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Synthesis of buprestins D, E, F, G and H; structural confirmation and biological testing of acyl glucoses from jewel beetles (Coleoptera: Buprestidae)

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ABSTRACT

A chemical and enzymatic synthesis was developed for five variant buprestins termed D, E, F, G and H found in jewel beetles (Coleoptera: Buprestidae). Selective acylation of the primary hydroxyl group of β-D-glucopyranose-1,2-bis(pyrrole-2-carboxylate) with substituted benzoic or cinnamic acid derivatives followed by deprotection gave the target compounds. Using coinjection the identity with the natural extracts was confirmed. The activity of the variant buprestins as deterrents for ants was assayed.

1. Introduction

The first isolation of acyl glucoses from Australian jewel beetles (Buprestidae) led to the characterization of two compounds named buprestins A and B.[1] Brief biotesting of these compounds showed a deterrent activity against ants.[2] We developed a chemical and enzymatic approach to the buprestins A and B in order to provide sufficient material for biotests.[3] In the original publication[2] the occurrence of various minor buprestins containing substituted cinnamoyl residues was indicated. However, no structural information was provided. In the course of our own investigations the variant buprestins were found in crude extracts from various jewel beetles.[4] LC–MS analysis of these variant buprestins suggested[4] that the variation was caused by the attachment of different acyl residues to O-6 of the 1,2-acylated glucose core (Fig. 1). In order to prove the structure of five variant buprestins by total synthesis we used the previously developed precursor **1**[3] with three OH groups as an intermediate. We herein describe the synthesis of the natural buprestins termed[4] D, E, F, G and H from the diacyl glucose precursor **1**.

2. Results and discussion

The synthesis of buprestins A and B by chemical and enzymatic methods allows the introduction of different acyl residues at O-6 of the triol **1** as the final step.[3] This approach should also give a direct access to variant buprestins with altered O-6 acyl moieties. In a recently disclosed thesis[4] from our lab the isolation of buprestins via an extraction from jewel beetles indicated the presence of other buprestins (acyl glucoses) with two pyrrole-2-carboxylic acid moieties and a variable third acyl group in the crude extracts. By deduction of the MS data obtained by LC–MS the structural variation was proposed to reside at O-6 with O-1 and O-2 acylated with pyrrole-2-carboxylic acid.[4] In order to prove this hypothesis and to verify the identity of the natural compounds by coinjection the synthesis of five hitherto uncharacterized buprestins was carried out. Access to the target molecules required the incorporation of hydroxylated cinnamoyl residues (buprestins D, E and F) or substituted benzoyl moieties (buprestins G and H). Selective acylation of the primary OH-group of triol **1** was carried out via a Mitsunobu reaction[5] employing O-acetylated cinnamic acid derivatives. The acetylation of OH-groups of the substituted cinnamic acids is crucial in order to avoid side reactions and low acylation yields.[3] Starting with commercially available *p*-acetoxy cinnamic acid the selective 6-O acylation of triol **1** under Mitsunobu conditions (2 equiv of acid, 3 equiv of triphenylphosphine and 1.5 equiv of diethylazodicarboxylate (DEAD)) gave compound **2** in an isolated yield of 51% (Fig. 2). The subsequent enzymatic deacetylation[6] using immobilized *Candida antarctica* lipase B (Novozym 435)[3] furnished the desired compound **D** (45% yield). Similarly, the above procedure was carried out with *p*-acetoxy-*m*-methoxy cinnamic acid giving compound **3** (54%), which was deprotected enzymatically yielding the feruloylated compound **E** (48%). In comparison

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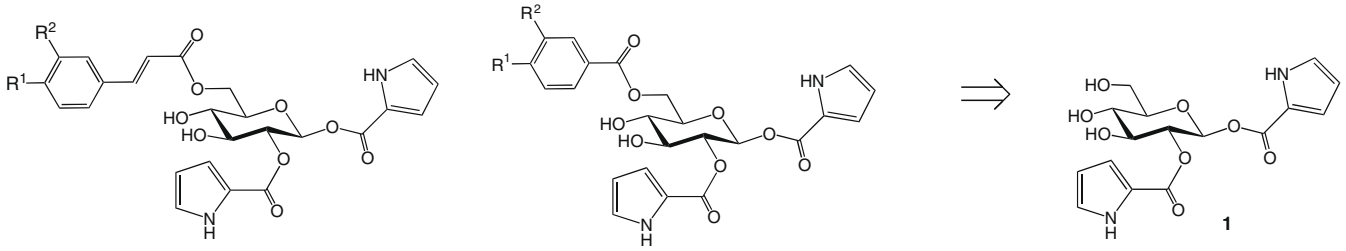


D (Buprestin D) R^1 = OH, R^2 = H
E (Buprestin E) R^1 = OH, R^2 = OMe
F (Buprestin F) R^1 = R^2 = OH

G (Buprestin G) R^1 = OH, R^2 = OMe
H (Buprestin H) R^1 = OMe, R^2 = H

Figure 1. Retrosynthetic analysis of buprestins D, E, F, G and H leading to the precursor **1**.

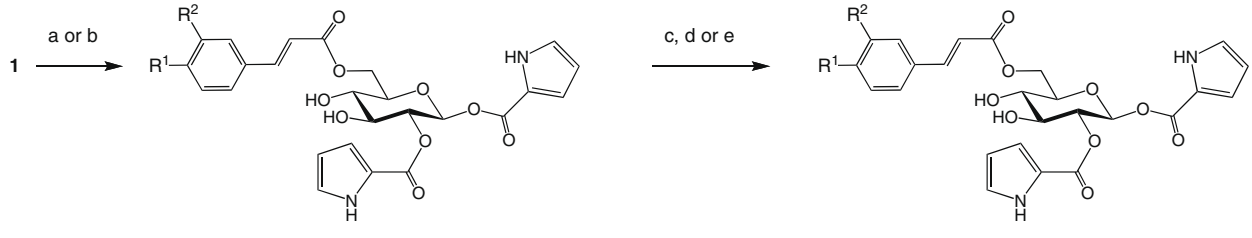
the deprotection of unrelated phenylpropanoid glycosides with a *p*-benzyl feruloyl moiety proved very difficult resulting in considerably lower yields.[7] In the case of compound **4** di-*O*-acetyl caffeic acid was synthesized initially[8] and coupled via the Mitsunobu protocol (60%). Unexpectedly the enzymatic deprotection of **4** gave only unsatisfactory results. Thus two alternative procedures were investigated. Careful alkaline hydrolysis of **4** using potassium carbonate in a dichloromethane-methanol mixture[9] afforded the deprotected caffeoyl derivative **F** (35%). In a second approach TBDMS protected caffeoyl chloride[10] was selectively introduced at the primary OH group of **1** giving intermediate **5** in 48% yield. TBAF mediated deprotection of **5** was not effective, however, the use of HF/Et_3N[11] rendered the target molecule **F** smoothly (63%). Surprisingly, when attempting the deacetylation of the intermediates **2** and **3** with potassium carbonate under the abovementioned conditions the isolated yield was very low.

The acylation of **1** with benzoic acid derivatives was less prone to side reactions compared with the α,β-unsaturated cinnamic acid derivatives. Starting from acetylated vanillic acid compound **6** was obtained (61%) and *p*-anisic acid directly furnished *p*-methoxybenzoylated **H** in 72% (Fig. 3). Enzymatic deacetylation of **6** led to compound **G** in 46% yield due to competing hydrolysis to triol **1**. All compounds were thoroughly characterized[12] by 2D NMR experiments.

In order to assess the identity of the synthetic compounds **D**, **E**, **F**, **G** and **H** with the natural buprestins specimens of *Anthaxia hungarica* and *Chalcophora mariana* were extracted according to the established procedure.[4] LC–MS analysis of the crude extracts showed the LC peaks and the corresponding mass spectra for the compounds **D**, **E**, **F** and **G** in *A. hungarica* and compounds **D**, **E**, **G** and **H** in *C. mariana*. LC–MS coinjection of each synthetic reference compound (**D**, **E**, **F**, **G** and **H**) with the crude jewel beetle extracts showed identical retention times for the natural compounds and the synthetic reference material. The only differences between the analytical data of the extracts and the synthetic compounds were occasional deviations in the intensity of the peaks and the type of adducts in the ESI-TOF mass spectra. This can be attributed to the low concentration of several variant buprestins in the natural samples and to the heterogeneity of the extracts. A common feature for all buprestins in ESI–TOF–MS was the occurrence of the base peak for a glycosyl cation fragment in which the anomeric pyrrole-2-carboxylate was cleaved. The molecular ions were found as adducts with ammonium or sodium in addition to dimers complexed with cations. The structures of the five variant buprestins differing only in their O-6 acyl groups suggest a common biosynthetic pathway, which remains to be elucidated.

In analogy to the biotests conducted by Moore and Brown for buprestins A and B we investigated the ability of the minor buprestins D, E, F, G and H to act as deterrents in a bioassay using the feeding behavior of ants. In order to examine quantitatively the acceptance/deterrency of the buprestins against *Lasius flavus* ants a choice test modified according to Hilker[13] was conducted within the formicarium. The bioassay started when 7 μl each of a test (0.15 mg of compound/20 mg of sucrose/1 ml water) and a control solution (20 mg of sucrose/1 ml water) were offered simultaneously on a glass slide. For a period of 10 min the number of ants feeding at the test and control solution was recorded. Surprisingly, at a concentration of 0.15 mg/ml the buprestins D, E, F, G, and H were not active, whereas synthetic buprestins A and B showed strong response even for solutions with a tenfold dilution.

In these experiments it became evident, that buprestins A and B exhibited a pronounced deterrency against ants as already shown by Moore & Brown.[2] Compared with buprestins A and B the buprestins D–H required more concentrated solutions in the test



2 (AcBuprestin D) R^1 = OAc, R^2 = H (51 %)
3 (AcBuprestin E) R^1 = OAc, R^2 = OMe (54 %)
4 (Ac_2Buprestin F) R^1 = R^2 = OAc (60 %)
5 ($TBDMS_2$Buprestin F) R^1 = R^2 = OTBDMS (48 %)

D (Buprestin D) R^1 = OH, R^2 = H (c: 45 %)
E (Buprestin E) R^1 = OH, R^2 = OMe (c: 48 %)
F (Buprestin F) R^1 = R^2 = OH (d: 35 %); (e: 63 %)

Figure 2. (a) Acid, PPh_3, DEAD, THF: *p*-acetoxy cinnamic acid (51% of **2**); *p*-acetoxy *m*-methoxy cinnamic acid (54% of **3**); *m*,*p*-diacetoxy cinnamic acid (60% of **4**); (b) $TBDMS_2$-caffeoyl chloride, toluene, pyridine, (48% of **5**); (c) *Candidia antarctica* lipase B, immobilized (Novozym 435), 0.5 M NH_4OAc/CH_3CN (9:1) pH 7.0, 40 °C, (45% of **D**; 48% of **E**); (d) 10 mM K_2CO_3 in $MeOH/CH_2Cl_2$ (1:10) (35% of **F**); (d) 1.6 M HF/Et_3N, pyridine (63% of **F**).

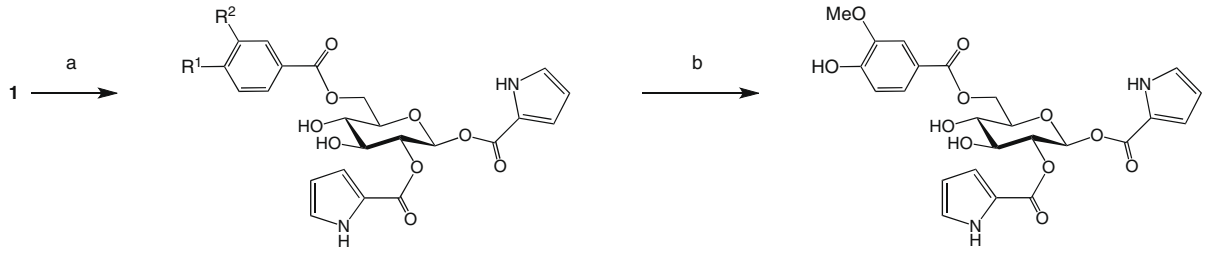


Figure 3. (a) Acid, PPh_3, DEAD, THF: *p*-methoxy benzoic acid (61% of **6**); *p*-acetoxy *m*-methoxy benzoic acid (72% of **H**); (b) *Candidia antarctica* lipase B, immobilized (Novozym 435), 0.5 M NH_4OAc/CH_3CN (9:1) pH 7.0, 40 °C, (46% of **G**).

as their biological activities were rather weak. Preliminary evaluations of the data indicated that buprestins F, G and H show no activity at all whereas buprestins D and E are even attractive for *L. flavus* ants as compared with the aqueous sugar controls. This suggests that the deterrent effect of buprestins is highly influenced by the individual carboxylic acid moieties at O-6.

3. Conclusion

In summary, a short chemical and enzymatic route was developed for the five novel buprestins D, E, F, G, and H. Due to the acid and base sensitivity of the buprestins mild conditions for deprotection were required. Based on extracts obtained from European jewel beetles the occurrence and the identity of five compounds corresponding to modified buprestins was confirmed by total synthesis and coinjection. These minor compounds do not display the known deterrent activity of the major buprestins A and B.

4. Experimental

4.1. General

Solvents were dried according to standard methods. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 589 nm. NMR spectra were recorded on Bruker AC 250, Avance 360 and AMX 500 instruments. Coupling constants are reported in Hz. ESI-TOF mass spectra were recorded on a Micromass LCT instrument coupled to an Agilent 1100 HPLC. Flash chromatography was performed on silica gel 60, (230–400 mesh, Merck Darmstadt). The reactions were monitored by thin layer chromatography on coated aluminum plates (silica gel 60 GF254, Merck Darmstadt). Spots were detected by UV-light or by charring with a 1:1 mixture of 2 N H_2SO_4 and 0.2% resorcine monomethylether in ethanol. Several colonies of *L. flavus* (Formicinae) where collected at Weidenberg (near Bayreuth/Northern Bavaria, Germany). Ants where kept in climate chamber at 25 °C (16L: 6D) at constant humidity.

4.2. 6-*O*-(*p*-Acetoxycinnamoyl)-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose (2)

Triol **1** (20 mg, 55 μmol), *p*-acetoxycinnamic acid (23 mg, 11 μmol) and triphenylphosphine (43 mg, 165 μmol) were dissolved in freshly distilled tetrahydrofuran (2 ml) and stirred under nitrogen for 40 min at 0 °C. Diethylazodicarboxylate (DEAD, 17 μl, 107 μmol) was added dropwise to the mixture, which was allowed to attain room temperature. After 19 h, an additional amount of DEAD (7.5 μl, 47 μmol) was slowly added to the mixture after cooling to 0 °C. After 24 h the reaction was terminated with methanol (1 ml). The mixture was concentrated and purified by flash chromatography (dichloromethane/methanol 45:1) affording 15.6 mg of **2** (51%). R_f = 0.35 (cyclohexane/ethyl acetate 1:2); $[\alpha]_D^{23} = -34.5$ (*c* 0.3, dichloromethane); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.98 (s, 1H, NH), 11.87 (s, 1H, NH′), 7.81, 7.78 (2s, 2H, Ar-2/6), 7.66 (d, J_{trans} = 16.0 Hz, 1H, =CH_β), 7.18, 7.16 (2s, 2H, Ar-3/5), 7.02, 6.97 (2s, 2H, Pyrr, Pyrr′), 6.73–6.67 (m, 3H, Pyrr, =CH_α, Pyrr′), 6.11 (m, 2H, Pyrr, Pyrr′), 5.85 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1), 5.61 (d, $J_{OH,4}$ = 5.6 Hz, 1H, OH-4), 5.57 (d, $J_{OH,3}$ = 5.6 Hz, 1H, OH-3), 4.99 (dd, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 8.7 Hz, 1H, H-2), 4.46 (dd, J_{gem} = 12.2 Hz, $J_{5,6a}$ < 2Hz, 1H, H-6a), 4.26 (dd, J_{gem} = 12.2 Hz, $J_{5,6b}$ = 5.6 Hz, 1H, H-6b), 3.75 (m, 1H, H-5), 3.68 (m, 1H, H-3), 3.46 (m, 1H, H-4), 2.27 (s, 3H, Ac); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 169.0 (C=O Ac), 166.1 (C=O Ar), 159.3, 158.4 (C=O Pyrr, Pyrr′), 152.0 (C-4 Ar), 143.9 (=CH_β), 131.6 (C-1 Ar), 129.7 (C-2/6 Ar), 122.4 (C-3/5 Ar), 121.5, 120.4 (Pyrr, Pyrr′), 117.9 (CH_α), 116.4, 115.3 (Pyrr, Pyrr′), 109.8, 109.4 (Pyrr, Pyrr′), 91.8 (C-1), 74.7 (C-5), 73.6 (C-3), 72.2 (C-2), 69.8 (C-4), 63.3 (C-6); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{27}H_{26}N_2O_{11}$ M_r (calcd) 554.15, M_r (found) 577.10 $(M+Na)^+$, 444.09 $(M-PyrrCO_2)^+$, 1131.23 $(2M+Na)^+$.

4.3. 6-*O*-(*p*-Acetoxy-*m*-methoxycinnamoyl)-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose (3)

Triol **1** (20 mg, 55 μmol), *p*-acetoxy-*m*-methoxycinnamic acid (26 mg, 110 μmol) and triphenylphosphine (43 mg, 165 μmol) were dissolved in freshly distilled tetrahydrofuran (2 ml) and stirred under nitrogen for 40 min at 0 °C. Diethylazodicarboxylate (DEAD, 17 μl, 107 μmol) was added dropwise to the mixture, which was allowed to attain room temperature. After 19 h, an additional amount of DEAD (7.5 μl, 47 μmol) was slowly added to the mixture after cooling to 0 °C. After 24 h the reaction was terminated with methanol (1 ml). The mixture was concentrated and purified by flash chromatography (dichloromethane/methanol 45:1) affording 17.3 mg of **3** (54%). R_f = 0.33 (cyclohexane/ethyl acetate 1:2); $[\alpha]_D^{23} = -22.1$ (*c* 0.4, dichloromethane); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.98 (s, 1H, NH), 11.86 (s, 1H, NH′), 7.64 (d, J_{trans} = 15.9 Hz, 1H, =CH_β), 7.56 (s, 1H, H-2' Ar), 7.29 (d, $J_{5',6'}$ = 8.1 Hz, 1H, H-5′ Ar), 7.11 (d, $J_{6'5'}$ = 8.1 Hz, 1H, H-6′ Ar), 7.03, 6.97 (2s, 2H, Pyrr, Pyrr′), 6.78 (d, J_{trans} = 16.0 Hz, 1H, =CH_α), 6.73, 6.70 (2s, 2H, Pyrr, Pyrr′), 6.10 (m, 2H, Pyrr, Pyrr′), 5.86 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1), 5.61 (d, $J_{OH,4}$ = 5.8 Hz, 1H, OH-4), 5.58 (d, $J_{OH,3}$ = 5.6 Hz, 1H, OH-3), 5.00 (dd, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 8.8 Hz, 1H, H-2), 4.46 (dd, J_{gem} = 12.2 Hz, $J_{5,6a}$ < 2 Hz, 1H, H-6a), 4.27 (dd, J_{gem} = 12.2 Hz, $J_{5,6b}$ = 5.7 Hz, 1H, H-6b), 3.82 (s, 3H, Me), 3.72 (m, 1H, H-5), 3.68 (m, 1H, H-3), 3.46 (m, 1H, H-4); 2.25 (s, 3H, Ac); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 168.3 (C=O Ac), 166.2 (C=O Ar), 159.3, 158.4 (C=O Pyrr, Pyrr′), 151.2 (C-4 Ar), 144.3 (=CH_β), 141.1 (C-3 Ar), 132.0 (C-1 Ar), 123.2, 122.0 (Pyrr,

Pyrr′), 121.5, 120.4 (C_i-Pyrr, C_i-Pyrr′), 118.1 (C-5 Ar), 116.4, 115.3 (Pyrr, Pyrr′), 111.8 (C-6 Ar), 109.8, 109.5 (Pyrr, Pyrr′), 91.8 (C-1), 74.7 (C-5), 73.5 (C-3), 72.2 (C-2), 69.8 (C-4), 63.3 (C-6), 56.0 (Me), 20.4 (Ac); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{28}H_{28}N_2O_{12}$ M_r (calcd) 584.16, M_r (found) 607.24 $(M+Na)^+$, 474.16 $(M-PyrrCO_2)^+$, 1191.50 $(2M+Na)^+$.

4.4. 6-*O*-(*m*,*p*-Diacetoxycinnamoyl)-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose (4)

Triol **1** (5 mg, 14 μmol), *m*,*p*-diacetoxycinnamic acid (7.4 mg, 28 μmol) and triphenylphosphine (11 mg, 42 μmol) were dissolved in freshly distilled tetrahydrofuran (2 ml) and stirred under nitrogen for 40 min at 0 °C. Diethylazodicarboxylate (DEAD, 10 μl, 63 μmol) was added dropwise to the mixture, which was allowed to attain room temperature. After 21 h, an additional amount of DEAD (5 μl, 32 μmol) was slowly added to the mixture after cooling to 0 °C. After 72 h the reaction was terminated with methanol (1 ml). The mixture was concentrated and purified by flash chromatography (dichloromethane/methanol 45:1) affording 5.1 mg of **4** (60%). R_f = 0.29 (cyclohexane/ethyl acetate 1:2); $[\alpha]_D^{23}$ = −28.7 (*c* 0.5, dichloromethane); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.98 (s, 1H, NH), 11.87 (s, 1H, NH′), 7.74 (s, 1H, H-2′ Ar), 7.70–7.67 (m, 1H, H-5′ Ar), 7.64 (d, J_{trans} = 16.3 Hz, 1H, =CH_β), 7.30 (d, $J_{5'6'}$ = 8.3 Hz, 1H, H-6′ Ar), 7.02, 6.97 (2s, 2H, Pyrr, Pyrr′), 6.74–6.70 (m, 3H, Pyrr, =CH_α, Pyrr′), 6.11 (m, 2H, Pyrr, Pyrr′), 5.85 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1), 5.61 (d, $J_{OH,4}$ = 5.8 Hz, 1H, OH-4), 5.57 (d, $J_{OH,3}$ = 5.6 Hz, 1H, OH-3), 4.99 (dd, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 8.9 Hz, 1H, H-2), 4.45 (dd, J_{gem} = 12.2 Hz, $J_{5,6a}$ < 2 Hz, 1H, H-6a), 4.26 (dd, J_{gem} = 12.2 Hz, $J_{5,6b}$ = 5.6 Hz, 1H, H-6b), 3.77 (m, 1H, H-5), 3.68 (m, 1H, H-3), 3.43 (m, 1H, H-4), 2.28, 2.27 (2s, 6H, Ac); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 168.1, 168.0 (C=O Ac), 165.9 (C=O Ar), 159.3, 158.4 (C=O Pyrr, Pyrr′), 143.5 (C-4 Ar), 143.1 (=CH_β), 142.3 (C-3 Ar), 132.8 (C-1 Ar), 127.0 (C-2 Ar), 125.6 (C-6 Ar), 124.1 (C-5 Ar), 124.1, 123.2 (Pyrr, Pyrr′), 121.5, 120.4 (C_i-Pyrr, C_i-Pyrr′), 118.9 (=CH_α), 116.4, 115.3 (Pyrr, Pyrr′), 109.8, 109.5 (Pyrr, Pyrr′), 91.8 (C-1), 74.7 (C-5), 73.6 (C-3), 72.2 (C-2), 69.8 (C-4), 63.3 (C-6), 56.0 (Me), 20.3 (Ac, Ac′); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{29}H_{28}N_2O_{13}$ M_r (calcd) 612.16, M_r (found) 634.93 $(M+Na)^+$, 501.93 $(M-PyrrCO_2)^+$.

4.5. 6-*O*-(*m*,*p*-Bis(*tert*-butyldimethylsilyloxy)cinnamoyl)-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose (5)

To a stirred solution of freshly prepared *tert*-butyldimethylsilyl-protected caffeoyl chloride (17 mg, 41 μmol) in toluene (10 ml) were added triol **1** (10 mg, 27 μmol) and pyridine (1.5 ml). The mixture was stirred at room temperature for two days. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (dichloromethane/methanol 60:1) affording 11 mg of **5** (56%). R_f = 0.20 (dichloromethane/methanol 24:1); $[\alpha]_D^{23}$ = −25.9 (*c* 0.3, dichloromethane); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.97 (s, 1H, NH), 11.87 (s, 1H, NH′), 7.56 (d, J_{trans} = 16.2 Hz, 1H, =CH_β), 7.25 (d, $J_{5',6'}$ = 8.3 Hz, 1H, H-5′ Ar), 7.20 (s, 1H, H-2′ Ar), 7.02, 6.96 (2s, 2H, Pyrr, Pyrr′), 6.86 (d, $J_{5'6'}$ = 8.3 Hz, 1H, H-6′ Ar) 6.72–6.70 (m, 2H, Pyrr, Pyrr′), 6.50 (d, J_{trans} = 15.8 Hz, 1H =CH_α), 6.11 (m, 2H, Pyrr, Pyrr′), 5.85 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1), 5.59 (d, $J_{OH,4}$ = 5.3 Hz, 1H, OH-4), 5.57 (d, $J_{OH,3}$ = 5.9 Hz, 1H, OH-3), 4.99 (dd, $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 9.0 Hz, 1H, H-2), 4.44 (dd, J_{gem} = 12.7 Hz, $J_{5,6a}$ < 2 Hz, 1H, H-6a), 4.22 (dd, J_{gem} = 12.7 Hz, $J_{5,6b}$ = 6.5 Hz, 1H, H-6b), 3.71 (m, 1H, H-5), 3.66 (m, 1H, H-3), 3.39 (m, 1H, H-4), 0.93–0.94 (m, 18H, *t*Bu), 0.19 (s, 12H, Me); ^{13}C NMR (67.5 MHz, DMSO-d_6), from HMQC-COSY): δ = 144.5 (=CH_β), 125.3 (C-2 Ar), 125.2, 124.0 (Pyrr, Pyrr′), 122.6 (C-5 Ar), 120.6 (C-6 Ar), 116.1, 115.3 (Pyrr, Pyrr′), 115.2 (=CH_α), 109.8, 109.5 (Pyrr, Pyrr′), 91.9 (C-1), 75.0 (C-5), 73.4 (C-3), 72.0 (C-2), 69.6 (C-4), 63.1 (C-6), 25.6 (tBu), 2.2 (Me); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{37}H_{52}N_2O_{11}Si_2$ M_r (calcd) 756.31, M_r (found) 779.22 $(M+Na)^+$, 774.25 $(M+NH_4)^+$, 535.21 $(M-PyrrCO_2H-PyrrCO_2)^+$, 646.21 $(M-PyrrCO_2)^+$, 1535. 46 $(2M+Na)^+$.

4.6. 6-*O*-(*p*-Acetoxy-*m*-methoxybenzoyl)-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose (6)

Triol **1** (5 mg, 14 μmol), *p*-acetoxy-*m*-methoxybenzoic acid (6 mg, 28 μmol) and triphenylphosphine (3 equiv, 11 mg) were dissolved in freshly distilled tetrahydrofuran (1 ml) and stirred under nitrogen for 40 min at 0 °C. Diethylazodicarboxylate (DEAD, 10 μl, 63 μmol) was added dropwise to the mixture, which was allowed to attain room temperature. After 21 h, an additional amount of DEAD (5 μl, 32 μmol) was slowly added to the mixture after cooling to 0 °C. After 72 h the reaction was terminated with methanol (0.5 ml). The mixture was concentrated and purified by flash chromatography (dichloromethane/methanol 45:1) affording 4.7 mg of **6** (61%). R_f = 0.31 (cyclohexane/ethyl acetate 1:2); $[\alpha]_D^{23}$ = −27.3 (*c* 0.3, dichloromethane); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.95 (s, 1H, NH), 11.87 (s, 1H, NH′), 7.59–7.58 (m, 2H, H-2′/5′ Ar), 7.27 (d, $J_{5,6}$ = 8.6 Hz, 1H, H-6′ Ar), 7.01, 6.97 (2s, 2H, Pyrr, Pyrr′), 6.74, 6.69 (2s, 2H, Pyrr, Pyrr′), 6.11 (m, 2H, Pyrr, Pyrr′), 5.84 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1), 5.65 (d, $J_{OH,4}$ = 5.8 Hz, 1H, OH-4), 5.56 (d, $J_{OH,3}$ = 5.8 Hz, 1H, OH-3), 5.01 (dd, $J_{1,2}$ = 8.3 Hz, $J_{2,3}$ = 8.9 Hz, 1H, H-2), 4.58 (dd, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ < 2 Hz, 1H, H-6a), 4.37 (dd, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 5.8 Hz, 1H, H-6b), 3.86–3.82 (m, 4H, H-5, Me), 3.70 (m, 1H, H-3), 3.47 (m, 1H, H-4), 2.28 (s, 3H, Ac); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 168.1 (C=O Ac), 164.9 (C=O Ar), 159.3, 158.4 (C=O Pyrr, Pyrr′), 151.0 (C-4 Ar), 143.3 (C-3 Ar), 128.4 (C-1 Ar), 125.6 (C-5 Ar), 124.2 (C-6 Ar), 123.3, 122.1 (Pyrr, Pyrr′), 121.5, 120.4 (C_i-Pyrr, C_i-Pyrr′), 116.5, 115.3 (Pyrr, Pyrr′), 113.1 (C-2 Ar), 109.8, 109.5 (Pyrr, Pyrr′), 91.9 (C-1), 74.7 (C-5), 73.7 (C-3), 72.2 (C-2), 70.0 (C-4), 63.9 (C-6), 56.0 (Me), 20.4 (Ac); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{26}H_{26}N_2O_{10}$ M_r (calcd) 558.15, M_r (found) 580.94 $(M+Na)^+$, 447.95 $(M-PyrrCO_2)^+$, 1138.89 $(2M+Na)^+$.

4.7. 6-*O*-(*p*-Anisoyl)-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose H

Triol **1** (20 mg, 55 μmol), *p*-anisic acid (17 mg, 110 μmol) and triphenylphosphine (43 mg 165 μmol) were dissolved in freshly distilled tetrahydrofuran (2 ml) and stirred under nitrogen for 40 min at 0 °C. Diethylazodicarboxylate (DEAD, 25 μl, 157 μmol) was added dropwise to the mixture, which was allowed to attain room temperature. After 4 h the reaction was terminated with methanol (1 ml). The mixture was concentrated and purified by flash chromatography (dichloromethane/methanol 45:1) affording 19.7 mg of **H** (72%). R_f = 0.22 (dichloromethane/methanol 24:1); $[\alpha]_D^{23}$ = −76.0 (*c* 0.4, MeOH); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.98 (s, 1H, NH), 11.87 (s, 1H, NH), 7.91 (d, *J* = 8.8 Hz, 2H, H-2′/6′ Ar), 7.06 (d, *J* = 8.8 Hz, 2H, H-3′/5′ Ar), 7.02 (s, 1H, Pyrr), 6.97 (s, 1H, Pyrr′), 6.74 (s, 1H, Pyrr), 6.70 (s, 1H, Pyrr′), 6.10 (m, 2H, Pyrr, Pyrr′), 5.85 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1), 5.64 (m, 1H, OH-4), 5.58 (d, $J_{OH,3}$ = 5.1 Hz, 1H, OH-3), 5.02 (dd, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 8.8 Hz, 1H, H-2), 4.52 (dd, J_{gem} = 12.1 Hz, $J_{5,6a}$ < 2 Hz, 1H, H-6a), 4.33 (dd, J_{gem} = 12.1 Hz, $J_{5,6b}$ = 5.2 Hz, 1H, H-6b), 4.12 (s, 3H, OMe), 3.82 (m, 1H, H-5), 3.69 (m, 1H, H-3), 3.49 (m, 1H, H-4); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 165.2 (C=O Ar), 163.2 (C-4 Ar), 159.3, 158.4 (C=O Pyrr), 131.3 (C-2/6 Ar), 125.5 (Pyrr), 124.2 (Pyrr′), 121.8, 121.5 (C_i-Pyrr, C_i-Pyrr′), 120.4 (C-1 Ar), 116.4 (Pyrr), 115.4 (Pyrr′), 114.0 (C-3/5 Ar), 109.8 (Pyrr), 109.5 (Pyrr′), 91.9 (C-1), 74.8 (C-5), 73.7 (C-3), 72.2 (C-2), 69.8 (C-4), 63.3 (C-6), 55.5 (OMe); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{24}H_{24}N_2O_{10}$ M_r (calcd) 500.14, M_r (found) 523.26 $(M+Na)^+$.

4.8. 6-*O*-Cumaroyl-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose D

Compound **2** (5 mg, 9 μmol) was suspended in a mixture of acetonitrile/0.5 M ammonium acetate, pH 7 (1 ml, 1:9) and stirred at 40 °C. To the milky suspension was added immobilized CAL B (20 mg) and stirring was continued at 40 °C. With progressing reaction the suspension cleared. After 3–4 h (monitored by LC–MS) the reaction was terminated by filtration. The solids were washed with water/acetonitrile (2 ml, 9:1) and the filtrate was lyophilized twice. The remainder was dissolved in water (10 ml) and passed over a SepPak C18 Classic cartridge (Waters). Elution was carried out using a step gradient of acetonitrile/water (10 ml each) with concentrations of 0–40% acetonitrile (5% steps). The target compound eluted in the fractions with 25–30% of acetonitrile. The fractions were combined and lyophilized giving 2 mg of **D** (45%). R_f = 0.61 (dichloromethane/methanol 7:1); $[\alpha]_D^{23} = -28.2$ (*c* 0.1, MeOH); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.97 (s, 1H, NH), 11.87 (s, 1H, NH′), 10.04 (s, 1H, OH-Ar), 7.65–7.53 (m, 2H, H-2′/6′ Ar), 7.55 (d, J_{trans} = 15.7 Hz, 1H, =CH$_\beta$), 7.08 (m, 1H, Pyrr), 7.02 (m, 1H, Pyrr′), 6.78–6.70 (m, 2H, H-3′/5′ Ar), 6.53 (d, J_{trans} = 15.9 Hz, 1H, =CH$_\alpha$), 5.84 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1), 5.58 (m, 2H, OH-4, OH-3), 4.99 (dd, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 8.8 Hz, 1H, H-2), 4.41 (dd, J_{gem} = 11.9 Hz, $J_{5,6a}$ < 2 Hz, 1H, H-6a), 4.37 (dd, J_{gem} = 11.9 Hz, $J_{5,6b}$ = 5.9 Hz, 1H, H-6b), 3.75 (m, 1H, H-5), 3.69 (m, 1H, H-3), 3.37 (m, 1H, H-4). ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 166.5 (C=O Ar), 159.9 (C-4 Ar), 159.3, 158.4 (C=O Pyrr, Pyrr′), 145.1 (=CH$_\beta$), 132.7, 130.4 (2H, C-2/6 Ar), 125.6 (Pyrr), 125.0 (C-1 Ar), 124.2 (Pyrr′), 121.5 (C$_i$-Pyrr), 120.4 (C$_i$-Pyrr′), 116. 5 (Pyrr), 115.8 (C-3/5 Ar), 115.3 (Pyrr′), 114.9 (1H, C-3/5 Ar), 113.8 (=CH$_\alpha$), 109.8, 109.5 (Pyrr, Pyrr′), 91.8 (C-1), 74.8 (C-5), 73.6 (C-3), 72.2 (C-2), 69.8 (C-4), 63.1 (C-6); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{25}H_{24}N_2O_{10}$ M_r (calcd) 512.14, M_r (found) 535.27 (M+Na)$^+$.

4.9. 6-*O*-Feruloyl-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose E

Compound **3** (5 mg, 8 μmol) was suspended in a mixture of acetonitrile/0.5 M ammonium acetate, pH 7 (1 ml, 1:9) and stirred at 40 °C. To the milky suspension was added immobilized CAL B (20 mg) and stirring was continued at 40 °C. With progressing reaction the suspension cleared. After 3–4 h (monitored by LC/MS) the reaction was terminated by filtration. The solids were washed with water/acetonitrile (2 ml, 9:1) and the filtrate was lyophilized twice. The remainder was dissolved in water (10 ml) and passed over a SepPak C18 Classic cartridge (Waters). Elution was carried out using a step gradient of acetonitrile/water (10 ml each) with concentrations of 0–40% acetonitrile (5% steps). The target compound eluted in the fractions with 20–30% of acetonitrile. The fractions were combined and lyophilized giving 2 mg of **E** (48%). R_f = 0.65 (dichloromethane/methanol 7:1); $[\alpha]_D^{23} = -49.3$ (*c* 0.4, MeOH); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.95 (s, 1H, NH), 11.84 (s, 1H, NH), 9.56 (s, 1H, OH Ar), 7.68 (m, 1H, H-5′ Ar), 7.54 (d, J_{trans} = 15.8 Hz, 1H, =CH$_\beta$), 7.35 (m, 1H, H-6′ Ar), 7.02 (s, 1H, H-2′ Ar), 6.96 (m, 2H, Pyrr, Pyrr′), 6.73 (m, 2H, Pyrr, Pyrr′), 6.53 (d, J_{trans} = 15.9 Hz, 1H, =CH$_\alpha$), 6.11 (m, 2H, Pyrr, Pyrr′), 5.85 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1), 5.64–5.49 (m, 2H, OH-4, OH-3), 4.99 (dd, $J_{1,2}$ = 8.3 Hz, $J_{2,3}$ = 9.3 Hz, 1H, H-2), 4.44 (dd, J_{gem} = 12.3 Hz, $J_{5,6a}$ < 2 Hz, 1H, H-6a), 4.23 (dd, J_{gem} = 12.3 Hz, $J_{5,6b}$ = 4.9 Hz, 1H, H-6b), 3.81 (s, 3H, OMe), 3,74 (m, 1H, H-5), 3.68 (m, 1H, H-3), 3.39 (m, 1H, H-4); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 166.6 (C=O Ar), 159.3, 158.4 (C=O Pyrr, Pyrr′), 149.4 (C-4 Ar), 148.0 (C-3 Ar), 145.4 (=CH$_\beta$), 125.6 (C-2 Ar), 125.4 (C-1 Ar), 124.2 (Pyrr), 123.5 (Pyrr′), 121.5 (C$_i$-Pyrr), 120.4 (C$_i$-Pyrr′), 116.5 (Pyrr), 115.4 (Pyrr′), 114.9 (C-5 Ar), 114.1 (=CH$_\alpha$), 111.0 (C-6 Ar), 109.8 (Pyrr), 109.5 (Pyrr′), 91.7 (C-1), 74.7 (C-5), 73.5 (C-3), 72.2 (C-2), 69.8 (C-4), 63.0 (C-6), 55.7 (OMe); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{26}H_{26}N_2O_{11}$ M_r (calcd) 542.15, M_r (found) 565.26 (M+Na)$^+$.

4.10. 6-*O*-Caffeoyl-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose F

*1. Deprotection of **4***: To a stirred solution of **4** (2 mg, 0.33 μmol) in dichloromethane (1 ml), a solution of K_2CO_3 in methanol (0.01 M, 25 μl) was added dropwise. The reaction was monitored by LC/MS and after each 24 h additional K_2CO_3-solution (25 μl) was added. After 4 days the reaction was terminated with acetic acid (50 μl). The mixture was dried in high vacuo and purified by RP-HPLC (Äkta Basic, Amersham, water/acetonitrile 10–95%, 9.5 ml/min, YMC ODS-A, 250 × 4.6 mm, 120 Å, S-5 μm) to afford 0.6 mg of **F** (35%).

*2. Deprotection of **5***: To a solution of **5** (9 mg, 12 μmol) in pyridine (2 ml), a solution of 3HF/Et_3N in pyridine (100 μl, 1.56 M) was added dropwise. The mixture was stirred for 20 h and the solvent was evaporated under reduced pressure. The residue was purified using RP-HPLC (Äkta Basic, Amersham, water/acetonitrile 10–95%, 9.5 ml/min, YMC ODS-A, 250 × 20 mm, 120 Å, S-5 μm) to afford 10 mg of **F** (63%). R_f = 0.68 (dichloromethane/methanol 7:1); $[\alpha]_D^{23} = -27.7$ (*c* 0.4, MeOH); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.94 (s, 1H, NH), 11.84 (s, 1H, NH′), 9.35 (m, 2H, OH-3/4 Ar), 7.47 (d, J_{trans} = 15.8 Hz, 1H, =CH$_\beta$), 7.02 (m, 1H, Pyrr), 7.00 (s, 1H, H-2′ Ar), 6.96 (m, 1H, Pyrr′), 6.76 (m, 1H, Pyrr), 6.73 (m, 1H, Pyrr′), 6.71 (m, 1H, H-5′ Ar), 6.70 (d, $J_{5',6'}$ = 1.3 Hz, 1H, H-6′ Ar), 6.30 (d, J_{trans} = 15.9 Hz, 1H, =CH$_\alpha$), 6.12–6.10 (m, 2H, Pyrr, Pyrr′), 5.84 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1), 5.53 (m, 2H, OH-4, OH-3), 4.99 (dd, $J_{1,2}$ = 8.3 Hz, $J_{2,3}$ = 8.6 Hz, 1H, H-2), 4.44 (dd, J_{gem} = 12.0 Hz, $J_{5,6a}$ < 2 Hz, 1H, H-6a), 4.20 (dd, J_{gem} = 12.0 Hz, $J_{5,6b}$ = 5.8 Hz, 1H, H-6b), 3.79 (m, 1H, H-5), 3.70 (m, 1H, H-3), 3.42 (m, 1H, H-4); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 166.5 (C=O Ar), 159.3, 158.4 (C=O Pyrr, Pyrr′), 148.5 (C-4 Ar), 145.6 (C-3 Ar), 145.5 (=CH$_\beta$), 125.6 (Pyrr), 125.4 (C-1 Ar), 124.1 (Pyrr′), 121.5 (C$_i$-Pyrr), 121.4 (C-2 Ar), 124.1 (C$_i$-Pyrr′), 116.5, 115.7 (Pyrr, Pyrr′), 115.3 (C-5 Ar), 115.0 (C-6 Ar), 113.6 (=CH$_\alpha$), 109.8, 109.5 (Pyrr, Pyrr′), 91.8 (C-1), 74.8 (C-5), 73.6 (C-3), 72.2 (C-2), 69.9 (C-4), 63.0 (C-6); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{25}H_{24}N_2O_{11}$ M_r (calcd) 528.14, M_r (found) 551.27 (M+Na)$^+$.

4.11. 6-*O*-Vanilloyl-1,2-di-*O*-(pyrrol-2-carbonyl)-β-D-glucopyranose G

Compound **6** (14 mg, 25 μmol) was suspended in a mixture of acetonitrile/0.5 M ammonium acetate, pH 7 (3 ml, 1:9) and stirred at 40 °C. To the milky suspension was added immobilized CAL B (20 mg) and stirring was continued at 40 °C. With progressing reaction the suspension cleared. After 1–2 h (monitored by LC–MS) the reaction was terminated by filtration. The solids were washed with water/acetonitrile (2 ml, 9:1) and the filtrate was lyophilized twice. The remainder was dissolved in water (10 ml) and passed over a SepPak C18 Classic cartridge (Waters). Elution was carried out using a step gradient of acetonitrile/water (10 ml each) with concentrations of 0–40% acetonitrile (5% steps). The target compound eluted in the fractions with 20–30% of acetonitrile. The fractions were combined and lyophilized giving 6mg of **G** (48%). R_f = 0.62 (dichloromethane/methanol 7:1); $[\alpha]_D^{23} = -60.7$ (0.3, MeOH); ^{1}H NMR (360 MHz, DMSO-d_6): δ = 11.91 (s, 1H, NH), 11.82 (s, 1H, NH′), 9.92 (s, 1H, OH Ar), 7.47 (d, $J_{5',6'}$ = 8.2 Hz, 1H, H-5′ Ar), 7.43 (s, 1H, H-2′ Ar), 7.01 (m, 1H, Pyrr), 6.96 (m, 1H, Pyrr′), 6.88 (d, $J_{5',6'}$ = 8.2 Hz, 1H, H-6′ Ar), 6.74 (m, 1H, Pyrr), 6.69 (m, 1H, Pyrr′), 6.10 (m, 2H, Pyrr, Pyrr′), 5.85 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1), 5.58 (d, $J_{OH,4}$ = 3.6 Hz, 1H, OH-4), 5.52 (d, $J_{OH,3}$ = 3.6 Hz, 1H, OH-3), 5.00 (dd, $J_{1,2}$ = 8.4 Hz, $J_{2,3}$ = 8.6 Hz, 1H, H-2), 4.56 (m, J_{gem} = 12.0 Hz, $J_{5,6a}$ < 2 Hz, 1H, H-6a) 4.28 (dd, J_{gem} = 12.0 Hz, $J_{5,6b}$ = 5.8 Hz, 1H, H-6b), 3.82 (m, 1H, H-5), 3.80 (s, 3H, OMe), 3.69 (m, 1H, H-3), 3.48 (m, 1H, H-4); ^{13}C NMR (67.5 MHz, DMSO-d_6): δ = 165.4 (C=O Ar), 159.4, 158.5 (C=O Pyrr),

151.9 (C-4 Ar), 147.4 (C-3 Ar), 125.6 (Pyrr), 124.2 (Pyrr′), 123.5 (C-2 Ar), 121.5, 120.4 (C_i-Pyrr, C_i-Pyrr′), 120.2 (C-1 Ar), 116.5 (Pyrr), 115.4 (Pyrr′), 115.2 (C-5 Ar), 112.6 (C-6 Ar), 109.9 (Pyrr), 109.5 (Pyrr′), 91.9 (C-1), 74.8 (C-5), 73.7 (C-3), 72.2 (C-2), 70.0 (C-4), 63.3 (C-6), 55.6 (OMe); ESI-MS (CH_3CN/H_2O, 0.1% HCOOH), $C_{24}H_{24}N_2O_{11}$ M_r (calcd) 516.14, M_r (found) 539.24 $(M+Na)^+$.

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