Synthesis of a Chiral Precursor for No-Carrier-Added (NCA) PET Tracer 6-[^{18}F]Fluoro- L-dopa Based on Regio- and Enantioselective Alkylation of 2,4-Bis(chloromethyl)-5-iodoanisole

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(2*S*,5*S*)-5-(3-Formyl-6-iodo-4-methoxybenzyl)-1-*t*-butoxycarbonyl-2-*t*-butyl-3-methyl-4-imidazolidinone (**11**), a chiral intermediate towards NCA PET tracer 6-[^{18}F]fluoro-L-dopa (**1**), was synthesized from 3-iodoanisole in four steps. 3-Iodoanisole was first bischloromethylated to 2,4-bis(chloromethyl)-5-iodoanisole (**14**). Regio- and enantio-selective alkylation of **14** with (*S*)-1-(*t*-butoxycarbonyl)-2-*t*-butyl-3-methyl-4-imidazolidinone (**12**) afforded **33**, which was then hydrolyzed and oxidized to the desired intermediate **11**.

6-[^{18}F]Fluoro-L-dopa (6FDOPA; **1**) is an established tracer for the elucidation of central dopaminergic system with Positron Emission Tomography (PET) (Chart 1), especially in studying the compromised nature of dopamine function in Parkinson's disease.[1] As a result, significant synthetic efforts have been made to optimize its production to reach the ease of the widely used agent [^{18}F]fluorodeoxyglucose (FDG). 6FDOPA is currently available by electrophilic fluorination as well as by nucleophilic fluoride displacement reactions.[2] The former method, though facile, produces a tracer with low specific activity. The latter method yields 6FDOPA as no-carrier-added (NCA) tracer, i.e., with higher specific activity, but the number of steps involved make it cumbersome.[3] Though our previous paper[4] reported an improved synthesis of 6FDOPA, we have been conceiving methods to improve the overall efficiency of its nucleophilic preparation. Thus taking into account the short half life of ^{18}F ($T_{1/2}$ = 110 min), it is essential to introduce radioactive [^{18}F]fluoride at a later stage of the synthesis. Especially chiral separation should be avoided since this involves loss of radioactivity in the form of biologically inactive enantiomer and also by decay during the 30 min it takes to run the HPLC separation. We describe here our efforts in synthesizing a chiral intermediate with an activating group located *para* to the leaving group so as to facilitate the preparation of enantiomerically pure 6FDOPA.

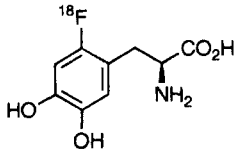

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Chart 1.

* Correspond with CK for the synthetic work described in this article.

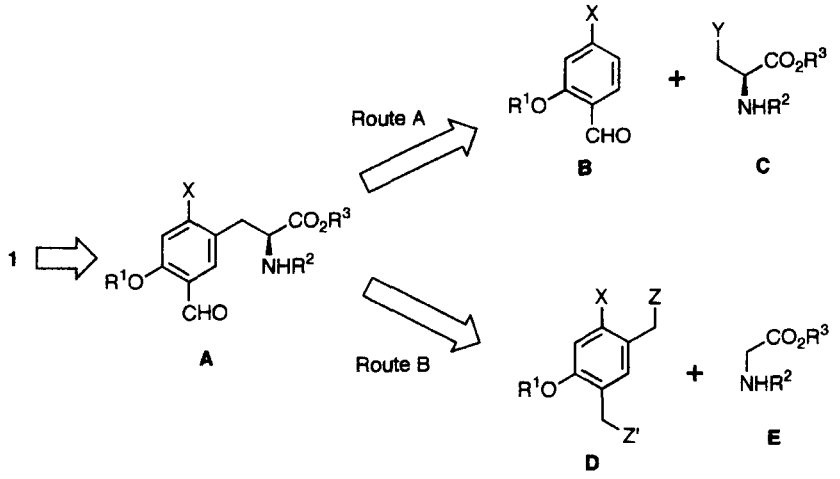
* Correspond with GNR for general information.

Results and Discussion

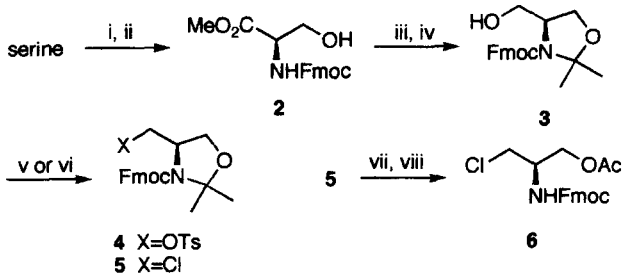
Retrosynthesis. We envisioned that compound **A** could be a key intermediate, wherein displacement of leaving group X with [^{18}F]fluoride could be carried out by the aid of *para*-formyl group (Scheme 1), followed by Baeyer–Villiger oxidation and deprotection to obtain 6FDOPA in chirally pure form. By this methodology, the necessary carbon skeleton can be constructed as well as the chiral center before introducing [^{18}F]fluoride. This would provide a simple and short-step method to produce 6FDOPA with high specific activity. In this paper, we describe our efforts in synthesizing compound **A** with iodine as the leaving group (X = I).[5]

We planned two basic strategies towards the synthesis of **A** (Scheme 1). The first route (Route A) involves Friedel–Crafts coupling of aromatic compound **B** and a chiral amino acid derivative **C**, and the second (Route B) alkylation of benzyl halide **D**, or its equivalent, with a chirally inducting glycine derivative **E**. Route A has an advantage that inexpensive serine derivative can be used as the chirality source, while the advantage of Route B is that benzylation is more effective than Friedel–Crafts alkylation for the coupling reaction.

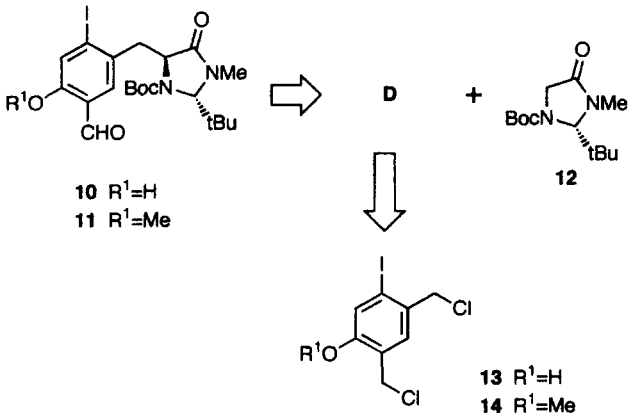
Route A. For the amino acid part **C**, compounds **4**, **5**, and **6** were synthesized as described in Scheme 2. Thus serine methyl ester protected with Fmoc (9-fluorenylmethoxycarbonyl) (**2**), obtained by protection of serine with Fmoc and subsequent esterification, was further protected as acetonide (97%) followed by reduction with $NaBH_4$/LiCl[6] to afford



Scheme 1.



Scheme 2. Reagents and conditions: i) FmocCl, Na_2CO_3 aq, dioxane, r.t.; ii) $SOCl_2$, MeOH, r.t.; iii) dimethoxypropane, TsOH, benzene, reflux; iv) $NaBH_4$, LiCl, THF, reflux; v) TsCl, pyridine, r.t.; vi) Ph_3P, CCl_4, reflux; vii) MeOH, PPTS, reflux; viii) Ac_2O, pyridine, r.t.



Scheme 3.

alcohol **3** (98%). The hydroxy group of **3** was converted to both tosylate **4** and chloride **5**, in 89 and 96% yield, respectively. The chloride **5** was then subjected to deprotection (98%), followed by acetylation to afford **6** (93%). However, Friedel–Crafts coupling of **4**, **5**, and **6** with 2-hydroxy-4-iodobenzaldehyde, obtained by Reimer–Tiemann reaction of 3-iodophenol (see Route B1), in the presence of $AlCl_3$ was unsuccessful. Only the deprotected chloride **7** was obtained when **4** or **5** was employed (Chart 2), while **6** gave a complex mixture. Varying the reaction conditions, such as solvents or Lewis acids, using **8** and **9** as model compounds did not result in the desired compound. Under tested conditions ($AlCl_3$, $ZnCl_2$, and $FeCl_3$ as Lewis acids; $MeNO_2$, CH_2Cl_2, and CS_2 as solvents), no coupling reaction took place. Finally, this route was abandoned since Route B proved to be successful, as described below.

Route B. As the target molecule of this route, we conceived compound **10** or **11** that could be obtained by benzylation of (*S*)-1-(*t*-butoxycarbonyl)-2-*t*-butyl-3-methyl-4-imidazolidinone (**12**) with **D** or its equivalent according to Seebach's method[7] (Scheme 3). The latter could be easily obtained from bis(chloromethyl) derivative **13** or **14**, but it is necessary to differentiate two chloromethyl groups. In order to achieve this differentiation, we conceived three strategies; stepwise alkylation (Route B1), selective protection (Route B2), and selective alkylation (Route B3).

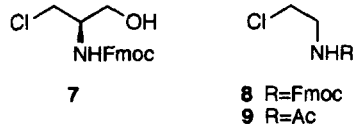
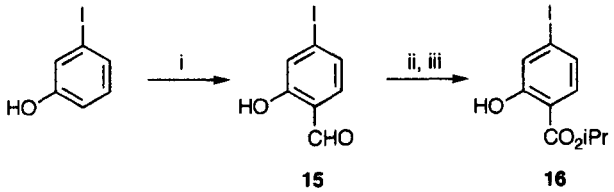


Chart 2.

Route B1. This route involves alkylation of **B**, and therefore is a variation of Route A. First, classical Reimer–Tiemann[8] reaction of 3-iodophenol was carried out by treatment with $CHCl_3$ and NaOH giving **15** in 14% yield (Scheme 4). Although the position of the formyl group was not determined at this stage, the aldehyde was oxidized and esterified to an ester, in order to avoid side products in the benzylation step. Thus carboxylic acid obtained by silver



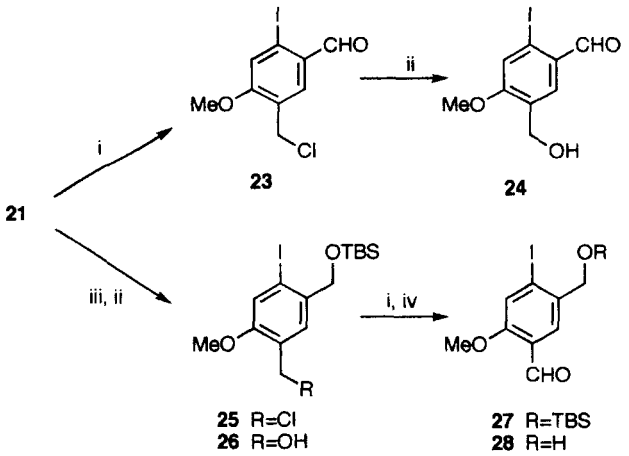
Scheme 4. Reagents and conditions: i) $CHCl_3$, NaOH, H_2O, 70 °C; ii) $AgNO_3$, KOH, H_2O, r.t.; iii) *i*PrOH, *N*,*N*′-carbonyldiimidazole, DBU, DMF, 40 °C.

oxidation of **15** (49%) was esterified to isopropyl ester[9] giving **16** in 39% yield. However, this route was abandoned without studying Friedel–Crafts alkylation of **16** in detail, since the corresponding compound was obtained easily by Route B3, as described below.

Route B2. In this route, an attempt was made to distinguish two hydroxymethyl groups of **19** by the formation of acetonide, taking advantage of the phenolic hydroxy group adjacent to one of the two hydroxymethyl groups (Scheme 5). Bischloromethylation[10] of 3-iodophenol with $ClCH_2OCH_3/AlCl_3$ was first attempted but without success. The phenolic hydroxy group was then protected with a pivaloyl group to give **17** (97%), which was subjected to bischloromethylation affording **18**. Hydrolysis of both chloride and pivaloyl group with KOH aq in EtOH afforded triol **19** in 66% yield from **17**. However, since several attempts at acetalization of **19** to **20** were not successful, this route was abandoned.

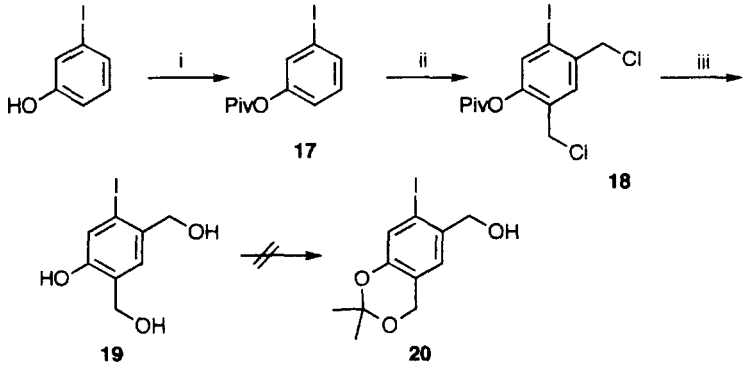
Route B3. Here a selective reaction with one of the two chloromethyl groups was attempted. 3-Iodoanisole was used as the starting material. When 3-iodoanisole was bischloromethylated with $AlCl_3$ and methoxychloromethane,[10] compound **14** was obtained in poor yield. However the yield was improved to 68% by using $TiCl_4$ instead of $AlCl_3$ (Scheme 6). As an explorative study of selective reaction, when **14** was treated under mild hydrolysis condition ($NaHCO_3$ aq, acetone), one of two chloromethyl groups was selectively hydrolyzed to afford **21** (57% yield based on consumed material). However, unfortunately, it was not possible at this stage to determine which chloromethyl group was hydrolyzed. It was difficult to distinguish two methylene signals of **21** in the ^1H NMR spectrum. The NOE spectrum of acetate **22** was also useless.

In order to establish the structure of **21**, this compound

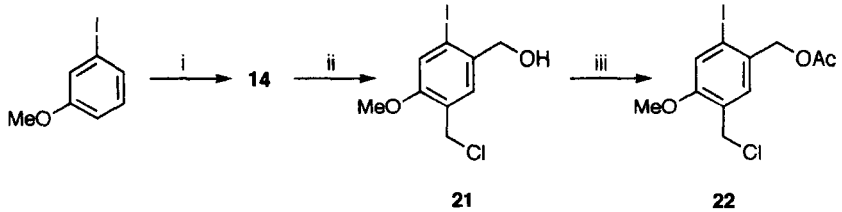


Scheme 7. Reagents and conditions: i) MnO_2, CH_2Cl_2, r.t.; ii) $AgNO_3$, H_2O, acetone, r.t.; iii) TBSCl, DMF, imidazole, r.t.; iv) TBAF, THF, H_2O, r.t.

was converted into two isomeric hydroxy aldehydes **24** and **28** (Scheme 7), and the structure was determined by comparing ^{13}C NMR data of these hydroxy aldehydes. Compound **24** was obtained by MnO_2 oxidation of benzyl alcohol (**23**, 76%), followed by hydrolysis of the other chloromethyl group (43%). Compound **28** was prepared by four-step reactions: protection of hydroxy group with *t*-butyldimethylsilyl (TBS) group (**25**, 81%), hydrolysis of chloromethy group (**26**, 78%), MnO_2 oxidation (**27**, 91%), and removal of TBS group (48%). The δ values of aromatic carbons for **24** and **28** are shown in Table 1. Good agreement was obtained when δ-values of aromatic carbons were compared with calculated values,[11] which were deduced from *o*-methoxybenzyl alcohlol (**29**) and *o*-iodobenzaldehyde (**30**) for **24**, and *o*-methoxybenzaldehyde (**31**) and *o*-iodobenzyl alcohol (**32**) for **28** (Table 2 and Chart 3). Here direct summa-



Scheme 5. Reagents and conditions: i) PivCl, pyridine, 0 °C; ii) $ClCH_2OCH_3$, $AlCl_3$, r.t.; iii) KOH aq, EtOH, r.t., then HCl aq.



Scheme 6. Reagents and conditions: i) $ClCH_2OCH_3$, $TiCl_4$, r.t.; ii) $NaHCO_3$, H_2O, acetone, r.t.; iii) Ac_2O, pyridine, r.t.

Table 1. ^{13}C NMR Data of **24** and **28**

Carbon[a]	24		28	
	Observed	Calcd ($\Delta\delta$)[b]	Observed	Calcd ($\Delta\delta$)[c]
C(1)	161.8	164.3 (+35.8)	160.5	162.5 (+34.0)
C(2)	121.8	122.2 (−6.3)	123.1	122.3 (−6.2)
C(3)	101.7	101.0 (−27.5)	106.6	112.2 (−16.3)
C(4)	128.6	127.2 (−1.3)	135.6	134.5 (+6.0)
C(5)	129.7	130.3 (+1.8)	127.7	128.3 (−0.2)
C(6)	130.4	129.3 (+0.8)	124.6	124.7 (−3.8)

a) Carbon number is not consistent with that of nomenclature. C(1) is the methoxy-bearing position; C(3) is the iodinated position. See Chart 3. b) Calculated from $\Delta\delta$ values of **29** and **30**, see Table 2. c) Calculated from $\Delta\delta$ values of **31** and **32**, see Table 2.

Table 2. ^{13}C NMR Data used for the Calculation of **24** and **28**

Carbon[a]	**29**[b,d]	**30**[c,d]	**31**[b,d]	**32**[b,d]
C(1)	157.3 (+28.8)	135.5 (+7.0)	161.8 (+33.3)	129.2 (+0.7)
C(2)	110.1 (−18.4)	140.6 (+12.1)	111.7 (−16.8)	139.1 (+10.6)
C(3)	128.8 (+0.3)	100.7 (−27.8)	135.9 (+7.4)	104.8 (−23.7)
C(4)	120.6 (−7.9)	135.1 (+6.6)	120.6 (−7.9)	142.4 (+13.9)
C(5)	128.6 (+0.1)	130.2 (+1.7)	128.4 (−0.1)	128.4 (−0.1)
C(6)	129.1 (+0.6)	128.7 (+0.2)	124.9 (−3.6)	128.3 (−0.2)

a) Carbon number is not consistent with that of nomenclature. See Table 1. b) Data were quoted from Aldrich's data book.[14] c) Synthesized by oxidation of **32**. d) $\Delta\delta$ (= δ − 128.5) in parenthesis.

29 R=CH_2OH
31 R=CHO

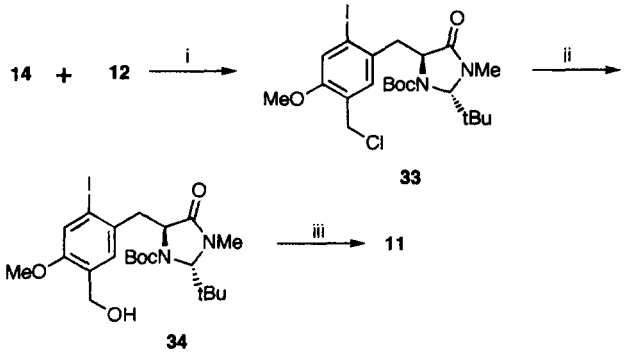
30 R=CHO
32 R=CH_2OH

Chart 3.

tion of substituent effects ($\Delta\delta$) causes a serious error due to *ortho*-substituent effect.[11] Therefore, the structure of **21** was established as 2-chloromethyl-4-hydroxymethyl-5-iodoanisole. The selectivity of one chloromethyl group over the other can be explained by the larger inductive effect of iodine than of the methoxy group.

It is possible to convert **21** into **D** or its equivalent. However, since we were convinced that the chloromethyl group adjacent to iodine would selectively react, **14** was treated with the enolate derived from chiral imidazolidinone **12** and LDA.[7] The alkylation reaction proceeded both regio- and stereo-selectively giving **33** in 39% yield from **12** (Scheme 8). Hydrolysis of **33** with KOH in EtOH aq gave alcohol **34** along with some by-products, while **34** was obtained as a sole product in 90% yield when **33** was treated with $AgNO_3$ in aqueous acetone.[12] Oxidation of **34** to **11** was achieved in 45% yield by treatment with MnO_2. However, when **34** was subjected to Swern oxidation, **11** was obtained in 75% yield.

Conclusion. The chiral key intermediate **11** for the synthesis of 6-[^{18}F]fluoro-L-dopa (**1**) was synthesized as enantiomerically pure form in four steps from 3-iodoanisole. It is possible to synthesize corresponding compounds having some other leaving group such as X = Cl or NO_2 by the



Scheme 8. Reagents and conditions: i) LDA, THF, −50 °C to r.t.; ii) $AgNO_3$, H_2O, acetone, r.t.; iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C to r.t.

same route. The one-pot displacement reaction of X group with [^{18}F]fluoride[5] followed by Baeyer–Villiger reaction[13] and deprotection into **1** is in progress. This method also affords a simple way to prepare the chirally pure compounds, for other needs. It was also established that, of two chloromethyl groups in 2,4-bis(chloromethyl)-5-iodoanisole, the one adjacent to iodine is more reactive than the other.

Experimental

General Procedures. Melting points were collected on a Laboratory Devices Mel-Temp apparatus. IR spectra were taken on a JASCO FT/IR-230 spectrometer. Both ^1H and ^{13}C NMR spectra were measured on a JEOL GSX-400 (400 MHz for ^1H; 100 MHz for ^{13}C) spectrometer. Chemical shifts are reported on the δ scale (ppm) with tetramethylsilane (Me_4Si = 0.00) as an internal standard. The signal of the solvent ($CHCl_3$ = 7.26 for ^1H; $CDCl_3$ = 77.0 for ^{13}C) was used an a standard for all compounds having TBS group. Both low-resolution mass spectra (MS) and

high-resolution mass spectra (HRMS) were obtained on a JEOL SX-102A mass spectrometer with EI method. Analytical TLC was done on precoated TLC plates (Kieselgel 60 F_{254}, layer thickness 0.2 mm). Wakogel C-200 was used for column chromatography.

2,4-Bis(chloromethyl)-5-iodoanisole (14). In a 100 cm^3 round-bottomed flask with a $CaCl_2$ drying tube attached was placed a solution of 3-iodoanisole (1.02 g, 4.36 mmol) in CH_3OCH_2Cl (20 cm^3). A solution of $TiCl_4$ in CH_2Cl_2 (10 cm^3, 10 mmol; 1.0 mol dm^{-3} solution) was added at 0 °C with stirring. After the mixture had been stirred at room temperature for 3 d, water was added, and the mixture was extracted with Et_2O. The ethereal layer was washed successively with saturated $NaHCO_3$ aq and brine, and then dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica-gel (30 g) column chromatography using hexane–AcOEt (24 : 1) as eluent afforded **14** (983.7 mg, 68%); mp 85—86 °C; IR (KBr) 1600, 1560, 1490, 1440, 1260, 1025, 975, and 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.88 (3H, s, OMe), 4.57 (2H, s, CH_2Cl), 4.66 (2H, s, CH_2Cl), 7.34 (1H, s, ArH), and 7.44 (1H, s, ArH); ^{13}C NMR ($CDCl_3$) δ = 40.6, 50.6, 56.1, 100.3, 122.1, 126.7, 131.5, 132.4, and 157.3; MS *m/z* (rel intensity) 334 (M^+ for $^{37}Cl_2$; 5%), 332 (M^+ for $^{35}Cl^{37}Cl$; 29), 330 (M^+ for $^{35}Cl_2$; 46), 297 (66), 295 (100), 138 (19), and 89 (18); HRMS [Found: *m/z* 329.9102 (M^+). Calcd for $C_9H_9Cl_2IO$: M, 329.9077]; Analysis [Found: C, 32.63; H, 2.70; Cl, 21.11%. Calcd for $C_9H_9Cl_2IO$: C, 32.66; H, 2.72; Cl, 21.42%].

2-Chloromethyl-4-hydroxymethyl-5-iodoanisole (21). To a stirred solution of **14** (900.9 mg, 2.72 mmol) in acetone (20 cm^3) were added H_2O (5 cm^3) and a saturated aqueous solution of $NaHCO_3$ (5 cm^3). The resulting suspension was stirred at room temperature for 3 d with TLC monitoring. Et_2O and H_2O were added, and the two layers were separated. After further extraction of aqueous layer, the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica-gel (20 g) column chromatography using hexane–AcOEt (95 : 5 and 90 : 10) as eluent afforded recovered **14** (808.5 mg) and **21** (49.4 mg, 57% based on consumed material). **21**: mp 148—150 °C; IR (Nujol) 3160, 1600, 1260, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.60 (1H, br, OH), 3.87 (3H, s, OMe), 4.59 (2H, s, CH_2Cl or $C\underline{H}_2OH$), 4.63 (2H, s, $C\underline{H}_2OH$ or CH_2Cl), 7.32 (1H, s, ArH), and 7.42 (1H, s, ArH); ^{13}C NMR ($CDCl_3$ = 77.0) δ = 40.9, 56.0, 68.6, 98.2, 121.7, 126.3, 130.2, 135.2, and 156.9; MS *m/z* (rel intensity) 314 (M^+ for ^{37}Cl; 18%), 312 (M^+ for ^{35}Cl; 56), 277 (100), 252 (13), 229 (17), 121 (28), and 91 (33); HRMS [Found: *m/z* 311.9449 (M^+). Calcd for $C_9H_{10}ClIO_2$: M, 311.9415].

3-Chloromethyl-6-iodo-4-methoxybenzaldehyde (23). In a 50 cm^3 round bottomed flask with a $CaCl_2$ drying tube attached was prepared a solution of **21** (35.0 mg, 0.112 mmol) in dry CH_2Cl_2 (10 cm^3; distilled from CaH_2). MnO_2 (311 mg) was added and the resulting suspension was stirred at room temperature for 21 h. After filtration through Celite, the solvent was evaporated off to give a crude mixture that was chromatographed on silica gel (3 g) using hexane–AcOEt (96 : 4) as eluent to afford **23** (26.3 mg, 76%); mp 109—110 °C; IR (Nujol) 1675, 1590, 1025, 985, 845, and 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.97 (3H, s, OMe), 4.58 (2H, s, CH_2Cl), 7.39 (1H, s, ArH), 7.90 (1H, s, ArH), and 9.91 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ = 40.3, 56.4, 102.9, 122.4, 127.2, 128.6, 131.8, 161.8, and 194.2; MS *m/z* (rel intensity) 312 (M^+ for ^{37}Cl; 32%), 310 (M^+ for ^{35}Cl; 96), 275 (100), 245 (17), and 118 (12); HRMS [Found: *m/z* 309.9256 (M^+). Calcd for $C_9H_8ClIO_2$: M, 309.9258].

3- Hydroxymethyl- 6- iodo- 4- methoxybenzaldehyde (24). Compound **23** (35.0 mg, 0.113 mmol) was dissolved in acetone (5 cm^3) and H_2O (2 cm^3), and to this solution was added $AgNO_3$ (300 mg) with stirring. The white precipitate was filtered off, and the filtrate was dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by silica-gel (1 g) column chromatography using hexane–AcOEt (96 : 4) as eluent gave **24** (14.0 mg, 43%); mp 114—116 °C; IR (Nujol) 3300, 1680, 1595, 1255, and 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.80 (1H, br, OH), 3.95 (3H, s, OMe), 4.67 (2H, s, $C\underline{H}_2OH$), 7.37 (1H, s), 7.88 (1H, s), and 9.92 (1H, s); ^{13}C NMR ($CDCl_3$) δ = 56.2, 60.8, 101.7, 121.8, 128.6, 129.7, 130.4, 161.8, and 194.5; MS *m/z* (rel intensity) 292 (M^+; 100%), 263 (61), 164 (12), 129 (14), 108 (14), and 69 (21); HRMS [Found: *m/z* 291.9583 (M^+). Calcd for $C_9H_9IO_3$: M, 291.9597].

4- *t*- Butyldimethylsilyloxymethyl- 2- chloromethyl- 5- iodoanisole (25). To a stirred solution of **21** (94.0 mg, 0.301 mmol) in dry *N*,*N*-dimethylformamide (15 cm^3, distilled from 4 Å molecular sieve) were added imidazole (100 mg) and TBSCl (200 mg) at once. After this mixture had been stirred at room temperature for 5 min, water was added, and the mixture was extracted with Et_2O. The ethereal layer was washed with diluted HCl and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (10 g) using hexane–AcOEt (95 : 5) as eluent, producing **25** (104 mg, 81%); an oil; IR (neat) 1600, 1565, 1490, 1260, 1105, 840, and 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.14 (6H, s, $SiMe_2$), 0.97 (9H, s, *t*Bu), 3.86 (3H, s, OMe), 4.59 (2H, s, CH_2OTBS or CH_2Cl), 4.61 (2H, s, CH_2Cl or CH_2OTBS), 7.28 (1H, s, ArH), and 7.46 (1H, s, ArH); ^{13}C NMR ($CDCl_3$) δ = −5.3 (2C), 18.4, 25.9 (3C), 41.2, 56.0, 68.7, 96.3, 121.2, 125.9, 129.2, 135.3, and 156.3; MS *m/z* (rel intensity) 413 (M^+−Me for ^{37}Cl; 8%), 411 (M^+−Me for ^{35}Cl; 21), 391 (M^+−Cl; 24), 370 (100), 295 (95), 229 (95), and 103 (22); HRMS [Found: *m/z* 411.0001 (M^+−Me). Calcd for $C_{14}H_{21}ClIO_2Si$: M, 411.0045].

4- *t*- Butyldimethylsilyloxymethyl- 2- hydroxymethyl- 5- iodoanisole (26). Compound **25** (20.0 mg, 0.0469 mmol) was subjected to the same conditions described for **24** to obtain the alcohol **26** (15.0 mg, 78%), after silica-gel (1 g) column chromatography using hexane–AcOEt (95 : 5) as eluent. **26**: an oil; IR (neat) 3380, 1600, 1570, 1490, 1255, and 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.13 (6H, s, $SiMe_2$), 0.95 (9H, s, *t*Bu), 1.75 (1H, br, OH), 3.84 (3H, s, OMe), 4.58 (2H, s, $C\underline{H}_2OH$ or CH_2Cl), 4.64 (2H, s, CH_2Cl or $C\underline{H}_2OH$), 7.26 (1H, s, ArH), and 7.38 (1H, s, ArH); ^{13}C NMR ($CDCl_3$) δ = −5.3 (2C), 18.4, 26.0 (3C), 55.7, 61.9, 68.8, 94.9, 120.7, 127.7, 129.2, 135.3, and 156.6; MS *m/z* (rel intensity) 351 (M^+−*t*Bu; 83%), 277 (32), 229 (15), 129 (21), 81 (47), and 69 (100); HRMS [Found: *m/z* 350.9880 (M^+−*t*Bu). Calcd for $C_{11}H_{16}IO_3Si$: M, 350.9914].

3-*t*-Butyldimethylsilyloxymethyl-4-iodo-6-methoxybenzaldehyde (27). Compound **26** (34.6 mg, 0.0847 mmol) was oxidized by the same procedure described for **23** to obtain the aldehyde (31.4 mg, 91%), after silica-gel (3 g) column chromatography using hexane–AcOEt (95 : 5) as eluent. **27**: mp 66—68 °C; IR (Nujol) 1675, 1595, 1260, 980, and 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.13 (6H, s, $SiMe_2$), 0.96 (9H, s, *t*Bu), 3.92 (3H, s, OMe), 4.59 (2H, s, $C\underline{H}_2OTBS$), 7.44 (1H, s, ArH), 7.86 (1H, s, ArH), and 10.14 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ = −5.3 (2C), 18.4, 25.9 (3C), 56.1, 68.5, 105.0, 122.5, 124.6, 127.1, 135.8, 160.0, and 189.2; MS *m/z* (rel intensity) 391 (M^+−Me; 6%), 349 (87), 333 (78), 319 (45), 275 (100), 207 (49), and 89 (19); HRMS [Found: *m/z* 391.0192 (M^+−Me). Calcd for $C_{14}H_{20}IO_3Si$: M, 391.0227].

3-Hydroxymethyl-4-iodo-6-methoxybenzaldehyde (28). To a stirred solution of **27** (34.4 mg, 0.0847 mmol) in tetrahydrofuran (THF) (2 cm^3) was added a solution of tetrabutylammonium fluoride (86.2 mg) in THF (1.5 cm^3). After this mixture had been stirred

at room temperature for 5 min, water was added, and the mixture was extracted with Et_2O and dried. Evaporation of the solvent, followed by silica-gel (1.5 g) column chromatography using hexane–AcOEt (8 : 2) as eluent, afforded **28** (11.8 mg, 48%); mp 112—114 °C, IR (Nujol) 3200, 1680, 1595, 1255, and 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.10 (1H, br, OH), 3.94 (3H, s, OMe), 4.66 (2H, s, C$\underline{H}_2$OH), 7.48 (1H, s, ArH), 7.83 (1H, s, ArH), and 10.40 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ = 56.2, 68.4, 106.6, 123.1, 124.6, 127.7, 135.6, 160.5, and 189.1; MS *m/z* (rel intensity) 292 (M^+; 46%), 274 (19), 263 (11), 137 (13), 81 (44), and 69 (100); HRMS [Found: *m/z* 291.9626 (M^+). Calcd for $C_9H_9IO_3$: M, 291.9597].

(2*S*,5*S*)-5-(3-Chloromethyl-6-iodo-4-methoxybenzyl)-1-*t*-butoxycarbonyl-2-*t*-butyl-3-methyl-4-imidazolidinone (33). To a stirred solution of LDA, prepared from *i*Pr_2NH (0.1 cm^3, 0.7 mmol) and BuLi (0.4 cm^3, 0.64 mmol; 1.6 mol dm^{-3} solution in hexane) in dry THF (1 cm^3; distilled from CaH_2) under Ar at −50 °C, was added dropwise a solution of (*S*)-1-*t*-butoxycarbonyl-2-*t*-butyl-3-methyl-4-imidazolidinone (**12**, 120.7 mg, 0.471 mmol) in THF (1 cm^3). After this mixture had been stirred at −50 °C for 30 min, a solution of **14** (185.1 mg, 0.559 mmol) in THF (1 cm^3) was added, and the mixture was stirred at room temperature overnight. A solution of saturated NH_4Cl aq was added, followed by extraction with Et_2O. The ethereal solution was washed with saturated $NaHCO_3$ aq and brine, and then dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica-gel (7 g) column chromatography using hexane–AcOEt (4 : 1) as eluent afforded **33** (100.8 mg, 39%); mp 133—134 °C; IR (KBr) 1700, 1695, 1595, 1490, 1385, 1255, and 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.97 (9H, s, CH*t*$\underline{Bu}$), 1.35 (9H, s, O*t*Bu), 2.94 (3H, s, NMe), 3.35 (1H, dd, *J* = 3, 15 Hz, ArC$\underline{H}$HCH), 3.45 (1H, br, ArCH$\underline{H}$CH), 3.81 (3H, s, OMe), 4.33 (1H, t-like, *J* = 4 Hz, $ArCH_2C\underline{H}$), 4.60 (1H, d, *J* = 12 Hz, ArC$\underline{H}$HCl), 4.62 (1H, d, *J* = 12 Hz, ArCH$\underline{H}$Cl), 4.98 (1H, br s, C$\underline{H}$*t*Bu), 7.01 (1H, s, ArH), and 7.21 (1H, s, ArH); ^{13}C NMR ($CDCl_3$) δ = 26.4 (3C), 28.0 (3C), 32.0, 40.8, 51.2, 55.9, 58.3, 80.9, 81.0, 96.8, 121.1, 126.7, 130.5, 131.4, 152.8 (br), 157.9, and 171.7; MS *m/z* (rel intensity) 515 (M^+−Cl; 11%), 493 (63), 477 (14), 437 (86), 393 (100), 357 (100), 295 (49), 256 (26), 230 (11), 138 (14), 103 (16), and 57 (100); HRMS [Found: *m/z* 515.1440 (M^+−Cl). Calcd for $C_{22}H_{32}IN_2O_4$: M, 515.1409]; Analysis [Found: C, 47.84; H, 5.74; N, 5.19%. Calcd for $C_{22}H_{32}ClIN_2O_4$: C, 47.97; H, 5.86; N, 5.09%].

(2*S*,5*S*)-5-(3-Hydroxymethyl-6-iodo-4-methoxybenzyl)-1-*t*-butoxycarbonyl-2-*t*-butyl-3-methyl-4-imidazolidinone (34). Compound **33** (115 mg, 0.209 mmol) was dissolved in acetone/H_2O (40 cm^3; 1 : 1 ratio), and to this was added $AgNO_3$ (146 mg, 0.86 mmol) with stirring. After this mixture had been stirred at room temperature for 1 h, the precipitate was filtered off through Celite, and the mixture was extracted with Et_2O and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded **34** (99.6 mg, 90%) which was not purified. **34**: mp 170—173 °C; IR (KBr) 3430, 1685, 1485, 1390, and 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.97 (9H, s, CH*t*$\underline{Bu}$), 1.31 (9H, s, O*t*Bu), 2.04 (1H, br OH), 2.96 (3H, s, NMe), 3.38 (2H, m, $ArC\underline{H}_2CH$), 3.80 (3H, s, OMe), 4.33 (1H, t-like, *J* = 4 Hz, $ArCH_2C\underline{H}$), 4.53 (1H, d, *J* = 12 Hz, ArC$\underline{H}$HOH), 4.55 (1H, d, *J* = 12 Hz, ArCH$\underline{H}$OH), 5.00 (1H, br s, C$\underline{H}$*t*Bu), 6.98 (1H, s, ArH), and 7.19 (1H, s, ArH); ^{13}C NMR ($CDCl_3$) δ = 26.4 (3C), 27.9 (3C), 32.1, 40.8, 55.7, 58.2, 68.7, 80.9 (2C), 94.5, 120.7, 125.9, 128.6, 134.6, 153.3 (br), 157.3, and 172.0; MS *m/z* (rel intensity) 515 (M^+−OH; 1%), 475 (100), 375 (75), 358 (77), 277 (60), 256 (26), 230 (19), and 57 (85); HRMS [Found: *m/z* 515.1427 (M^+−OH). Calcd for $C_{22}H_{32}IN_2O_4$: M, 515.1409].

(2*S*,5*S*)-5-(3-Formyl-6-iodo-4-methoxybenzyl)-1-*t*-butoxycarbonyl-2-*t*-butyl-3-methyl-4-imidazolidinone (11). To a stirred solution of $(COCl)_2$ (0.2 cm^3, 2.29 mmol) in dry CH_2Cl_2 (10 cm^3; distilled from CaH_2) was added dimethyl sulfoxide (0.2 cm^3, 2.82 mmol) at −60 °C under Ar. After this had been stirred for 5 min, a solution of **34** (42.6 mg, 0.0800 mmol) in CH_2Cl_2 (3 cm^3) was added, and the stirring was continued for 1 h. Et_3N (0.8 cm^3, 5.69 mmol) was added, and the mixture was allowed to warm to room temperature over 40 min. The reaction was quenched by the addition of water, followed by extraction with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated to give an oily residue, which was chromatographed on silica gel (6 g) using hexane–AcOEt (4 : 1) as eluent to afford **11** (32.0 mg, 75%); mp 153—155 °C; $[\alpha]_D^{23}$ +17° (*c* = 0.246); IR (KBr) 1710, 1700, 1680, 1595, 1360, 1250, and 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.99 (9H, s, CH*t*$\underline{Bu}$), 1.27 (9H, s, O*t*Bu), 3.06 (3H, s, NMe), 3.30 (1H, dd, *J* = 2, 16 Hz, ArC$\underline{H}$HCH), 3.60 (1H, br, ArCH$\underline{H}$CH), 3.90 (3H, s, OMe), 4.36 (1H, br, $ArCH_2C\underline{H}$), 5.05 (1H, br s, C$\underline{H}$*t*Bu), 7.27 (1H, s, ArH), 7.42 (1H, s, ArH), and 9.84 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ = 26.4 (3C), 27.9 (3C), 32.2, 40.8, 56.1, 57.8, 80.9, 81.2, 100.3, 121.5, 127.2, 128.0, 129.3, 152.6 (br), 162.6, 171.9, and 194.4; MS *m/z* (rel intensity) 531 (M^++H; 3%), 475 (100), 447 (43), 431 (17), 374 (74), 304 (76), 275 (42), 247 (13), 217 (7), and 89 (6); HRMS [Found: *m/z* 531.1367 (M^++H). Calcd for $C_{22}H_{32}IN_2O_5$: M, 531.1358]; Analysis [Found: C, 49.91; H, 5.99; N, 5.24; I, 23.55%. Calcd for $C_{22}H_{32}IN_2O_5$: C, 49.82; H, 5.89; N, 5.28; I, 23.93%].

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