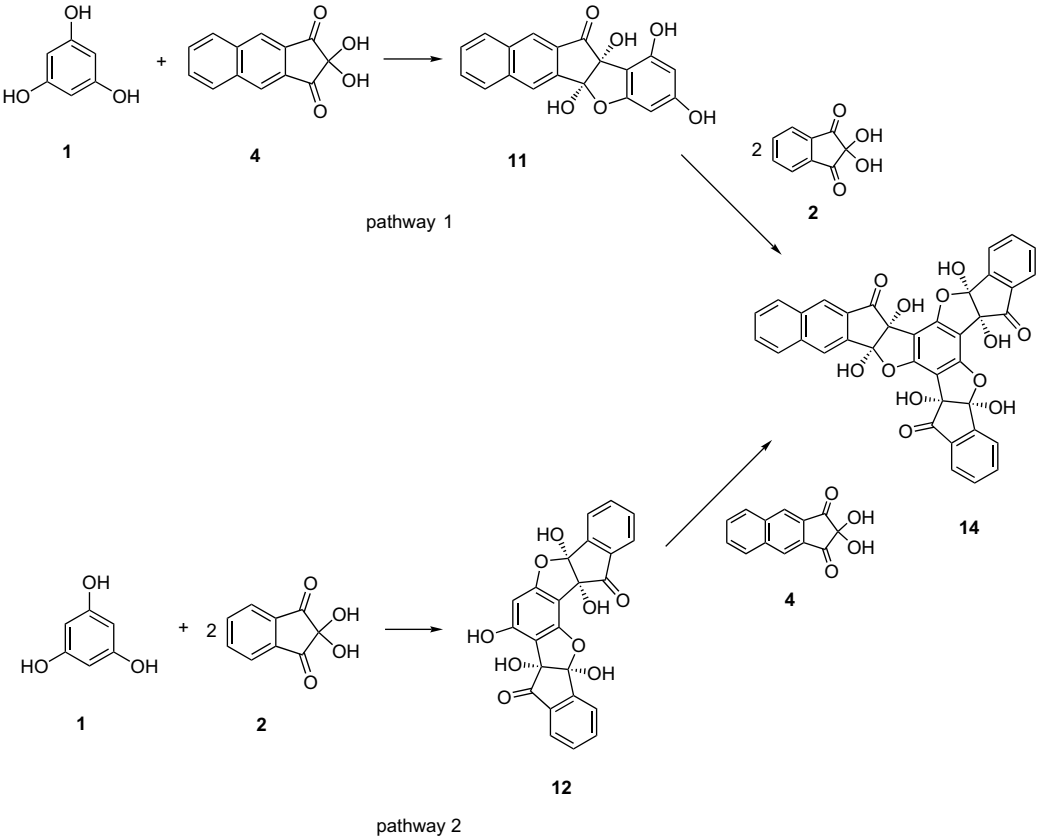
5. Experimental

5.1. General

Ninhydrin bowl (**3**) was prepared using the previously reported procedure.[3] Benzo[*f*]ninhydrin (**4**) was prepared according to the literature procedure.[4] Ninhydrin mono-adduct (**10**) was prepared according to Kim[3] with one modification: it was purified by crystallization from acetonitrile, without column chromatography. Deuterated solvents for NMR spectroscopy were obtained from Cambridge Isotope Laboratories. All other commercially available chemicals were obtained from Sigma–Aldrich. Flash chromatography was performed with silica gel (230–400 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica gel plates (Merck, Kieselgel 60 F_{254}). The melting points were determined using an Electrothermal apparatus. An Alpha model spectrometer, equipped with a single reflection diamond ATR sampling module, manufactured by Bruker, was used to record the FTIR spectra. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker DRX 400 and on a 500 MHz Bruker Ultrashield Plus instruments. UV–vis spectra were recorded on a Varian Cary 100 Bio spectrophotometer. API mass spectrometer—an LCQ_{DUO} mass spectrometer (Thermo-Finnigan, San Jose, CA, USA) with ESI interface using direct infusion was used.

5.2. X-ray crystallography

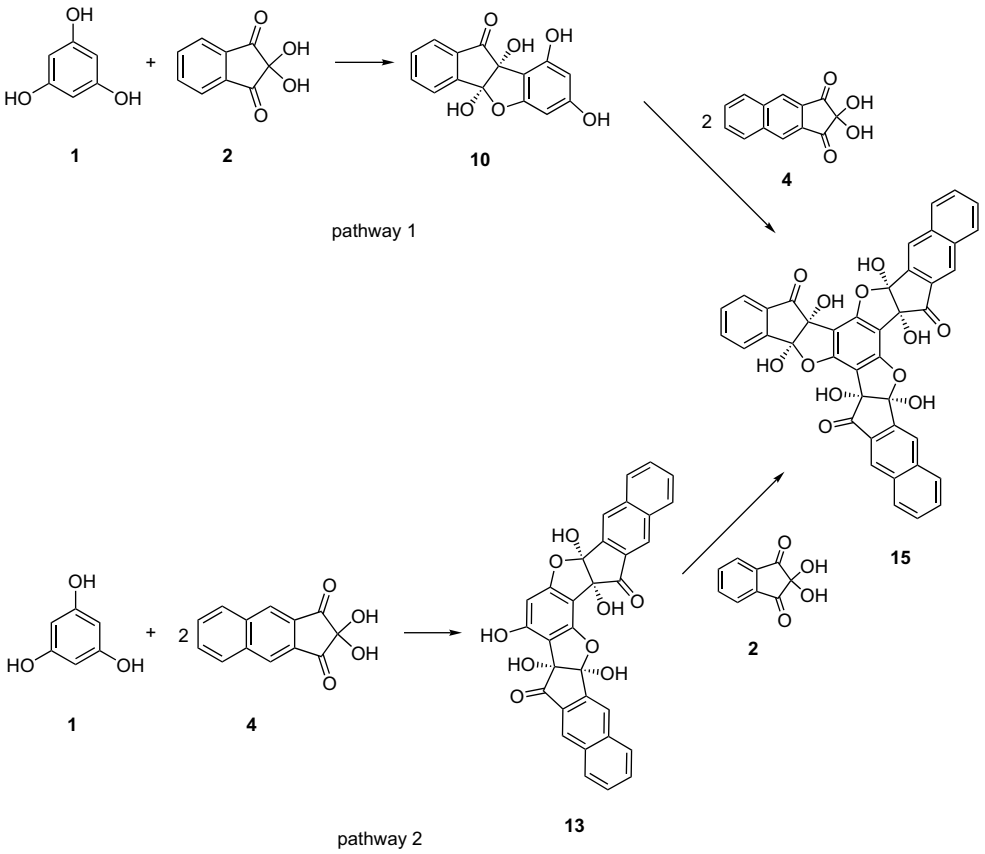
A single crystal of each sample was attached to a glass fiber, with epoxy glue and transferred to a Bruker SMART APEX CCD X-ray



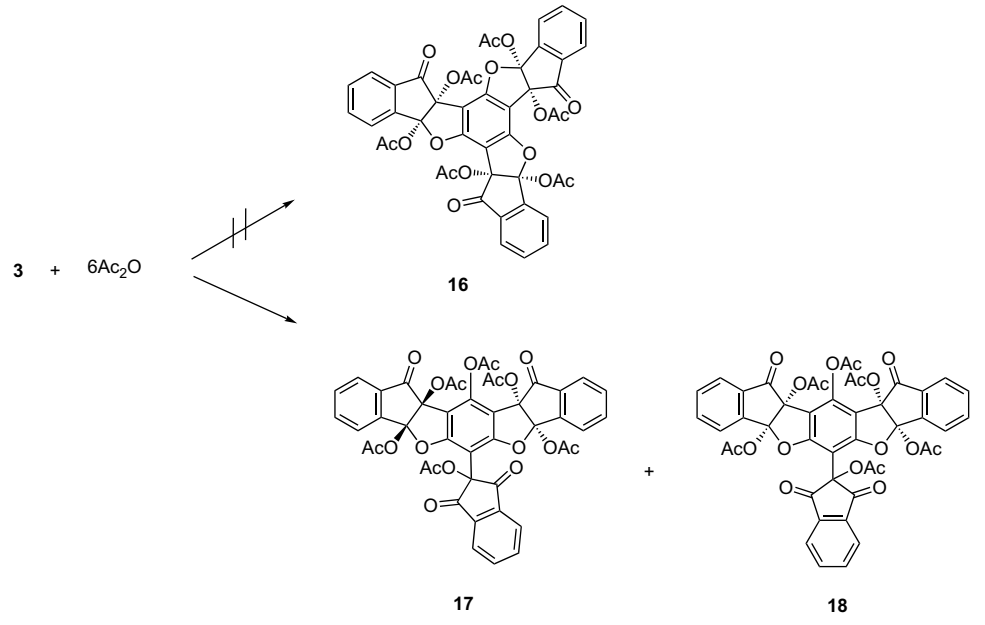
Scheme 2. Formation of a 'mixed bowl' consisting of two ninhydrin and one benzo[*f*]ninhydrin units.

The new compounds, which we tentatively name *vasarenes* (from 'vase'), are currently being tested as potential hosts or ligands for small molecules and metallic ions. Initial results will be reported in a forthcoming paper.

diffractometer equipped with a graphite-monochromator and using Mo Kα radiation (λ=0.71073 Å). The system was controlled by a pentium-based PC running the SMART software package.[9] Maintaining the crystal at low temperature was done with a Bruker



Scheme 3. Formation of a 'mixed bowl' consisting of one ninhydrin and two benzo[*f*]ninhydrin units.



Scheme 4. Formation of hexaacetyl derivatives in presence of $CuSO_4 \cdot 5H_2O$ catalyst.

KRYOFLEX nitrogen cryostat. Immediately after collection, the raw data frames were transferred to a second PC computer for integration and reduction by the SAINT program package.[10] The structures were solved and refined by the SHELXTL software package.[11]

5.3. Benzo[*f*]ninhydrin bowl (5)

A solution of benzo[*f*]ninhydrin (**4**)[4] (1000 mg, 4.38 mmol) and phloroglucinol (**1**) (184 mg, 1.46 mmol) in acetic acid (180 mL) was stirred at room temperature for 2 days. The solid was filtered and

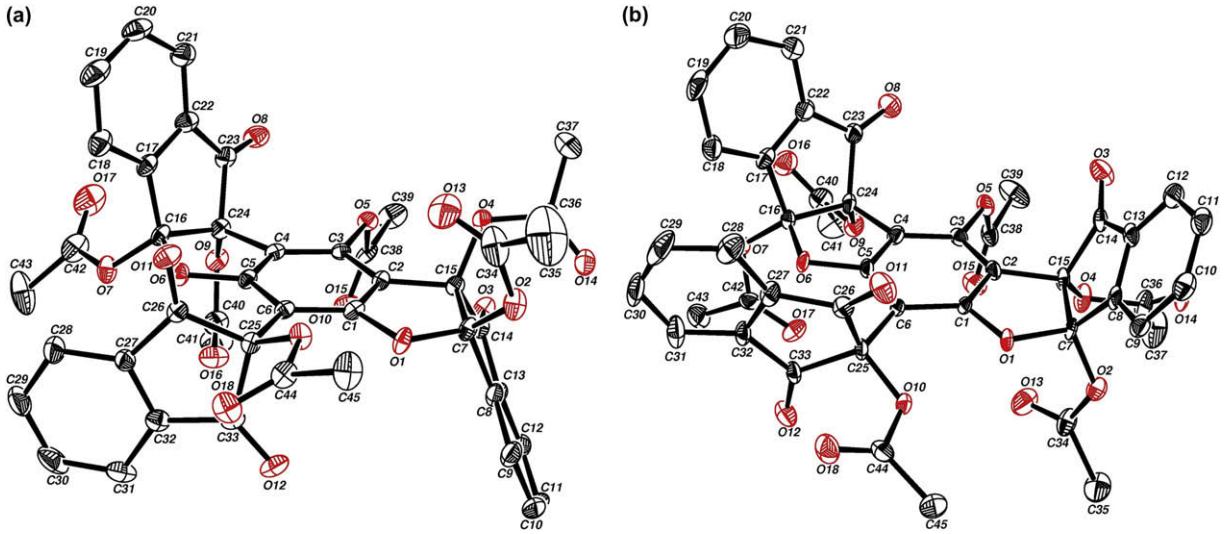


Figure 3. ORTEP drawing of 'hexaacetyl derivatives': (a) '*cis–trans*' (**17**) and (b) '*cis–cis*' (**18**).

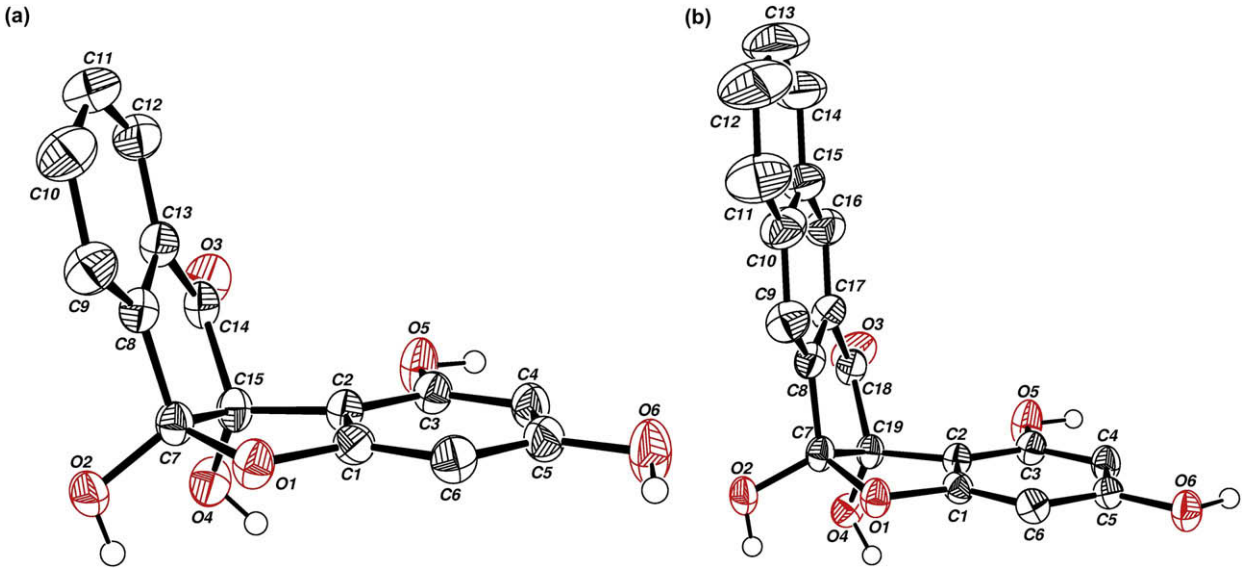
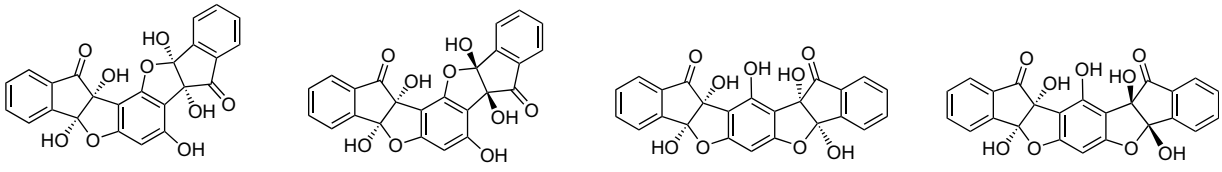


Figure 4. ORTEP drawing of: (a) ninhydrin mono-adduct (**10**) and (b) benzo[*f*]ninhydrin mono-adduct (**11**). The thermal ellipsoids are scaled to 50% probability. Solvent molecules were hidden for clarity.



12

"*cis-trans*"
aliphatic hydroxyls
pointing in the same
directions;
carbonyls pointing
in opposite directions.

"*trans-trans*"
aliphatic hydroxyls
pointing in opposite
directions;
carbonyls pointing
in opposite directions.

19

"*cis-cis*"
aliphatic hydroxyls
pointing in the same
directions;
carbonyls pointing
in the same directions.

"*trans-cis*"
aliphatic hydroxyls
pointing in opposite
directions;
carbonyls pointing
in the same directions.

Scheme 5. Possible bis-adducts obtained by the reaction of ninhydrin (**2**) and mono-adduct (**10**). Compounds **12** and **19** have been isolated and characterized.

washed with acetic acid followed by diethyl ether to produce a white solid (909.6 mg, 82%). Crystallization (DMF/EtOH) afforded colorless crystals, mp 242–245 °C (dec); UV (EtOH, λ_{max}): 221, 269 nm; IR 3743, 3327, 1728, 1626, 1558, 1505, 1457, 1261, 1141, 1010, 891, 807, 752 cm^{-1}; ^1H NMR (500 MHz; DMSO-d_6) δ 6.13 (1H, s, OH), 6.30 (1H, s, OH), 6.42 (1H, s, OH), 7.48 (1H, m), 7.59 (1H, m), 7.63 (1H, m), 7.67 (1H, m), 7.38 (1H, m), 7.79 (1H, m), 7.87 (1H, d, *J* 8.5), 7.91 (1H, s, OH), 8.10 (1H, s, OH), 8. 12 (2H, d), 8.13 (1H, s, OH), 8.17 (1H, s), 8.22 (1H, d, *J* 8.5), 8.25 (1H, d, *J* 8.0), 8.28 (1H, d, *J* 8.1), 8.31 (1H, s), 8.41 (1H, s), 8.45 (1H, s), 8.47 (1H, s), and 8.56 (1H, s);

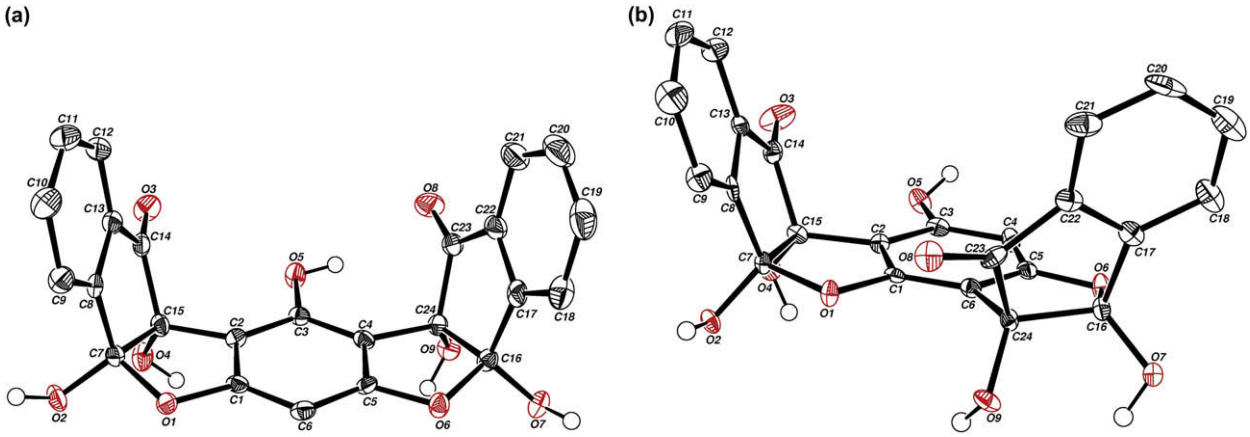
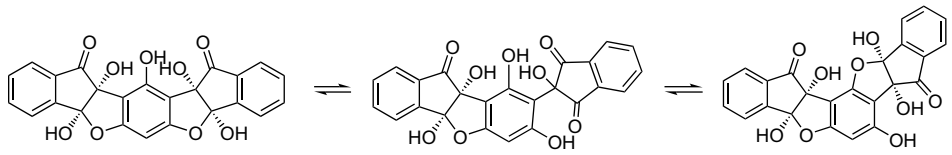


Figure 5. ORTEP drawing of: (a) ninhydrin '*cis–cis*' bis-adduct (**19**) and (b) ninhydrin '*cis–trans*' bis-adduct (**12**). The thermal ellipsoids are scaled to 50% probability. Solvent molecules were hidden for clarity.



19 **12**

Scheme 6. Formation of a '*cis–trans*' bis-adduct (**12**) from the initially formed '*cis–cis*' bis-adduct (**19**).

^{13}C NMR (125 MHz, DMSO-d_6) δ 82.95, 83.18, 83.41, 101.92, 102.13, 102.20, 112.20, 112.66, 112.85, 123.65, 124.12, 124.33, 124.58, 125.06, 125.10, 127.82, 128.00, 128.04, 129.08, 129.19, 129.24, 129.30, 129.55, 129.62, 130.19, 130.57, 130.61, 131.77, 131.89, 131.94, 133.77, 133.93, 134.08, 137.25, 137.34, 137.50, 142.87, 143.13, 143.30, 185.22, 197.11, 197.61, and 197.69. Anal. Calcd for $C_{45}H_{28}O_{14}$ (adduct+2H_2O): C, 68.18; H, 3.56. Found: C, 67.91; H, 3.30.

5.4. Indanedione tris-adduct (7)

A solution of 1,2-indanedione (**6**)[†] (2.0 g, 12.18 mmol) and phloroglucinol (**1**) (0.51 g, 4.06 mmol) in acetic acid (30 mL) was stirred at room temperature for 4 days. The solid was filtered and washed with cold acetic acid followed by cold diethyl ether (1.11 g, 49%). Crystallization (MeOH) afforded white crystals, mp >238 °C (dec); UV (EtOH, λ_{max}): 208, 242 nm; IR ν 3394, 3161, 3039, 1688, 1625, 1466, 1300, 1249, 1131, 1099, 1070, 951, 918, 766, 723, 617, 450 cm^{-1}; ^{1}H NMR (400 MHz; DMSO-d_6) δ 3.20 (2H, d, J 16), 3.28 (1H, d, J 16), 3.42 (1H, d, J 16), 3.60 (2H, d, J 16), 5.14–5.50 (3H, 3OH), 6.53–7.80 (15H, m, 2OH+12H), 10.49 (1H, aromatic H).[3,7,12] Anal. Calcd for $C_{33.5}H_{26}O_{9.5}$ (indanedione tris-adduct+0.5CH_3OH): C, 69.31; H, 4.51. Found: C, 69.18; H, 4.20; *m/z* LC/MS negative mode ESI 563.3 $[M-H]^-$, 564.3 $[M]^-$, 599.1 $[M+Cl]^-$, 1127.0 $[2M-H]^-$, 1128.0 $[2M]^-$, 1162.7 $[2M+Cl]^-$; positive mode ESI 547.1 $[M-OH]^+$, 582.1 $[M+NH_4]^+$, 1146.0 $[2M+NH_4]^+$, 1147.0 $[2M+H_3O]^+$.

5.5. Benzo[*f*]ninhydrin mono-adduct (11)

A solution of benzo[*f*]ninhydrin (**4**)[4] (1.70 g, 7.45 mmol) and phloroglucinol (**1**) (2.82 g, 22.35 mmol) in acetic acid (30 mL) was heated to 90 °C for 0.5 h. After cooling to room temperature the solid was filtered and washed with acetic acid followed by diethyl ether (2.02 g, 81%). Crystallization (CH_3CN) afforded yellow crystals, mp 247–249 °C (dec); UV (EtOH, λ_{max}): 212, 249 nm; IR ν 3227, 3115, 1693, 1610, 1405, 1235, 1139, 1084, 1037, 985, 888, 822, 568 cm^{-1}; ^{1}H NMR (500 MHz; DMSO-d_6) δ 5.69 (1H, d, J 2), 5.82 (1H, d, J 2), 6.26 (1H, s, OH), 7.61 (1H, m), 7.69 (1H, m), 7.73 (1H, s, OH), 8.16 (2H, d, J 9), 8.40 (1H, s), 8.43 (1H, s), 9.02 (1H, s, OH) and 9.44 (1H, s, OH); ^{13}C NMR (125 MHz; DMSO-d_6) δ 84.13, 89.57, 96.41, 103.23, 110.92, 118.49, 124.13, 124.53, 127.85, 129.11, 129.37, 130.52, 132.08, 133.99, 137.42, 143.73, 157.17, 159.74, 161.83 and 198.89. Anal. Calcd for $C_{21}H_{15}NO_6$ (adduct+1CH_3CN): C, 66.84; H, 4.01; N, 3.71. Found: C, 66.61; H, 3.94; N, 3.37.

5.6. Alloxan 'tray' (9)

A solution of alloxan monohydrate (**10**) (5.93 g, 37.04 mmol) and phloroglucinol (**1**) (1.56 g, 12.35 mmol) in acetic acid (120 mL) was stirred at room temperature for 24 h. During the reaction, an off-white solid precipitated in the reaction vessel. The solid was filtered and washed with acetic acid followed by diethyl ether. Due to its hygroscopic nature, (**11**) was dried in vacuum (5.93 g, 87%). Crystallization (EtOH) afforded off-white crystals, mp 210–214 °C; UV (EtOH, λ_{max}): 210 nm; IR ν 3624, 3358, 3122, 2852, 1798, 1729, 1679, 1258, 1084, 957 cm^{-1}; ^{1}H NMR (400 MHz; DMSO-d_6) δ 11.38 (6H, s, NH), 10.37 (3H, s, OH of phloroglucinol) and 9.31 (3H, s, OH); ^{13}C NMR (125 MHz; DMSO-d_6) δ 75.08, 100.85, 150.44, 156.32 and 170.45. Anal. Calcd for $C_{18}H_{22}N_6O_{20}$ (adduct+5H_2O): C, 33.65; H, 3.45; N, 13.08. Found: C, 33.74; H, 3.35; N, 12.73.

5.7. Ninhydrin bis-adducts (12 and 19)

Ninhydrin bis-adducts were prepared according to Kim's procedure[3] with an additional separation stage. The reaction afforded several structural isomers. The white powder, which separated from the reaction mixture was crystallized (MeOH) to afford colorless crystals of the '*cis–trans*' adduct **12**, mp >208 °C (dec); IR ν 3544, 3404, 3219, 1708, 1632, 1602, 1449, 1380, 1229, 1152, 1089, 884, 862, 770 cm^{-1}; ^{1}H NMR spectrum showed complex peaks,

[†] 1,2-Indanedione is produced as a latent fingerprint reagent at The Casali Institute of Applied Chemistry, The Hebrew University of Jerusalem. It is commercially available from this institute.

which could not be assigned precisely.[3,7,12] Anal. Calcd for $C_{24.5}H_{16}O_{9.5}$ (adduct+0.5MeOH): C, 59.04; H, 4.04. Found: C, 59.35; H, 3.64.

After separating **12**, a second crop precipitated from the filtrate affording colorless crystals of the '*cis*–*cis*' bis-adduct (**19**), mp >200 °C (dec); IR ν 3484, 3373, 1716, 1631, 1605, 1450, 1347, 1236, 1154, 1090, 1002, 856, 776, 619 cm^{-1}; ^1H NMR spectrum showed complex peaks, which could not be assigned precisely.[3,7,12] Anal. Calcd for $C_{24}H_{17}O_{10.5}$ (adduct+1.5H_2O): C, 60.89; H, 3.62. Found: C, 61.27; H, 3.66.

5.8. Benzo[*f*]ninhydrin bis-adduct (13)

A solution of mono-adduct (**9**) (400 mg, 1.19 mmol) and benzo[*f*]ninhydrin (**4**)[4] (271.4 mg, 1.19 mmol) in acetic acid (15 mL) was heated to 90 °C for 2 h. After cooling to room temperature the solid was filtered and washed with acetic acid followed by methylene chloride. The solid was purified by column chromatography (silica gel), eluent: methanol/ethyl acetate 1:3, to afford the bis-adduct as yellow solid (160 mg, 25%). Crystallization (MeOH) afforded yellow crystals, mp >200 °C (dec); UV (EtOH, λ_{max}): 214, 252, 312 nm; IR ν 3359, 1705, 1617, 1454, 1242, 1138, 884, 747, 468 cm^{-1}; ^1H NMR (400 MHz; DMSO-d_6) δ 5.73–5.87 (1H), 6.20–6.66 (2H, br, OH), 7.48–8.57 (14H, m, 12H+2OH), 9.47 (1H, br, OH).[3,7,12] Anal. Calcd for $C_{34}H_{26}O_{11}$ (adduct+2CH_3OH): C, 66.88; H, 4.29. Found: C, 67.03; H, 4.18.

5.9. Mixed bowl 1 (14): procedure 1

A solution of ninhydrin (**2**) (530 mg, 2.98 mmol) and benzo[*f*]-ninhydrin mono-adduct (**9**) (500 mg, 1.49 mmol) in acetic acid (30 mL) was heated to 90 °C for 2 days. After cooling to room temperature the solid was filtered and washed with acetic acid followed by methylene chloride to give a white solid (873 mg, 89%). Crystallization (MeOH) afforded colorless crystals, mp 224–226 °C (dec); UV (EtOH, λ_{max}): 206, 251 nm; IR ν 3244, 1713, 1631, 1444, 1236, 1139, 1078, 998, 920, 866, 772, 620, 474 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$+10 drops of THF) δ 2.88 (6H, br s, OH), 7.20 (1H, m), 7.27 (1H, m), 7.33 (1H, d, *J* 8.0), 7.35 (1H, m), 7.39 (1H, d, *J* 7.5), 7.45 (1H, m), 7.51 (1H, m), 7.58 (1H, m), 7.71 (1H, d, *J* 8.5), 7.75 (1H, d, *J* 8.0), 7.81 (1H, d, *J* 8.0), 7.92 (1H, d, *J* 8.0), 7.99 (1H, s) and 8.23 (1H, s); ^{13}C NMR (125 MHz; $CDCl_3$+10 drops of THF) δ 80.59, 80.62, 81.43, 101.17, 101.20, 101.22, 114.14, 114.15, 114.37, 123.24, 123.27, 124.55, 124.78, 125.11, 125.16, 127.35, 128.74, 129.00, 129.88, 131.00, 131.08, 131.36, 134.27, 134.28, 134.31, 136.23, 136.27, 137.75, 141.86, 147.45, 147.51, 157.27, 157.31, 157.45, 196.36, 196.37 and 196.58. Anal. Calcd for $C_{37}H_{28}O_{16}$ (adduct+4H_2O): C, 60.99; H, 3.87. Found: C, 60.66; H, 3.83.

5.10. Mixed bowl 1 (14): procedure 2

A solution of benzo[*f*]ninhydrin (**4**)[4] (511 mg, 2.24 mmol) and ninhydrin bis-adduct (**12**) (1000 mg, 2.24 mmol) in acetic acid (15 mL) was heated to 90 °C for 2 h. After cooling to room temperature the solid was filtered and washed with acetic acid followed by diethyl ether. The product was crystallized from DMF and recrystallized from MeOH to afford colorless crystals. The melting point and all spectroscopic data are identical with those of the compound obtained by procedure 1.

5.11. Mixed Bowl 2 (15): procedure 1

A solution of benzo[*f*]ninhydrin (**4**)[4] (1.91 g, 8.38 mmol) and ninhydrin mono-adduct (**8**) (1.20 g, 4.19 mmol) in acetic acid (70 mL) was heated to 90 °C for 3 days. After cooling to room temperature the solid was filtered and washed with cold acetic acid followed by cold diethyl ether to give a white solid (2.69 g, 91%). Crystallization (EtOH) afforded colorless crystals, mp >236 °C (dec); UV (EtOH, λ_{max}): 212, 252, 299, 311 nm; IR ν 3309, 1713, 1629, 1442, 1406, 1251, 1190, 1142, 1086, 930, 873, 757, 611, 472 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$+10 drops of THF) δ 4.38 (6H, br s, OH), 7.21 (1H, m), 7.32 (1H, m), 7.33 (1H, d, *J* 7.2), 7.38 (1H, m), 7.45 (1H, m), 7.51 (1H, m), 7.55 (1H, m), 7.65 (1H, d, *J* 8.8), 7.72 (1H, d, *J* 8.4), 7.81 (1H, d, *J* 7.6), 7.92 (1H, d, *J* 8.4), 7.94 (1H, s), 7.98 (1H, d, *J* 8.4), 8.00 (1H, s), 8.23 (1H, s), 8.28 (1H, s); ^{13}C NMR (125 MHz; $CDCl_3$+10 drops of THF) δ 80.58, 81.38, 81.40, 101.12, 101.14, 101.17, 113.90, 113.91, 114.12, 123.10, 124.31, 124.32, 124.58, 124.65, 124.98, 127.06, 127.17, 128.51, 128.60, 128.76, 128.83, 129.63, 129.72, 130.82, 131.19, 131.25, 134.00, 134.09, 134.16, 136.05, 137.51, 137.59, 141.62, 141.79, 147.36, 157.35, 157.50, 157.53, 192.21, 196.43 and 196.46. Anal. Calcd for $C_{43}H_{32}O_{15}$ (adduct+1C_2H_5OH+2H_2O): C, 65.48; H, 4.09. Found: C, 65.44; H, 4.03.

5.12. Mixed bowl 2 (15): procedure 2

A solution of benzo[*f*]ninhydrin bis-adduct (**13**) (130 mg, 0.24 mmol) and ninhydrin (**2**) (43.5 mg, 0.24 mmol) in acetic acid (9 mL) was heated to 90 °C for 3 days. After cooling to room temperature the solid was filtered and washed with cold acetic acid followed by methylene chloride to give a white solid (124 mg, 72%). The melting point and all spectroscopic data are identical with those of the compound obtained by procedure 1.

5.13. Hexaacetyl derivatives (17, 18)

A mixture of ninhydrin bowl (**3**) (480 mg, 0.8 mmol), acetic anhydride (5.0 mL, 0.05 mol), and $CuSO_4 \cdot 5H_2O$ (50 mg, 0.2 mmol) was stirred at room temperature for 24 h. Upon completion of the reaction (monitored by TLC) the mixture was diluted with aq sodium bicarbonate (10%, 15 mL) and extracted with methylene chloride (3×20 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated to dryness to afford a mixture of hexaacetylated products as a white solid (298 mg). Crystallization (CH_3CN/H_2O) afforded colorless crystals of **17**, mp >305 °C (dec); IR ν 1779, 1731, 1604, 1368, 1223, 1154, 995, 905, 762, 584 cm^{-1}; ^1H NMR spectrum showed complex peaks, which could not be assigned precisely.[3,7,12] Anal. Calcd for $C_{45}H_{32}O_{19}$ (adduct+1H_2O): C, 61.65; H, 3.68. Found: C, 61.83; H, 3.46.

The filtrate afforded a second crop: colorless crystals of **18**, mp >202 °C (dec); IR ν 1782, 1727, 1615, 1369, 1225, 1188, 1154, 1013, 905, 727, 585 cm^{-1}; ^1H NMR spectrum showed complex peaks, which could not be assigned precisely.[3,7,12] Anal. Calcd for $C_{45}H_{36}O_{21}$ (adduct+3H_2O): C, 59.21; H, 3.98. Found: C, 59.76; H, 3.76.

5.14. Determination of the crystal structures of compounds 3, 5, 9, 10, 11, 12, 14, 15, 17, 18, and 19 by X-ray diffraction

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 699916–699922, CCDC 712134–712137. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). Abbreviated crystallographic data are given below.

Ninhydrin bowl (**3**). $C_{33}H_{18}O_{12} \cdot C_3H_7NO \cdot H_2O$, MW=697.59, triclinic, *P*-1, a=11.1873(9) Å, b=11.7658(9) Å, c=12.756(1) Å, α=102.803(1)°, β=93.018(1)°, γ=109.234(1)°, V=1531.5(2) $Å^3$, Z=2, T=123 K, μ=0.118 mm^{-1}, ρ_{calcd}=1.513 Mg m^{-3}, GOF on F^2=1.308, R=0.0939, R_w=0.1934 [$I>2\sigma(I)$].

Benzo[*f*]ninhydrin bowl (**5**). $C_{45}H_{24}O_{12}\cdot 3(C_3H_7NO)$, MW=975.93, triclinic, *P*-1, *a*=11.0321(6) Å, *b*=13.797(8) Å, *c*=16.5109(9) Å, α=80.902(1)°, β=74.641(1)°, γ=74.154(1)°, *V*=2321.3(2) Å^3, *Z*=2, *T*=295 K, μ=0.103 mm^{-1}, ρ_{calcd}=1.396 Mg m^{-3}, GOF on F^2=0.915, *R*=0.0652, R_w=0.1176 [$I>2\sigma(I)$].

Alloxan tray (**9**). $2(C_{18}H_{12}N_6O_{15})\cdot C_2H_4O_2\cdot 9(H_2O)$, MW=1326.87, triclinic, *P*-1, *a*=11.918(2) Å, *b*=12.094(2) Å, *c*=20.186(4) Å, α=73.307(3)°, β=79.696(3)°, γ=78.795(3)°, *V*=2710.2(8) Å^3, *Z*=2, *T*=173 K, μ=0.150 mm^{-1}, ρ_{calcd}=1.626 Mg m^{-3}, GOF on F^2=1.091, *R*=0.0820, R_w=0.1928 [$I>2\sigma(I)$].

Ninhydrin mono-adduct (**10**). $C_{15}H_{10}O_6\cdot 2(C_2H_3N)$, MW=368.34, monoclinic, $P2_1/c$, *a*=8.0794(6) Å, *b*=14.359(1) Å, *c*=15.673(1) Å, β=94.117(1)°, *V*=1813.6(2) Å^3, *Z*=4, *T*=295 K, μ=0.102 mm^{-1}, ρ_{calcd}=1.349 Mg m^{-3}, GOF on F^2=1.033, *R*=0.0426, R_w=0.1175 [$I>2\sigma(I)$].

Benzo[*f*]ninhydrin mono-adduct (**11**). $C_{19}H_{12}O_6\cdot H_2O$, MW=354.30, monoclinic, $P2_1/c$, *a*=14.6275(9) Å, *b*=8.2732(5) Å, *c*=14.5983(9) Å, β=111.538(1)°, *V*=1643.3(2) Å^3, *Z*=4, *T*=295 K, μ=0.111 mm^{-1}, ρ_{calcd}=1.432 Mg m^{-3}, GOF on F^2=1.171, *R*=0.0545, R_w=0.1300 [$I>2\sigma(I)$].

'*cis–trans*' Bis-adduct (**12**). $C_{24}H_{14}O_9\cdot 2(CH_4O)$, MW=510.44, triclinic, *P*-1, *a*=7.913(1) Å, *b*=11.808(2) Å, *c*=12.691(2) Å, α=97.510(2)°, β=97.312(2)°, γ=103.497(2)°, *V*=1127.6(3) Å^3, *Z*=2, *T*=173 K, μ=0.119 mm^{-1}, ρ_{calcd}=1.503 Mg m^{-3}, GOF on F^2=1.261, *R*=0.0989, R_w=0.1725 [$I>2\sigma(I)$].

Mixed ninhydrin bowl (**14**). $C_{37}H_{20}O_{12}\cdot CH_4O\cdot 0.8(C_3H_7NO)\cdot 0.2(H_2O)$, MW=734.67, triclinic, *P*-1, *a*=11.5719(16) Å, *b*=11.728(2) Å, *c*=13.646(2) Å, α=87.978(2)°, β=79.753(2)°, γ=75.131(2)°, *V*=1761.4(4) Å^3, *Z*=2, *T*=173 K, μ=0.109 mm^{-1}, ρ_{calcd}=1.423 Mg m^{-3}, GOF on F^2=1.136, *R*=0.0728, R_w=0.1652 [$I>2\sigma(I)$].

Mixed ninhydrin bowl (**15**). $C_{41}H_{22}O_{12}\cdot 3(C_2H_3N)$, MW=829.75, monoclinic, $P2_1/c$, *a*=10.9136(9) Å, *b*=27.079(2) Å, *c*=13.2059(11) Å, β=97.144(2), *V*=3872.4(6) Å^3, *Z*=4, *T*=173 K, μ=0.104 mm^{-1}, ρ_{calcd}=1.423 Mg m^{-3}, GOF on F^2=1.414, *R*=0.1252, R_w=0.2301 [$I>2\sigma(I)$].

Hexaacetyl derivative (**17**). $C_{45}H_{30}O_{18}\cdot C_2H_3N$, MW=899.74, triclinic, *P*-1, *a*=11.241(2) Å, *b*=13.164(2) Å, *c*=17.538(2) Å, α=105.725(3)°, β=99.462(3)°, γ=106.742(3)°, *V*=2308.1(5) Å^3, *Z*=2, *T*=173 K, μ=0.101 mm^{-1}, ρ_{calcd}=1.295 Mg m^{-3}, GOF on F^2=1.213, *R*=0.1183, R_w=0.2910 [$I>2\sigma(I)$].

Hexaacetyl derivative (**18**). $C_{45}H_{30}O_{18}\cdot C_2H_3N$, MW=899.74, triclinic, *P*-1, *a*=12.857(2) Å, *b*=12.859(2) Å, *c*=14.400(2) Å, α=84.080(2)°, β=86.107(2)°, γ=62.509(2)°, *V*=2100.2(4) Å^3, *Z*=2, *T*=173 K, μ=0.111 mm^{-1}, ρ_{calcd}=1.423 Mg m^{-3}, GOF on F^2=1.269, *R*=0.1176, R_w=0.2387 [$I>2\sigma(I)$].

'*cis–cis*' Bis-adduct (**19**). $C_{24}H_{14}O_{19}\cdot 4(CH_4O)$, MW=574.52, triclinic, *P*-1, *a*=7.7586(9) Å, *b*=12.018(2) Å, *c*=15.834(2) Å, α=68.407(2)°, β=86.148(2)°, γ=81.302(2)°, *V*=1356.9(3) Å^3, *Z*=2, *T*=173 K, μ=0.112 mm^{-1}, ρ_{calcd}=1.406 Mg m^{-3}, GOF on F^2=1.196, *R*=0.0712, R_w=0.1464 [$I>2\sigma(I)$].

Acknowledgements

This project was financially supported by a joint grant of The Israel Atomic Energy Commission and The Israel Council of Higher Education.

The authors are indebted to Professor Silvio Biali of the Institute of Chemistry, The Hebrew University of Jerusalem, for helpful discussions.

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12. ^{1}H NMR/^{13}C NMR spectrum showed broad and complex peaks, which could not be assigned precisely. The reason for the rather complex and broad pattern might be the presence of regioisomeric and/or stereoisomeric and/or partial ring-opened compounds in the solution depending on the specific solvent.