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Synthesis and revised stereochemistry assignment of *C*-allyl glucopyranosides and derivatives

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Abstract: α - and β -*C*-allylglucopyranosides and ~~some anomerically pure~~ hydroxy-, bromo- and azido- derivatives were prepared through allylation at C-1 of methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside or 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose and subsequent chemical modifications of the alkene on the anomeric arm. However, we picked out some discordance between some recent published studies and our results. After a thorough work of characterisation and NMR analysis, we unambiguously confirmed α and β stereochemistry of the two series of compounds and fully described for the first time β -*C*-propyl alcohol, bromide and azide of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose.

Keywords: *C*-glycoside, allylation, functionalizable alkene, NMR attribution.

1. Introduction

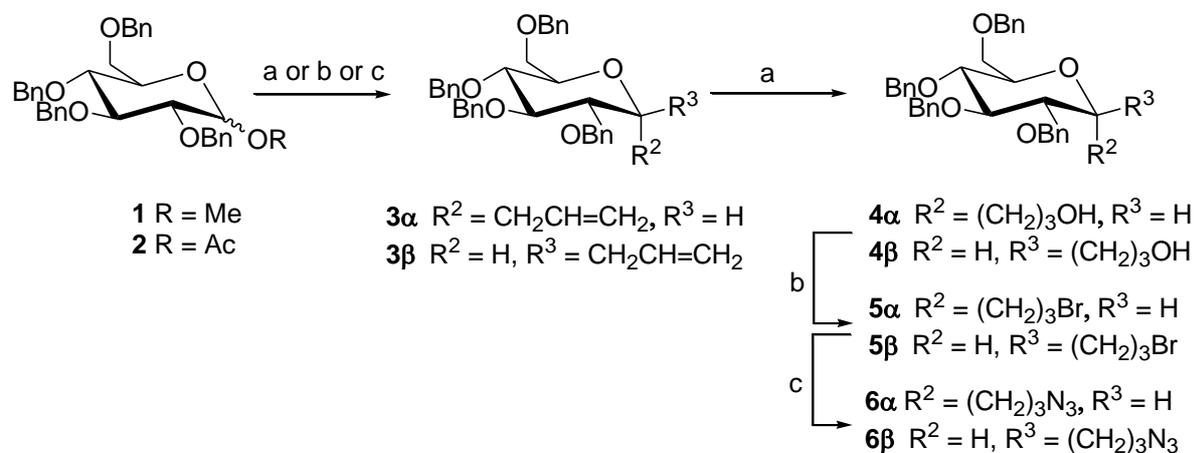
For more than 30 years, the synthesis of *C*-glycosidic derivatives has been an exciting research issue for organic chemists due to the numerous chemical, biological and physical properties of these compounds. In particular, *C*-glycosyl compounds are well known as enzyme inhibitors and as subunits of biologically active natural products, the *C*-glycosidic bond being resistant to acidic and enzymatic hydrolysis.¹

C-glycosyl derivatives has a long standing interest in our group, especially as intermediates in the preparation of new glycoamino acids and bioactive compounds.² Moreover, we are also interested in the conjugation of biomolecules with carbohydrate derivatives by copper(I) catalyzed azide-alkyne cycloaddition (CuAAC), click version of the Huisgen cycloaddition, between a propargylated peptide and an azido sugar.³

In connection with this ongoing work, we were thus interested in the synthesis of *C*-glycosyl derivatives derived from D-glucose and bearing a functionalized arm at the anomeric center, especially α - and β - anomers of *C*-allyl-D-glucopyranoside which were key building blocks for our study. Among the numerous methods used for *C*-glycosyl compounds synthesis, we investigated the nucleophilic addition of the allyl group on the oxonium ion derived from tetra-*O*-benzyl-D-glucopyranose derivatives initially described by Kishi *et al.*⁴ and leading to α -anomer in an highly stereoselective manner. For β -anomer, a one-pot procedure recently developed by Gervay-Hague *et al.* was used.⁵ Nevertheless, when we turned to functionalization of the double bond, an examination of the literature allowed us to find confusing data in recent published works. In this note, we thus would like to give **the full characterization *C*-propyl alcohol of glucopyranoside, to correct compound characterization and stereochemical assignment of *C*-propyl azide** derivative and to describe the synthesis and the full characterization of new α - and β -*C*-propyl bromide derivative.

2. Results and discussion

We first planned to obtain α -*C*-allyl-glucopyranoside **3 α** starting from methyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **1**⁶ or 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **2**, **in the α - or β - predominantly configuration depending on experimental conditions**^{7,8} (Scheme 1). Kishi *et al.* first achieved stereoselective and efficient preparation of α -*C*-allylglucopyranosides⁴ using allylsilane and boron trifluoride etherate (BF₃.Et₂O) in acetonitrile. Hosomi *et al.* proposed the replacement of BF₃.Et₂O by trimethylsilyl triflate (TMSOTf) by keeping excellent stereoselectivity.⁹ These procedures were commonly used for the preparation of α -*C*-allyl-glucopyranosides.¹⁰ As expected, allylation of **1** and **2** according to Hosomi *et al.*⁹ and Kishi *et al.*⁴ procedures respectively afforded a 90:10 mixture of **3 α :3 β** (Scheme 1).



Scheme 1: Alkylation and alkene functionalization. Reagents and conditions: a) AllylTMS, TMSOTf, CH₃CN, 0°C to r.t., 24h, 77% from **1**, α:β 90:10; b) AllylTMS, BF₃·Et₂O, CH₃CN, 0°C to r.t., 24h, up to 74% from **2**, α:β 90:10; c) TMSI, CH₂Cl₂, 0°C, 1h, then AllylMgBr, 0°C to r.t., 3h, up to 90% from **2**, α:β 95:5. a) 1) 9-BBN, THF, Δ, 4h; 2) EtOH, NaOH, H₂O₂, **4α** 93%, **4β** 89%; b) PPh₃, CBr₄, CH₂Cl₂, 0°C, 1h, **5α** 94%, **5β** 90%; c) NaN₃, DMF, **6α** 91%, **6β** 89%.

We were next interested in obtaining the β-*C*-allylglucopyranoside **3β** in an highly stereoselective manner which is more challenging. Several approaches were reported in the literature.^{4,10f,12} Recently, Gervay-Hague *et al.* described the stereoselective Grignard reaction between an allyl magnesium halide and galactosyl iodide.⁵ A one-pot procedure has been developed, allowing the preparation of the α-iodide from the galactopyranosylacetate and its direct transformation into the β-*C*-allylgalactoside *via* an S_N2-type pathway by treatment with allylmagnesium bromide. Only a single anomer was obtained in excellent yield (85% over two steps). This one-pot procedure was carried out on compound **2**. We slightly modified the procedure by using toluene instead of benzene for azeotropic evaporation to remove TMSOAc. Reaction of the crude with allyl magnesium bromide furnished a 5:95 mixture of **3α**:**3β** (Scheme 1).

Both anomers were separated by column chromatography on silica gel and the anomeric configuration was confirmed by NMR spectroscopy and measurement of optical rotations. The analytical data of the two compounds are in accordance with the literature,^{11,10f} especially NMR chemical shifts of anomeric carbon and hydrogen and optical rotation (see SI, Table S1). To further confirm these assignments, NOESY spectra of **3α** and **3β** were recorded. A correlation between H5 and H4 was observed for the major isomer, confirming the cis axial-

equatorial configuration of these two protons and thus the stereochemistry assigned for **3 α** (Figure 1). For the minor compound, the NOESY-spectrum showed a correlation between H8, H6 and H4, corroborating the **axial**-configuration of these three axial protons and therefore the stereochemistry of **3 β** .



Figure 1: NOE correlations in **3 α and **3 β** .** Atom numbering is consistent with **3 β** chemical name and for clarity it is also used for **3 α** .

We next turned to the functionalization of alkenes **3 α** and **3 β** (Scheme 1). Alcohols **4 α** and **4 β** were obtained in excellent yields by hydroboration with 9-BBN in THF (93% and 89% respectively). In connection with our work on the conjugation of biomolecules with sugars derivatives by cycloaddition reaction, we envisioned the preparation of azido derivatives. For this purpose, we focused to convert alcohols **4** in **brominated derivatives 5** using carbon tetrabromide and triphenylphosphine in dichloromethane. Compounds **5 α** and **5 β** were so obtained in 94% and 90% yield respectively. Azidation with sodium azide in DMF led to compounds **6 α** and **6 β** in excellent yields (91 % and 89% yields respectively). This procedure leads to azides **6** in two steps from alcohols **4** with an excellent overall yield (up to 80%). All these compounds were fully characterized and it is worthy to note a consistent trend in NMR for anomeric proton and carbon. Indeed, in compounds **3 α -6 α** , chemical shifts for the anomeric protons H-4 were significantly downfield compared to compounds **3 β -6 β** . In ^{13}C -NMR, signals for the anomeric carbon of α -configured compounds appeared upfield (see SI, Table 1).

The alcohols **4** and azides **6** have already been described.^{10e,13-16} However, we found confusing data in published works. Indeed, Gardiner *et al.* reported in 2010 the preparation of C-allylglycosides according to the procedure initially described by Hosomi *et al.*,⁹ *i.e.* allylTMS and TMSOTf in MeCN.¹³ **With methyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside** as starting material, the authors described a mixture of 10:90 α : β ratio, which is in opposition with results obtained by us and others.^{9,10b,10e} After examination of the SI, it appeared that

NMR data effectively matched with those of compound **3 α** but the β -configuration was assigned by Gardiner *et al.* This mistake has spread in the stereochemical assignment of C-glycopyranosides **4 β** ¹³ and **6 β** ¹⁶ whereas **4 α** ^{10e,15} and **6 α** ¹⁴ has been correctly characterized. Indeed, Xu *et al.* described the preparation of *O*-, *S*-, *N*- and *C*- β -glucose-fipronil conjugates to assay their hydrolysis by β -glucosidase.¹⁶ These compounds were prepared according to the procedure described by Gardiner *et al.*, their configuration proved to be the α -one and not the β -one. Comparison between our data for compounds **4 α** , **4 β** and **6 α** , **6 β** and those reported by Xu *et al.* clearly showed that Xu's products are α -C-glycopyranosides (see SI Table S1). Even if two others groups¹⁷ prepared **4 β** in a multistep synthesis, they never gave a full characterization of this compound. The only data referenced by Chemical Abstract Service for **4 β** and **6 β** are those given by Gardiner (N° CAS of **4 β** : 173829-80-6, **6 β** : 1255526-26-1), which are in fact α -derivatives. We would like thus to give full analytical data for **4 β** and to correct those of **6 β** .

3. Conclusion

To conclude, we were thus interested in the synthesis of C-glycosyl derivatives from D-glucose and bearing a functionalized arm at the anomeric position. According to the original work of Kishi *et al.* and Gervay-Hague *et al.*, the C-allylation reaction proceeded with the anticipated anomeric selectivities. Nevertheless, when we next turned to the functionalization of alkenes, we picked out mistakes in the literature concerning stereochemistry assignment of C-glycopyranosides and derivatives. In this note, we thus would like to give the correct characterizations of β -C-propyl alcohol and azide glycopyranosides **4 β** and **6 β** and to describe the synthesis and the full characterization of new α - and β -C-propyl bromide derivatives **5 α** and **5 β** .

4. Experimental part

4.1. General methods

All reactions were carried out in commercially available dry solvents. TLC analyses were performed using standard procedures on Kieselgel 60 F254 plates (Merck). Compounds were visualized using UV light (254 nm) and (or) 30% methanolic H₂SO₄/heat as developing agent. Column chromatography was performed on silica gel SI 60 (63-200 μ m) (Merck) using hexanes (H), cyclohexane (cycloH) or ethyl acetate (EA) mixtures. FTIR spectra were recorded on a Perkin-Elmer spectrum 1000 on NaCl windows. Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured on

an Anton Paar MC300 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer DPX250 (250 MHz and 62.9 MHz, respectively) and Avance III400 (400 MHz and 100.6 MHz, respectively). For complete assignment of ^1H and ^{13}C signals, two-dimensional ^1H , ^1H COSY and ^1H , ^{13}C correlation spectra were recorded. Chemical shifts (δ) are given in ppm relative to the solvent residual peak. For clarity, atom numbering is that given on Figure 1 rather than resulting from the IUPAC naming of compounds given in SI. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad signal and app=apparent multiplicity. MS spectra were recorded on a Waters Platform and HRMS on a Bruker MicroTOFQ apparatus.

4.2. 4,8-anhydro-2,3-dideoxy-5,6,7,9-tetra-*O*-benzyl-*D*-glycero-*D*-gulo-nonitol (4 β)

mp = 81-83°C (EtOH/H₂O). TLC (R_f): 0.28 (Ethyl acetate/cyclohexane, 3/7). $[\alpha]_D^{20} = +3.4$ (c 1.04, CHCl₃). IR: film (ν , cm⁻¹): 3393, 3028, 2903, 2857, 1497, 1452, 1356, 1092, 1057. ^1H NMR (400 MHz, CDCl₃) δ 1.56 (m, 1H, H-3a), 1.74 (m, 2H, H-2), 1.93-2.05 (m, 2H, H-3b and H_{OH}), 3.31-3.34 (m, 2H, H-4 et H-5), 3.47 (ddd, 1H, $J_{8,7} = 9.5$ Hz, $J_{8,9a} = 5.0$ Hz, $J_{8,9b} = 2.0$ Hz, H-8), 3.61 (app t, 1H, $J_{7,8} = J_{7,6} = 9.5$ Hz, H-7), 3.63-3.74 (m, 5H, H-1, H-6 and H-9), 4.56 (d, 1H, $J_{\text{CH}_2} = 12.0$ Hz, CH₂Ph), 4.57 (d, 1H, $J_{\text{CH}_2} = 11.0$ Hz, CH₂Ph), 4.62 (d, 1H, $J_{\text{CH}_2} = 12.0$ Hz, CH₂Ph), 4.68 (d, 1H, $J_{\text{CH}_2} = 11.0$ Hz, CH₂Ph), 4.84 (d, 1H, $J_{\text{CH}_2} = 11.0$ Hz, CH₂Ph), 4.90-4.94 (m, 3H, CH₂Ph), 7.17-7.19 (m, 2H, H_{Ar}), 7.28-7.37 (m, 18H, H_{Ar}). ^{13}C NMR (100.6 MHz, CDCl₃) δ 28.7 (C-3), 29.4 (C-2), 63.0 (C-1), 69.1 (C-9), 73.6 (CH₂Ph), 75.2 (CH₂Ph), 75.5 (CH₂Ph), 75.7 (CH₂Ph), 78.7 (C-7), 78.8 (C-8), 79.5 (C-5), 82.1 (C-4), 87.4 (C-6), 127.8 (2 C_{Ar}), 127.9 (2 C_{Ar}), 127.9 (C_{Ar}), 128.0 (C_{Ar}), 128.0 (2 C_{Ar}), 128.1 (2 C_{Ar}), 128.1 (2 C_{Ar}), 128.5 (2 C_{Ar}), 128.6 (2 C_{Ar}), 128.6 (2 C_{Ar}), 128.6 (2 C_{Ar}), 138.1 (C_{q-Ar}), 138.2 (C_{q-Ar}), 138.2 (C_{q-Ar}), 138.7 (C_{q-Ar}). HRMS (ESI): calcd for C₃₇H₄₂O₆Na [M+Na]⁺: 605.2879, found: 605.2871.

4.3. 2,6-anhydro-9-bromo-7,8,9-trideoxy-1,3,4,5-tetra-*O*-benzyl-*D*-glycero-*L*-gulo-nonitol (5 α)

mp = 65-67°C (EtOH). TLC (R_f): 0.40 (Ethyl acetate/cyclohexane, 1/9). $[\alpha]_D^{20} = +30.2$ (c 0.98, CHCl₃). IR: film (ν , cm⁻¹): 3028, 2902, 2862, 1452, 1354, 1061. ^1H NMR (400 MHz, CDCl₃) δ 1.85-1.95 (m, 3H, H-3 and H-2a), 2.02 (m, 1H, H-2b), 3.45-3.55 (m, 2H, H-1), 3.57-3.66 (m, 2H, H-8 and H-7), 3.67 (dd, 1H, $J_{9a,8} = 2.0$ Hz, $J_{9a,9b} = 10.5$ Hz, H-9a), 3.72 (dd,

1H, $J_{9b,8} = 3.5$ Hz, H-9b), 3.77 (dd, 1H, $J_{5,4} = 5.5$ Hz, $J_{5,6} = 9.5$ Hz, H-5), 3.81 (m, 1H, H-6), 4.05 (m, 1H, H-4), 4.50 (d, 1H, $J_{CH_2} = 11.0$ Hz, CH₂Ph), 4.51 (d, 1H, $J_{CH_2} = 12.0$ Hz, CH₂Ph), 4.65 (d, 2H, $J_{CH_2} = 12.0$ Hz, CH₂Ph), 4.74 (d, 1H, $J_{CH_2} = 11.5$ Hz, CH₂Ph), 4.83 (d, 1H, $J_{CH_2} = 11.0$ Hz, CH₂Ph), 4.85 (d, 1H, $J_{CH_2} = 11.0$ Hz, CH₂Ph), 4.95 (d, 1H, $J_{CH_2} = 11.0$ Hz, CH₂Ph), 7.14-7.17 (m, 2H, H_{Ar}), 7.28-7.39 (m, 18H, H_{Ar}). ¹³C NMR (100.6 MHz, CDCl₃) δ 23.1 (C-3), 28.8 (C-2), 33.8 (C-1), 69.0 (C-9), 71.2 (C-8), 73.3 (CH₂Ph), 73.5 (CH₂Ph), 73.5 (C-4), 75.1 (CH₂Ph), 75.5 (CH₂Ph), 78.1 (C-7), 80.1 (C-5), 82.5 (C-6), 127.6 (C_{Ar}), 127.7 (C_{Ar}), 127.8 (C_{Ar}), 127.9 (C_{Ar}), 127.9 (4 C_{Ar}), 128.0 (2 C_{Ar}), 128.0 (2 C_{Ar}), 128.4 (2 C_{Ar}), 128.4 (4 C_{Ar}), 128.5 (2 C_{Ar}), 138.0 (C_{q-Ar}), 138.2 (C_{q-Ar}), 138.2 (C_{q-Ar}), 138.8 (C_{q-Ar}). **Anal. Calcd for C₃₇H₄₁O₅Br: C, 68.83; H, 6.40%; Found: C, 69.20; H, 6.39%.** HRMS (ESI): calcd for C₃₇H₄₁O₅BrK [M+Na]⁺: 667.2035, found: 667.2000.

4.4. 4,8-anhydro-1-bromo-1,2,3-trideoxy-5,6,7,9-tetra-*O*-benzyl-D-glycero-D-gulo-nonitol (5β)

mp = 94-96°C (EtOH). TLC (R_f): 0.35 (Ethyl acetate/cyclohexane, 9/1). $[\alpha]_D^{20} = -3.6$ (c 0.90, CHCl₃). IR: film (ν, cm⁻¹): 2909, 2868, 1495, 1450, 1433, 1358. ¹H NMR (400 MHz, CDCl₃) δ 1.58 (m, 1H, H-3a), 1.90-2.15 (m, 3H, H-3b et H-2), 3.27 (m, 1H, H-4), 3.30 (app t, 1H, $J_{5,4} = J_{5,6} = 9.5$ Hz, H-5), 3.41 (ddd, 1H, $J_{8,7} = 9.5$ Hz, $J_{8,9a} = 4.0$ Hz, $J_{8,9b} = 2.0$ Hz, H-8), 3.45 (t, 2H, $J_{1,2} = 7.0$ Hz, H-1), 3.63 (app t, 1H, $J_{7,6} = J_{7,8} = 9.5$ Hz, H-7), 3.69 (dd, 1H, $J_{9a,9b} = 11.0$ Hz, H-9a), 3.71 (app t, 1H, H-6), 3.71 (dd, 1H, H-9b), 4.57 (d, 1H, $J_{CH_2} = 12.0$ Hz, CH₂Ph), 4.59 (d, 1H, $J_{CH_2} = 12.0$ Hz), 4.64 (d, 1H, $J_{CH_2} = 12.0$ Hz, CH₂Ph), 4.68 (d, 1H, $J_{CH_2} = 11.0$ Hz, CH₂Ph), 4.85 (d, 1H, $J_{CH_2} = 12.0$ Hz, CH₂Ph), 4.90-4.93 (m, 3H, CH₂Ph), 7.19-7.21 (m, 2H, H_{Ar}), 7.28-7.38 (m, 18H, H_{Ar}). ¹³C NMR (100.6 MHz, CDCl₃) δ 29.3 (C-3), 30.5 (C-2), 34.2 (C-1), 69.2 (C-9), 73.6 (CH₂Ph), 75.1 (CH₂Ph), 75.5 (CH₂Ph), 75.7 (CH₂Ph), 78.7 (C-7), 78.8 (C-4), 79.0 (C-8), 82.1 (C-5), 87.4 (C-6), 127.8 (C_{Ar}), 127.8 (C_{Ar}), 127.9 (2 C_{Ar}), 127.9 (3 C_{Ar}), 128.1 (3 C_{Ar}), 128.3 (2 C_{Ar}), 128.5 (2 C_{Ar}), 128.6 (2 C_{Ar}), 128.6 (2 C_{Ar}), 128.6 (2 C_{Ar}), 138.1 (C_{q-Ar}), 138.3 (C_{q-Ar}), 138.3 (C_{q-Ar}), 138.7 (C_{q-Ar}). HRMS (ESI): calcd for C₃₇H₄₁O₅BrK [M+K]⁺: 683.1774, found: 683.1778.

4.5. 4,8-anhydro-1-azido-1,2,3-trideoxy-5,6,7,9-tetra-*O*-benzyl-D-glycero-D-gulo-nonitol (6β)

mp = 44-46°C (EtOH). TLC (R_f): 0.38 (Ethyl acetate/cyclohexane, 1/9). $[\alpha]_D^{20} = -4.9$ (c 1.07, CHCl₃). IR: film (ν, cm⁻¹): 302

8, 2909, 2855, 2083, 1494, 1452, 1358, 1086, 1047. ¹H NMR (400 MHz, CDCl₃) δ 1.52 (m, 1H, H-2a), 1.69 (m, 1H, H-3a), 1.83 (m, 1H, H-3b), 1.93 (m, 1H, H-2b), 3.24-3.33 (m, 4H, H1, H-5 and H-4), 3.42 (ddd, 1H, $J_{8,7} = 9.5$ Hz, $J_{8,9a} = 4.0$ Hz, $J_{8,9b} = 2.0$ Hz, H-8), 3.64 (app t, 1H, $J_{7,8} = J_{7,6} = 9.5$ Hz, H-7), 3.67-3.74 (m, 2H, H-9a and H-6), 3.74 (dd, 1H, $J_{9b,9a} = 11.0$ Hz, H-9b), 4.57 (d, 1H, $J_{CH_2} = 12.0$ Hz, CH₂Ph), 4.60 (d, 1H, $J_{CH_2} = 12.0$ Hz, CH₂Ph), 4.64 (d, 1H, $J_{CH_2} = 12.0$ Hz, CH₂Ph), 4.67 (d, 1H, $J_{CH_2} = 11.0$ Hz, CH₂Ph), 4.85 (d, 1H, $J_{CH_2} = 11.0$ Hz, CH₂Ph), 4.90-4.96 (m, 3H, CH₂Ph), 7.18-7.21 (m, 2H, H_{Ar}), 7.28-7.37 (m, 18H, H_{Ar}). ¹³C NMR (100.6 MHz, CDCl₃) δ 25.2 (C-3), 28.7 (C-2), 51.5 (C-1), 69.0 (C-9), 73.5 (CH₂Ph), 75.0 (CH₂Ph), 75.3 (CH₂Ph), 75.6 (CH₂Ph), 78.6 (C-7), 78.8 (C-4), 78.9 (C-8), 82.0 (C-5), 87.3 (C-6), 127.6 (C_{Ar}), 127.6 (C_{Ar}), 127.7 (2 C_{Ar}), 127.7 (3 C_{Ar}), 127.9 (C_{Ar}), 127.9 (2 C_{Ar}), 128.1 (2 C_{Ar}), 128.4 (2 C_{Ar}), 128.4 (2 C_{Ar}), 128.4 (2 C_{Ar}), 128.5 (2 C_{Ar}), 138.0 (C_{q-Ar}), 138.1 (C_{q-Ar}), 138.2 (C_{q-Ar}), 138.6 (C_{q-Ar}). **Anal. Calcd for C₃₇H₄₁N₃O₅: C, 73.12; H, 6.80; N, 6.91%; Found: C, 73.61; H, 6.75; N, 6.75%.** HRMS (ESI): calcd for C₃₇H₄₁N₃O₅Na [M+Na]⁺: 630.2944 found: 630.2952.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at

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