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Novel pyridyl macrocyclic triarylmethanes: synthesis by ring-closing metathesis and chemical analysis

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Abstract:

In the present work, we described the synthesis of eight original pyridyl macrocyclic triarylmethanes using an efficient 3-steps synthetic strategy. The bisalkylated 4,4'-(pyridin-X-ylmethylene) diphenols (X=2-4) were prepared by ring-closing metathesis, as macrocyclization key step, using Grubbs second generation catalyst. The pyridyl macrocyclic triarylmethanes were obtained with moderate to good yields. The introduction of a pyridine *N*-oxide moiety before the macrocyclization proved to be interesting to afford higher yield of the corresponding metathesis product. FT-IR, ¹H NMR, ¹³C NMR and X-Ray diffraction analysis have been used for the characterization of the synthesized compounds.

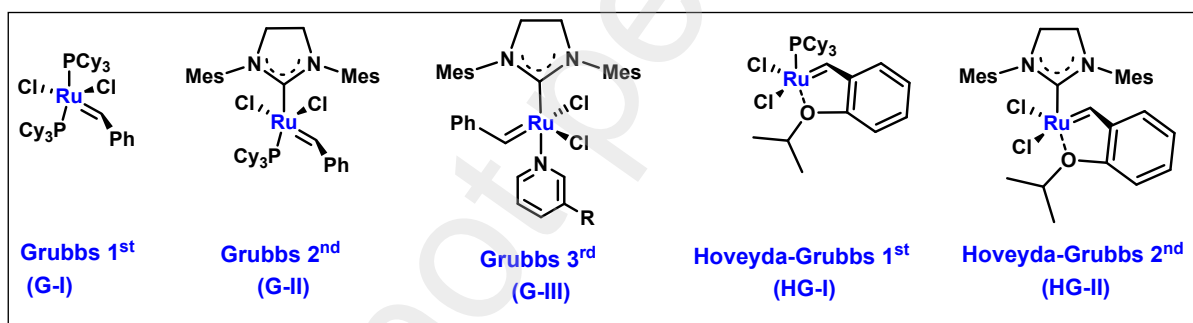
Keywords: Ring closing metathesis • triarylmethanes • macrocyclization • Grubb's catalysis • Pyridine *N*-oxide

30 1. Introduction

31
32 The olefin metathesis has become one of the most important tools for the construction
33 of C-C double bonds [1–3]. This reaction is widely applied to the synthesis of high value
34 added products such as polymers [4–5], natural [6–9], pharmaceuticals and
35 agrochemicals [10].

36 In particular, ring-closing olefin metathesis (RCM) has received a great deal of attention
37 for the synthesis of small (5- and 6), medium (7–9) and larger (>9)-membered ring
38 systems [11–15]. Actually, macrocyclic compounds constitute a privileged source for
39 the development of compounds with interesting biological properties [9, 10, 16–23]. The
40 use of RCM has been extended owing to the compatibility of the process with
41 heteroatoms in the newly created ring systems like nitrogen, oxygen and sulfur [24]. In
42 addition, the stable, well-defined and highly chemoselective catalysts are
43 commercially available including the 1st, 2nd and 3rd generation Grubbs (G-I, G-II and
44 G-III) catalysts as well as the Grubbs-Hoveyda 1st and 2nd generation catalysts (H-G I
45 and H-G II). (Figure 1) [25–27].

46



47

48 **Figure 1.** Grubbs and Hoveyda Grubbs catalysts used in metathesis

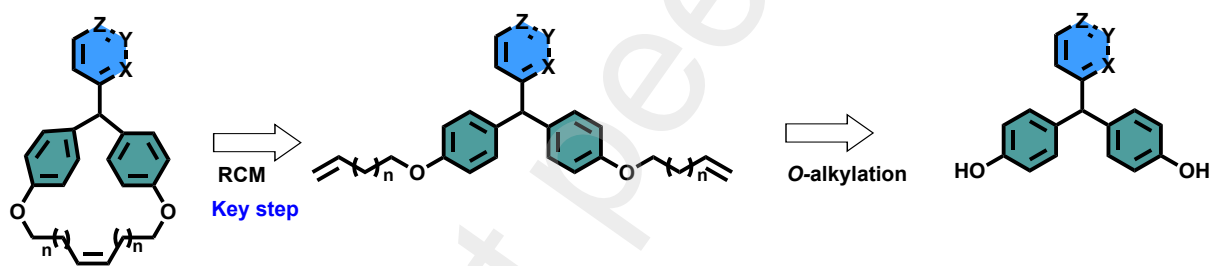
49 Metathesis is an efficient method for the development of macrocyclic compounds
50 which is being extensively investigated notably for medicinal chemistry. The RCM is
51 being widely used due to its suitability by linking olefinic double bonds under affordable
52 experimental conditions. This reaction allow to obtain the macrocycles, regardless of
53 their size, hard to prepare by other alternative routes [28,29,30–32].

54 However, the use of a substrate holding a Lewis base character such as pyridine or
55 free amine can be problematic because of the coordination of the nitrogen to the
56 ruthenium center which may cause the deactivation of the catalyst [31][33]. For years,

57 many studies have been addressing the deactivation of the ruthenium-centered
58 catalysts which have been reported it in the literature [19, 29–31].

59 The use of pyridine-containing compounds in metathesis remains challenging [33].
60 Several studies have proposed appropriate approaches to overcome catalyst
61 deactivation such as the nitrogen functionalization [37], the introduction of a hindered
62 [29] or electron-withdrawing group such as halogens in C2-substituted *N*-heterocycles
63 [38–40] or even the preparation of ammonium salts [28][40–42]. Consequently,
64 pharmaceutically interesting macrocycles such as Muscopyridine, quinoxalinones
65 have been efficiently developed using this method [28,29,43].

66 As part of our medicinal chemistry program, directed toward the development of new
67 anticancer agents, and encouraged by the high interest of macrocycles systems and
68 the triarylmethane scaffold, we decided to implement an efficient synthesis of new
69 macrocyclic triarylmethanes from commercially available reagents using RCM as key
70 step (Scheme 1) [44–46].



72 **Scheme 1.** Retrosynthetic pathway for the synthesis of macrocyclic triarylmethanes

73 2. Experimental

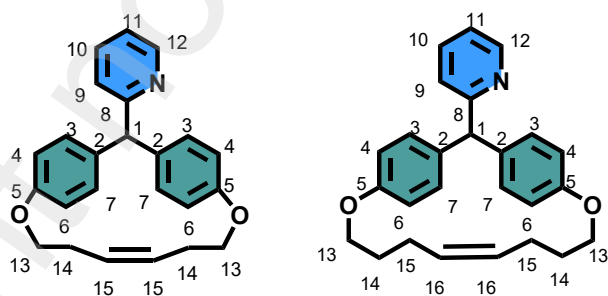
74 2.1. Materials

75 All reagents were obtained from commercial sources unless otherwise noted and used
76 as received. Heated experiments were conducted using thermostatically controlled oil
77 baths and were performed under an oxygen-free atmosphere in oven-dried glassware
78 when necessary. The reactions were monitored by analytical Thin Layer
79 Chromatography (TLC). TLC was performed on aluminium sheets precoated silica gel
80 plates (60 F254, Merck). TLC plates were visualized using irradiation with light at 254
81 nm. Flash column chromatography (FCC) was carried out when necessary, using silica
82 gel 60 (particle size 0.040 - 0.063 mm, Merck). Cary 630 FTIR/ ATR/ ZnSe
83 spectrometer.

84

85 2.2. Characterization

86 The structures of the products were checked by comparison of NMR, IR and MS data
87 and by the TLC behaviour. ^1H - and ^{13}C -NMR spectra were recorded on a Bruker
88 BioSpin GmbH spectrometer (400 MHz), at room temperature. Chemical shifts are
89 reported in δ units, parts per million (ppm). Coupling constants (J) are measured in
90 Hertz (Hz). Splitting patterns are designed as followed: d : doublet ; dd : doublet of
91 doublet ; ddd : doublet of doublet of doublets ; dt : doublet of triplet ; dq : doublet of
92 quadruplet ; m : multiplet ; qt : quadruplet of triplet ; s : singlet ; t : triplet ; td : triplet of
93 doublet. DEPT experiments and various 2D techniques such as COSY, HSQC and
94 HMBC were used to establish the structures and to assign the signals. Infrared spectra
95 were recorded over the 400-4000 cm^{-1} range with an Agilent Technologies.
96 X-Ray diffraction experiments of the macrocycles **7b**, **8b**, **8c** were performed with an
97 in-house setup of the Charles Coulomb laboratory, Montpellier University, France. A
98 high brightness low power X- ray tube, coupled with aspheric multilayer optic (GeniX3D
99 from Xenocs) was employed. It delivers an ultralow divergent beam (0.5 mrad, $\lambda =$
100 0.15418 nm). Scatter less slits were used to give a clean 0.6 mm beam diameter with
101 a flux of 35 Mphotons/s at the sample. We worked in a transmission configuration and
102 scattered intensity was measured by a 2D "Pilatus" 300K pixel detector by Dectris
103 (490*600 pixels) with pixel size of $172 \times 172 \mu\text{m}^2$, at 0.2 m from the sample. All
104 Intensities were corrected by transmission and the empty cell contribution was
105 subtracted.



106

107 **Figure 2.** Convention adopted to assign signals of ^1H and ^{13}C -NMR spectra

108 2.3. Synthesis of (4,11-dioxa-1,3(1,4)-dibenzenacycloundecaphan-7-en-2-yl)pyridine 109 7a

110
111 To a solution of 2-(bis(4-(but-3-en-1-yloxy)phenyl)methyl) pyridine **5a** (0.39 mmol, 1
112 equiv, 151 mg), in anhydrous DCM (15 mL) Grubbs II catalyst was added (0.037 mmol,
113 0.1 equiv, 32 mg), under argon. The reaction mixture was stirred during 25 h at 60 $^{\circ}\text{C}$
114 and controlled by TLC. After reaction completion, the mixture was cooled to room

115 temperature and then concentrated under vacuum. The crude residue was purified by
116 FCC on silica gel (Cyhex/EtOAc: 6/4) to afford the desired product **7a** as a brown oil in
117 65% yield (90 mg).

118 TLC: CyHex/EtOAc: 60/40, $R_f = 0.4$, $^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) : 8.64 - 8.56
119 (m, 1H, H_{12}), 7.59 - 7.74 (m, 1H, H_{10}), 7.22 - 7.08 (m, 2H, H_9 , H_{11}), 7.04 (d, 4H, $J_{3-4} =$
120 $J_{7-6} = 8.0$ Hz, H_3 , H_7), 6.80 (d, 4H, $J_{4-3} = J_{6-7} = 8.0$ Hz, H_4 , H_6), 5.74 - 5.47 (m, 3H, H_1 ,
121 H_{15}), 3.95 (t, 4H, $J_{13-14} = 6.5$ Hz, H_{13}), 2.58 - 2.42 (m, 4H, H_{14}). $^{13}\text{C NMR}$ (100 MHz,
122 CDCl_3) δ (ppm) : 157.5 (C_5), 149.4 (C_{12}), 136.3 (C_{10}), 131.0 (C_2), 130.2 (C_3 , C_7), 128.4
123 (C_{15}), 126.1 (C_8), 123.6 - 121.2 (C_9 , C_{11}), 114.5 (C_4 , C_6), 67.4 (C_{13}), 57.6 (C_1), 32.5
124 (C_{14}). IR ν (cm^{-1}) : 2917, 2852 ($\nu_{\text{Csp}3\text{-H}}$), 1608, 1507, 1468 ($\nu_{\text{C=C ar.}}$), 1238, 1026 ($\nu_{\text{C-O-}}$
125 c), 1110 ($\nu_{\text{C-N}}$), 909 ($\delta_{\text{C-H}}$), 821 ($\delta_{\text{Csp}2\text{-H para}}$).

126

127 *2.4. Synthesis of 3-(4,11-dioxa-1,3(1,4)-dibenzenacycloundecaphan-7-en-2-* 128 *yl)pyridine 7b*

129

130 To a solution of 3-(bis(4-(but-3-en-1-yloxy)phenyl)methyl) pyridine **5b** (0.18 mmol, 1
131 equiv, 68.4 mg), in anhydrous DCM (7 mL) Grubbs II catalyst was added (0.018 mmol,
132 0.1 equiv, 15.7 mg), under argon. The reaction mixture was stirred during 72 h at 60 °C
133 and controlled by TLC. After reaction completion, the mixture was cooled to room
134 temperature and then concentrated under vacuum. The crude residue was purified by
135 FCC on silica gel (Cyhex/EtOAc: 6/4) to afford the desired product **7b** as a brown oil
136 in 45% yield (28.7 mg). TLC: CyHex/EtOAc: 60/40, $R_f = 0.3$, $^1\text{H NMR}$ (400 MHz, CDCl_3)
137 δ (ppm) : 8.50 - 8.45 (m, 1H, H_{12}), 8.40 - 8.38 (m, 1H, H_{10}), 7.40 - 7.38 (m, 1H, H_{11}),
138 7.22 - 7.17 (m, 1H, H_9), 6.99 - 6.94 (m, 4H, H_3 , H_7), 6.84 - 6.79 (m, 4H, H_4 , H_6), 5.43
139 (s, 1H, H_1), 5.20 - 5.00 (m, 2H, H_{15}), 4.01 - 3.89 (m, 4H, H_{13}), 2.50 - 2.40 (m, 4H, H_{14}). ^{13}C
140 NMR (100 MHz, CDCl_3) δ (ppm) : 158.0 (C_5), 150.7 (C_{10}), 147.4 (C_{12}), 136.5 (C_{11}),
141 135.1 (C_8), 130.1 (C_3 , C_7), 130.1 (C_2), 123.1 (C_9), 114.4 (C_4 , C_6), 134.3 (C_{15}), 67.1 (C_{13}),
142 52.8 (C_1), 29.7 (C_{14}). IR ν (cm^{-1}) : 2923, 2856 ($\nu_{\text{Csp}3\text{-H}}$), 1671 ($\nu_{\text{C=C}}$), 1608, 1507 - 1469
143 ($\nu_{\text{C=C ar.}}$), 1240, 1028 ($\nu_{\text{C-O-C}}$), 1113 ($\nu_{\text{C-N}}$), 916 ($\delta_{\text{C-H}}$), 823 ($\delta_{\text{Csp}2\text{H para}}$).

144

145 *2.5. Synthesis of 2-(4,13-dioxa-1,3(1,4)-dibenzenacyclotridecaphan-8-en-2-yl)pyridine* 146 *8a*

147

148 To a solution of 2-(bis(4-(pent-4-en-1-yloxy)phenyl)methyl) pyridine **6a** (0.37 mmol, 1
149 equiv, 151 mg), in anhydrous DCM (15 mL) Grubbs II catalyst was added (0.037 mmol,

150 0.1 equiv, 33 mg), under argon. The reaction mixture was stirred during 30 h at 60 °C
151 and controlled by TLC. After reaction completion, the mixture was cooled to room
152 temperature and then concentrated under vacuum. The crude residue was purified by
153 FCC on silica gel (Cyhex/EtOAc: 8/2) to afford the desired product **8a** as a brown oil in
154 64% yield (91 mg). TLC: CyHex/EtOAc: 60/40, $R_f = 0.4$, $^1\text{H NMR}$ (400 MHz, CDCl_3) δ
155 (ppm) : 8.60 - 8.55 (m, 1H, H_{12}), 7.75 - 7.66 (m, 1H, H_{10}), 7.22 - 7.15 (m, 1H, H_{11}), 7.15
156 - 7.10 (m, 1H, H_9), 7.06 - 6.99 (m, 4H, H_3 , H_7), 6.84 - 6.74 (m, 4H, H_4 , H_6), 5.67 (s, 1H,
157 H_1), 5.56 - 5.35 (m, 2H, H_{16}), 3.98 - 3.78 (m, 4H, H_{13}), 2.28 - 2.11 (m, 4H, H_{15}), 1.96 -
158 1.89 (m, 4H, H_{14}). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ (ppm) : 159.7 (C_5), 149.3 (C_{12}), 136.4
159 (C_{10}), 130.1 (C_3 , C_7 , C_{16}), 128.7 (C_2), 126.9 (C_8), 123.7 (C_9), 121.2 (C_{11}), 114.3 (C_4 ,
160 C_6), 67.2 (C_{13}), 57.6 (C_1), 29.0 (C_{14}), 28.9 (C_{15}). IR ν (cm^{-1}) : 2924 - 2855 ($\nu_{\text{Csp}^3\text{-H}}$),
161 1609, 1508, 1468 ($\nu_{\text{C=C ar.}}$), 1243, 1037 ($\nu_{\text{C-O-C}}$), 1116 ($\nu_{\text{C-N}}$), 909 ($\delta_{\text{C-H}}$), 823 ($\delta_{\text{Csp}^2\text{H para}}$).
162

163 2.6. Synthesis of 3-(4,13-dioxo-1,3(1,4)-dibenzenacyclotridecaphan-8-en-2-yl)pyridine 164 **8b**

165 To a solution of 3-(bis(4-(pent-4-en-1-yloxy)phenyl)methyl) pyridine **6b** (0.36 mmol, 1
166 equiv, 147 mg), in anhydrous DCM (15 mL) Grubbs II catalyst was added (0.034, 0.09
167 equiv, 30 mg), under argon. The reaction mixture was stirred during 30 h at 60 °C and
168 controlled by TLC. After reaction completion, the mixture was cooled to room
169 temperature and then concentrated under vacuum. The crude residue was purified by
170 FCC on silica gel (Cyhex/EtOAc: 6/4) to afford the desired product **8b** as a brown oil
171 in 77% yield (106 mg). TLC: CyHex/EtOAc: 60/40, $R_f = 0.2$, $^1\text{H NMR}$ (400 MHz, CDCl_3)
172 δ (ppm) : 8.50 - 8.45 (m, 1H, H_{12}), 8.36 - 8.34 (m, 1H, H_{10}), 7.66 - 7.62 (m, 1H, H_{11}),
173 7.47 - 7.43 (m, 1H, H_9), 6.92 - 6.86 (m, 4H, H_3 , H_7), 6.72 - 6.78 (m, 4H, H_4 , H_6), 5.44 -
174 5.32 (m, 1H, H_1), 5.20 - 5.00 (m, 2H, H_{16}), 3.89 - 3.82 (m, 4H, H_{13}), 2.18 - 2.08 (m, 4H,
175 H_{15}), 1.83 - 1.71 (m, 4H, H_{14}). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ (ppm) : 158.0 (C_5), 146.8
176 (C_{12}), 138.1 (C_9), 134.8 (C_8), 131.3 (C_{11}), 130.2 (C_2), 130.2 (C_3 , C_7), 128.7 (C_{10}), 114.7
177 (C_4 , C_6), 129.9 (C_{15}), 67.3 (C_{13}), 52.7 (C_1), 30.9 (C_{14}). IR ν (cm^{-1}) : 2922, 2854 ($\nu_{\text{Csp}^3\text{-H}}$),
178 1684 ($\nu_{\text{C=C}}$), 1608, 1508, 1470 ($\nu_{\text{C=C ar.}}$), 1242, 1027 ($\nu_{\text{C-O-C}}$), 1113 ($\nu_{\text{C-N}}$), 917 ($\delta_{\text{C-H}}$),
179 822 ($\delta_{\text{Csp}^2\text{H para}}$).
180

181 2.7. Synthesis of 4-(4,13-dioxo-1,3(1,4)-dibenzenacyclotridecaphan-8-en-2-yl)pyridine 182 **8c**

183

184 To a solution of 4-(bis(4-(pent-4-en-1-yloxy)phenyl)methyl)pyridine **6c** (0.48 mmol, 1
185 equiv, 200 mg), in anhydrous DCM (20 mL) Grubbs II catalyst was added (0.048 mmol,
186 0.1 equiv, 42 mg), under argon. The reaction mixture was stirred during 48 h at 60 °C
187 and controlled by TLC. After reaction completion, the mixture was cooled to room
188 temperature and then concentrated under vacuum. The crude residue was purified by
189 FCC on silica gel (Cyhex/EtOAc: 8/2; 7/3 ; 6/4) to afford the desired product **8c** as a
190 brown oil in 69% yield (127.8 mg, $R_f = 0.30$ Cyhex/EtOAc : 6/4). $^1\text{H NMR}$ (400 MHz,
191 CDCl_3) δ (ppm) : 8.48 - 8.45 (m, 2H, H_{10}), 7.05 - 6.90 (m, 2H, H_9), 6.97 (d, 4H, $J_{3-4} =$
192 $J_{7-6} = 7.0$ Hz, H_3 , H_7), 6.89 - 6.83 (m, 4H, H_4 , H_6), 5.37 (s, 1H, H_1), 5.06 - 5.00 (m, 2H,
193 H_{16}), 3.95 - 3.32 (m, 4H, H_{13}), 2.28 - 2.17 (m, 4H, H_{15}), 1.90 - 1.74 (m, 4H, H_{14}). ^{13}C
194 NMR (100 MHz, CDCl_3) δ (ppm) : 158.3 (C_5), 150.1 (C_{10}), 134.9 (C_2), 130.6 (C_3 , C_7),
195 130.5 (C_{16}), 125.0 (C_9), 124.2 (C_8), 114.9 (C_4 , C_6), 67.6 (C_{13}), 55.1 (C_1), 30.6 (C_{15}),
196 28.9 (C_{14}). IR ν (cm^{-1}) : 3025 ($\nu_{\text{Csp}2\text{-H}}$), 2924, 2865 ($\nu_{\text{Csp}3\text{-H}}$), 1607, 1507, 1470 ($\nu_{\text{C=C ar.}}$),
197 1239, 1027 ($\nu_{\text{C-O-C}}$), 1112 ($\nu_{\text{C-N}}$), 914 ($\delta_{\text{C-H}}$), 821 ($\delta_{\text{Csp}2\text{-H para}}$).

198

199 *2.8. Synthesis of 2-(4,11-dioxa-1,3(1,4)-dibenzenacycloundecaphan-7-en-2-* 200 *yl)pyridine 1-oxide 11*

201

202 To a solution of 2-(bis(4-(but-3-en-1-yloxy)phenyl)methyl) pyridine 1-oxide **9a** (0.17
203 mmol, 1 equiv, 70 mg) in anhydrous DCM (7 mL), Grubbs II catalyst was added (0.017
204 mmol, 0.1 equiv, 15 mg) under argon. The reaction mixture was stirred during 36 h at
205 60 °C and controlled by TLC. After reaction completion, the mixture was cooled to room
206 temperature and then concentrated under vacuum. The crude residue was purified by
207 FCC on silica gel (DCM/MeOH.NH₃ (7N): 98/2) to afford the desired product **11** as a
208 black solid in 76% yield (48 mg). TLC: DCM/MeOH (7N): 95/5, $R_f = 0.8$, $^1\text{H NMR}$ (400
209 MHz, CDCl_3) δ (ppm) : 8.58 - 8.56 (m, 1H, H_{12}), 7.57 - 7.50 (m, 1H, H_{10}), 7.17 - 7.08
210 (m, 2H, H_{11} , H_9), 7.06 - 7.00 (m, 4H, H_3 , H_7), 6.83 - 6.77 (m, 4H, H_4 , H_6), 5.67 - 5.51
211 (m, 3H, H_1 , H_{15}), 3.99 - 3.88 (m, 4H, H_{13}), 2.51 - 2.48 (m, 4H, H_{14}). ^{13}C NMR (100 MHz,
212 CDCl_3) δ (ppm) : 164.1 (C_8), 157.8 (C_5), 149.4 (C_{12}), 136.1 (C_{10}), 135.0 (C_2), 130.3 (C_3 ,
213 C_7), 128.2 (C_{15}), 123.7 - 121.4 (C_9 , C_{11}), 114.6 (C_4 , C_6), 67.3 (C_{13}), 57.6 (C_1), 29.7 (C_{14}).
214 IR ν (cm^{-1}) : 2927 - 2855 ($\nu_{\text{Csp}3\text{-H}}$), 1680 ($\nu_{\text{C=C}}$), 1608 - 1509 - 1469 ($\nu_{\text{C=C ar.}}$), 1245 ($\nu_{\text{N}^+ \text{-O}^-}$),
215 1026 ($\nu_{\text{C-O-C}}$), 1131 ($\nu_{\text{C-N}}$), 968 ($\delta_{\text{C-H}}$), 823 ($\delta_{\text{Csp}2\text{-H para}}$).

216

217 *2.9. Synthesis of 2-(4,13-dioxa-2.9. 1,3(1,4)-dibenzenacyclotridecaphan-8-en-2-* 218 *yl)pyridine 1-oxide 12*

219

220 Method 1

221 To a solution of 2-(4,13-dioxa-1,3(1,4)-dibenzenacyclotridecaphan-8-en-2-yl) pyridine
222 **8a** (0.20 mmol, 1 equiv, 77 mg) in anhydrous DCM (2 mL), was added m-CPBA (0.22
223 mmol, 1.1 equiv, 53 mg) under argon. The reaction mixture was stirred during 48 h at
224 room temperature and controlled by TLC. After reaction completion, the mixture was
225 neutralized with a solution of KOH (40%) until pH = 7 - 8, washed with water and then
226 extracted with DCM. The organic phase was dried under anhydrous MgSO₄, filtered
227 and concentrated under vacuum. The crude residue was purified by FCC on silica gel
228 (DCM/MeOH.NH₃ (7N) : (99/1) ; (98/2) ; (96/4) ; (95/5) and then (93/7) to afford the
229 desired product **12** as a brown oil in 36% yield (36 mg).

230 Method 2

231 To a solution of 2-(bis(4-(but-3-en-1-yloxy)phenyl)methyl) pyridine 1-oxide **10a** (0.37
232 mmol, 1 equiv, 160 mg) in anhydrous DCM (16 mL) was added Grubbs II catalyst
233 (0.037, 0.1 equiv, 32.5 mg) under argon. The reaction mixture was stirred during 24 h
234 at 60 °C and controlled by TLC. After reaction completion, the mixture was cooled to
235 room temperature and then concentrated under vacuum. The crude residue was
236 purified by FCC on silica gel (DCM/MeOH.NH₃ (7N): 98/2; 95/5) to afford the desired
237 product **12** as a brown oil in 91% yield (135 mg, R_f = 0.30 Cyhex/EtOAc : 6/4). TLC:
238 Cyhex/EtOAc : 60/40, R_f = 0.3

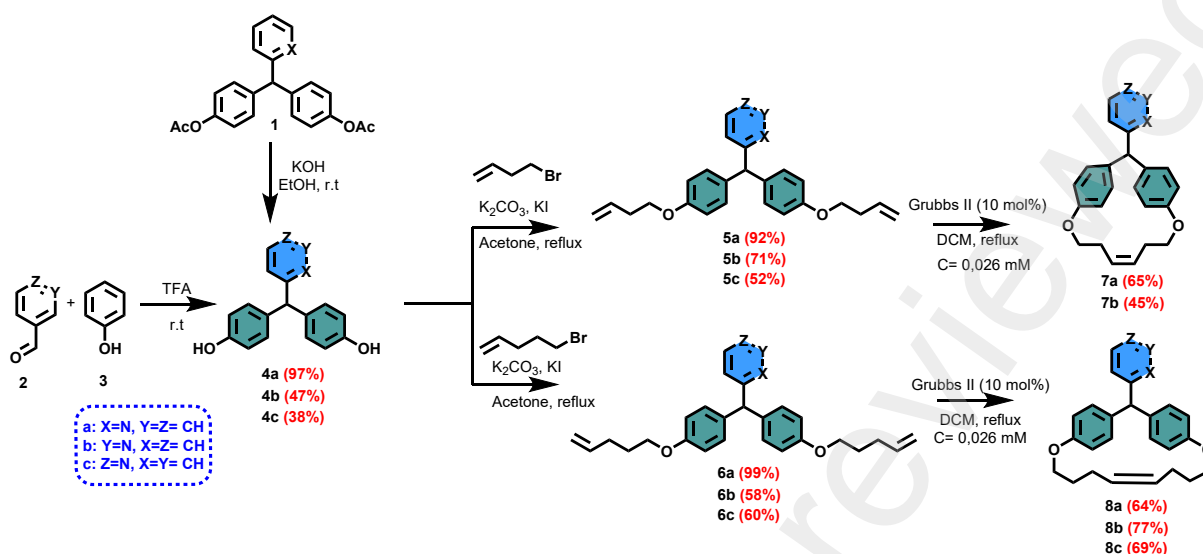
239 ¹H NMR (400 MHz, CDCl₃) δ (ppm) : 8.56 - 8.52 (m, 1H, H₁₂), 7.56 - 7.52 (m, 1H, H₁₀),
240 7.14 - 7.09 (m, 2H, H₁₁, H₉), 7.03 - 7.02 (m, 4H, H₃, H₇), 6.80 - 6.78 (m, 4H, H₄, H₆),
241 5.56 - 5.41 (m, 3H, H₁, H₁₆), 3.95 - 3.87 (m, 4H, H₁₃), 2.00 - 1.60 (m, 8H, H₁₅, H₁₄).

242 ¹³C NMR (400 MHz, CDCl₃) δ (ppm) : 164.0 (C₈), 157.9 (C₅), 149.5 (C₁₂), 136.4 (C₁₀),
243 130.2 (C₃, C₇), 130.1 (C₁₆), 130.0 (C₂), 123.6 - 121.3 (C₉, C₁₁), 114.4 (C₄, C₆), 67.1
244 (C₁₃), 58.0 (C₁), 30.9 (C₁₄, C₁₅). IR ν (cm⁻¹) : 3061 (ν_{Csp2-H}), 2926 - 2852 (ν_{Csp3-H}), 1609,
245 1585, 1508 - 1447 (ν_{C=C ar.}), 1242 (ν_{N⁺-O⁻}), 1035 (ν_{C-O-C}), 1112 (ν_{C-N}), 969 (δ_{C-H}), 850
246 (δ_{Csp2-H para}).

247 **3. Results and Discussion**

248 New pyridyl macrocyclic triarylmethanes were synthesized from the corresponding
249 alkene functionalized triarylmethanes using ring closing metathesis. The alkyl
250 functionalized triarylmethanes were previously prepared by alkylation from the
251 corresponding 4,4'-(pyridin-X-ylmethylene)diphenol (X=2-4)[47]. The macrocyclization
252 was carried out using the second-generation Grubbs catalyst (Grubbs II). General

253 synthetic strategy to obtain the target compounds is outlined in Scheme 2. Details
 254 about the synthetic protocol and chemical characterization of all intermediates are
 255 given in the Supplementary information (SI-1).



256

257 **Scheme 2.** Synthesis strategy for the preparation of macrocyclic triarylmethanes

258 Two procedures were considered to synthesize the diphenylpyridylmethanes **4**.
 259 Compound **4a** was prepared by saponification of commercially available bisacodyl **1**,
 260 and obtained in 97% yield [44]. Nonetheless, compounds **4b** and **4c** were synthesized
 261 by Friedel-Crafts hydroxyalkylation between phenol and the corresponding
 262 commercially available pyridinecarboxaldehydes under acid catalysis (TFA, H₂SO₄) at
 263 room temperature. Our first attempts with concentrated sulfuric acid as acid led to the
 264 compounds **4b** and **4c** in low yields (less than 15%). This result is probably due to the
 265 fastidious treatment protocol conducting to the formation of emulsions and salts difficult
 266 to remove. Consequently, in order to improve the yields and make the workup easier,
 267 we carried out a Friedel-Crafts hydroalkylation under TFA catalysis. In general, the
 268 reaction was straightforward, avoiding the use of organic solvents and other costly
 269 acidic systems. The *p,p*-regioisomers **4b** and **4c** were obtained with 47% and 62%
 270 yields respectively. The formation of *o,p*-regioisomers was observed and, when
 271 possible, they were isolated and characterized. It should be noticed that the separation
 272 of regioisomers was only possible by recrystallization in ethyl acetate. NMR analysis
 273 confirmed these results showing that the *p,p*-regioisomers presented a more shielded
 274 proton compared to the proton belonging to the *o,p* isomer regioisomers (Figure 3).

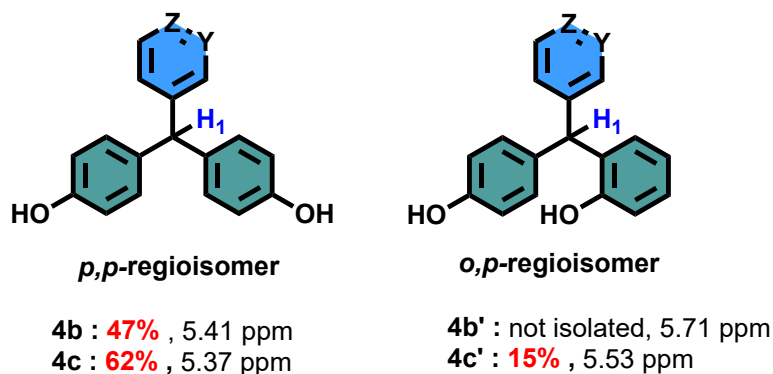


Figure 3. ^1H NMR chemical shifts of H_1 of *p,p*- regioisomers (**4b** and **4c**) and *o, p* regioisomers (**4b'** and **4c'**)

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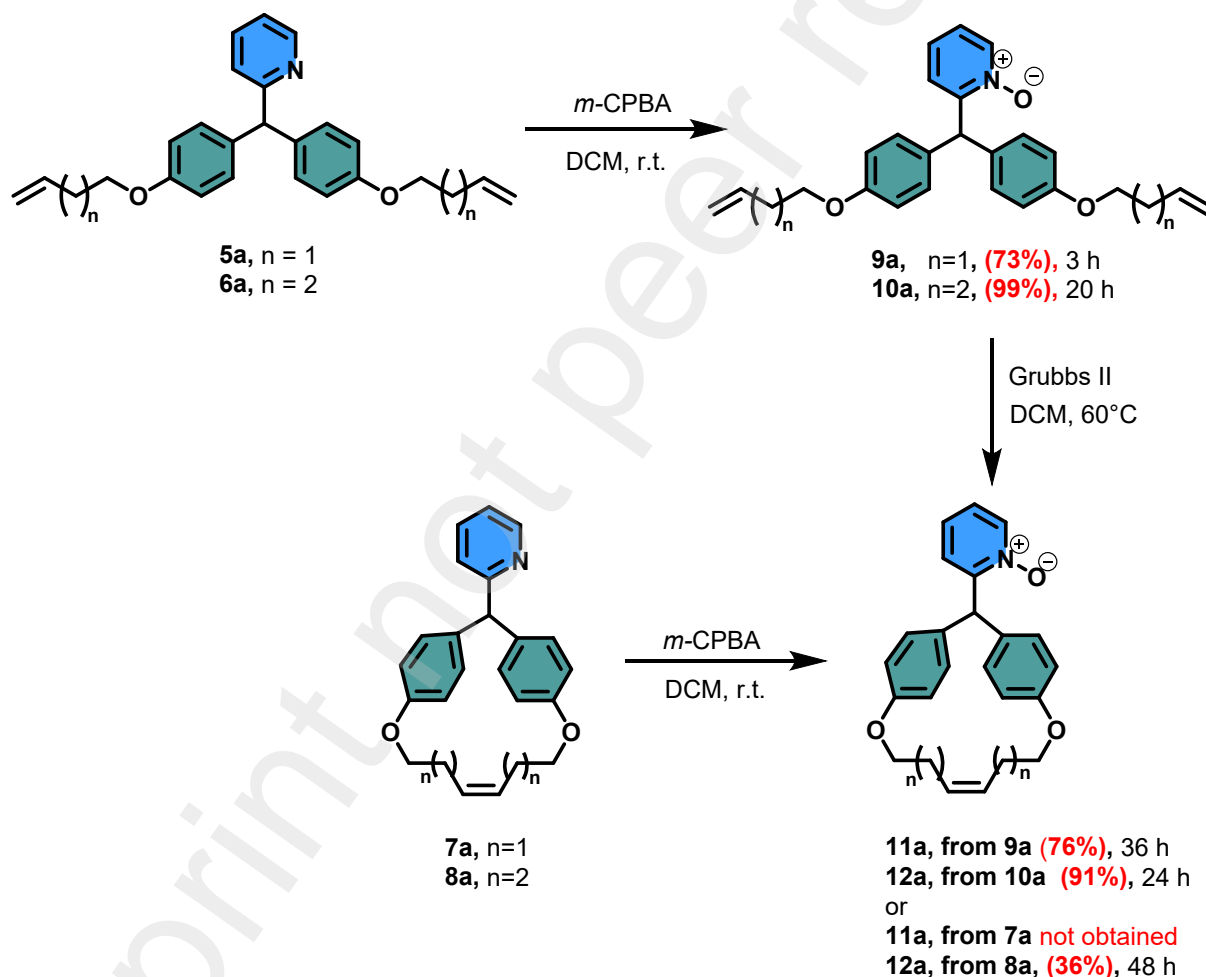
278 Alkylated diphenylpyridylmethanes **5** and **6** were obtained by treating the
 279 corresponding diphenylpyridylmethanes **4** with 4-bromo-1-butene and 5-bromo-1-
 280 pentene in the presence of K_2CO_3 and KI in acetone at 60°C [48]. After workup and
 281 purification the corresponding expected products **5a-c** and **6a-c** were isolated in yields
 282 between 52% and 99% yields respectively (Scheme 2).

283 The key step to access macrocyclic triarylmethanes involved the ring closing
 284 metathesis. RCM was performed on symmetrically alkylated diphenylpyridylmethanes
 285 **5** and **6** in the presence of Grubbs II catalyst in dichloromethane at reflux. In the
 286 literature have been described the deactivation of the ruthenium-based catalyst in the
 287 presence of a substrate containing a free amine or pyridine in metathesis reaction [24,
 288 [31] 38]. The deactivation involves the coordination of the nitrogen to the ruthenium
 289 center of catalyst. To circumvent this problem, amino substrates have been
 290 transformed into carbamates, amides, sulfonamides or imidazolium or pyridinium salts
 291 in order to decrease the nucleophilic ability or the Lewis basicity of the amine
 292 function[37].[38][24].[42]. Alternatively, increasing the steric hindrance of the amine has
 293 also been considered [49].

294 We decided to perform the metathesis reaction of pyridyl intermediates **5a-c** and **6a-c**.
 295 The expected macrocyclic compounds **7** and **8** were obtained with yields between 45%
 296 and 77% except when the substrate **5c** was used. In this case, no conversion was
 297 observed and compound **5c** was entirely recovered after 48 h of reaction. The best
 298 results were obtained for macrocyclic triarylmethanes **8a-c** isolated in 64%, 77% and
 299 69% yields respectively.

300 These results suggested that the pyridyl substrates **5** and **6** do not poison the
 301 ruthenium catalyst by coordination to the metal center as previously described in some
 302 cases from the literature [24]. We can also suggest that the pyridyltriarylmethane

303 scaffold could induce steric constraints that prevent the deactivation of the catalyst
 304 Grubbs II, facilitating the metathesis reaction as describe also in literature [28,50].
 305 We were also interested in preparing macrocyclic triarylmethanes containing pyridine
 306 *N*-oxides moieties. In recent years, pyridine-based *N*-oxides have appeared as very
 307 versatile compounds. They have been used as Lewis's base catalysts as well as
 308 ligands for metal complexes. It has been also described as an attractive group to
 309 increase the metabolic stability and bioavailability of bioactive molecules [45,51,52].
 310 In the preparation of pyridyl macrocyclic triarylmethanes *N*-oxides, two synthetic
 311 strategies have been considered. The first one concerned the oxidation of the pyridyl
 312 macrocycles triarylmethane at the end of the synthesis. The second one concerned
 313 the ring closing metathesis of the corresponding alkylated diphenylpyridylmethanes *N*-
 314 oxides previously prepared from the compounds **5** and **6**. (Scheme 3)



315
 316 **Scheme 3.** Synthesis of pyridyl macrocyclic triarylmethanes *N*-oxides by ring closing
 317 metathesis proceeding

318 Macroyclic triarylmethanes **7** and **8** were oxidized using *m*-CPBA in dichloromethane.
 319 After 48 h of the reaction at room temperature only the pyridyl macrocyclic
 320 triarylmethane *N*-oxide **12a** was isolated in 36% yield. Unfortunately, the *N*-oxidation

321 of compound **7a** never occurred. Considering the unsatisfying results obtained in the
322 *N*-oxidation step of the first strategy, we performed the preparation of the alkylated
323 triarylmethane *N*-oxide **9a** and **10a** with 1.2 ring of *m*-CPBA in dichloromethane at room
324 temperature. The expected products **9a** and **10a** were obtained in 73% and 99% yields,
325 respectively. Ring closing metathesis of *N*-oxide triarylmethanes **9a** and **10a** was
326 carried out in the conditions previously used with 10% of Grubbs II catalyst in
327 dichloromethane at 60 °C. The expected *N*-oxide macrocyclic triarylmethanes **11a** and
328 **12a** were afforded after purification by flash column chromatography on silica gel in
329 76% and 91% yields respectively.

330 RCM reaction carried out on the *N*-oxidized alkylated diphenylpyridylmethanes **9a** and
331 **10a** led to better yields than metathesis performed on the non-*N*-oxidized alkylated
332 diphenylpyridylmethanes **5a** and **6a** (76% and 91% vs 65% and 64%). These results
333 confirmed that the metathesis reaction is more efficient when it is carried out on a
334 substrate containing quaternary nitrogen endorses that the protected nitrogen atom
335 prevents poisoning of catalyst and is therefore advantageous for the metathesis
336 reaction.

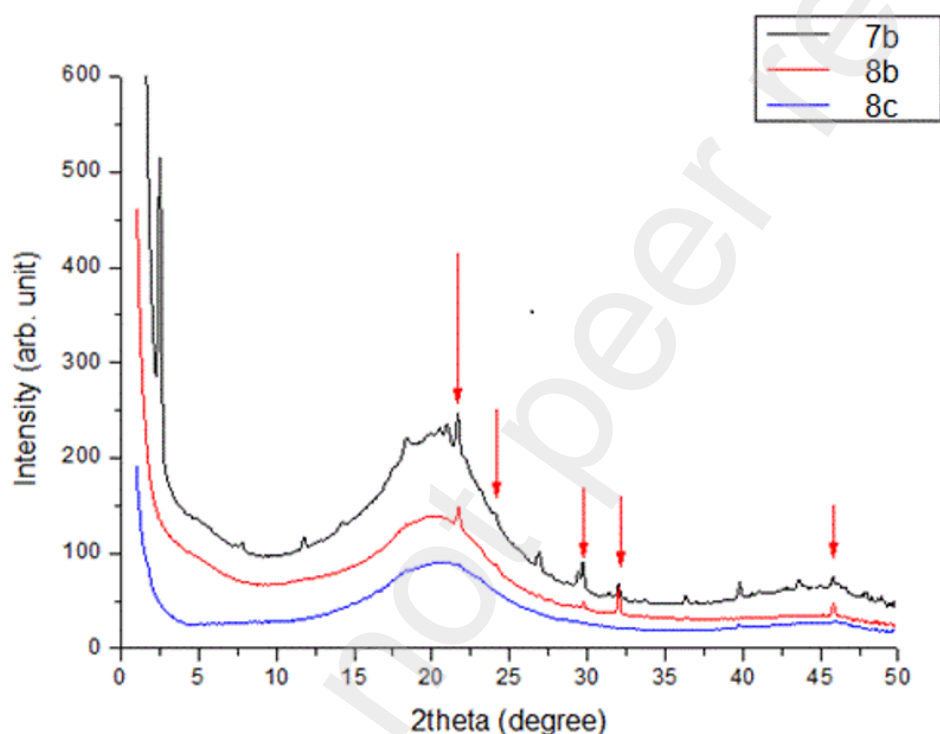
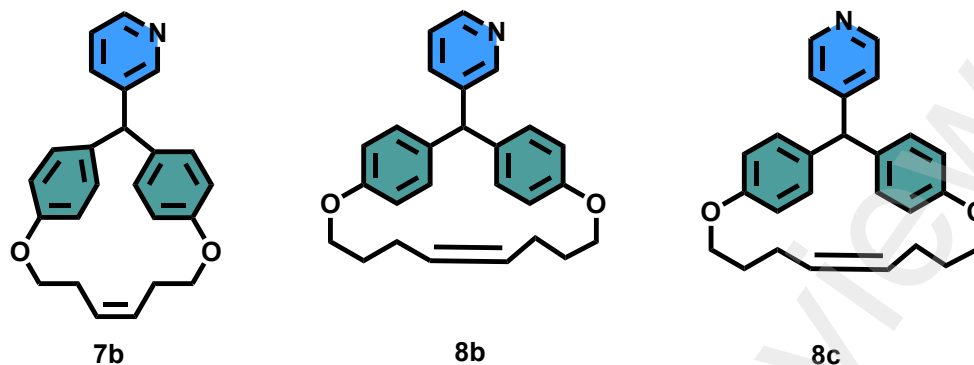
337

338 **4. X-Ray diffraction analysis**

339 As complementary study, to determine the presence of a possible crystalline phase
340 within the samples, and to be able to compare them from a structural point of view, X-
341 Ray diffraction analysis (XRD) of the macrocycles **7b**, **8b**, **8c** was performed. The
342 measured intensity is the result of the average of 8 measurements, in two different
343 experimental configurations to access large diffraction angles, up to 50° (2theta). The
344 obtained results are gathered in the Figure 3, where the XRD patterns displayed a
345 broad peak around 2theta = 20° for all three samples, indicating their amorphous
346 nature.

347 A first analysis seems to indicate that compound **8c** is totally disordered (no crystal
348 structure is present). On the other hand, we observe the existence of a few narrow
349 peaks that overlap the scattered intensity for macrocycles **7b** and **8b**. These peaks
350 indicate the existence of at least two crystalline structures in the amorphous matrix.
351 The position of the three most visible peaks of the structure of compound **8b**, also
352 present for **7a** sample, located at the large angles, corresponds to an elementary mesh
353 of small dimension of $(8.3 \pm 0.3) \text{ \AA}$, probably formed by small molecules and/or
354 molecular stacking. On the other hand, for compound **7b**, the first peak appears at the

355 small angles, around 2.5° , which corresponds to a distance about 35 Angstrom
356 characteristic of the crystal structure of the order of magnitude of the size of the
357 elementary macromolecule.



359
360

361 **Figure 4.** X-ray diffraction analysis of compounds **7b**, **8b**, **8c**

362

363 5. Conclusion

364 To our knowledge, we describe in this work, for the first time, the use of RCM to reliably
365 prepare pyridyl macrocyclic triarylmethanes. Eight novel macrocycles have been
366 efficiently synthesized including three compounds containing pyridine *N*-oxide moiety
367 with good yields. The introduction of a pyridine *N*-oxide moiety before the
368 macrocyclization step led to a higher yield of the corresponding metathesis product.

369 This synthetic strategy offers an efficient alternative to prepare macrocyclic
370 triarylmethanes of different sizes.

371

372 **Declaration of Competing Interest**

373

374 There are no conflicts to declare.

375

376 **CRedit authorship contribution statement**

377 **A. H. Mohamed:** Methodology, Data analysis, Writing-original draft, Editing. **C.**

378 **Coutant:** Methodology, Data analysis. **M. Masaddek:** Data analysis, Review

379 Supervision, Resources. **M.Sylla-Iyarreta Veitia:** Writing-original draft, Data analysis,

380 Review & Editing, Supervision, Resources, Project administration.

381

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389

390 **Supplementary materials**

391

392 Supplementary material associated with this article can be found, in the online version.

393

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