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Discovery of disubstituted phenanthrene imidazoles as potent, selective and orally active mPGES-1 inhibitors

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ABSTRACT

Phenanthrene imidazoles **26** and **44** have been identified as novel potent, selective and orally active mPGES-1 inhibitors. These inhibitors are significantly more potent than the previously reported chlorophenanthrene imidazole **1** (**MF63**) with a human whole blood IC_{50} of 0.20 and 0.14 μM, respectively. It exhibited a significant analgesic effect in a guinea pig hyperalgesia model at oral doses as low as 14 mg/kg. Both active and selective mPGES-1 inhibitors (**26** and **44**) have a relatively distinct pharmacokinetic profile and are suitable for clinical development.

Prostaglandin E_2 (PGE_2), a prostanoid, is widely recognized as a key mediator in fever, pain and the inflammatory response.[1] PGE_2 is produced by sequential conversion of arachidonic acid to PGH_2 by cyclooxygenases (COX-1/COX-2) followed by the isomerization of PGH_2 to PGE_2 by mPGES-1, a microsomal, glutathione-dependent, inducible enzyme.[2] Selective inhibition of mPGES-1 would be expected to preclude PGE_2 production[3] without any potential side effects, resulting from the inhibition of PGD_2, PGF2α, PGI_2 and TXA_2 biofunctions.[4]

We recently reported that the phenanthrene imidazole **1** (**MF63**) is a potent and selective mPGES-1 inhibitor (Fig. 1).[5] This inhibitor is significantly more potent than our previously reported mPGES-1 inhibitors[6] with an intrinsic inhibitory potency[7] of IC_{50} = 0.001 μM on the recombinant human mPGES-1 enzyme. Furthermore, it has a PGE_2 whole cell inhibition[8] in A549 cells of 0.42 μM (see Fig. 1) and a human whole blood (HWB) activity of 1.3 μM.[9] It also exhibited an analgesic effect in a guinea pig hyperalgesia model when dosed orally at 100 mg/kg.[10]

Despite its interesting activity profile, the phenanthrene imidazole **1** demonstrated less than desirable pharmacokinetics which precluding its development. The mPGES-1 inhibitor **1** has a short half life of 1.5 h when dosed at iv in rats. A short half life was also observed in the rhesus monkey (1.3 h).

Herein, we report the identification of two potent, selective and orally active phenanthrene imidazole inhibitors (compounds **26** and **44**), showing an improved pharmacokinetic profile and superior in vitro and in vivo activities compared to inhibitor **1**.[11]

Based on the discovery of inhibitor **1** (**MF63**), both the phenanthrene imidazole core and the phenyl ring bearing a bis-cyano ortho substitution is optimal and is crucial for potency. Our initial medicinal chemistry approach was to find the optimal structure–activity relationship (SAR) for the substitution of the phenanthrene backbone. For ease of synthesis, the previously reported 2-chloro-6-fluorophenyl group was selected in this initial study. As we can see from the Table 1, substitution at the 6′-position leads to more active inhibitors (compounds **3** and **5**) compared to 4′, 5′ and 7′ substituted analogues (compounds **4**, **6**, **7** and **8**). The bromo substituted inhibitor **5** has increased enzyme activity compared to the chloro analogue (compound **3**) and maintained whole cell activity. Substitution at the 9′-position is tolerated, as observed in the symmetrical dibromo inhibitor **9**. Since this inhibitor is equipotent to the mono substituted analogue **5**, we decided to further characterize this position through SAR. For ease of synthesis, the 6′-bromo substituent was selected and a variety of 9′-substituted analogues were generated. In order to explain the phenomena we observed, a selection of protypical inhibitors are described in Table 1. Although equipotent on the enzyme, the presence of a lipophilic isopropyl group at 9′ leads to a diminished potency in the whole cell assay (compound **10**). The introduction of a group

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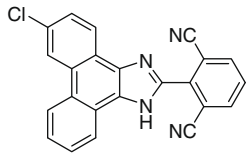
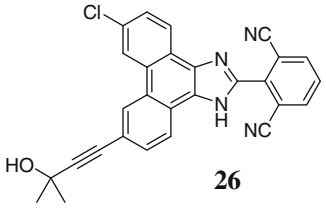
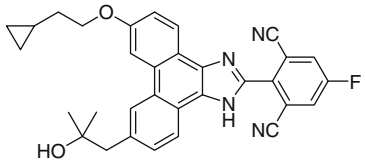


	IC_{50} (μM)
h-mPGES-1	0.001
A549 PGES	0.42
HWBA	1.3

1 (MF63)



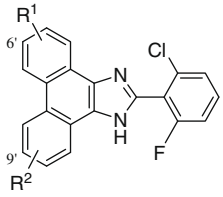
26



44

Figure 1. mPGES-1 inhibitors.

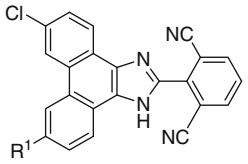
Table 1
mPGES-1IC_{50} data for mono- and bis-substituted phenanthrene imidazoles

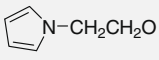
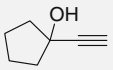


Compd	R^1	R^2	mPGES-1 inhibition	A549, 50% FBS PGE_2
			IC_{50}[a] (μM)	
2	H	H	0.036	2.6
3	6′-Cl	H	0.005	0.71
4	5′-Cl	H	0.011	4.3
5	6′-Br	H	0.002	1.1
6	4′-Br	H	0.11	5.0
7	5′-Br	H	0.025	7.4
8	7′-Br	H	0.008	3.0
9	6′-Br	9′-Br	0.003	1.0
10	6′-Br	9′-*i*Pr	0.004	2.0
11	6′-Br	9′-OMe	0.006	0.73
12	6′-Br	9′-COMe	0.008	0.33
13	6′-Br	9′-$C(CF_3)_2OH$	0.001	0.45
14	6′-Br	9′-$C(CH_3)_2OH$	0.007	0.28
15	6′-Me	9′-Me	0.007	1.1
16	6′-COMe	6′-COMe	0.122	>50
17	9′-$C(CH_3)_2OH$	9′-$C(CF_3)_2OH$	0.045	2.3

[a] Values are means of at least two experiments.

Table 2
mPGES-1 IC_{50} data for 9′-substituted chlorophenanthrene imidazoles



Compd	R_1	mPGES-1 inhibition	A549, 50% FBS PGE_2	HWB PGE_2
		IC_{50}[a] (μM)		
1	H	0.001	0.42	1.3
18	$HO(CH_3)_2C$	0.004	0.034	1.4
19	$MeSO_2$	0.009	0.11	>10
20	$NCCH_2CH_2CH_2O$	0.001	0.038	0.38
21		0.001	0.021	0.38
22	*p*-$MeSO_2C_6H_4$	0.002	0.045	0.41
23	$MeOCH_2C{\equiv}C$	0.002	0.060	1.1
24	3-PyridylC≡	0.001	0.057	0.53
25	4-PyridylC≡C	0.001	0.075	0.39
26	$HO(CH_3)_2CC{\equiv}C$	0.001	0.013	0.20
27		0.001	0.027	0.26

[a] Values are means of at least two experiments.

containing a heteroatom such as a methoxy, a methylketone or a tertiary alcohol (compounds **11–14**) increases activity in the whole cell assay. Conversely, the presence of two lipophilic substituents such as in compound **15** or two heteroatom containing groups (compound **17**) is detrimental to the activity. The right balance of one lipophilic group and one slightly polar substituent in an unsymmetrical fashion is optimal and leads to potent inhibitors having a reduced cellular shift. Based on these observations we further investigated the SAR at the 9′-position with the less lipophilic chloro substituent at the 6′-position and the optimal bis-orthocyano group found in mPGES-1 inhibitor **1** (**MF63**).

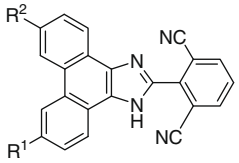
The structure–activity relationship of the 6′-chloro-9′-substituted inhibitors is summarized in Table 2. These analogues contain the more potent bis-cyanophenyl group found inhibitor **1** and previously disclosed.[5] Looking at the SAR we can observe that the presence of a tertiary alcohol (compound **18**) or a methylsulfonyl group (compound **19**) provides inhibitors with good whole cell potencies, however, they are highly shifted in presence of protein. Then we examined a number of phenol ether inhibitors exemplified by inhibitors **20** and **21**. In general, all analogues benefited from increased A549 whole cell and human whole blood activities. Rigidifying the substituent by the introduction of a phenyl or an alkyne group was also explored. Reduced whole cell and human whole blood activities were seen with methyl phenyl sulfone **22**, methyl propargyl ether **23**, 3-ethynylpyridyl **24** and the 4-ethynylpyridyl **25**. On the other hand, tertiary alcohol substituted alkynes demonstrated increased whole cell and whole blood activities (compounds **26** and **27**). Phenanthrene imidazole **26** proved to be the most potent mPGES-1 inhibitor we have prepared thus far. It

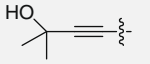
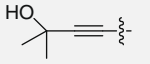
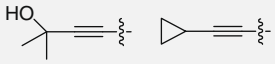
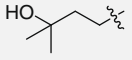
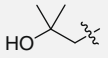
has a human whole blood activity of 0.20 μM with no concomitant TXB_2, PGF2α and PGI_2 inhibitions (Table 5) and PGD_2 inhibition (data not shown).

The general synthetic route for phenanthrene imidazole analogues is outlined in Scheme 1. The synthesis started with a Perkin condensation of 4-bromophenylacetic acid **28** with 4-chloro-2-nitrobenzaldehyde to afford the (*E*)-arylcinnamic acid **29** in 60% yield.[12] Nitro reduction with iron provided the amine **30** which underwent a diazotization and a subsequent intramolecular Pschorr[13] cyclization resulting in the formation of the phenanthrene **31** in 95% yield. Oxidation and decarboxylation in the presence of chromium (IV) oxide in acetic acid at 110 °C afforded the corresponding quinone **32** in 60% yield. The core of the molecule was assembled by the reaction of phenanthrenedione **32**, 2,6-dibromobenzaldehyde and ammonium acetate in acetic acid which provided the phenanthrene imidazole **33** in 85% yield. The dibromo intermediate **33** was then treated with CuCN in DMF at 80 °C to afford the bis-nitrile **34** in 80% yield.[14] Finally, installation of the acetylinic tertiary alcohol group under Sonogashira conditions provided the desired target compound **26** in 70% yield.

The selective mPGES-1 inhibitor **26** demonstrated oral in vivo efficacy in a LPS-induced hyperalgesia guinea pig model (guinea pig mPGES-1 whole blood = 0.10 μM) with a ED_{50} of 30 mg/kg.[10] Pharmacokinetic (PK) studies in rat revealed a long half life of 20 h and slow absorption rate (C_{max} @ 6 h). This correlates well with the rat hepatocyte incubation studies that showed very little metabolism (3%, see Table 5) after the 2 h incubation period at 37 °C. Similarly, the human hepatocyte incubation studies demonstrated minimal metabolism (3%). The main cytochrome P450's responsible for metabolism were identified to be the extrahepatic CYP1A1 and CYP2J2, suggesting a potentially long half life in humans. Furthermore, excretion studies showed that the phenanthrene imidazole **26** was mainly eliminated as the parent in the bile, supporting low metabolism. Although, the phenanthrene imidazole **26** is selective, potent and orally active, further SAR studies to identify a mPGES-1 inhibitor with a shorter half life.

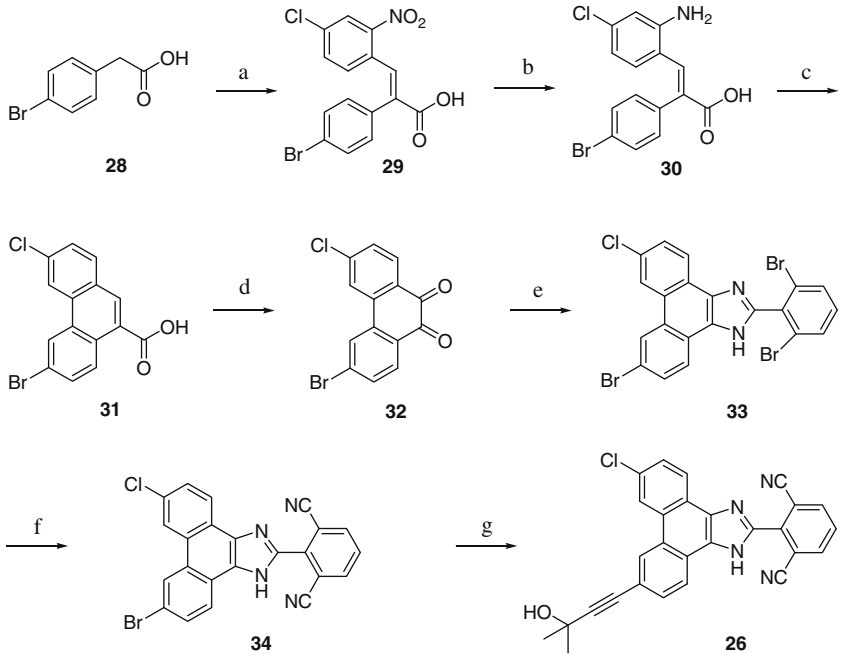
Table 3
SAR at the 6′- and 9′-positions of the phenanthrene imidazole



Compd	R^1	R^2	mPGES-1 inhibition	HWB PGE_2	Rat $t_{1/2}$[a] (h)
			IC_{50}[b] (μM)		
26		Cl	0.001	0.2	20
35		Et	0.001	0.37	7.0
36			0.001	0.076	40
37		Cl	0.001	0.20	14
38		Cl	0.002	0.25	8.4

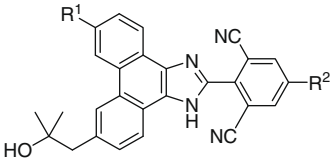
[a] Rat half life after single iv dosing at 5 mg/kg.
[b] Values are means of at least two experiments.

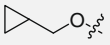
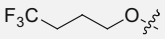
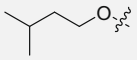
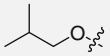
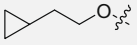
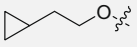
As shown in Table 3, keeping the propargylic alcohol in place and modifying the lipophilic group afforded a mean of modulation for the pharmacokinetics. For example, inhibitor **35** in which the chloro was replaced by an ethyl group demonstrated a much shorter half life compared to inhibitor **36**. Saturating the triple bond as a



Scheme 1. Reagents and conditions: (a) 4-chloro-2-nitrobenzaldehyde, K_2CO_3, Ac_2O, 100 °C, 60%; (b) Fe, AcOH, H_2O 50 °C, 96%; (c) (i) $NaNO_2$, NaOH, 0 °C (ii) H_2SO_4, H_2NSO_3, $FeCp_2$, 0 °C, 95%; (d) CrO_3, AcOH, 110 °C, 60%; (e) 2,6-dibromobenzaldehyde, NH_4OAc, AcOH, reflux, 85%; (f) CuCN, DMF, 80 °C, 80%; (g) 2-methyl-3-butyn-2-ol, $Pd(Ph_3)_4$, iPr_2NH, DMF, CuI, 70 °C, 70%.

Table 4
SAR at the 6′-position of the 9′-(2-methyl-2-propanol) phenanthrene imidazole



Compd	R^1	R^2	mPGES-1 inhibition IC_{50}[d] (μM)	HWB PGE_2	Rat $t_{1/2}$[a] (h)	% F[b]	% of Parent remaining[c] Rat	Human
39		H	0.003	0.35	5.5	36	n.d.[e]	>99
40		H	0.001	0.25	3.3	85	92	98
41		H	0.0004	0.15	4.8	46	8	30
42		H	0.003	0.29	1.3	30	n.d.	n.d.
43		H	0.0009	0.22	1.6	76	n.d.	n.d.
44		F	0.001	0.14	2.3	68	68	81

[a] Rat half life after single iv dosing at 5 mg/kg.
[b] Bioavailability in the rat after single po dosing at 20 mg/kg.
[c] % of parent remaining after 2 h of incubation in presence of hepatocytes.
[d] Values are means of at least two experiments.
[e] Not determined.

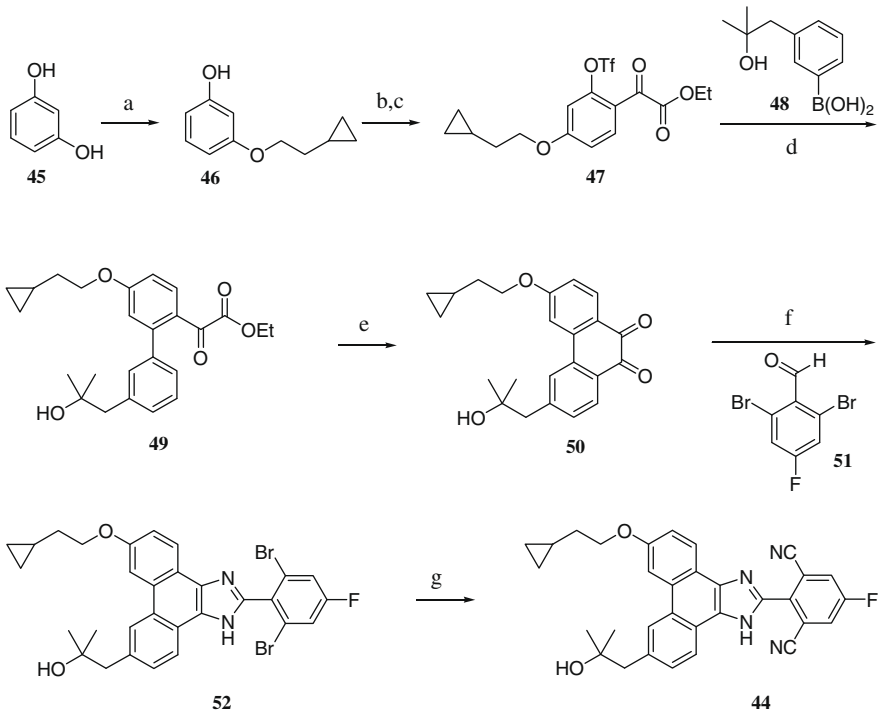
mean to introduce a metabolic soft spot provided the potent inhibitor **37**, however its inherent pharmacokinetics revealed a long half life of 14 h. Interestingly, the shortened tertiary alcohol found in inhibitor **38** had in vivo activities comparable to **26**. This pharmacophore provided an inhibitor with a shorter half life, but unfortunately this inhibitor exhibited CYP 3A4 induction. Encouraged by these findings and our desire to address this undesired property, further SAR investigations were initiated while maintaining the 2-methyl-2-propanol group in the hydrophilic region and modifying the lipophilic region (see Table 4).

The introduction of a cyclopropylmethyl ether or a 3-trifluorobutyl group leads to potent inhibitors with an adequate half life (compounds **39** and **40**). Unfortunately, as previously seen with phenanthrene imidazole **26**, these inhibitors showed little metabolism after an incubation period in the presence of human hepatocytes. Conversely, the incorporation of a 3-methylbutylether group (compound **41**) led to an inhibitor having a very good in vitro profile and pharmacokinetics, however, it had a high degree of metabolism in rat (92%) and human hepatocytes (70%) incubation studies. Introduction of 2-methylpropylether and cyclopropylethyl ether groups (compounds **42** and **43**) give rise to inhibitors that possess good overall in vivo activities and good bioavailabilities. More interestingly, the incorporation of a *para*-fluoro on the biscyanophenyl ring resulted in the identification of phenanthrene imidazole **44**, our most active mPGES-1 inhibitor to date. The phenanthrene imidazole **44** has a half life in the rat of 2.3 h and bioavailability of 68%. In the human hepatocyte metabolism studies, phenanthrene imidazole **44** was more extensively metabolized than its predecessors with 81% parent remaining after the 2 h incubation period at 37 °C compared to 97% for the inhibitor **26**. The main cytochrome P450 responsible for the metabolism of **44** is the hepatic CYP 3A4. The shorter rat half life observed along with an increased metabolism compared to inhibitor **26** support our confidence in avoiding an excessively long half life in humans. Overall, this inhibitor was found to have excellent in vivo activities, mPGES-1 enzymatic activity of 0.001 μM and a human whole blood activity of 0.14 μM. Furthermore, it does not inhibit the biosynthesis of PGD_2, $PGF2\alpha$, PGI_2 and TXA_2. The selective inhibitor **44** is thermally stable as a tosylate salt and showed a fast absorption rate in rat, reaching C_{max} after 1 hour.[15] Conversely, the inhibitor **26** had potential stability issues since dehydration of the tertiary alcohol was detected in thermal stability analysis of several salt

Table 5
Comparative data of mPGES-1 inhibitors **1**, **26** and **44**

Enzyme or cell assay	IC_{50}[a] (μM) **1**	**26**	**44**
Human mPGES-1	0.001	0.001	0.0009
Guinea pig mPGES-1 whole blood	0.10	0.10	n.d.
Human mPGES-2	>30	>30	>30
TX synthase	3.0	0.8	30
A549 cells, PGE_2, 50% FBS	0.42	0.020	0.010
A549 cells, $PGF_{2\alpha}$, 50% FBS	>40	>40	>40
Human whole blood, PGE_2	1.3	0.20	0.14
Human whole blood, TXB_2	>40	>40	>40
In vitro and in vivo data			
Rat $t_{1/2}$ (h)	1.5	20	2.3
Rat hepatocyte metabolism (parent remaining)	n.d.	97%	68%
Human hepatocyte metabolism (parent remaining)	90%	97%	81%
Guinea Pig hyperalgesia model ED_{50} (mg/kg)	100	30	14

[a] Values are means of at least two experiments.



Scheme 2. Reagents and conditions: (a) 2-cyclopropylethyl methanesulfonae, K_2CO_3, acetone, reflux, 78%; (b) $TiCl_4$, $ClCOCO_2Et$, CH_2Cl_2, −78 °C, 53%; (c) Tf_2O, Et_3N, CH_2Cl_2, −78 °C, 99%; (d) **48**, $PdCl_2(dppf)\cdot CH_2Cl_2$, K_2CO_3, DME, 70 °C; (e) (i) NaOH, H_2O, MeOH, THF, rt (ii) CDI, CH_2Cl_2, 50 °C, rt (iii) $TiCl_4$, CH_2Cl_2, rt, 0 °C; (f) **51**, NH_4OH, AcOH, 85 °C, (60%, five steps); (g) CuCN, DMF, 80 °C, 80%.

forms. The mPGES-1 inhibitor **44** demonstrated enhanced oral in vivo efficacy over its predecessors in the LPS-induced hyperalgesia guinea pig model with a ED_{50} of 14 mg/kg (see Table 5).

The synthesis of **44** started with the mono-alkylation of commercially available resorcinol **45** with 2-cylclopropylethyl methanesulfonate. The phenol **46** underwent a Friedel–Crafts reaction in the presence of ethyl oxalyl chloride. The intermediate was then submitted to triflic anhydride in the presence of triethylamine in dichloromethane affording the corresponding oxalyl ester **47** in an overall yield of 53%. The biaryl **49** is generated by the palladium cross-coupling of **47** with the boronic acid **48**.[16] Ester hydrolysis under basic conditions followed by activation in the presence of carbonyl diimidazole and a subsequent Friedel–Crafts reaction provided the quinone **50**. Product elaboration was accomplished as described previously by the addition of the quinone **50** in the presence of 2,6-dibromo-4-fluorobenzaldehyde[17] **51** and ammonium acetate affording the phenanthrene imidazole **52** in an overall yield of 60% for the five reaction steps. Finally, the cyano groups were incorporated by reacting the dibromo precursor **52** with CuCN in DMF at 80 °C which provided the target inhibitor **44** in 80% yield (see Scheme 2).

In summary, we have identified two potent, selective and orally active mPGES-1 phenanthrene imidazole inhibitors (compounds **26** and **44**). These new inhibitors showed in vitro and in vivo superiority over the previously reported phenanthrene imidazole **1**. In particular, a 10-fold increase in whole blood activity and in vivo efficacy is demonstrated with the mPGES-1 inhibitor **44**. Finally, the mPGES-1 inhibitors **26** and **44** demonstrate distinct pharmacokinetic profiles where both are suitable for further pre-clinical studies.

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15. Improved rate of absorption under certain conditions. For example, following dosing in rats at 20 mg/kg in PEG400, the respective t_{max} were 1 h and greater than 6 h for **38** and **20**, respectively.
16. The boronic acid **48** is prepared by first forming the Grignard of 3-bromobenzyl bromide in the presence of magnesium in ether followed by the addition of acetone. The tertiary alcohol intermediate is then treated with *n*-butyllithium and trimethyl borate providing after acidic treatment the boronic acid **48** in a 70% yield.
17. *Synthesis of benzaldehyde* **51** *is as follows*: Diazotization of 4-amino-2,6-dibromotoluene in the presence of sodium nitrite and hydrochloric acid followed by fluoronation with HPF_6 at 200 °C provides the 2,6-dibromo-4-fluorotoluene in 85% yield. Bromination with NBS followed by oxidation in the presence of trimethylamine oxide (TMNO) and DMSO in dichloromethane affords the aldehyde **51** in 80% yield.