Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Fluorine Chemistry 126 (2005) 1002–1008
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Polyhalogenated heterocyclic compounds Part 52. [1] Macrocycles from 3,5-dichloro-2,4,6-trifluoropyridine

Richard D. Chambers [a,*], Ali Khalil [a], Christopher B. Murray [a], Graham Sandford [a,1], Andrei S. Batsanov [b], Judith A.K. Howard [b]

[a] *Department of Chemistry, University of Durham, South Road, Durham DH13LE, UK*
[b] *Chemical Crystallography Group, Department of Chemistry, University of Durham, South Road, Durham DH13LE, UK*

Received 30 November 2004; accepted 24 January 2005
Available online 9 March 2005

Dedicated to Professor Herbert W. Roesky on the occasion of his 70th birthday.

Abstract

Model studies show that displacement of fluorine, rather than chlorine, occurs upon reaction of 3,5-dichloro-2,4,6-trifluoropyridine with sodium methoxide and phenoxide. Subsequent hydro-dechlorination can be achieved by reaction with lithium aluminium hydride whereas reaction of sodium in *iso*-propanol leads to formation of the tri-*iso*-propoxy pyridine derivative, via nucleophilic substitution of the methoxy group, rather than the dechlorinated products. Macrocycles can be synthesised by reactions of appropriate difunctional oxygen nucleophiles with 3,5-dichloro-2,4,6-trifluoropyridine, one of which was characterised by X-ray crystallography.

Keywords: Heterocycle; Macrocycle; Perfluoroheterocycle; Nucleophilic aromatic substitution; Pyridine; X-ray structure

1. Introduction

Nucleophilic displacement of fluorine in highly fluorinated pyridine and related heteroaromatic systems occurs very readily because the heterocyclic ring is activated strongly both by the presence of the nitrogen heteroatom and by the activating influence of the fluorine substituents themselves [2–4] (Scheme 1). The orientating influence of the fluorine atom substituents for nucleophilic substitution processes has also been well established [2–4].

Recently, pentafluoropyridine **1** and related derivatives have been used as substrates for the construction of various macrocycles [1,5,6] by exploiting this reactivity in reactions involving appropriate difunctional nucleophiles, as illustrated in Scheme 2.

3,5-Dichloro-2,4,6-trifluoropyridine **2** is directly available [7] from pentachloropyridine **3** and, in principle, a variety of non-halogenated macrocyclic systems **4** could be obtained from **2**, by subsequent removal of chlorine from **5**, Scheme 3.

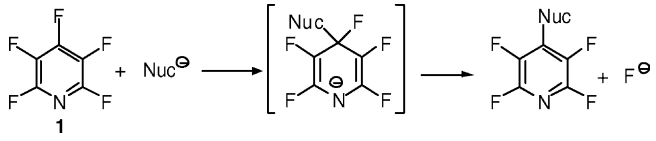
Here, we first describe reactions of appropriate model perhalogenated pyridine compounds to assess the feasibility of this approach and then demonstrate the formation of macrocycles corresponding to type **5**.

2. Results and discussion

The results of reactions of **2** with both sodium methoxide and phenoxide are collated in Table 1 and it is clear that reactions of **2** with these nucleophiles are much less selective than analogous reactions involving pentafluoropyridine **1** which gives only a single mono-substituted product arising from highly selective attack at the 4-position [2,8].

* Corresponding author. Tel.: +44 191 3342039; fax: +44 191 3844737.
E-mail addresses: r.d.chambers@durham.ac.uk (R.D. Chambers), graham.sandford@durham.ac.uk (G. Sandford).
[1] Co-corresponding author. Tel.: +44 191 334 2020; fax: +44 191 384 4737.

0022-1139/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2005.01.018



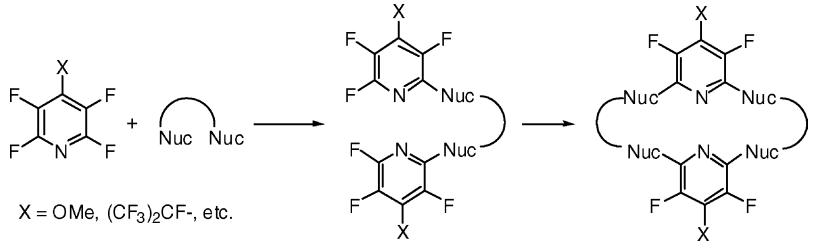
Scheme 1.

In **2**, the 4-position is obviously more sterically hindered towards nucleophilic attack by the presence of the adjacent chlorine atoms. Consequently, mixtures of both derivatives **6** and **7** arising from attack at both 4- and 2-positions respectively are present in the monosubstituted products and disubstituted products **8** are formed from further nucleophilic attack at either of the remaining 2- and 4-carbon fluorine sites, respectively. It is worth emphasising that some disubstitution products **8** are obtained even when a deficiency (0.6 equiv.) of nucleophile is used and this is at first sight puzzling. However, this is a further manifestation of the fact that attack at the 4-position is inhibited by steric effects and it is probable that most of **8a** and **8b** arise from further attack at the 2-position in compound **6a** and **6b**, respectively, in competition for the nucleophile with attack at the crowded 4-position in **2**. However, reaction of **2** with a large excess of methoxide gave trisubstituted compound **9** in high yield and this provided a useful model compound for studies concerning reductive displacement of chlorine.

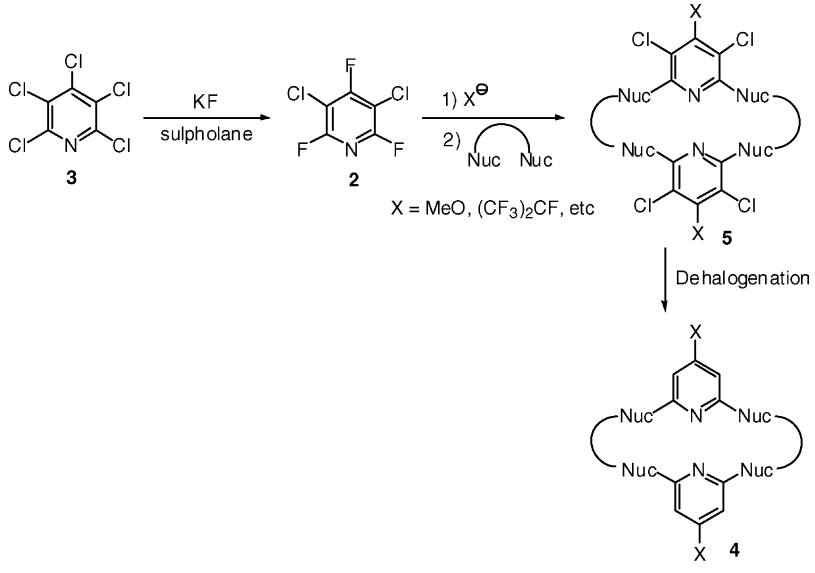
Use of sodium in *iso*-propanol is a well-established process for the dechlorination of saturated chlorocarbons but, with **9** as the substrate, no significant dechlorination was detected and, to our surprise, **9** had been converted to the corresponding tri-*iso*-propyl derivative **10** (Scheme 4). This clearly demonstrates that introduction of methoxy and other alkoxy groups into heterocyclic ring systems can be reversible in appropriate circumstances.

In contrast, reduction of **9** with lithium aluminium hydride occurred to give a mixture of **11** and **12**. Although we have not optimised this reductive dechlorination reaction, the results are sufficient to demonstrate the feasibility of the approach that we outlined in Scheme 2.

Subsequently, we carried out a series of reactions of **6a** with the difunctional oxygen nucleophiles generated from the corresponding silyl derivatives **13**, shown in Table 2, by reaction with cesium fluoride in monoglyme following methodology similar to that we reported previously [6]. The two-step process is illustrated in Table 2 and the macrocycles **15** shown were purified from the corresponding bridged precursors **14** by a combination of column chromatography and recrystallisation.

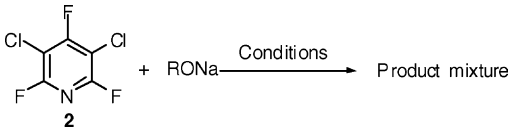


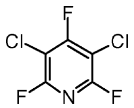
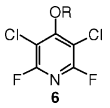
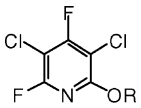
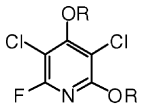
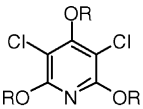
Scheme 2.

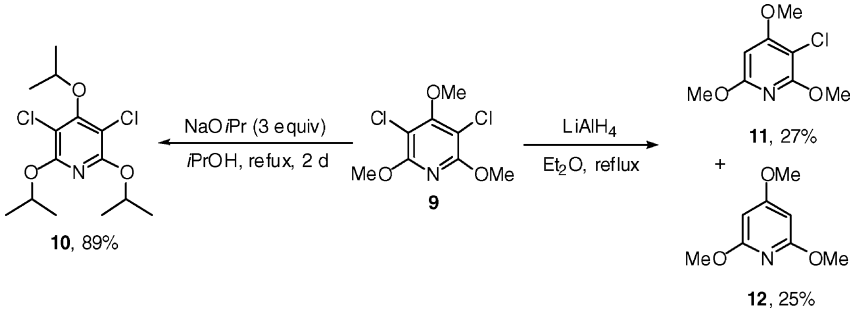


Scheme 3.

Table 1
Reactions of **2** with sodium methoxide phenoxide



Rona	Conditions	Product mixture composition (%)				
		 **2**	 **6**	 **7** **a**, R = Me **b**, R = Ph	 **8**	 **9**
MeONa	0.6 equiv. MeOH	27	**6a**, 59	**7a**, 9	**8a**, 4	–
MeONa	2 equiv. MeOH	2	**6a**, 61	**7a**, 7	**8a**, 29	–
MeONa	20 equiv. MeOH	–	–	–	–	**9**, 99
PhONa	0.6 equiv. THF	44	**6b**, 44	–	**8b**, 12	–
PhONa	2 equiv. THF	–	**6b**, 37	–	**8b**, 63	–



Scheme 4.

Characterisation of macrocycles **15** was largely carried out by NMR. but a full single-crystal X-ray analysis was performed on **15c** to reveal a 32-membered ring (Fig. 1) formed from two units each of **13c** and **14c**. The molecule has crystallographic C_4 symmetry where the dihedral angles between adjacent pyridine and benzene rings alternate between 30.0° and 84.4°, resulting in a tightly folded molecular conformation.

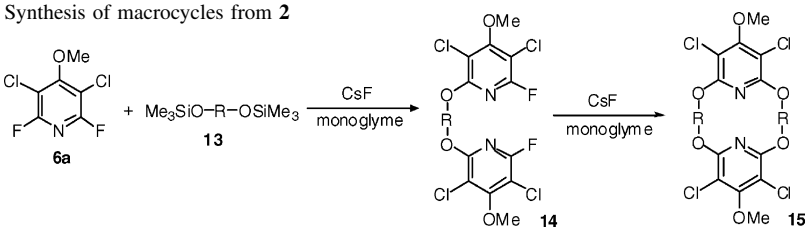
At this point, however, we have been unable to apply the reduction process efficiently, largely due to the low order of solubility of the macrocycles **15**.

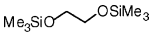
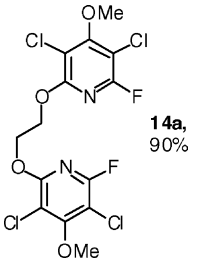
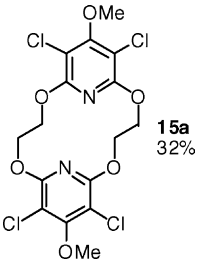
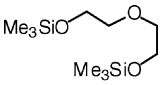
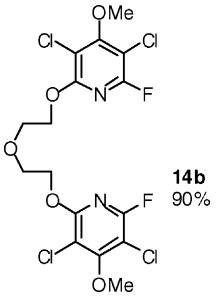
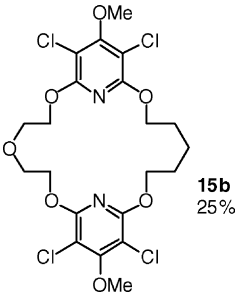
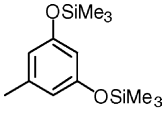
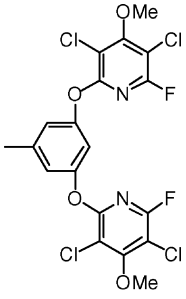
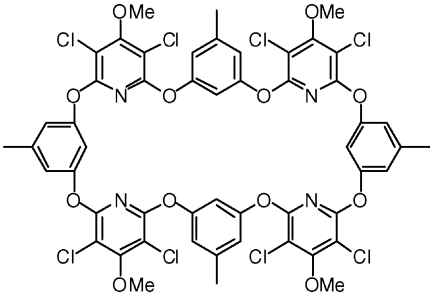
3. Experimental

All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem) All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer operating at 400 MHz (^{1}H NMR), 376 MHz (^{19}F NMR) and 100 MHz (^{13}C NMR) with tetramethylsilane and trichlorofluoromethane as internal standards. Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25 m HP1 (methylsilicone) column. Elemental analyses were obtained on a Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. The progress of reactions was monitored by either 19F NMR or gas-chromatography on an Shimadzu GC8A system using an SE30 column. Distillation was performed using a Fischer Spaltrohr MS220 microdistillation apparatus. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040–0.063 mm) and TLC analysis was performed on silica gel TLC plates (Merck).

X-ray diffraction experiment was carried out on a Siemens 3-circle diffractometer with a SMART 1K CCD area detector, using graphite-monochromated Mo Kα radiation ($\bar{\lambda} = 0.71073$ Å) and a Cryostream (Oxford Cryosystems) open-flow N_2 cryostat. The structure was solved by direct methods and refined by full-matrix least squares (non-H atoms refined in anisotropic, all H atoms in isotropic approximation) against F^2 of all reflections, using SHELXTL software (version 6.12, Bruker AXS, Madison, WI, USA, 2001).

Table 2
Synthesis of macrocycles from **2**



13	14	15
 13a	 **14a**, 90%	 **15a** 32%
 **13b**	 **14b** 90%	 **15b** 25%
 **13c**	 **14c**, 90%	 **15c**, 25%

3.1. Model reactions of **2** with oxygen nucleophiles

3.1.1. General procedure

A three-necked flask was charged with sodium alkoxide and the appropriate solvent and heated to reflux temperature with continual stirring. 3,5-Dichloro-2,4,6-trifluoropyridine **2** was added rapidly and the mixture heated to reflux for 18 h. The reaction mixture was poured into an equal volume of water, extracted with dichloromethane and dried ($MgSO_4$). The solvent was evaporated to afford the crude product, which could be purified by column chromatography if required.

3.1.2. Reaction with sodium methoxide

3.1.2.1. 0.6 equivalents. Compound **2** (2.0 g, 9.9 mmol) and sodium methoxide (0.32 g, 5.9 mmol) in methanol (30 ml) gave the crude product as a straw-coloured oil (0.77 g). Characterisation by GC/MS and ^{19}F NMR showed **2**, **6a**, *3,5-dichloro-2-methoxy-4,6-difluoropyridine* **7a** [δ_F −72.7 (1F, d, F-6), −98.6 (1 F, d, F-4)] and **8a** in the ratio 27:59:9:4 by ^{19}F NMR. Spectral and physical data of products below.

3.1.2.2. 2 equivalents. Compound **2** (2.0 g, 9.9 mmol) and sodium methoxide (1.06 g, 19.8 mmol) in methanol (30 ml) gave the crude product as a pale yellow oil (2.27 g). Analysis

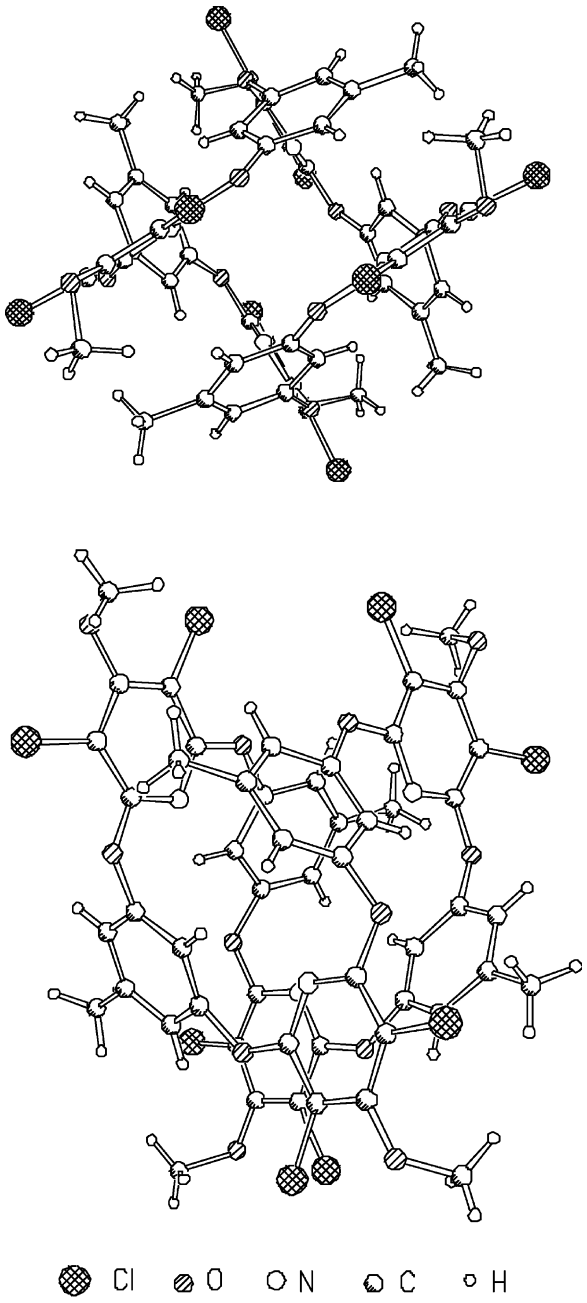


Fig. 1. X-ray crystal structure of **15c**; (above) viewed down the four-fold axis, (below) side view (four-fold axis vertical).

by GC/MS and ^{19}F NMR revealed **2**, **6a**, **7a** and **8a** in the ratio 2:61:7:29 by ^{19}F NMR. Column chromatography of the crude product on silica gel (25 g) using hexane-10% DCM as eluant gave *3,5-dichloro-4-methoxy-2,6-difluoropyridine* **6a** (0.70 g, 33%) as a very pale yellow liquid; b.p. 217–219 °C (Siwoloboff) (lit., [8] 213–214 °C); R_F 0.22. (Found: C, 33.6; H, 1.4; N, 6.7. $C_6H_3Cl_2F_2NO$ requires C, 33.7; H, 1.4; N, 6.5%); δ_H 4.13 (m, OCH_3); δ_F −71.5 (s, F-2); δ_C 61.7 (s, OMe), 108.2 (dd, $^2J_{CF}$ 24.04, $^4J_{CF}$ 16.39, C-3), 155.4 (dd, $^1J_{CF}$ 244.49, $^3J_{CF}$ 17.60, C-2), 164.8 (t, $^3J_{CF}$ 4.6, C-4); *m/z* (EI^+) 213 (M^+, 100%), 215 (M^++2, 69.70%), 217 (M^++4, 11.88%), and *3,5-dichloro-2,4-dimethoxy-6-fluoropyridine* **8a** (0.27 g, 12.1%) as pale straw coloured needles; mp 66.9–67.1 °C (from dichloromethane) (lit., [8] 65–67 °C); R_F 0.18. (Found: C, 37.2; H, 2.7; N, 6.1. $C_7H_6Cl_2FNO_2$ requires: C, 37.2; H, 2.7; N, 6.2%); δ_H 3.96 (3H, s, CH_3), 4.02 (3H, s, CH_3); δ_F −74.1 (s); δ_C {H} 55.2 (s, 4-OMe), 61.2 (s, 2-OMe), 102.9 (d, $^2J_{CF}$ 34.70, C-5), 108.4 (d, $^4J_{CF}$ 8.05, C-3), 156.2 (d, $^1J_{CF}$ 238.05, C-6), 157.2 (d, $^3J_{CF}$ 15.99, C-2), 163.4 (d, $^3J_{CF}$ 4.63, C-4); *m/z* (EI^+) 225 (M^+, 100%), 227 (M^++2, 64.06%), 229 (M^++4, 10.94%).

3.1.2.3. 20 equivalents. A mixture consisting of **2** (11.3 g, 0.05 mol) and sodium methoxide (5.4 g, 0.1 mol) in methanol (50 ml) was heated under reflux with continual stirring. After 48 h, the resulting material was poured into cold water and the white solid was precipitated which was extracted into methylene dichloride. The organic layer was separated, dried ($MgSO_4$), and evaporated to give a crude product which was shown by gc/ms to consist of one component. Recrystallisation from light petroleum gave *3,5-dichloro-2,4,6-trimethoxypyridine* **9** (11.7 g, 99%) as white crystals; m.p. 99–100 °C (lit., [9] 97.8–98 °C). (Found: C, 40.4; H, 3.8; N, 5.8. $C_8H_9Cl_2NO_3$ requires C, 40.3; H, 3.8; N, 5.88%); δ_H 3.93 (3H, s, CH_3), 3.95 (6H, s, CH_3); δ_C 54.32 (s, CH_3), 60.7 (s, CH_3), 103.0 (s, C-3), 156.5 (s, C-2), 161.8 (s, C-4); *m/z* (EI^+) 240 (10%, M^+), 239 (62%, M^+), 238 (41, M^+), 237 (100, M^+), 208 (59), 194 (28), 144 (24), 87 (27).

3.1.3. Reaction with sodium phenoxide

3.1.3.1. 0.6 equivalents. Sodium (0.13 g, 5.6 mmol), phenol (0.70 g, 7.4 mmol), **2** (2.0 g, 9.9 mmol) in THF (50 ml) gave the crude product as an extremely viscous bright yellow oil (1.455 g). Analysis of the crude product revealed **2**, **6b** and **8b** in the ratio 44:44:12 by ^{19}F NMR. Spectral and physical data of products below.

3.1.3.2. 2 equivalents. Sodium metal (0.39 g, 16.9 mmol), phenol (1.9 g, 20.2 mmol), **2** (2.0 g, 9.9 mmol) in THF (50 ml) gave the crude product as an extremely viscous bright yellow oil (2.94 g). Analysis of the crude product by GC/MS and ^{19}F NMR revealed **6b** and **8b** in the ratio of 1:2 by ^{19}F NMR. Column chromatography on silica gel using hexane-10% DCM as eluant gave *3,5-dichloro-4-phenoxy-2,6-difluoropyridine* **6b** (0.57g, 6%) as translucent white crystals; R_F 0.28. (Found C, 47.7; H, 1.7; N, 5.0. $C_{11}H_5Cl_2F_2NO$ requires C, 47.8; H, 1.8; N, 5.1); δ_H 6.8–7.4 (m, Ar-H); δ_F −70.4 (s); δ_C 109.6 (m, C-3), 115.7 (s, Ar), 124.2 (s, Ar), 130.0 (s, Ar), 155.3 (s, Ar), 155.6 (dd, $^1J_{CF}$ 245.7, $^3J_{CF}$ 17.2, C-2), 160.2 (t, $^3J_{CF}$ 4.6, C-4); *m/z* (EI^+) 275 (M^+, 33%), 277 (M^++2, 17 %), 279 (M^++4, 3%); and, *3,5-dichloro-2,4-diphenoxy-6-fluoropyridine* **8b** (1.81 g, 18%) as a viscous bright yellow oil, which slowly yielded an amorphous white solid on standing (1–2 weeks); mp 65–68 °C; R_F 0.14. (Found C, 58.6; H, 2.8; N, 4.1. $C_{17}H_{10}Cl_2FNO_2$ requires C, 58.3; H, 2.9; N, 4.0); δ_H 6.9–7.5 (m, ArH); δ_F −71.2 (s); δ_C 105.7 (d, $^2J_{CF}$ 35.40, C-5), 110.5 (d, $^4J_{CF}$ 7.64, C-3), 115.5 (s, Ar), 121.3 (s, Ar), 123.7

(s, Ar), 125.8 (s, Ar), 129.7 (s, Ar), 129.9 (s, Ar), 152.5 (s, Ar), 155.6 (s, Ar), 155.9 (d, $^1J_{CF}$ 241.1, C-6), 156.2 (d, $^3J_{CF}$ 15.3, C-2), 158.9 (d, $^3J_{CF}$ 4.6, C-4); *m/z* (EI$^+$) 349 (M^+, 19%), 351 (M^++2, 12%), 353 (M^++4, 2%).

3.2. Reactions of 3,5-dichloro-2,4,6-trimethoxypyridine *9*

3.2.1. 3,5-Dichloro-2,4,6-triisopropoxypyridine *10*

A mixture consisting of **9** (6 g, 0.025 mol) and sodium (4.6 g, 0.2 mole) in isopropanol (50 ml) was heated under reflux with continual stirring. After 6 days, the resulting material was poured into cold water and extracted into methylene dichloride. The organic layer was separated, dried ($MgSO_4$), and evaporated to give crude material (5.7 g) which was shown by gc/ms to consist of three components in the ratio 0.5:1.5:17.5. Column chromatography on silica gel using light petroleum:CH_2Cl_2 (8:2) as eluent, gave *3,5-dichloro-2,4,6-tri-isopropoxypyridine* **10** (5.1 g, 89%) as a colourless liquid; b.p. 259–260 °C, Rf 0.52. (Found C, 52.5; H, 6.7; N, 4.5 $C_{14}H_{21}Cl_2NO_3$ requires: C, 52.2; H, 6.5; N, 4.3%); δ_H 1.3 (6H, d, $^3J_{HH}$ 6.0, CH_3), 1.3 (12H, d, $^3J_{HH}$ 6.4, CH3, C-8), 4.7 (1H, sept, $^3J_{HH}$ 6.0, CH at C-4), 5.1 (2H, sept, $^3J_{HH}$ 6.0, CH at C-7); δ_C 22.0 (s, CH_3), 22.5 (s, CH_3), 69.9 (s, CH), 77.5 (s, CH), 103.6 (s, C-3), 155.9 (s, C-2), 160.3 (s, C-4); *m/z* (EI+) 323 (10%, M^++2) 321 (15%, M^+), 239 (10), 237 (16), 197 (59), 195 (100), 43 (51).

3.2.2. 3-chloro-2,4,6-trimethoxypyridine *11* and 2,4,6-trimethoxypyridine *12*

To cold (0 °C), stirred solution of **9** (5 g, 24 mmol) in ether was added 0.32 N $LiAlH_4$ in ether (32 gm in 40 ml). On completion of addition the reaction mixture was heated under reflux with continually stirring. After 6 h, cooled (0 °C) and 2N H_2SO_4 acid (10 ml) was added slowly. The resulting material was poured into cold water and extracted into methylene dichloride. The organic layer was separated, dried ($MgSO_4$) and evaporated to give a crude product (2 g) which was shown by gc/ms to consist of two compounds (ratio 1:1). Column chromatography on silica gel using hexane:dichloromethane ratio (8:2) as eluent, gave *3-chloro-2,4,6-trimethoxypyridine* **11** (0.5 g, 27%) as a colourless liquid; b.p. 65–66 °C, Rf 0.28. (Found: C, 47.1; H, 4.9; N, 6.8. $C_8H_{10}ClNO_3$ requires C 47.2; H, 4.9; N, 6.9%); δ_H 3.9 (3H, d, $^5J_{HH}$ 2, C-8), 3.9 (3H, d, $^5J_{HH}$ 2, C-9), 4.0 (3H, d, $^5J_{HH}$ 2, C-7), 5.9 (1H, d, $^5J_{HH}$ 2.8, C-5); δ_C 53.5 (s, C-9), 54.1 (s, C-7), 56.3 (s, C-8), 86.3 (s, C-5), 96.4 (s, C-3), 158.4 (s, C-6), 161.5 (s, C-2), 164.3 (s, C-4); *m/z* (EI$^+$) 205 (28%, M^++3), 204 (36%, M^++2), 203 (89%, M^++1), 202 (100%, M^+), 174 (33), 173 (27), 160 (14), 110 (11), 69 (18), 53 (20); and, *2,4,6-trimethoxypyridine* **12** (0.4 g, 25%) as colourless liquid; b.p. 45–47 (lit., [10] 47–48 °C), Rf 0.18. (Found: C, 53.6; H, 6.1; N, 7.8. $C_8H_{11}NO_3$ requires C, 56.8; H, 6.5; N, 8.2%); δ_H 3.8 (3H, m, C-8), 3.9 (6H, m, C-7), 5.9 (2H, m, C-3); δ_C 53.6 (s, 2-OMe), 55.3 (s, 4-OMe), 87.3 (s, C-3), 164.3 (s, C-2), 170.1 (s, C-4); *m/z* (EI$^+$) 170 (7%, M^++1), 168 (65%, M^+), 169 (100%, M^+-1), 140 (16), 139 (29), 69 (21).

4. Synthesis of bridged oxygen derivatives 14

4.1. General procedure

A mixture consisting of **6a**, bis-silyl derivative **13** and CsF in monoglyme (50 ml) was heated at reflux temperature and stirred for 3 days. The resulting mixture was poured into cold water and extracted with dichloromethane. The organic layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a crude product which was purified by either distillation, recrystallisation or column chromatography on silica gel.

4.2. 6-[2-(3,5-Dichloro-6-fluoro-4-methoxy(2-pyridyloxy))ethoxy]-3,5-dichloro-2-fluoro-4-methoxypyridine *14a*

6a (6.5 g, 30 mmol), **13a** (3 g, 12 mmol) and CsF (3.5 g, 23 mmol) in monoglyme (50 ml), after recrystallisation from *n*-hexane, gave *6-[2-(3,5-dichloro-6-fluoro-4-methoxy(2-pyridyloxy))ethoxy]-3,5-dichloro-2-fluoro-4-methoxypyridine* **14a** (6.0 g, 90%) as a white solid; m.p. 146–148 °C. (Found: C, 37.4; H, 2.2; N, 6.2. $C_{14}H_{10}Cl_4F_2N_2O_4$ requires C, 37.3; H, 2.2; N, 6.2%); δ_H 4.0 (3H, s, OCH3), 4.7 (2H, s, CH2); δ_F −74.0 (s); δ_C 61.2 (s, CH_3), 65.5 (s, CH_2), 103.3 (d, $^2J_{CF}$ 34.2, C-3), 108.7 (d, $^4J_{CF}$ 7.6, C-5), 156.1 (d, $^3J_{CF}$ 15.9, C-4), 155.7 (d, $^1J_{CF}$ 237, C-2), 163.3 (d, $^3J_{CF}$ 4.6, C-6); *m/z* (EI$^+$) 454 (M^+, 1%), 452 (M^+, 3%), 450 (M^+, 5%), 448 (M+, 4%), 242 (11), 240 (65), 239(10), 238 (100).

4.3. 6-{2-[2-(3,5-Dichloro-6-fluoro-4-methoxy(2-pyridyloxy)) ethoxy]ethoxy}-3,5-dichloro-2-fluoro-4-methoxypyridine *14b*

6a (6.5 g, 30 mmol), **13b** (3 g, 12 mmol) and CsF (3.5 g, 23 mmol) in monoglyme (50 ml), after recrystallisation from petroleum ether 40–60, gave *6-{2-[2-(3,5-dichloro-6-fluoro-4-methoxy(2-pyridyloxy))ethoxy]ethoxy}-3,5-dichloro-2-fluoro-4-methoxy pyridine* **14b** (6.6 g, 90%) as white solid; m.p. 98–100 °C. (Found: C, 38.9; H, 2.8; N, 5.7. $C_{16}H_{14}Cl_4F_2N_2O_5$ requires C, 38.9; H, 2.8; N, 5.7%); δ_H 3.9 (2H, m, CH_2OCH_2), 4.0 (3H, s, OCH_3), 4.4 (2H, m, Ar-OCH_2); δ_F −74.1(s); δ_C 61.2 (s, CH_3), 67.4 (s, CH_2OCH_2), 69.2 (s, Ar-OCH_2), 103.0 (d, $^2J_{CF}$ 34.2, C-3), 108.5 (d, $^4J_{CF}$ 8.0, C-5), 155.8 (d, $^1J_{CF}$ 237, C-2), 156.4 (d, $^3J_{CF}$ 15.6, C-4), 163.2 (d, $^3J_{CF}$ 5.0, C-6); *m/z* (EI$^+$) 496 (3%, M^+), 494 (6%, M^+), 492 (4%, M^+), 242 (11), 240(65), 239(11), 238 (100), 213 (18), 212 (13), 211(28).

4.4. 6-[3-(3,5-Dichloro-6-fluoro-4-methoxy(2-pyridyloxy)) 5-methylphenoxy]-3,5-dichloro-2-fluoro-4-methoxypyridine *14c*

6a (5.35 g, 25 mmol), 1-methyl-3,5-bis-trimethylsilanyloxy-benzene **13c** (2.68 g, 10 mmol) and CsF (2.28 g,

15 mmol) in monoglyme (50 ml), after recrystallisation from dichloromethane, gave *6-[3-(3,5-dichloro-6-fluoro-4-methoxy(2-pyridyloxy))5-methylphenoxy]-3,5-dichloro-2-fluoro-4-methoxypyridine* **14c** (5.7 g, 90%) as a straw yellow solid; m.p. 55–56 °C. (Found: C, 44.2; H, 2.3; N, 5.4. $C_{19}H_{12}Cl_4F_2N_2O_4$ requires C, 44.5; H, 2.3; N, 5.4%); δ_H 2.4 (3H, s, Ar-CH_3), 4.1 (6H, s, OCH_3), 6.7 (1H, m, H-2′), 6.8 (2H, m, H-4′); δ_F −74.8 (s); δ_C 21.5 (s, Ar-CH_3), 61.4 (s, OCH_3), 105.2 (d, $^2J_{CF}$ 34.5, C-3), 109.8 (d, $^4J_{CF}$ 7.6, C-5), 111.7 (s, C-2′), 119.0 (s, C-4′), 140.9 (s, C-5′), 153.2 (s, C-1′), 155.5 (d, $^3J_{CF}$ 15.5, C-4), 155.7 (d, $^1J_{CF}$ 239.0 C-2), 163.9 (d, $^3J_{CF}$ 4.5, C-6); *m/z* (EI^+) 516 (M^+, 12%), 515 (M^+, 11), 514 (M^+, 50), 513 (M^+, 24), 512 (M^+, 100), 511 (M^+, 21), 510 (M^+, 78), 302 (3), 301 (10), 299 (13), 265 (20).

5. Synthesis of macrocycles 15

5.1. General procedure

A mixture consisting of the bridged bi-pyridine **14**, bis-silyl derivative **13** and CsF in monoglyme (50 ml) was heated at reflux temperature for 3 days. The resulting mixture was poured into cold water and extracted into dichloromethane. The organic layer was separated, dried ($MgSO_4$), and solvent was removed under reduced pressure to give a crude product which was purified by column chromatography on silica gel.

5.2. 19,20-Diaza-7,9,16,18-tetrachloro-8,17-dimethyl-2,5,11,14-tetraoxatricyclo[13.3.1.1<6,10>]icosa-1(18),6,8,10,(20),15 (19),16-hexane *15a*

14a (4.5 g, 0.01 mol), **13a** (2.28 g, 0.015 mol) and CsF (2.28 g, 0.015 mol) in monoglyme (50 ml), after recrystallisation from light petroleum, gave *19,20-diaza-7,9,16,18-tetrachloro-8,17-dimethyl-2,5,11,14-tetraoxatricyclo[13.3.1.1<6,10>]icosa-1(18),6,8,10,(20), 15(19),16-hexane* **15a** (1.5 g, 32%) as a white solid**;** 204–206 °C, δ_H 3.9 (6H, m, OCH_3), 4.6 (8H, s, CH_2); δ_C 60.8 (s, CH_3), 65.0 (s, C-8), 103.9 (s, C-1), 155.8 (s, C-2), 162.3 (s, C-6); *m/z* (EI^+) 476 (4%, M^++2), 474 (15%, M^++2), 472 (27%, M^+), 470 (21), 264(32), 262(50), 239 (15), 238 (36), 237 (69), 236 (59), 235 (100), 210 (11), 102 (13), 87 (12), 77 (19), 73(22), 70 (19).

5.3. 25,26-Diaza-10,12,22,24-tetrachloro-11,23-dimethoxy-2,5,8,14,17,20-hexaoxatricyclo[19.3.1.1<9,13>]hexacosa-1(24),9,11,13(26),21(25), 22-hexaene *15b*

14b (4.96 g, 0.01 mol), **13b** (3.75 g, 0.015 mole) and CsF (2.28 g, 0.015 mole) in monoglyme (50 cm^3), after recrystallisation from light petroleum ether, gave *25,26-diaza-10,12,22,24-tetrachloro-11,23-dimethoxy-2,5,8,14,17,20-hexaoxatricyclo [19.3.1.1<9,13>]hexacosa-1(24),9,11, 13(26),21(25), 22-hexaene* **15b** (1.4 g, 25%) as a white solid; mp 186–187 °C. (Found: C, 43.1; H, 4.1; N, 4.9. $C_{20}H_{22}Cl_4N_2O_8$ requires C, 42.9; H, 4.9; N, 5.0); δ_H 4.5 (8H, t, $^3J_{HH}$ 5.6, $2CH_2$, C-8), 3.9 (6H, s, OCH_3), 3.8 (4H, t, $^3J_{HH}$ 5.6, $2CH_2$, C-8); δ_C 60.7 (s, CH_3), 65.4 (s, C-9), 69.1 (s, C-8), 103.5 (s, C-1), 155.8 (s, C-2), 162.2 (s, C-6); *m/z* (EI^+) 564 (4%, M^++2), 562 (16%, M^++2), 560 (34%, M^+), 558 (25), 264(10), 262(16), 240 (12), 239 (16), 238 (61), 237 (62), 236 (100), 223 (35), 137 (18), 132(14), 103 (16).

5.4. Macrocycle *15c*

14c (1.03 g, 2 mmol), **13c** (0.81 g, 3 mmol) and CsF (0.45 g, 15 mmol) in monoglyme (500 ml), after recrystallisation from *n*-hexane, gave macrocycle **15c** (0.3 g, 25%) as white crystals; mp 299–300 °C. (Found: C, 52.2; H, 3.1; N, 4.4. $C_{52}H_{36}Cl_8N_4O_{12}$ requires: C, 52.4; H, 3.0; N, 4.6%); δ_H 2.2 (3H, s, CH_3), 4.0 (3H, s, OCH_3), 6.3–6.6 (3H, m, ArH); δ_C 21.1 (s, CH_3), 61.0 (s, OCH_3), 105.3 (s, CCl), 113.2 (s, Ar), 119.7 (s, Ar), 140.1 (s, *C*-CH_3), 153.3 (s, Ar-O), 156.3 (s, C-2), 162.8 (s, C-4); *m/z* (EI^+) 596 (100).

5.4.1. Crystal data

$C_{52}H_{36}Cl_8N_4O_{12}$**15c**[2], $M = 1192.45$, $T = 110$ K, tetragonal, space group $P4_2/n$ (No. 86), $a = 13.470(1)$, $c = 13.986(1)$ Å, $V = 2537.5(7)$ Å^3, $Z = 2$, $D_c = 1.552$ g cm^{-3}, $\mu = 0.51$ mm^{-1}, 27,785 reflections with $2\theta \leq 55^\circ$, 2926 unique, $R_{int} = 0.056$, final $R = 0.040$ [2242 data with $F^2 \geq \sigma(F^2)$], w$R(F^2) = 0.116$ (all data). CCDC 255962.

References

[1] R.D. Chambers, A. Khalil, P. Richmond, G. Sandford, D.S. Yufit, J.A.K. Howard, J. Fluorine Chem. 125 (2004) 715–720.
[2] R.D. Chambers, C.R. Sargent, Adv. Heterocycl. Chem. 28 (1981) 1–71.
[3] G.M. Brooke, J. Fluorine Chem. 86 (1997) 1–76.
[4] R.D. Chambers, Fluorine in Organic Chemistry, Blackwell, Oxford, 2004.
[5] R.D. Chambers, P.R. Hoskin, A. Khalil, P. Richmond, G. Sandford, D.S. Yufit, J.A.K. Howard, J. Fluorine Chem. 116 (2002) 19–22.
[6] R.D. Chambers, P.R. Hoskin, A.R. Kenwright, A. Khalil, P. Richmond, G. Sandford, D.S. Yufit, J.A.K. Howard, Org. Biomol. Chem. 1 (2003) 2137–2147.
[7] R.D. Chambers, J. Hutchinson, W.K. Musgrave, J. Chem. Soc. (1964) 3573–3576.
[8] R.D. Chambers, J. Hutchinson, W.K. Musgrave, J. Chem. Soc. (1964) 5634–5640.
[9] X. Xu, X. Qian, Z. Li, G. Song, J. Fluorine Chem. 88 (1998) 9–14.
[10] C. Kaneko, K. Uchiyama, M. Sato, N. Katagiri, Chem. Pharm. Bull. 9 (1986) 3658–3671.

[2] CCDC 255962 contains the supplementary crystallographic data for this paper. These data can be viewed free of charge via http://www.ccdc.cam.ac.uk/cont/retrieving.html or from the CCDC, 12 Union Road, Cambridge, CB21EZ; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk.