Synthesis of New [(2*S*)-*N*-(*p*-Tolylsulfonyl)-2-Pyrrolidinyl]Propyl 2,3,4-Tri-*O*-Acetyl- and 2,3,4-Tri-*O*-Benzyl-β-L-Fucopyranosides

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ABSTRACT

Synthesis of two new glycoheterocyclic compounds, [(2*S*)-*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]propyl 2,3,4-tri-*O*-acetyl- and 2,3,4-tri-*O*-benzyl-β-L-fucopyranosides **1a** and **1b,** starting from δ-amino alcohol (-)-[(2*S*)-*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl]propan-1-ol **2** and *O*-α-L-fucosyltrichloroacetimidates **3a** or **3b** as glycosyl donor is described. Hitherto δ-aminoalcohol **2** was synthesized from L-proline without any racemization during its preparation.

Keywords: L-Proline, δ-amino alcohol, *O*-α-L-fucosyltrichloroacetimidate, β-L-fucopyranoside, glycosylation

The ongoing research program in this laboratory is concentrated on the synthesis of glycoheterocyclic compounds for biological screening.[1,2] Attention was concentrated on pyrrolidinyl moiety and its congeners as aglycones, since they possess interesting biological activities.[1-3] Pyrrolidine moiety attached to fucose is present in natural products.[4] L-Fucose (6-deoxy-L-galactose) is a constituent of certain naturally occurring substances including bacterial lipopolysaccharides, blood group substances and mammalian glycosphingolipids.[5] One of the pyrrolidine derivatives bearing *N*-tosyl function prepared by us earlier shows very promising antiangiogenic properties.[6] Because of the above-mentioned properties, we became interested to prepare other compounds containing *N*-tosylpyrrolidinyl moiety with possible anti-cancer screening. Unfortunately, the screening experiment could not be done due to the meager quantity and less number of the substances. Initially, we concentrated our attention on alcohol **2** (**Scheme 1**), which could be coupled with protected fucose derivatives **3a** and **3b**, to furnish the α or β glycosides **1**. Removal of the fucose-protecting groups in **1** should furnish compound **4a.** Additionally, *N*-detosylation of **1** by the known procedures[7,8] followed by *N*-methylation and removal of deprotecting groups should furnish a fucoside **4b** having a propylene-bridge between pyrrolidine and fucose (**Figure 1**). The reason for designing this kind of propylene-bridge between the above-mentioned heterocyclic rings was that a somewhat closer spacer (a substituted isopropyl group) has been found in a fucose-containing natural alkaloid isolated from the leaves of *Schizantus integrifolius* Phil.[4] The last compound is of

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interest for us due to our ongoing work on a total synthesis of the pyrrolidine alkaloid analogs of 1-methyl-2-(1-methyl-2-pyrrolidinyl) ethyl 6-deoxy-3-*O*-[(Z)-2-methyl-2-butenoyl]-α-galactopyranoside isolated from *Schizanthus integrifolius* Phil leaves.[1] Thus, the synthesis of **2** and its coupling with two fucosyl donors **3a** and **3b** to get **1a** and **1b** is reported in this paper (**Figure 1**).

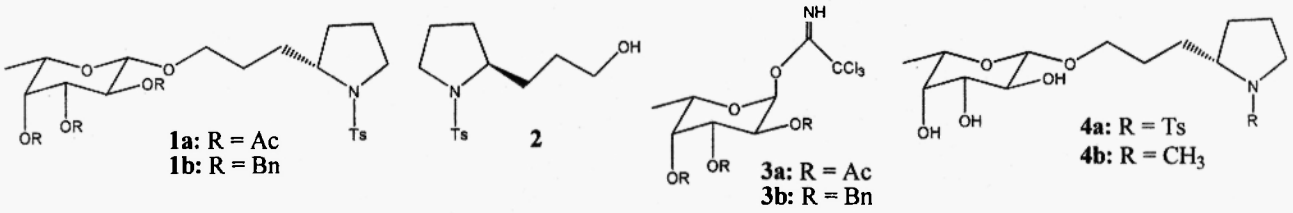
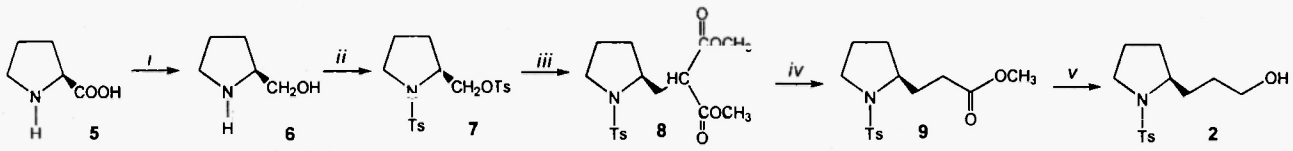


Fig. 1:

RESULTS AND DISCUSSION

δ-Amino alcohol **2** was synthetized in five steps starting from L-proline[2] **5** as shown in **Scheme 1** without any detectable racemization.

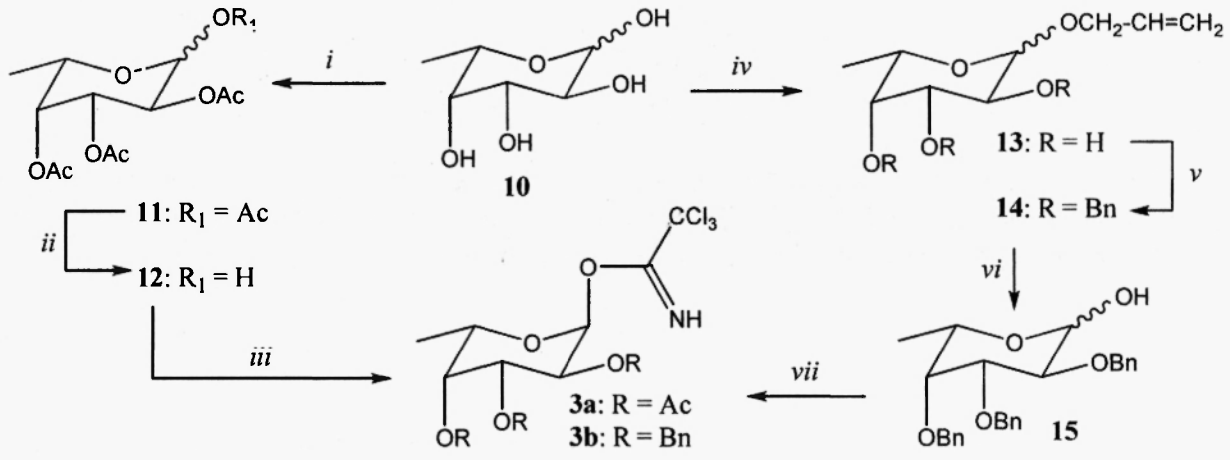


i: $Zn(BH_4)_2$, THF, Δ, 10h, 61%;
ii: TsCl, Py, rt, 12h, 89%;
iii: NaH, $CH_2(CO_2CH_3)_2$, DMF, 100°C, 10h, 80%;
iv: LiCl, H_2O, DMSO, 100°C, 24h, 52%;
v: $LiAlH_4$, ether, rt, 1.5h, 77%.

Scheme 1. Synthesis of (-)-[(2*S*)-*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl] propan-1-ol **2**.

Compound **2** is an oil and was found to be enantiomerically pure by ^1H NMR spectroscopy as evidenced by its behavior with the chiral shift reagent Europium (III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] $Eu(hfc)_3$. Successive addition of this reagent followed by measuring the spectrum caused the shifts of the proton signals, however no separation of the H-2 signal was observed. This clearly indicated the existence of only one enantiomer. Next, we directed our attention to synthesize α-L-fucosyltrichloroacetimidates **3a** and **3b**. Both of them were obtained, according to the known procedure, from L-fucose **10** via 2,3,4-tri-*O*-protected intermediates **12** and **15** as shown in **Scheme 2**.[1,9-12] Compounds **12** or **15** with free anomeric hydroxyl groups were treated with CCl_3CN and DBU in CH_2Cl_2 to furnish the α configured intermediates **3a** and **3b**, respectively. This did occur as evidenced from their ^1H NMR spectra. Thus, the spectrum of **3a** showed a dublet at 6.56 ppm with $J_{1,2}$ = 3.4Hz belonging to H-1, whereas the corresponding signal of **3b** is a dublet at 6.52 ppm with $J_{1,2}$ = 3.4Hz. These values are in agreement with the literature data and prove the anomeric α configuration in both cases.[5,13] Since both 2,3,4-tri-*O*-acetyl- or 2,3,4-tri-*O*-benzyl-protected fucose **12** and **15** used in the reactions to obtain **3a** and **3b** are mixtures of α and β anomers, formation of pure

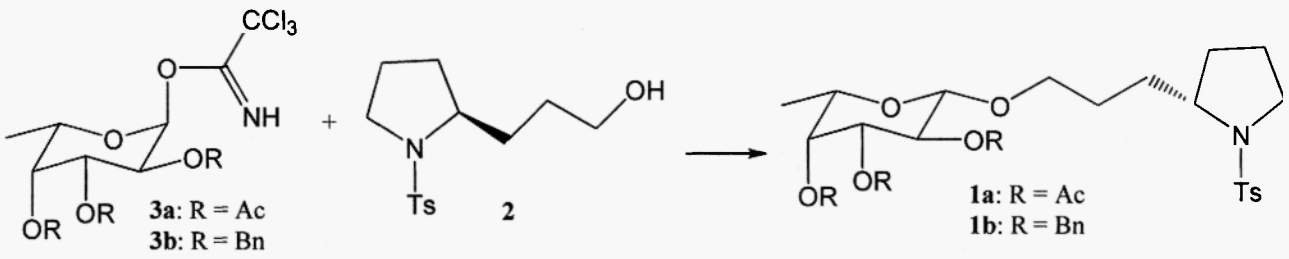
α anomers of **3a** and **3b** implies a strong thermodynamic control during their formation. The same behavior for the formation of trichloroamidates has been noticed earlier.[5,14] Both glycosyl donors **3a** and **3b** were subsequently coupled with alcohol **2** in the presence of trimethylsilyl triflate[14], Scheme 3, and furnished products **1a** and **1b**, respectively, which unexpectedly show the same β anomeric configuration. This configuration can easily be judged from the coupling constants between the vicinal protons H-1 and H-2: $J_{1,2}$=7.9Hz (at δ 4.45 ppm) in **1a** and $J_{1,2}$ = 7.7Hz (at δ 4.33 ppm) in **1b**, which demonstrate *trans* diaxial disposition of the H-1 and H-2 protons in the target compounds **1a** and **1b**.



i: Ac_2O, py, 4°C, 12h, 97%;
ii: $NH_2NH_3^+ {}^-OOCCH_3$, DMF, 50°C, 4h, 63%;
iii: $CNCCl_3$, DBU, CH_2Cl_2, rt, 12h, 74.5%;
iv: CH_2=$CHCH_2OH$, Dowex-H^+, 75°C, 24h, 61.5%;
v: BnBr, NaH, DMF, rt, 2.5h, 78%;
vi: $PdCl_2$, MeOH, rt, 2h, 80%; *vii:* CCl_3CN, DBU, CH_2Cl_2, rt, 3h, 69%.

Scheme 2. Synthesis of *O*-α-L-fucosyltrichloroacetimidates **3a** and **3b**.

One would expect that the glycosyl donor **3b** which bears a non-participating group at the C-2 position, would furnish the most stable α anomer, whereas the other donor **3a** with a participating group at the C-2 atom, would furnish the opposite β anomer. This kind of work has been investigated before.[15-17] In these situations, there may be no relation between the configuration of the newly formed glycosidic bond and the participating/non-participating nature of the protecting group present at the C-2 position of the glycosyl donor. Mechanistically, these facts strongly suggest that the glycosylation step may proceed via a tight ion-pair, and that the inversion of configuration takes place at the anomeric center irrespective of the participating or non-participating character of the protecting group present at the *O*-2 atom. Contrary to this, if the glycosylation step proceeds via a loose ion-pair, one can expect the influence of a participating or a non-participating group.[18] In some cases, the acidic catalyst was able to epimerize the kinetically formed β-glycoside and to yield the most stable α anomer.[19] Evidently, the TMSOTf used throughout this work was unable to promote such transformation, particularly because the short reaction time and the low temperature. Attempts to remove the *N*-tosyl group in **1a** using $LiAlH_4$ in THF[7] or Na/naphthalene in DME[8] unexpectedly failed.



For **1a**: CH_2Cl_2, TMSOTf, -30°C, 1h, 79%. For **1b**: Ether, TMSOTf, -30°C, 1h, 69%.

Scheme 3. Synthesis of the *β*-L-fucopyranosides **1a** and **1b**.

Two new β-L-fucopyranosides **1a** and **1b** bearing [(*2S*)-*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl] propan-1-yl group as aglycone were obtained in good yields. The anomeric configuration of both products was independent of the participating or non-participating nature of the *O*-2-protecting groups present in the fucosyl donors.

EXPERIMENTAL

Melting points were determined on an Electrothermal digital melting point apparatus (model IA9100) and are uncorrected. Specific rotations were measured with a Perkin-Elmer polarimeter model 241. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrophotometer using TMS as an internal standard. High resolution mass spectral measurements were done using the Finnigan MAT 95 XL spectrometer. Silica Gel 60 (230 – 400 mesh, Merck) was used for liquid chromatography. Petroleum ether used in the present work had the boiling range of 40-65°C.

(-)-[(S)-N-(p-Tolylsulfonyl)-2-pyrrolidinyl] methyl dimethylmalonate (8)

Dimethylmalonate (1.43mL, 12.22 mmol) and 60% NaH (293.4mg, 12.22mmol) in dry DMF (25mL) were stirred for 30min at room temperature. Addition of (-)-(*S*)-*N*,*O*-bis(*p*-tolylsulfonyl)-2-pyrrolidyl methanol **7** (1.0g, 2.44mmol) to this malonate suspension followed by stirring for 8h at 100°C completed the reaction. Further addition of water to the reaction contents, extraction with dichloromethane, drying over Na_2SO_4 and solvent removal provided the crude product. Purification by column chromatography over silica gel using a mixture of petroleum ether and ethyl acetate (7:3) gave 0.72g (80%) of **8** as solid having R_f value of 0.58 (petroleum ether:ethyl acetate, 7:3), mp. 115-117°C, $[\alpha]_D^{25}$ = –64.6 (*c* 1, CH_2Cl_2). EI: m/z Calc. for $C_{17}H_{23}NO_6S$: 370.1323, Found: 370.1324. ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, 2H, *J* = 8.1Hz, H-7 and H-11), 7.31 (d, 2H, *J* = 7.9Hz, H-8 and H-10), 3.89-3.82 (m, 2H, H-2 and H-2′), 3.78 (s, 3H, H-4′), 3.75 (s, 3H, H-4′′), 3.40-3.32 (m, 1H, H-5), 3.22-3.13 (m, 1H, H-5), 2.41 (s, 3H, H-12), 2.12-2.03 (m, 2H, H-1′), 1.85-1.74 (m, 1H, H-3) and 1.53-1.35 (m, 3H, H-3 and H-4). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.60 (C-3′), 170.14 (C-3′′), 143.93(C-6), 134.79 (C-9), 130.05 (C-7 and C-11), 127.96 (C-8 and C-10), 58.66 (C-2), 53.01 (C-4′), 52.98 (C-4′′), 49.06 (C-5), 49.04 (C-2′), 35.29 (C-1′), 31.55 (C-3), 24.26 (C-4) and 21.91 (C-12).

Methyl (-)-[(S)-N-(p-tolylsulfonyl)-2-pyrrolidinyl] propionate (9)

(-)-[(*S*)-*N*-(*p*-Tolylsulfonyl)-2-pyrrolidinyl] methyl dimethylmalonate **8** (0.70g, 1.90mmoles) was dissolved in dry DMSO (10mL). To the solution, water (0.035mL, 1.90mmol) and LiCl (161mg, 3.79mmol) were added followed by stirring for 24h at 105°C. Addition of saturated brine solution to the contents, extraction with dichloromethane, drying

over Na_2SO_4 and solvent removal provided the crude product. Purification by column chromatography over silica gel using petroleum ether and ethyl acetate (7:3) gave 0.31g (52%) of 9 as oil having R_f value of 0.64 (petroleum ether:ethyl acetate, 7:3), $[\alpha]_D^{25}$ = −80.8 (*c* 1.05, CH_2Cl_2). Anal. Calc. for $C_{15}H_{21}NO_4S$: C = 57.85%, H = 6.79%; Found: C = 57.42%, H = 6.96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 2H, J = 8.1Hz, H-7 and H-11), 7.33 (d, 2H, J = 8.1Hz, H-8 and H-10), 3.77-3.72 (m, 1H, H-2), 3.70 (s, 3H, H-4′), 3.42-3.34 (m, 1H, H-5), 3.25-3.19 (m, 1H, H-5), 2.51-2.46 (m, 2H, H-2′), 2.43 (s, 3H, H-12), 2.03-1.48 (m, 6H, H-1′, H-3 and H-4). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.26 (C-3), 143.75 (C-6), 135.08 (C-9), 130.04 (C-7 and C-11), 127.96 (C-8 and C-10), 59.90 (C-2), 52.00 (C-4′), 49.20 (C-5), 31.39 (C-2′), 31.24 (C-1′), 30.99 (C-3), 24.37 (C-4) and 21.89 (C-12).

(-)-[(S)-N-(p-Tolylsulfonyl)-2-pyrrolidinyl] propan-1-ol (2)

To a stirred solution of methyl (-)-[(*S*)-*N*-(*p*-tolylsulfonyl)-2-pyrrolidinyl] propionate 9 (0.29g, 0.93mmol) in ether (6.0mL) at 0°C was added $LiAlH_4$ (35mg, 0.93mmol) and agitation continued for 1h at room temperature. One drop of water was added to this and stirring was maintained for 1h more. Filtration and solvent removal provided the crude product. Purification by column chromatography over silica gel using 6:4 petroleum ether and ethyl acetate gave 0.20g (77%) of **2** as an oil having R_f value of 0.3 (petroleum ether:ethyl acetate, 6:4), $[\alpha]_D^{25}$ = −98.6 (*c* 1.11, CH_2Cl_2). IR (Film): 3660-3110 cm^{-1} (OH). Anal. Calc. for $C_{14}H_{21}NO_3S$: C = 59.33%, H = 7.47%, O = 16.94%; Found: C = 59.14%, H = 7.73%, O = 17.07%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, 2H, J = 8.0Hz, H-7 and H-11), 7.33 (d, 2H, J = 8.1Hz, H-8 and H-10), 3.71-3.69 (m, 3H, H-2 and H-3′), 3.43-3.36 (m, 1H, H-5), 3.24-3.15 (m, 1H, H-5), 2.44 (s, 3H, H-12) and 1.90-1.44 (m, 8H, H-3, H-4, H-1′ and H-2′). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 143.71 (C-6), 135.17 (C-9), 130.04 (C-7 and C-11), 127.90 (C-8 and C-10), 63.17 (C-3′), 60.59 (C-2), 49.29 (C-5), 33.12 (C-1′), 31.26 (C-3), 24.46 (C-4), 29.41 (C-2′) and 21.91 (C-12).

(-)-[(S)-N-(p-Tolylsulfonyl)-2-pyrrolidinyl] propyl 2,3,4-tri-O-acetyl-β-L-fucopyranoside (1a)

To a cold (-30°C) suspension of **2** (0.1g, 0.35mmol) and trichloroacetoimidate **3a** (0.23g, 0.53mmol) in dry dichloromethane (10mL) containing a small quantity of molecular sieves (4Å) under argon atmosphere was added TMSOTf (30µL). After stirring for 1.5h, the reaction mixture was treated with 1.0g of $NaHCO_3$ and filtered. Brine was then added and the mixture was extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and the solvent was removed. The crude product was purified by column chromatography over silica gel using 6:4 petroleum ether and ethyl acetate to give 156mg (79%) of **1a** as a syrup having R_f value of 0.6 (petroleum ether:ethyl acetate 1:1), $[\alpha]_D^{25}$ = −57 (*c* 0.665, CH_2Cl_2). HRFABMS $[M+H]^+$ Calc. 556.2217; Found 556.2212. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, 3H, $J_{6,5}$ = 6.4Hz, H-6′), 1.38-1.83 (m, 8H, H-3, H-4, H-6, H-7), 1.98 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.17 (s, 3H, CH_3CO), 2.43 (s, 3H, H-15), 3.11-3.19 (m, 1H, H-5), 3.31-3.36 (m, 1H, H-5), 3.37-3.51 (m, 1H, H-2), 3.54-3.62 (m, 1H, H-8), 3.84 (q, 1H, $J_{5,6}$ = 6.4Hz, H-5′), 3.91-3.98 (m, 1H, H-8), 4.45 (d, 1H, $J_{1,2}$ = 7.9Hz, H-1′), 5.02 (dd, 1H, $J_{3,2}$ = 10.5Hz and $J_{3,4}$ = 3.4Hz, H-3′), 5.19 (dd, 1H, $J_{2,1}$ = 7.9Hz and $J_{2,3}$ = 10.5Hz, H-2′), 5.22 (d, 1H, $J_{4,3}$ = 3.4Hz, H-4′), 7.30 (d, 2H, J = 8.2Hz, H-11 and H-13) and 7.70 (d, 2H, J = 8.1Hz, H-10 and H-14). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.46 (C-6′), 21.02 (CH_3), 21.09 (CH_3), 21.25 (CH_3), 21.88 (C-15), 24.40 (C-4), 26.52 (C-7), 31.11 (C-3), 33.11 (C-6), 49.23 (C-5), 60.58 (C-2), 69.43 (C-3′ and C-5′), 70.18 (C-8), 70.73 (C-4′), 71.77 (C-2′), 101.57 (C-1′), 127.86 (C-11 and C-13), 130.02 (C-10 and C-14), 135.13 (C-12), 143.66 (C-9), 170.02 (CO), 170.60 (CO) and 171.09 (CO).

(-)-[(S)-N-(p-Tolylsulfonyl)-2-pyrrolidinyl] propyl 2,3,4-tri-O-benzyl-β-L-fucopyranoside (1b)

To a cold (-30°C) suspension of **2** (0.02g, 0.08mmol) and trichloroacetoimidate **3b** (0.07g, 0.11mmol) in dry ether (8mL) containing a little molecular sieves (4Å) under argon atmosphere was added TMSOTf (15µL). After stirring for

1h, the reaction mixture was treated with 0.2g of $NaHCO_3$ and filtered. Solvent removal provided the crude product. Purification by column chromatography over silica gel using 3:1 petroleum ether and ethyl acetate gave 37mg (69%) of **1b** as a syrup having R_f value of 0.5 (petroleum ether:ethyl acetate 3:1), $[\alpha]_D^{25}$ = –64.8 (*c* 1.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (d, 3H, $J_{6,5}$ = 6.4Hz, H-6′), 1.40-1.86 (m, 8H, H-3, H-4, H-6, H-7), 2.40 (s, 3H, H-15), 3.11-3.20 (m, 1H, H-5), 3.27-3.35 (m, 1H, H-5), 3.42-3.61 (m, 5H, H-2, H-8, H-3′, H-4′, H-5′), 3.81(dd, 1H, $J_{2,1}$ = 7.7Hz and $J_{2,3}$ = 9.6Hz, H-2′), 4.00 (m, 1H, H-8), 4.33 (d, 1H, $J_{1,2}$ = 7.7Hz, H-1′), 4.68-4.99 (m, 6H, -CH_2-), 7.26-7.36 (m, 17H, H-10, H-13 and Ar) and 7.71 (d, 2H, *J* = 8.1Hz, H-10 and H-14). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.28 (C-6′), 21.89 (C-15), 24.43 (C-4), 26.90 (C-3), 31.11 (C-7), 33.48 (C-6), 49.22 (C-5), 60.70 (C-2), 70.02 (C-8), 70.67 (C-5′), 73.59 (-CH_2-), 74.95 (-CH_2-), 75.44 (-CH_2-), 76.76 (C-3′), 79.89 (C-4′), 82.93 (C-2′), 104.27 (C-1′), 127.87 (C-11 and C-13), 127.92, 127.97, 128.33, 128.43, 128.52, 128.58, 128.68, 128.77, 128.83 and 128.93 (15C, Ar), 130.01 (C-10 and C-14), 135.33(C-12), 139.03, 139.08 and 139,33 (3C, Ar), 143.58 (C-9).

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