Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXI, No. 4

SYNTHETIC STRATEGIES IN THE PREPARATION OF REGIOSPECIFICALLY CHLORINE-37 LABELED POLYCHLORINATED DIBENZO-P-DIOXINS[1]

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Summary

A series of thirteen regiospecifically chlorine-37 labeled polychlorodibenzo-p-dioxins were synthesized via the Sandmeyer reaction. Nitrochlorodibenzodioxins which were obtained by a base promoted condensation of catechols and dinitropolyhalobenzenes were reduced and converted to the diazonium salts. Chlorine-37 was introduced using cuprous chloride-37. The isotopic enrichment was in the range 75-96%.

Key words: Chlorine-37 labeled polychlorinated dibenzo-p-dioxin

Introduction

Polychlorinated dibenzo-p-dioxins (PCDDs) have been the subject of intense investigation for several years. These research efforts have been spurred by their surprisingly high toxicity[2]. Although the focus has been on the highly toxic 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), the fact that PCDDs are more common in the environment has increased interest in other members of this class of compounds[2c,3]. This interest has lead to the development of analytical and synthetic procedures to study these compounds in the laboratory.

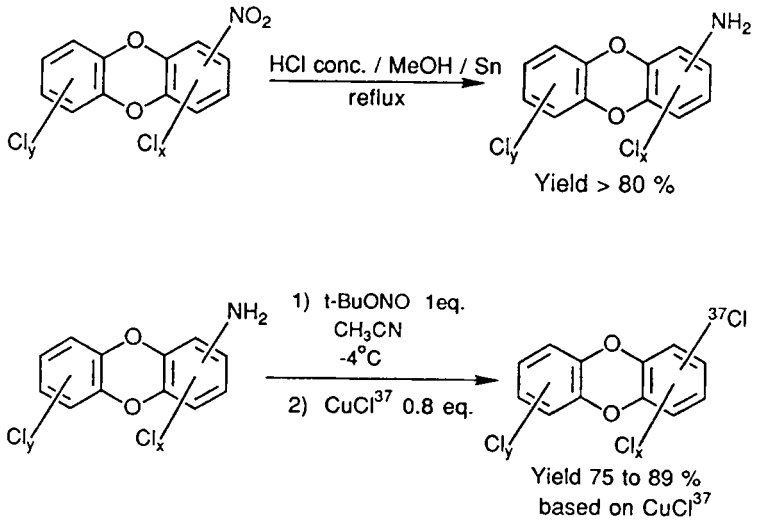
Our research efforts have been mainly directed at an understanding of the mechanism of one electron reduction of PCDDs under electron capture negative chemical ionization mass-spectrometry conditions (ECNI-MS) and the development of analytical procedures for their analyses that are both sensitive and specific with respect to positional isomers. We have shown, for example, that there exists a correlation between the molecular radical anions observed and the LUMO energy for PCDDs and polychlorinated dibenzofurans (PCDBFs) under ECNI-MS

0362–4803/92/040261–27$13.50

Received 26 September, 1991
Revised 16 December, 1991

conditions[4]. A subsequent study also has revealed a linear correlation between the branching ratio, log [(M-Cl)$^-$]/[Cl$^-$], and the calculated energies of the products formed when PCDDs were subjected to ECNI-MS conditions[5]. It was hypothesized that the one electron reductive dehalogenation of the PCDDs and PCDBFs under ECNI-MS conditions should be regioselective[6], and testing this hypothesis requires that one knows from which position the chlorine atom or chloride ion is lost during dissociative electron capture. This requirement led to the synthesis of regiospecific chlorine-37 labeled PCDDs. The methodology employed to obtain these labeled compounds is described below.

The two most common general procedures for preparing PCDDs are self-condensation of salts of ortho-halophenols and condensation of catechols with halonitrobenzene or polyhalobenzenes[7]. However, both processes give a mixture of products due to the Smiles rearrangement[8]. This rearrangement is rendered degenerate if at least one of the reactants is symmetrical[9]. Even though nitro-polychlorodibenzo-p-dioxins (nitro- PCDDs) have received only limited attention, they are key intermediates for the introduction of functional groups via reduction and subsequent diazotization[10-12]. This strategy was adopted for introducing the chlorine-37 label regiospecifically (Scheme 1).



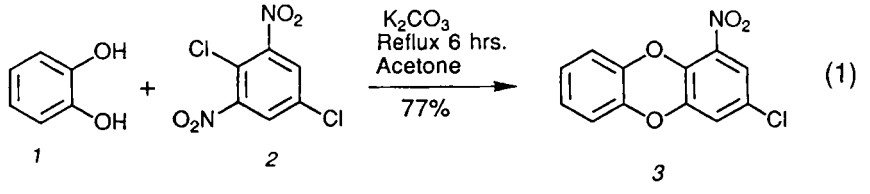
Scheme 1.

RESULTS AND DISCUSSION

The condensation of catechol with halodinitrobenzene was found to be the most convenient method to prepare nitro-PCDDs[10,12-15]. Oliver has shown that these compounds also can be obtained by the nitration of the corresponding PCDDs[15,16]. This latter method, however, lacks the regiospecificity that is essential to the present work; therefore, it was not employed. We also have reported that surface chlorination of nitro-dibenzofuran (nitro-DBF) afforded nitro-PCDBFs in good yield[17]. However, when this approach was extended to nitro-dibenzodioxins no reaction was observed. Thus, the nitro-PCDDs described in this paper were all obtained by the condensation of catechols with dinitropolyhalobenzenes.

Monochloromononitrodibenzo-p-dioxins.

As reported previously[15] the base promoted condensation of catechol (**1**) with 2,4-dichloro-1,3-dinitrobenzene (**2**) in refluxing acetone[13] afforded 3-chloro-1-nitrodibenzo-p-dioxin (**3**) in good yield (eq.1). Using the same method 1-chloro-4-nitrodibenzo-p-dioxin (**5**) and 1-chloro-2-nitrodibenzo-p-dioxin (**6**) were prepared as a mixture (7:3) in one step (eq. 2). 2-Chloro-3-nitrodibenzo-p-dioxin (**8**) was obtained in 80% yield by the condensation of (**1**) with 2,4-dichloro-1,5-dinitrobenzene (**7**) as described by Oliver[15] (eq. 3).



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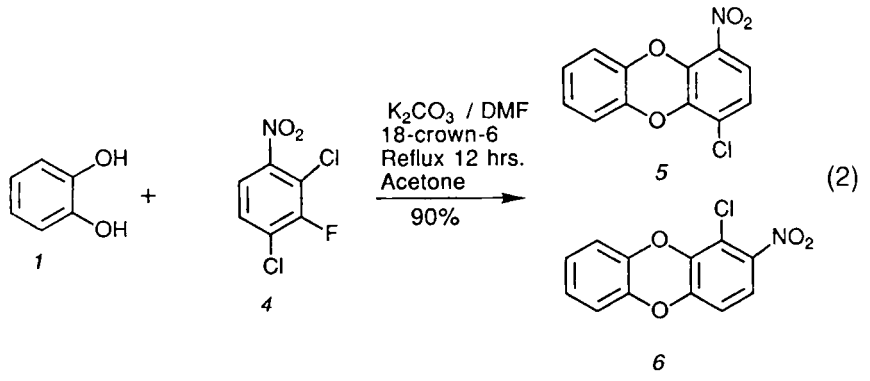

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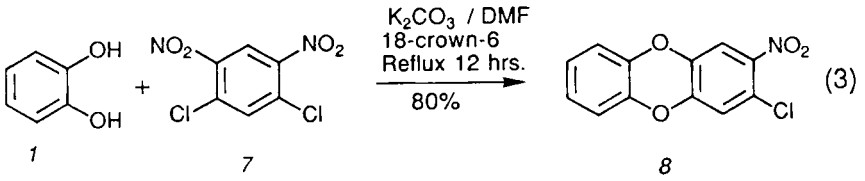
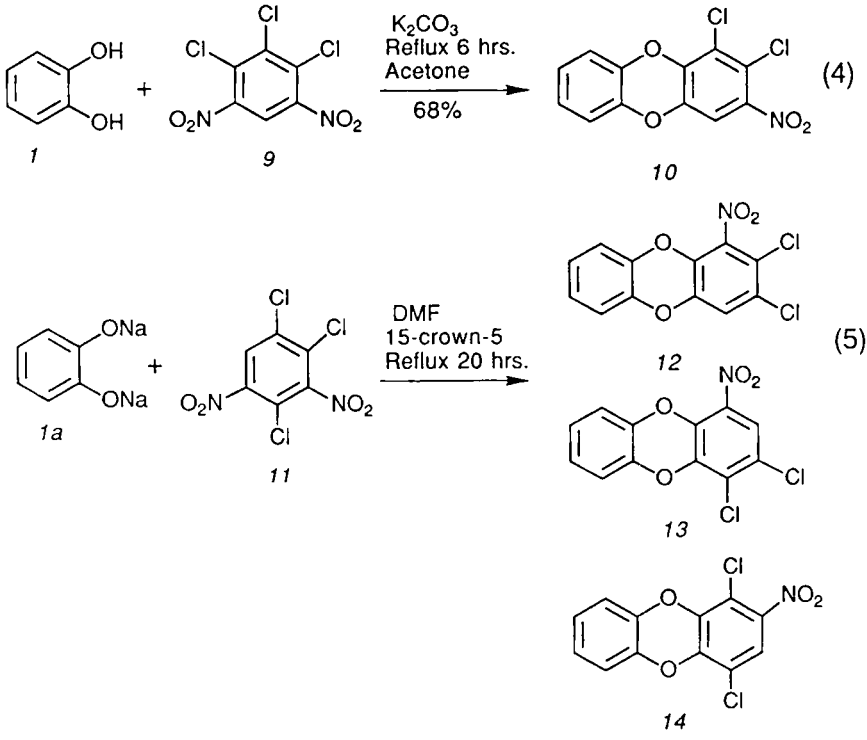


1 7 8

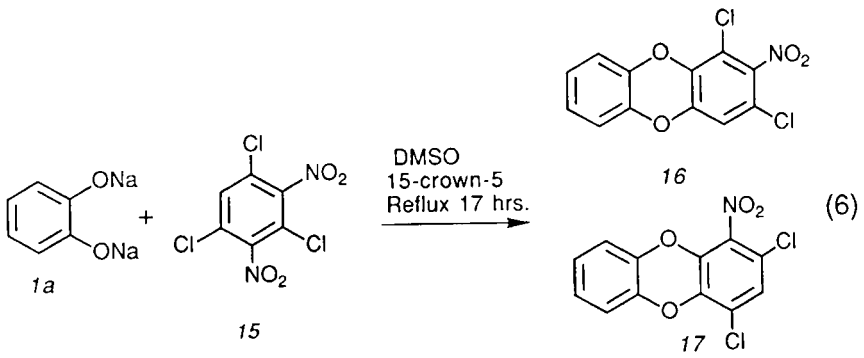
Dichloromononitrodibenzo-p-dioxins.

The condensation of **1** or its di-sodium salt (**1a**) with the appropriate dinitrotrichlorobenzene was carried out as described by Chae et al.[14] to give the desired dichloromononitrodibenzo-p-dioxins in relatively good yields. Condensation of **1** with **9**, for example, occurs at relatively low temperature in refluxing acetone (eq. 4). However, the condensation of **1** with either **11** or **15** in acetone failed. Thus, the reactions were carried out with the di-sodium salt (**1a**) at higher temperatures (eq. 5 and 6). It was found also that addition of a crown ether increases the yields substantially. The desired compounds **10** and **12** were isolated and purified by chromatographic techniques.



1 9 10

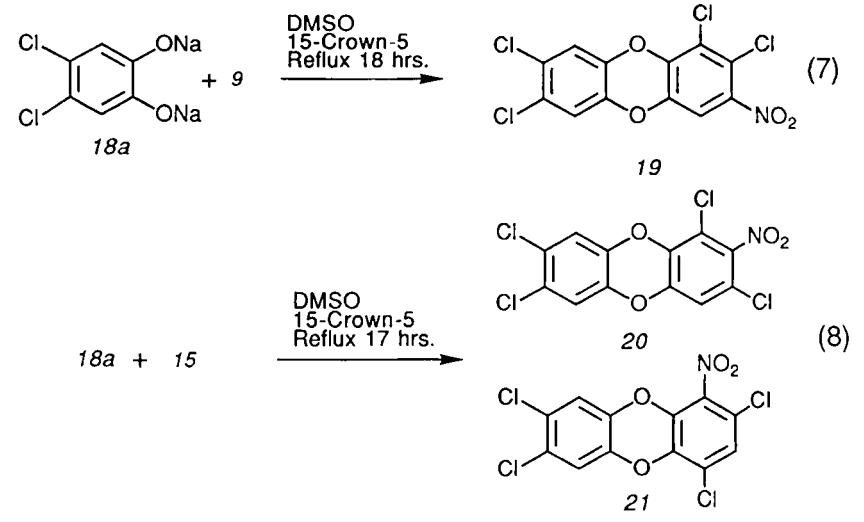
1a 11 12 13 14



(6)

Mononitrotetrachlorodibenzo-p-dioxins.

The goal in this series was to introduce a chlorine-37 label at the different isomeric positions of 1,2,3,7,8-pentachlorodibenzo-p-dioxin. A procedure developed by Chae et al. was employed[14]. As shown (eqs. 7-9) the condensation of the di-sodium salt of 4,5-dichlorocatechol (**18a**) with various dinitrochlorobenzenes is a versatile method to prepare mononitrotetrachlorodibenzo-p-dioxins. A substantial decrease in the yield was observed upon use of the catechol rather than the di-sodium salt. Compounds **19**, **20**, and **21** were isolated and purified by chromatographic techniques. The condensation of the di-sodium salt of 3,4,5-trichlorocatechol (**25a**) with 2,4-dichloro-1,5-dinitrobenzene (**7**) afforded compounds **26** and **27** in good yield (eq. 10), but all attempts to separate the two isomers were unsuccessful.



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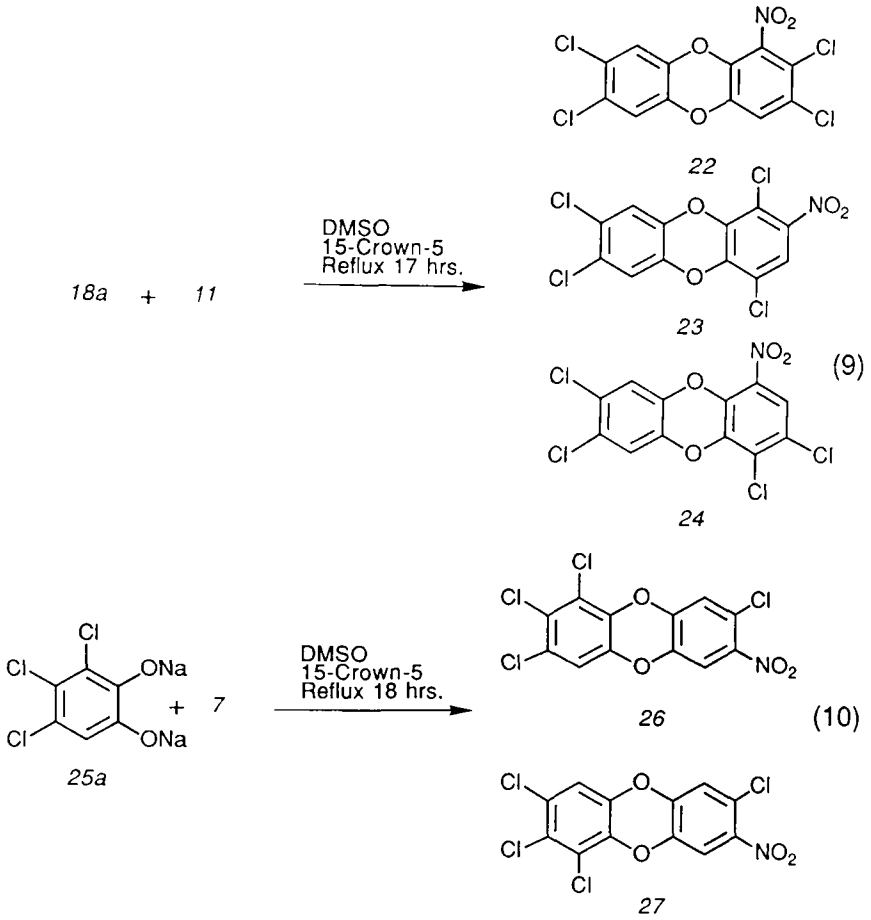
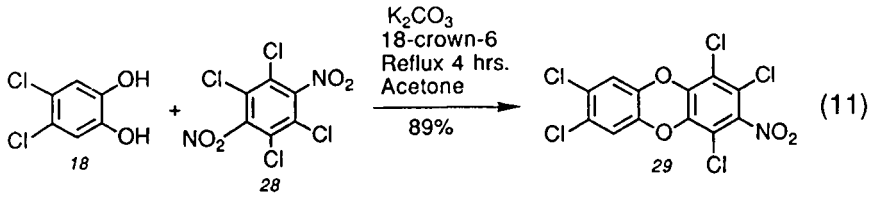
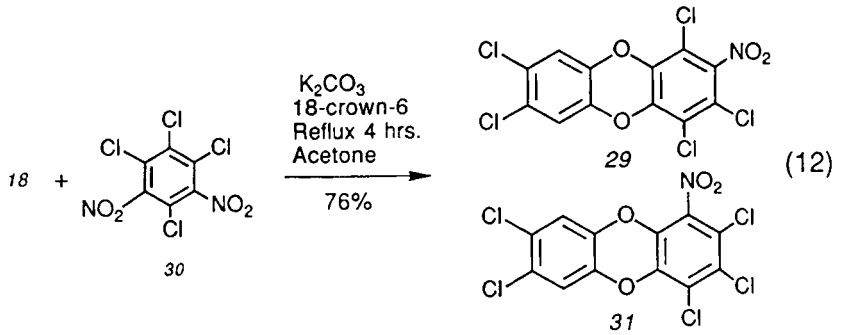


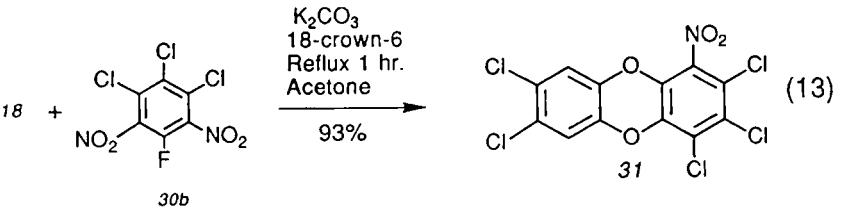
Mononitropentachlorodibenzo-p-dioxins.

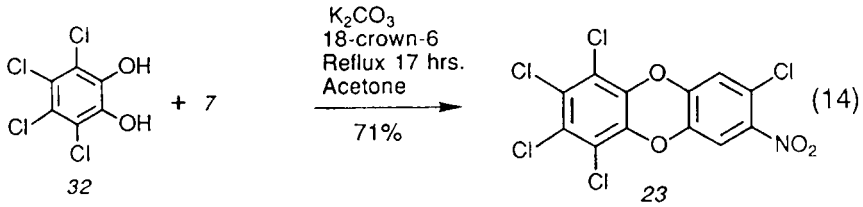
2-Nitro-1,3,4,7,8-pentachlorodibenzo-p-dioxin (**29**) was prepared in high yield by the condensation of 4,5-dichlorocatechol (**18**) and 1,4-dinitrotetrachlorobenzene (**28**) (eq. 11). Safe et al. prepared this compound by the nitration of 1,2,4,7,8-PCDD[18] which in turn was prepared by the condensation of **18** with 2,3,5,6-tetrachloronitrobenzene[18]. The method employed in the present work has two advantages: it is one step shorter and does not require the handling of large amounts of PCDD. The 2-nitro-3,6,7,8,9-pentachlorodibenzo-p-dioxin (**33**) was obtained in good yield upon condensation of tetrachlorocatechol (**32**) with 2,4-dichloro-1,5-dinitrobenzene (**7**) (eq. 14). All attempts to extend this approach to the preparation of 1-nitro-2,3,4,7,8-pentachlorodibenzo-p-dioxin (**31**) failed, however. The condensation of **18** with 1,3-

dinitrotetrachlorobenzene (**30**) led to the formation of a mixture of products **29** and **31** in a 20:1 ratio (eq. 12). Due to the tedious nature of the separation procedure the approach shown in equation 12 was abandoned and we elected to synthesize compound **31** using 1,3-dinitro-2-fluoro-4,5-trichlorobenzene (**30b**) (eq. 13). This procedure gave an excellent yield of compound **31**. The successful syntheses of compounds **29**, **31**, and **33** provided isomers with the label in the three possible isomeric positions.









Reduction of the mononitropolychlorodibenzo-p-dioxins.

Several procedures have been used to reduce nitro and nitropolychlorodibenzo-p-dioxins to their corresponding amino derivatives. These include: catalytic reduction over palladium on charcoal[12], stannous chloride-hydrochloric acid[14] hydrazine-Raney nickel[16,19] and zinc-hydrochloric acid[14]. We elected to utilize the well known tin-hydrochloric acid procedure. In the reduction of nitropolychlordibenzofurans with tin-hydrochloric acid a substantial amount (up to 20%) of nuclear chlorination has been observed[17]. However, no nuclear chlorination products were detected in the reduction of any of the mononitropolychlordibenzo-p-dioxins by this method.

The structures of the amines have been confirmed by retention times of the deaminated products with those of authentic standards (Ultra Scientific). NMR and MS analysis also were used to establish the structures of these deaminated products and, hence, the structures of the amines.

Strategy of Chlorine-37 labeling

The Doyle et al.[20] modification of the Sandmeyer-type chlorination was employed to introduce the chlorine-37 label. The utilization of Sandmeyer reactions to convert aromatic amines into chloroaromatics is a well known and a very efficient process[21]. The amines were converted to the diazonium salts by t-butyl nitrite. The diazonium salt was then treated with chlorine-37 enriched cuprous chloride[22]. Excess amines and t-butyl nitrite were used relative to enriched cuprous chloride to ensure maximum chlorine-37 incorporation.

The replacement of the diazo group by halogens is known to be regiospecific[23,24]. However, in a control experiment 1-amino-3-chlorodibenzo-p-dioxin was deaminated in the presence of 95% enriched cuprous chloride-37. EI-MS analysis of the purified 2-chlorodibenzo-p-dioxin showed no chlorine-37 enrichment. This supports the view that the chlorine-37 enrichment via the Sandmeyer reaction is regiospecific.

The chlorine-37 enrichment was obtained by comparing the intensities of isotope peaks (P_m, P_{m+2}, P_{m+4}) of the molecular ion cluster in the EI-MS spectrum with predicted intensities obtained from the binomial expansion shown below[26].

$$(a + b)^m (c + d)^n \qquad \text{(eq. 18)}$$

a: Natural relative abundance of ^{35}Cl (75.7705 ± 0.04).

b: Natural relative abundance of ^{37}Cl (24.2295 ± 0.04)

m: Number of natural chlorine atoms present in the molecule.

n: Number of chlorine-37 labels introduced. (For the present work n = 1)

c: Relative abundance of ^{35}Cl at the enriched position.

d: Relative abundance of ^{37}Cl at the enriched position.

Simulated spectra were generated by varying c and d (eq. 18). The smallest value for the sum of the square of the residues (difference between intensity of experimental and simulated isotope peak clusters) was used as criterion for best fit.

NMR Studies

Proton resonance assignments for the chlorinated dioxins (Table 2) were made wherever possible on the basis of chemical shifts and splitting patterns. In many cases it was not possible to make unambiguous assignments, because the chemical shifts fall within a very narrow range, i.e. 7.2-6.8ppm and the chlorinated and non-chlorinated compound resonances are not very different. The compounds are insoluble in aromatic solvents and it was therefore not possible to spread the resonances out. Finally, NOE and relay experiments were not successful.

Carbon-13 NMR data (Table 3) likewise were not sufficiently unambiguous to make all the assignments, because of the relative insolubility of the compounds and the quadrupole effect of the chlorines which results in very weak signals for the chlorinated carbons. For unsymmetrical compounds there were generally fewer than twelve resonances because the resonace peaks

Table 1. Spectroscopic Properties of Synthetic amino-polychlorodibenzo-p-dioxins

No.	Dibenzo-p-dioxin	Yield (%)	NMR	EIMS
3a	1-amino-3-chloro-	87	^{1}H δ 6.86 (m, 4H), 6.35 (d, 1H, J=2.3 Hz), 6.26 (d, 1H, J=2.3 Hz), 3.83 (bs, 2H)	m/z 233 (100, M$^+$), 198(26), 170(22), 116(12)
8a	2-amino-3-chloro-	86	^{1}H δ 6.88 (m, 2H), 6.82 (m, 2H), 6.79 (s, 1H) 6.31 (s, 1H), 3.83 (bs, 2H)	m/z 233 (100, M$^+$), 198(17), 170(51), 116(22)
5a	1-amino-4-chloro-	88	^{1}H δ 6.92 (m, 4H), 6.76 (d, 1H, J=8.7 Hz), 6.30 (d, 1H, J=8.8 Hz), 3.78 (bs, 2H)	m/z 233 (100, M$^+$), 205(8), 198(41), 170(43)
6a	2-amino-1-chloro-	77	^{1}H δ 6.96 (m, 4H), 6.61 (d, 1H, J=8.7 Hz), 6.32 (d, 1H, J=8.8 Hz), 3.69 (bs, 2H)	m/z 233 (100, M$^+$), 198(23), 170(79)
12a	1-amino-2,3-dichloro-	94	^{1}H δ 6.89 (m, 2H), 6.85 (m, 2H), 6.43 (s, 1H) 4.29 (bs, 2H)	m/z 267 (100, M$^+$), 232(20), 204(15), 189(8), 140(11)
10a	3-amino-1,2-dichloro-	80	^{1}H δ 6.93 (m, 3H), 8.84 (m, 1H), 6.26 (s, 1H), 3.72 (bs, 2H)	m/z 267 (100, M$^+$), 232(47), 204(43), 189(3), 140(8)
22a	1-amino-2,3,7,8-tetrachloro-	78	^{1}H δ 7.02 (s, 1H), 6.98 (s, 1H), 6.44 (s, 1H), 4.31 (bd, 2H)	m/z 335 (72, M$^+$), 300(22), 272(14), 257(8), 237(8)
20a	2-amino-1,3,7,8-tetrachloro-	86	^{1}H δ 7.09 (s, 1H), 6.95 (s, 1H), 6.80 (s, 1H), 4.30 (bs, 2H)	m/z 335 (73, M$^+$), 300(19), 272(38), 237(6)
19a	3-amino-1,2,7,8-tetrachloro-	80	^{1}H δ 7.07 (s, 1H), 6.97 (s, 1H), 6.26 (s, 1H) 4.39 (bs, 2H)	m/z 335 (83, M$^+$), 300(32), 272(45)
31a	1-amino-2,3,4,7,8-pentachloro-	85	^{1}H δ 7.13 (s, 1H), 7.04 (s, 1H), 4.31 (bs, 2H)	m/z 369 (52, M$^+$), 334(29), 306(4), 184(4)
29a	2-amino-1,3,4,7,8-pentachloro-	90	^{1}H δ 7.11 (d, 2H J=4.9 Hz), 4.45 (bs, 2H)	m/z 369 (58, M$^+$), 334(26), 306(9), 184(2)
33a	2-amino-3,6,7,8,9-pentachloro-	88	^{1}H δ 6.97 (s, 1H), 6.45 (s, 1H), 3.97 (bs, 2H)	m/z 369 (65, M$^+$), 334(5), 306(17), 184(4)
34a	1-amino-2,3,4-trichloro-	84	^{1}H δ 6.97 (m, 3H), 6.91 (m, 1H) 4.29 (bs, 2H)	m/z 301 (100, M$^+$), 266(16), 238(12), 223(8), 200(32)

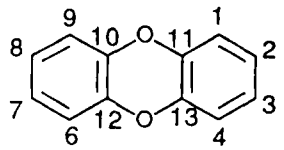
Table 2. Properties of Synthetic Regiospecifically Chlorine-37 Enriched polychlorodibenzo-p-dioxins

No.	Dibenzo-p-dioxin	yield (%)	Enrichment[a]	^{1}H NMR Chemical Shift (δ)	EIMS
3b	1(^{37}Cl) 3-Dichloro-	89	96.2 ± 0.4	(Acetone-d_6) 7.13 (d,1H,J=2.2 Hz) [H_4]; 7.02 (m, 3H); 6.95 (m, 2H)	m/z 254 (100, M$^+$), 219(6), 191(25), 163(5), 126(37)
8b	2(^{37}Cl) 3-Dichloro-	86	94.9 ± 0.3	6.93 (m, 4H) [H_1,H_4,H_6,H_9]; 6.85 (m, 2H) [H_7,H_8]	m/z 254 (100, M$^+$), 219(4), 191(23), 163(8), 126(35)
5b	1(^{37}Cl) 4-Dichloro-	87	91.2 ± 0.1	(Acetone-d_6) 6.96 (m, 4H) [H_6,H_7,H_8,H_9]; 6.90 (S, 2H) [H_2,H_3]	m/z 254 (100, M$^+$), 219(4), 191(22), 163(4), 126(32)
6b	1,2(^{37}Cl)-Dichloro-	79	93.1 ± 0.4	6.99 (m, 4H) [H_6,H_7,H_8,H_9]; 6.93 (d, 1H, J=8.2 Hz) [H_3]; 6.71 (d, 1H, J=8.8 Hz) [H_4]	m/z 254 (100, M$^+$), 219(2), 191(24), 163(9), 126(33)
12b	1(^{37}Cl) 2,3-Trichloro-	80	94.9 ± 0.2	6.98 (m, 3H), 6.94 (s, 1H) [H_4]; 6.87 (m, 1H)	m/z 288 (100, M$^+$), 253(5), 225(29), 197(6), 162(14)
10b	1,2,3(^{37}Cl)-Trichloro-	80	94.0 ± 0.8	6.98 (m, 3H), 6.93 (s, 1H) [H_4]; 6.87 (m, 1H)	m/z 288 (100, M$^+$), 253(7), 225(35), 197(8), 162(21)
22b	1(^{37}Cl) 2,3,7,8-Pentachloro-	75	78.7 ± 0.4	7.12 (s, 1H) [H_4]; 7.00 (s, 1H); 6.96 (s, 1H)	m/z 356 (97, M$^+$), 321(8), 293(37), 230(16)
20b	1,2(^{37}Cl) 3,7,8-Pentachloro-	68	92.8 ± 0.9	7.13 (s, 1H) [H_4]; 7.00 (s, 1H); 6.95 (s, 1H)	m/z 356 (95, M$^+$), 321(7), 293(29), 230(16)
19b	1,2,3(^{37}Cl) 7,8-Pentachloro-	71	90.1 ± 0.6	7.13 (s, 1H) [H_4]; 7.00 (s, 1H),; 6.96 (s, 1H)	m/z 356 (94, M$^+$), 321(8), 293(31), 230(16)
31b	1(^{37}Cl) 2,3,4,7,8-Hexachloro-	77	85.0 ± 0.2	7.15 (s) [H_6, H_9]	m/z 390 (80, M$^+$), 355(8), 327(40), 264(35)
29b	1,2(^{37}Cl) 3,4,7,8-Hexachloro-	69	72.2 ± 0.5	7.15 (s) [H_6, H_9]	m/z 390 (82, M$^+$), 355(5), 327(28), 264(31)
33b	2(^{37}Cl) 3,6,7,8,9-Hexachloro-	67	74.7 ± 0.8	7.15 (s) [H_6, H_9]	m/z 390 (79, M$^+$), 355(11), 327(43), 264(35)
34b	1(^{37}Cl) 2,3,4-Tetrachloro-	85	94.4 ± 0.4	(Acetone-d_6) 7.10 (s, 4H) [H_6, H_7, H_8, H_9]	m/z 322 (77, M$^+$), 287(7), 259(43), 231(12), 196(37)

[a] Replicate determinations

Table 3. Carbon-13 NMR Chemical Shift (δ) for Chlorinated dibenzodioxins.

No.	Dibenzo-p-dioxin	C 1,4,6,9	C 2,3,7,8	C 10,11,12,13
3b	1(^{37}Cl) 3-Dichloro-	117.33 (C1); 117.06 (C4); 116.13 (C6,C9)	124.85 124.61	143.72 (C11) 141.49 141.36
8b	2(^{37}Cl) 3-Dichloro-	118.00 (C1,C4); 116.63 (C6,C9)	126.24 (C2,C3) 123.91 (C7,C8)	143.01 141.89
5b	1(^{37}Cl) 4-Dichloro-	116.87	124.43 (C2,C3) 123.97 (C7,C8)	143.08 (C11,C13) 141.60 (C10,C12)
6b	1,2(^{37}Cl)-Dichloro-	116.83 116.11 115.21	126.67 (C2) 125.22 (C3) 124.08 (C7,C8)	142.87 (C11) 141.76 141.60
12b	1(^{37}Cl) 2,3-Trichloro-	119.67 (C1) 116.92 (C6,C9)	127.28 (C2) 124.92 (C3) 124.13 (C7,C8)	141.34 140.90
10b	1,2,3(^{37}Cl)-Trichloro-	119.67 (C1) 116.92 (C6,C9)	127.28 (C2) 124.92 (C3) 124.13 (C7,C8)	141.34 140.90
19b	1,2,3(^{37}Cl)-7,8-Pentachloro-	120.45 (C1) 119.58 (C4) 118.91 (C6,C9)	126.62 126.22	141.20 140.07
31b	1,2,3,4,7,8-hexachloro-	120.51 (C1,C4) 118.26 (C6,C9)	126.42 126.30	141.39 140.27
34b	1(^{37}Cl)-2,3,4-tetrachloro-	120.17 (C1,C4) 117.02 (C6,C9)	126.90 (C2,C3) 125.23 (C7,C8)	140.89 (C11,C13) 139.24 (C10,C12)



were either unresolved or simply missing even after 12-18 hour pulse exeriments. There are three distinct regions in the carbon-13 NMR spectra[9] which have been helpful for making assignments. These are the resonances due to the larteral carbons (C2,C3,C7,C8) which apper around 119ppm, the resonances due to the peri postitions (C1,C4,C6,C9) which fall around 125ppm and the resonances due to the ring junction carbons (C10,C11,C12,C13) which appear around 141ppm. Chlorinated carbons are shifted downfield about 4ppm relative to the non-chlorinated carbons. Carbons ortho to chlorinated carbons also are generally shifted downfield by about 2ppm, but carbons meta to chlorinated carbons are shifted upfield slightly.

Conclusion

The base promoted condensation of catechols with polynitropolyhalobenzene is a very efficient method for the preparation of nitropolychlorodibenzo-p-dioxins. Utilization of substrates bearing fluorine at key positions enhances both yield and regiospecificity. The replacement of the nitro group with other substituents via reduction and diazotization is a very effective method for introducing a variety of functional groups onto the dibenzo-p-dioxin ring systems. We have successfully applied this strategy for the preparation of regiospecifically chlorine-37 labeled polychlorinated dibenzo-p-dioxins in good yields.

Experimental

Caution: Most of the compounds described here are highly toxic. All of the halogenated dibenzo-p-dioxins should be handled with extreme care using precautions that parallel work with radioactive compounds. Contact or absorption of toxic dioxins may lead to acne, chloracne and irreversible liver damage.

Instrumentation: Melting points were measured with a Büchi melting point apparatus in open glass capillaries and are uncorrected. NMR spectra were recorded on Bruker AM-400 or AC-300 MHz instruments. TMS was used as reference and deuteriochloroform as solvent unless stated otherwise. Analytical GC-MS analyses were performed on a Finnigan 4023 (4500 Ion Source)

quadrupole mass spectrometer in the EI mode. A 30m DB-1301 or SE 54 (J & W, 0.25mm id) capillary column with splitless injection technique was used. The HPLC analyses and separations were carried out using a Beckman 421 HPLC equipped with a dual pump system and a variable UV detector (254 nm wavelength). A preparative reverse-phase column (Sephadex C-18, 250 x 10 mm) was employed.

Materials: HPLC grade solvents were used without further purification. The other solvents and reagents were purified by standard procedures before use[27]. 4,5-Dichloroguaiacol[28] and 3, 4, 5-trichloroguaiacol[28] were available from previous work. $Na^{37}Cl$ (95.6% ^{37}Cl enriched) was purchased from EG & G Mound Applied Technologies (Miamisburg, OH).

Enriched Cuprous Chloride-37.

The procedure developed by Tubandt et al. for preparation of cuprous iodide was employed to prepare the cuprous chloride-37[22]. In a three neck flask equipped with a stir bar were put equimolar amounts of anhydrous cupric sulfate (Aldrich) 2.66 g, (16.7 mmol), enriched sodium chloride-37 (1 g, 16.7 mmol) and 5 mL of deionized water. Sulfur dioxide (Matheson) was bubbled slowly through the well stirred solution. Cuprous chloride-37 precipitated as a white powder which was collected by filtration and washed with a saturated aqueous solution of sulfur dioxide. The powdered product was dried in a vacuum oven maintained at 90°C to give 1.17 g (70%) of pale greenish powder. High resolution mass spectrometry in the negative FAB mode was used to measure the ^{37}Cl enrichment. It was found to be 95.4%.

*4, 5-Dichlorocatechol (**18**).*

This compound was obtained by the demethylation of 4, 5-dichloroguaiacol by the method of Deinzer et. al[28] in 75% yield. NMR: ^{1}H δ 6.97 (s,2H), 5.54 (s,2H). ^{13}C δ 142.74, 123.72, 116.85. EIMS: m/z 178(85, M^{+}) 149(15), 113(10), 97(66), 85(34).

3,4,5-Trichlorocatechol (25).

Trichlorocatechol was obtained in 78% yield by demethylation of 3,4,5-trichloroguaiacol[28] using the same method employed in the preparation of 4,5-dichlorocatechol[28]. NMR: ^{1}H. δ 7.02 (s,1H), 5.63 (s,1H), 5.54 (s,1H). ^{13}C 143.25, 139.22, 125.00, 121.94, 119.62, 115.41. EIMS: m/z 212(100, M^{+}) 176(29), 148(26), 113(67), 85(31).

2,4-Dichloro-1,5-dinitrobenzene (7).

This dichloro-dinitrobenzene was prepared in 60% yield by the method of Buriks[29]. NMR: ^{1}H :δ 8.57 (s,1H). C^{13} δ 145.44, 135.18, 132.38, 123.33. EIMS: m/z 236(100, M^{+}) 206(20), 144(41), 109(38), 74(45).

2,5-Dichloro-1,3-dinitrobenzene (2).

Preparation of this compound by the method of Hammond and Modic[30] gave a low yield(~ 30%). However, our modification increased the yield substantially. 1.9 g (0.989 mol) of 1,4-dichloro-2 nitrobenzene, 4.2 mL of fuming nitric acid and 3.8 mL of concentrated sulfuric acid was stirred at room temperature overnight. The mixture was poured onto ice and the precipitate was collected. It was dissolved in chloroform and washed with a 5% sodium bicarbonate solution and rinsed with water. After the removal of the solvent 2.1 g of the pale yellow solid was obtained. The desired compound was isolated and purified by column chromatography on neutral alumina (activity I) using 3% acetone in hexane to give 1.17 g (56%) of product. NMR:^{1}H δ 8.00 (s). EIMS: m/z 236(M^{+}, 80), 162(11), 144(64), 109(80), 74(100).

2,3,4-Trichloro-1,5-dinitrobenzene (9).

The method described by Hüffer[31] was used to prepare this compound in 94% yield. It was recrystallized twice from 95% ethanol, mp 93-93.5 °C, lit[31] 92-93 °C. NMR:^{1}H δ 8.28 (s). ^{13}C δ 146.58, 137.90, 131.59, 119.35. EIMS: m/z 270 (98, M^{+}), 240(16), 178(65), 143(53), 131(29), 108(76), 84(14).

1,3,5-Trichloro-2,4-dinitrobenzene (15).

The nitration of 1,3,5-trichlorobenzene carried out according to the method of Hüffer[31] afforded the desired compound in 96% yield. It was recrystallized twice from 95% ethanol, mp 128-129.5°C, lit[31] 129-130°C. NMR:^{1}H δ 7.70 (s). ^{13}C 146.98, 130.75, 128.74, 120.82. EIMS: m/z 270(69, M^+), 240(31), 175(78), 143(64), 131(57), 108(100), 96(17).

1,2,4-Trichloro-3,5-dinitrobenzene (11).

This compound was obtained in 92% yield by the method described by Hüffer[31], mp 102-103.5°C, lit[31,14] 102.5-103.5°C. NMR:^{1}H δ 8.22 (s). ^{13}C δ 150.10, 146.00, 137.96, 134.15, 132.95, 127.24. EIMS: m/z 270 (38, M^+), 236(100), 206(14), 143(35), 108(100), 84(20).

1,4-Dinitrotetrachlorobenzene (28).

The nitration procedure developed by Berkman and Holleman[32] was utilized to prepare 1,3-dinitrotetrachlorobenzene in 90% yield after recrystallization from ethanol, mp 228-229°C, lit[14] 227-228°C. NMR: ^{13}C δ 149.36, 126.10. EIMS: m/z 304(77, M^+), 230(14), 177(45), 142(83), 130(17), 118(35), 95(12), 71(16).

1,3-Dinitrotetrachlorobenzene (30).

The procedure described by Berkman and Holleman was utilized[32]. Compound **38** was obtained in 98% yield, mp 161-161.5°C, lit[32] 161-162°C. NMR: ^{13}C δ 147.31, 134.66, 128.74, 117.85. EIMS: m/z 304(79, M^+), 274(9), 209(40), 200(18), 177(60), 142(73), 118(35), 107(45).

3,4,5-Trichlorofluorobenzene.

3,4,5-Trichloroaniline was converted to 3,4,5-trichlorofluorobenzene via a Balz-Schiemann reaction[33]. In a beaker equipped with a stir bar and immersed in ice/salt bath (below -4°C) was put 2.0 g (10.2 mmol) of 3,4,5-trichloroaniline, 3 mL of water and 3 mL of concentrated hydrochloric acid. To the cooled and well stirred mixture was added dropwise 871 mg (12.6 mmol) of sodium nitrite in 2 mL of water at a rate to keep the temperature below -3°C. After the

addition was completed the solution was stirred for 10 minutes at -4 °C. Then 3 mL of chilled 50% aqueous fluoroboric acid (Fluka) was added and stirred for 10 more minutes. The white precipitate was collected by filtration and washed with cold water and chilled ether. After drying under vacuum 2.5 g (83%) of diazonium tetrafluoroborate salt was obtained. The decomposition of the diazonium fluoroborate salt was carried out as follows[34]. A 1 L three-neck round bottom flask equipped with a nitrogen inlet and a Friedrichs condenser was connected to a 500 mL three-neck round bottom receiving flask with a glass adapter. The receiving flask was immersed in dry ice/acetone bath and connected to a trap containing 20% aqueous sodium hydroxide. The salt was introduced into the decomposition flask and ice cooled water was pumped through the condenser. The decomposition flask was then heated with an open flame under nitrogen (low flow). The receiving flask, the glass adaptor and the condenser were washed thoroughly with chloroform. The residue in the decomposition flask was first-treated with 10% aqueous sodium hydroxide solution and then extracted with chloroform. The combined chloroform solution was washed with 10% aqueous sodium hydroxide solution and with water, then dried over anhydrous sodium sulfate. The solvent was removed and the compound was purified via silica gel column chromatography eluting with 10% dichloromethane in hexane. 1.31 g (77%) of pure 3,4,5-trichlorofluorobenzene was obtained. NMR: ^{1}H δ 7.16 (d, J=7.8 Hz). ^{13}C δ 159.77 (d, J=252.1 Hz), 134.79 (d, J=11.5 Hz), 127.52 (d, J=4.6 Hz), 116.56 (d, J=25.6 Hz). EIMS: m/z 198(100, M^{+}), 163(23), 128(13).

*1,3-Dinitro-2-fluoro-4,5,6-trichlorobenzene (**30b**).*

The method of Berkman and Holleman originally developed for the preparation of dinitrotetrachlorobenzene[32] was adopted to prepare compound **30b**. In a 25 mL round bottom flask equipped with a stir bar and a reflux condenser were introduced 1 g (5.1 mmol) of 3,4,5-trichlorofluorobenzene, 3 mL of fuming nitric acid and 3 mL of fuming sulfuric acid containing 33% sulfur trioxide. The mixture was refluxed overnight. After cooling, the reaction mixture was poured onto ice, and the precipitate was collected by filtration. The solid was then recrystallized from 95% ethanol-water and dried under vacuum to give 1.21 g (83%) of pure **30b**. NMR: ^{13}C

δ 144.85 (d, J=271.3 Hz), 138.13 (d, J=13.5 Hz), 131.70 (d, J=4.7 Hz), 129.58 (d, J=0.9 Hz). EIMS: m/z 288 (71, M^+), 196(100), 161(93), 126(80).

3-Chloro-2-nitrodibenzo-p-dioxin (8).

This compound was prepared by the method described by Oliver[15]. However, the reaction was carried out in acetone solvent[13] rather than N,N'-dimethylformamide. In a dried 50 mL three neck round bottom flask equipped with a stir bar, a nitrogen inlet and a reflux condenser connected to a bubbler were introduced 46.7 mg (0.4 mmol) of catechol (**1**), 0.123 g (0.9 mmol) of potassium carbonate and 16 mL of dried acetone. The mixture was heated while stirring under nitrogen. After 30 minutes a solution of 0.100 g (0.4 mmol) of 2,4-dichloro-1,5-dinitrobenzene (**7**) in 5 mL of dry acetone was added. The reaction mixture was refluxed for six hours. After cooling, ice and water were added and the yellow precipitate was filtered and dried. The desired product was isolated by column chromatography on silica eluting with 50% dichloromethane in hexane. After removal of solvent 89.2 mg (80%) of a pale yellow solid was obtained. mp: 165-167°C lit[15] 164-166°C. NMR: ^1H δ 7.39 (s,1H), 7.05-7.5 (m,3H), 6.90-6.95 (m,2H). ^{13}C δ 145.88, 140.73, 140.38, 125.31, 124.88, 123.06, 119.04, 116.83, 116.70, 116 67, 114.32. EIMS: m/z 263(100, M^+), 217(83), 205(22), 182(23).

3-Chloro-1-nitrodibenzo-p-dioxin (3).

2,5-Dichloro-1,3-dinitrobenzene (**2**) and catechol (**1**) were allowed to react according to the method used to prepare **8**. It was obtained in 77% yield after purification on a silica column with 20% ethyl acetate in hexane as eluting solvent. NMR: ^1H δ 7.52 (d, 1H, J=2.6 Hz), 7.08 (d, 1H, J=2.6 Hz), 6.98 (m, 3H), 6.88 (m, 1H). ^{13}C δ 144.05, 140.64, 140.28, 137.89, 136.45, 127.68, 125.45, 125.06, 121.00, 119.55, 117.11, 116.47. EIMS: m/z 263(100, M^+), 217(58), 126(27).

4-Chloro-1-nitrodibenzo-p-dioxin (5) and 1-Chloro-2-nitrodibenzo-p-dioxin (6).

In a dried 25 mL three neck round bottom flask equipped with a stir bar, a nitrogen inlet

and a reflux condenser connected to a bubbler were put 52.4 mg (0.5 mmol) of catechol (**1**), 0.138 g (1 mmol) of potassium carbonate and 3 mL of dried N,N′-dimethylformamide. The mixture was warmed while stirring under nitrogen for 30 minutes. A solution of 100 mg (0.5 mmol) of 2,4-dichloro-3-fluroronitrobenzene (**4**) (Ishihara Sangyo Kaihsa, Ltd.) in 2 mL of dried N,N′-dimethylformamide was added and the mixture refluxed overnight under nitrogen. After cooling, ice and water were added and the precipitate was collected by filtration and dried. The two compounds were isolated as a mixture in 90% yield by column chromatography on silica using 50% dichloromethane/hexane. These two compounds were separated by HPLC on a C18 column and eluted with 30% water in acetonitrile. Their respective physical data are as follows: 1-Chloro-4-nitrodibenzo-p-dioxin (**5**). NMR: ^{1}H δ 7.51 (d, 1H, J=9.4 Hz), 7.06 (d, 1H, J=8.8 Hz), 7.00 (m, 4H). ^{13}C 146.53, 140.64, 140.16, 138.58, 136.31, 126.76, 125.54, 125.25, 123.51, 119.42, 117.02, 116.70. EIMS: m/z 263(100 M+), 217(38), 189(9), 182(7), 126(29). 1-Chloro-2-nitrodibenzo-p-dioxin (**6**). NMR: ^{1}H δ 7.56 (d, 1H, J=8.8 Hz), 6.87 (m, 4H), 6.82 (d, 1H, J=8.8 Hz). ^{13}C 142.19, 140.40, 140.12, 139.95, 136.22, 125.60, 125.14, 120.73, 116.79, 116.38, 114.00. EIMS: m/z 263(100, M^+), 217(46), 189(4), 182(8), 126(35).

*2,3-Dichloro-1-nitrodibenzo-p-dioxin (**12**).*

The method described by Chae et al.[14] for the preparation of 1-nitro-2,3,7,8-tetrachlorodibenzo-p-dioxin (**22**) was adopted to prepare compound **12**. The disodium salt of catechol (**1a**) was refluxed with 1,2,4-trichloro-3,5-dinitrobenzene (**11**) in dry DMF under nitrogen for 20 hours. After cooling the reaction mixture was absorbed on silica gel packed column and eluted with 1 L of hexane. Evaporation of solvent afforded 0.1578 g (72% yield). GC/MS analysis showed three compounds with molecular ion peaks at m/z 297. The desired product was isolated by preparative TLC; the plate was eluted twice with hexane. The second band contained the desired compound (76.4 mg). GC/MS analysis showed one single product with M^+ at m/z 297. NMR: ^{1}H δ 7.10 (s, 1H), 7.98 (q, 2H, J=2.4, 9.7 Hz), 6.91 (m, 2H). ^{13}C δ 141.65, 140.33, 139.85, 134.53, 127.73, 125.60, 125.22, 118.514, 117.02, 116.77. EIMS m/z 297 (100, M^+), 251(61), 239(8), 223(17), 216(16), 195(7), 160(51), 125(17), 108(16), 74(11).

1,2 Dichloro-3-nitrobenzo-p-dioxin (10).

This compound was obtained by the condensation of catechol (**1**) and 2,3,4-trichloro 1,5-dinitrobenzene (**9**) in the presence of potassium carbonate in acetone according to the procedure described for the preparation of **15**. The compound was purified by silica gel column chromatography using 30% dichlormethane in hexane (114.4 mg, 68%). NMR: ^{1}H δ 7.38 (s, 1H), 6.99 (m, 3H), 6.89 (m, 1H). ^{13}C δ 143.33, 140.86, 140.20, 125.77, 125.16, 123.03, 122.32, 117.02, 116.54, 111.88. EIMS: m/z 297(100, M^{+}), 251(38), 160(30), 108(27).

1-Nitro-2,3,7,8-tetrachlorodibenzo-p-dioxin (22).

This compound was obtained by the condensation of **18a** and 1,2,4-trichloro-3,5-dinitrobenzene (**11**) in dimethyl sulfoxide as described by Chae et al[14]. GC/MS analysis of the crude product mixture showed three compounds with molecular weights 365. These compounds were separated using silica gel column chromatography. The desired 1-nitro-2,3,7,8-tetrachlorodibenzo-p-dioxin (**22**) (63 mg, 53%) was eluted with 80 mL of 17% dichloromethane/hexane. The 1-nitro-3,4,7,8-tetrachlorodibenzo-p-dioxin (**24**) (31 mg, 30%) and 2-nitro-1,4,7,8-tetrachlorodibenzo-p-dioxin (**23**) (10.5 mg, 8%) were eluted with 500 mL and 400 mL of 25% and 30% dichloromethane in hexane respectively. Our physical data for compound **22** matched exactly those of Chae et al. for this compound[14]. NMR: ^{1}H δ 7.13 (s, 1H), 7.06 (s, 1H), 7.04 (s, 1H). ^{13}C δ 140.55, 139.20, 138.23, 133.49, 128.77, 128.61, 128.36, 229.50, 118.74, 228.50, 118.23. EIMS: m/z 365 (100, M^{+}), 319(61), 309(11), 284(24), 228(74), 193(22), 183(12), 143(32), 107(9), 84(22).

2-Nitro-1,3,7,8-tetrachlorodibenzo-p-dioxin (20).

Compound **20** was obtained by the procedure described for 1-nitro-2,3,7,8-tetrachlorodibenzo-p-dioxin (**22**)[14]. GC/MS analysis showed that the crude reaction mixture contained two compounds in a ratio of 10:1 with a molecular ion m/z 365. The two compounds were separated by silica gel column chromatography using 15% dichloromethane in hexane as eluting solvent. The desired product was obtained in 71% yield (148.3 mg). GC/MS analysis

showed a single compound with a molecular ion m/z 365. NMR: ^{1}H δ 7.14 (s, 1H), 7.04 (s, 1H), 6.96 (s, 1H). ^{13}C δ 142.85, 139.19, 139.11, 128.54, 128.46, 120.87, 118.41, 118.07, 116.18. EIMS: m/z 365(72, M^{+}), 335(11), 319(36), 309(12), 291(8), 284(15), 228(31), 143(9), 183(4), 143(10), 108(23), 84(120).

*3-Nitro-1,2,7,8-tetrachlorodibenzo-p-dioxin (**19**).*

The procedure of Chae[14] was employed to prepare this compound. The purification was carried out on a silica gel column. The compound was eluted with 50% dichloromethane in hexane (131.8 mg, 61%). NMR: ^{1}H δ 7.43 (s, 1H), 7.17 (s, 1H), 7.04 (s, 1H). ^{13}C δ 142.25, 139.96, 139.14, 139.05, 128.87, 128.27, 123.03, 118.55, 118.03, 114.88, 112.01. EIMS: m/z 365(100, M^{+}), 335(37), 319(60), 291(9), 284(20), 228(38), 193(12), 143(12), 108(25), 84(12).

*1-Nitro-2,3,4,7,8-pentachlorodibenzo-p-dioxin (**31**).*

This compound was obtained by the condensation of **18** and 1,3-dinitro-2-fluoro-4,5,6-trichlorobenzene (**30b**). In a 25 ml three neck-round bottom flask equipped with a stir bar, a nitrogen inlet and a reflux condenser connected to a bubbler were introduced 61.8 mg (0.34 mmol) of 4,5-dichlorocatechol, potassium carbonate 100 mg (3.5 mmol) and 10 mL of dry acetone. 18-Crown-6 was added and the mixture heated while stirring under nitrogen for 30 minutes. To this mixture, 100 mg (3.5 mmol) of **30b** in 5 mL of dry acetone was added. After 2 minutes a yellowish precipitate was obtained. The reaction mixture was refluxed for one hour and cooled. Ice-water was added and the yellow precipitate was collected and dried. Compound **31** was purified by silica gel column chromatography eluting with 20% dichloromethane in hexane. The product (128.8 mg, 93%) was obtained on evaporation of the solvent. NMR: ^{1}H δ 7.18 (s, 1H), 7.09 (s, 1H). ^{13}C δ 138.94, 138.34, 133.72, 129.12, 128.93, 128.61, 124.08, 120.15, 118.59, 118.43. EIMS: m/z 399(64, M^{+}), 353(19), 318(8), 262(19).

*2-Nitro-1,3,4,7,8-pentachlorodibenzo-p-dioxin (**29**).*

Compound **29** was obtained by the condensation of **18** (100 mg, 0.6 mmol) and 1,4-

dinitrotetrachlorobenzene (**28**) (171.3 mg, 0.6 mmol) in the presence of K_2CO_3 (1.32 mmol) and 18-crown-6 (1.32 mmol) in refluxing acetone[13]. The yield was 201 mg (89%) after purification by silica gel column using 20% dichloromethane in hexane as eluting solvent. NMR: ^1H δ 7.17 (d, J=4.7 Hz). ^{13}C δ 142.99, 140.62, 138.85, 138.71, 138.11, 129.02, 128.87, 120.86, 118.43, 118.31, 117.09, 113.36. EIMS: m/z 399(57, M^+), 371(12), 353(20), 318(11), 262(14).

*2-Nitro-3,6,7,8,9-pentachlorodibenzo-p-dioxin (**33**).*

The potassium carbonate promoted condensation of tetrachlorocatechol (**32**) and 1,5-dichloro-2,4-dinitrobenzene (**7**) was successfully employed to prepare this compound. The reaction was carried out in refluxing acetone[13] in the presence of 18-crown-6. The compound was purified via silica gel column chromatography using 20% dichloromethane in hexane as eluting solvent. Upon evaporation of the solvent, 144.3 mg (71%) of pale yellow solid was obtained. NMR: ^1H δ 7.72 (s,1H), 7.23 (s, 1H). ^{13}C 143.28, 139.04, 137.43, 137.21, 136.82, 129.49, 128.86, 124.50, 120.78, 119.68, 114.77, 114.04. EIMS: m/z 399(55, M^+), 353(25), 262(12).

*1-Nitro-2,3,4-trichlorodibenzo-p-dioxin (**34**).*

The procedure described for the preparation of **31** was employed to prepare compound **34**. Using **1** and **30b** as reactants, 1-Nitro-2,3,4-trichlorodibenzo-p-dioxin (**34**) was obtained in 92% yield after purification via silica gel chromatography eluting with 20% dichloromethane in hexane. NMR: ^1H δ 7.01 (m,3H), 6.92 (m,1H). ^{13}C δ 139.44, 139.24, 139.04, 134.5, 127.61, 126.33, 125.76, 125.61, 123.58, 119.17, 117.17, 116.97, 116.81. EIMS: m/z 331(100, M^+), 296(4), 285(57), 256(7), 250(29), 194(58).

Preparation of the Amino derivatives.

Nitropolychlorodibenzo-p-dioxins were reduced to the amino derivatives in good yield by tin and hydrochloric acid in refluxing methanol. The procedure is illustrated for the reduction of

3-chloro-1-nitrodibenzo-p-dioxin (**3**). A list of amino polychlorodibenzo-p-dioxins prepared by this procedure is shown (Table 1).

1-Amino-3-chlorodibenzo-p-dioxin (3a).

3-Chloro-1-nitrodibenzo-p-dioxin (**3**) 100 mg (0.4 mmol) was dissolved in 10 mL of methanol[35]. Granular tin (Aldrich 30 mesh) 300 mg (2.5 mmol) was added. To this well stirred solution 5 mL of concentrated HCl was added over a 10 minute period. This mixture was refluxed for 2 hours and the progress of the reaction was monitored by TLC analysis of aliquots after work up. The reaction mixture was cooled. The flask was immersed in an ice/water bath and the pH adjusted to about 8 with 5 M KOH solution. The mixture was extracted with chloroform. The organic layer was washed and dried over granular anhydrous sodium sulfate. Evaporation of solvent afforded 80.3 mg of crude product. The amine was purified by silica gel preparative TLC eluting with 30% dichloromethane in hexane (77.3 mg, 87%). NMR: ^{1}H δ 6.86 (m, 4H), 6.35 (d, 2H, J=2.3 Hz), 6.26 (d, 2H, J=2.3 Hz), 3.83 (bs, 2H). EIMS m/z 233(100, M^+), 198(26), 170(22), 116(12).

Preparation of the chlorine-37 labeled derivatives.

The replacement of the amino group by chlorine-37 was achieved with the Doyle *et al.* modification[20] of the Sandmeyer reaction. The amino derivatives containing two chlorines or less were allowed to react with cuprous chloride-37 at room temperature. Higher chlorinated amine derivatives were first diazotized at -2°C; then allowed to react with cuprous chloride-37 at room temperature. The reaction mixtures were stirred at room temperature for 1 hour and then heated to 50°C for 15 minutes. The yields were found to decrease as the steric hindrance around the amino group increased. The procedure is illustrated below using 1-amino-3-chlorodibenzo-p-dioxin as an example. The chlorine-37 enrichments and spectroscopic properties for the chlorine-37 enriched polychlorodibenzo-p-dioxins are shown (Table 2).

*1-(^{37}Cl),3-Dichlorodibenzo-p-dioxin (**3b**).*

In a 25 ml round bottom flask equipped with a stir bar was put 12 mg (51.5 μmol) of 1-amino-3-chlorodibenzo-p-dioxin in 5 mL of HPLC grade acetonitrile. To the well stirred solution was added 7.4 μL (61.8 μmol) of t-butyl nitrite. After 2 minutes the solution became dark, then 4.2 mg (41.2 μmol) of cuprous chloride-37 (95% enriched) in 1 mL of acetonitrile was added and the mixture stirred for 1 hour at room temperature. The mixture was then stirred at 50°C for an additional 15 minutes. The cooled mixture was passed through a small alumina column to remove the inorganic salts and starting materials. The solvent was removed and the desired product was isolated by silica gel preparative TLC eluting with hexane. Compound **3b** was purified by HPLC using 30% water in acetonitrile. GCMS analysis showed one single compound with m/z 254. The yield of product obtained was 9.3 mg (89%). NMR: (Acetone-d_6) ^{1}H δ 7.13 (d, 1H, J=2.2 Hz), 7.02 (m,3H), 6.95 (m,2H). EIMS: m/z 254 (100, M^+), 219(6), 191(25), 163(5), 126(37).

Acknowledgement

We gratefully acknowledge the support from the National Institutes of Health, NIEHS ES00040 and NIEHS ES00210. We also thank Brian Arbogast and Donald Griffin for their help with the MS analysis. We extend our gratitude to Dr. H. Takagai (Ishihara Sangyo Kaihsa, Ltd. Japan) for providing us with 2,4-dichloro-3-fluoronitro-benzene. The Bruker AM400 and AC300 NMR instruments were purchased in part through grants from the National Science Foundation (CHE-821690) and the M.J. Murdock Charitable Trust to Oregon State University. This is Oregon Agricultural Experiment Station publication No. 9582.

References

1. Partial presentation at the joint *45th Northwest/10th Rocky Mountain Regional Meeting of the American Chemical Society*, Salt Lake City, Utah, June 13-15, 1990.

2. a) *Environmental Health Perspectives*, No. 5 (1973).

b) McConnell E.E. and Moore J.A. - *Toxicol. Appl. Pharmacol.* 37:146(A130) (1976).

c) Hites R.A. - *ACC Chem. Res.* 23:194 (1990).

3. Nestrick T.J., Lamparksi L.L., Shadeoff L.A., and Peters T.L. - *Human and Environmental Risk of Chlorinated Dioxins and Related Compounds*, Tucker R.E., Young A.L. and Grey A.P. Eds., Plenum Press, New York, 1983 and references cited therein.

4. Laramée J.A., Chang Y.-S., Arbogast B.C., and Deinzer M.L. - *Biomed. Environ. Mass Spectrom.* 17:63 (1988).

5. Laramée J.A., Arbogast B.C., and Deinzer M.L. - *Anal. Chem.* 60:1937 (1988).

6. Preliminary results presented at the *38th ASMS Conference on Mass Spectrometry and Allied Topics*, Tucson, Arizona, June 3-8, 1990.

7. Gray A.P., Cepa S.P., Solomon I.J., and Aniline O. - *J. Org. Chem.* 41:2435 (1976) and references cited therein.

8. a) Gray A.P., Cepa S.P., and Cantrell J.S. - *Tetrahedron. Lett.* 2873 (1975).

b) Kende A.S. and DeCampe M. - *Tetrahedron. Lett.* 2877 (1975).

9. Kende A.S., Wade J.J., Ridge D., and Pohland A. - *J. Org. Chem.* 39:931 (1974) and references cited therein.

10. Tomita M. - *J. Pharm. Soc. Japan* 55:1060 (1935).

11. Ueo S. - *Bull. Chem. Soc. Japan* 16:177 (1941).

12. Loudon J.D. and McCaptra F. - *J. Chem. Soc.* 1899 (1959).

13. Pohland A.E. and Young G.C. - *J. Agr. Food Chem.* 20:1093 (1972).

14. Chae K., Cho L.K. and McKinney J.D. - *J. Agr. Food Chem.* 25:1207 (1977).

15. Oliver J.E. - *J. Heterocyclic Chem.* 21:1073 (1984).

16. Oliver J.E. and Ruth J.M. - *Chemosphere* 12:1497 (1983).

17. Chang Y.-S. and Deinzer M.L. - *J. Labelled Compounds and Radiopharm* XXIX:43 (1991).

18. Donnelly K.C., Jones D.H. and Safe S. - *Mutation Research* 17:169 (1985).

19. Leggetter B.E. and Brown R.K. - *Can. J. Chem.* 38:2363 (1960).

20. Doyle M.P., Siegfried B.S. and Dellaria J.F. - *J. Org. Chem.* 42:2426 (1977).

21. a) Meerwein H., Buchner E. and Van Emster K. - *J. Prakt. Chem.* 152:237 (1939).
b) Dickerman S.C., Weiss K. and Ingberman A.K. - *J. Org. Chem.* 152:380 (1956).
c) Dickerman S.C., Desouza D.J. and Jacobsen N.J. - *J. Org. Chem.* 34:710 (1969).

22. Tubandt C., Rindtorff E. and Jost W. - *Z. Anorg. Allgen. Chem.* 165:195 (1927).

23. Danek O., Snoble D. and Nouzouva S. - *Coll. Czech. Chem. Commun.* 32:1642 (1967).

24. Wulfman D.S. - *The Chemistry of Functional Groups: The Chemistry of Diazonium and Diazo Groups Part 1*, Patai S. Ed., John Wiley & Sons, Bristol, Great Britain, 1978, pp. 247.

25. Biemann K. - *Mass Spectrometry: Organic Chemical Applications*, McGraw-Hill, New York, 1962, Chapters 3 and 5.

26. Tarpley, A.R. and Goldstein, J.H. - *J. Mol. Spectros.* 37:432 (1991).

27. Perrin D.D., Armarego W.L.F. and Perrin D.R. - *Purification of Laboratory Chemicals*, 2nd Ed., Pergamon Press, New York, 1984.

28. Kolonko K.J., Deinzer M.L. and Miller T.L. - *Synthesis* 133 (1981).

29. Boyer H.J and Buriks R.S - *Org. Syn.* 40:96.

30. Hammond G.S. and Modic F.J. - *J. Am. Chem. Soc.* 75:1385 (1953).

31. Hüffer E.J.E. - *Recl. Trav. Chim. Pays-Bas* 40:451 (1921).

32. Berckmans V.S.F. and Holleman A.F. - *Recl. Trav. Chim. Pays-Bas* 44:851 (1925).

33. a) Suschitzky H. - *Advances in Fluorine Chemistry Vol IV*, Stacy M., Tatlow J.C., and Sharpe A.G., Eds., Butterworths, London, 1965, pp. 1-30.
b) Roe A. - *Organic Reactions Vol V*, Adams R., Ed., Wiley, New York, 1949, p. 193 and references cited therein.

34. The decomposition of the diazonium tetrafluoroborate must be carried out in a very efficient hood. BF_3 is generated.

35. For compounds bearing the nitro group at either 2,3,7, or 8 position, benzene was used as co-solvent to increase the solubility.