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Nitrogen versus Oxygen Group Protection in Hydroxypropylbenzimidazoles

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In order to convert 1′*H*-benzimidazol-2′-ylpropanols into aryl ethers using Mitsunobu coupling, it was necessary to protect the benzimidazole nitrogen in the starting alcohols. Selective protection at nitrogen was achieved through *N*-benzyl derivatives, but attempts to protect the nitrogen directly through *tert*-butoxycarbonyl, acetyl, trityl, or tetrahydropyranyl derivatives were complicated either by selective reactions at oxygen or by the formation of bis-protected compounds. Transformations of some oxygen-protected derivatives are discussed, and in particular the conversion of the acetates of 1′*H*-benzimidazol-2′-ylpropanols to *N*-tetrahydropyranyl derivatives is described. Mitsunobu coupling involving the *N*-benzyl and *N*-tetrahydropyranyl derivatives and methyl 4-hydroxybenzoate were achieved, and thus afforded synthetic routes to the desired propylbenzimidazole aryl ethers.

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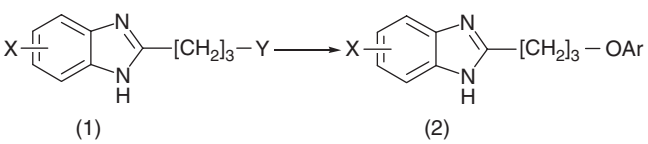
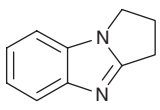
Introduction

As part of a study relating to the development of tripeptide mimics for the diagnosis and treatment of metastatic tumours, we required aryloxypropyl benzimidazoles of the type (2). Since we desired a number of aryloxy derivatives, it was preferable to start from a common benzimidazole and the most convenient general approach would involve ether synthesis as shown in Scheme 1. However, any attempt to react compounds of the type (1) (where Y is a suitable leaving group) resulted in cyclization to the pyrrolobenzimidazole (3) (Diagram 1). Since the functionality we required in groups X and Ar (2) were incompatible with strong acids, we thus needed to explore methods for the *N*-protection of benzimidazoles if the ether synthesis (Scheme 1) was to be employed, and we report here on a variety of alternatives.



(1) (2)

Scheme 1.



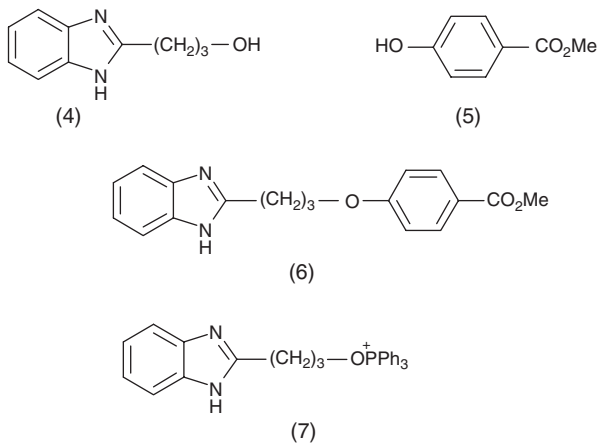
(3)

Diagram 1.

Results and Discussion

*Reactions of 1′*H*-Benzimidazol-2′-ylpropanol (4)*

Reaction of *o*-phenylenediamine with γ-butyrolactone afforded the required benzimidazole (4) (Diagram 2),[1] which on reaction with methyl 4-hydroxybenzoate (5) and triphenylphosphine/diethyl azodicarboxylate (Mitsunobu conditions) gave the pyrrolobenzimidazole (3) in 44% yield. None of the required ether (6) was detected. When the above reaction was repeated in the absence of the phenol (5), the pyrrolobenzimidazole (3) was formed in 68% yield. This indicated that the Mitsunobu intermediate (7) underwent



(4) (5)

(6)

(7)

Diagram 2.

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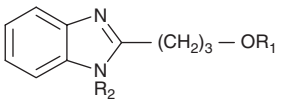
Table 1. Protecting group selectivity for the hydroxybenzimidazole (4)
Yields are isolated yields; – indicates product not formed

Protecting group	*N*-Protection	*O*-Protection	*N*- and *O*-Protection
BOC	–	–	(8) 42%
Acetyl	–	(9) 66%	(10) 27%
Trityl	–	(11) 75%	–
Benzyl	(12) 42%	–	–
Tetrahydropyranyl	(13) 5%	(14) 25%	(15) 5%



(8) R_1=R_2=CO.OBu^t
(9) R_1=CO.CH_3; R_2=H
(10) R_1=R_2=CO.CH_3
(11) R_1=C(Ph_3)$_3$; R_2=H
(12) R_1=H; R_2=CH_2Ph
(13) R_1=H; R_2=THP
(14) R_1=THP; R_2=H
(15) R_1=R_2=THP
(16) R_1=THP; R_2=CO.OBu^t
(17) R_1=CO.CH_3; R_2=CO.OBu^t
(18) R_1=CO.OBu^t; R_2=H
(19) R_1=CO.CH_3; R_2=THP

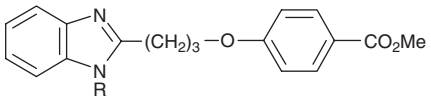
Diagram 3.

intramolecular cyclization, and the result is not surprising since a number of examples of this type of cyclization for 2-propylbenzimidazoles with suitable leaving groups are known.[1–3]

It was thus necessary to protect the nitrogen on the benzimidazole. For this heterocycle many protecting groups have been reported including *o*-nitrobenzyl,[4] vinyl,[5] trimethylsilylethylmethoxy,[6] ethylpyridyl,[7] hydroxymethyl,[8] trimethylsilylethanesulfonyl,[9] trityl,[10] tetrahydropyranyl (THP),[11] and *tert*-butoxycarbonyl (Boc).[12] However, in none of the examples has there been a neighbouring hydroxyl group which not only raises issues of nitrogen versus oxygen selectivity, but also which may influence the reaction through neighbouring-group chemistry.

Potential protecting groups for the hydroxybenzimidazole (4) were thus explored and the results are indicated in Table 1. Thus selective protection of the nitrogen was achieved through the benzyl group to give (12) (Diagram 3), and the oxygen was selectively protected with the trityl group to give (11). On the other hand both the nitrogen and oxygen groups reacted with Boc anhydride/*N*,*N*-dimethylaminopyridine (DMAP) and gave the bis-Boc derivative (8), while treatment of the hydroxybenzimidazole (4) with acetic anhydride gave the *O*-acetate (9) and the *N*,*O*-acetate (10) in the ratio of 2.5 : 1. Finally, when the hydroxybenzimidazole (4) was treated with 3,4-dihydropyran in the presence of *p*-toluenesulfonic acid catalyst a mixture of the *N*-protected (13), *O*-protected (14), and bis-protected (15) derivatives was formed.

Further reactions of some of the *O*-protected derivatives were undertaken in order to obtain *N*-protected analogues. For example, the tetrahydropyranyl ether (14) was treated with Boc-anhydride in the presence of DMAP to afford



(20) R=CH_2Ph
(21) R=THP

Diagram 4.

the carbamate (16), but attempted selective removal of the tetrahydropyranyl group was unsuccessful and the only product isolated was the original hydroxybenzimidazole (4). Here it is to be noted that even though there are many examples of the selective removal of tetrahydropyranyl protecting groups in the presence of Boc-protected amines,[13–16] none of the amines are part of a benzimidazole (or imidazole) moiety which on mechanistic grounds would indeed be likely to be quite labile.

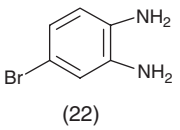
In another attempt to convert an *O*-protected analogue of the hydroxybenzimidazole (4) into an *N*-protected analogue, the monoacetate (9) was treated with Boc-anhydride/DMAP to afford the carbamate (17). However, base-catalyzed hydrolysis of this *O*-acetyl carbamate afforded the Boc-carbonate (18). While this transformation of a Boc-carbamate to a Boc-carbonate may at first seem surprising, in fact there are precedents in the literature in cases where alkoxide intermediates are generated in the presence of Boc-carbamates although, as in our case, the nitrogen involved is part of a good leaving group (an amide[17] or a vinylogous amide[18]).

However, treatment of the acetate (9) with dihydropyran/*p*-toluenesulfonic acid afforded the tetrahydropyranyl derivative (19) in satisfactory yield and subsequent base-catalyzed hydrolysis of this product gave the *N*-tetrahydropyranyl protected alcohol (13) in excellent yield. We thus had two suitably *N*-protected derivatives of (4), namely the *N*-benzyl derivative (12) and the *N*-tetrahydropyranyl derivative (13), on which to explore the desired ether synthesis (Scheme 1). In both cases, Mitsunobu coupling with methyl 4-hydroxybenzoate proceeded smoothly and gave the ethers (20) and (21) respectively (Diagram 4).

*Reactions of Bromo-1′*H*-benzimidazol-2′-ylpropanols*

For our eventual diagnostic studies, we required either a bromo or iodo group in the benzimidazole moiety, and so needed now to build on the methodology just outlined.

Accordingly, 4-bromo-1,2-phenylenediamine (22) (Diagram 5) was treated with γ-butyrolactone to afford the 5-bromobenzimidazole (23), which on reaction with benzyl bromide/potassium carbonate gave the benzylamines (24) and (25) in a 1 : 1 ratio. While these regioisomers, generated as a result of the protecting group, could be separated by flash chromatography, this was of no consequence as the protecting group would eventually be removed. We chose, therefore, to react the mixture of benzylamines (24) and (25) under Mitsunobu conditions with methyl 4-hydroxybenzoate and this afforded the ethers (26) and (27). Disappointingly, attempted hydrogenolysis of the benzyl group preferentially removed the bromine atom and the unbrominated ether (20) resulted.



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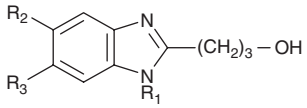
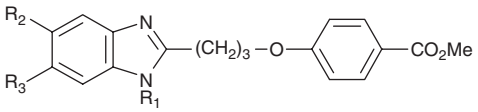
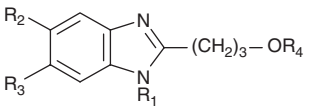


(23) R_1=R_3=H; R_2=Br
(24) R_1=CH_2Ph; R_2=H; R_3=Br
(25) R_1=CH_2Ph; R_2=Br; R_3=H

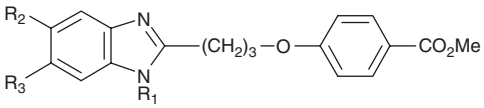


(26) R_1=CH_2Ph; R_2=H; R_3=Br
(27) R_1=CH_2Ph; R_2=Br; R_3=H

Diagram 5.



(28) R_1=R_2=H; R_3=Br; R_4=$CO.CH_3$
(29) R_1=THP; R_2=H; R_3=Br; R_4=$CO.CH_3$
(30) R_1=THP; R_2=Br; R_3=H; R_4=$CO.CH_3$
(31) R_1=THP; R_2=H; R_3=Br; R_4=H
(32) R_1=THP; R_2=Br; R_3=H; R_4=H



(33) R_1=THP; R_2=H; R_3=Br
(34) R_1=THP; R_2=Br; R_3=H
(35) R_1=R_2=H; R_3=Br

Diagram 6.

It was necessary to explore reactions where the nitrogen was protected with a tetrahydropyranyl group, and thus the alcohol (23) was converted via the acetate (28) (Diagram 6) into the mixture of bromo tetrahydropyranyl acetates (29) and (30). Base-catalyzed hydrolysis of these acetates then afforded the corresponding alcohols (31) and (32), which on Mitsunobu coupling with methyl 4-hydroxybenzoate afforded the ethers (33) and (34). Finally, removal of the protecting group gave the desired 1*H*-benzimidazolylpropyl aryl ether (35).

The ethers (33) and (34) were separated by flash chromatography and so it was necessary to determine the structures of the less-polar compound (a white solid) and the more-polar compound (an oily solid). Both compounds had the same splitting pattern in the benzimidazole ring, and the doublets with *meta*-coupling only (J 1.8 Hz) arising from the less-polar compound and from the more-polar compound appeared at δ 7.82 and δ 7.77 respectively. A two-dimensional nuclear Overhauser effect spectroscopy (2D NOESY) experiment on the less-polar compound showed no correlation between the signal at δ 7.82 and the signals from the protons at C2 and C3 in the tetrahydropyranyl ring, and so

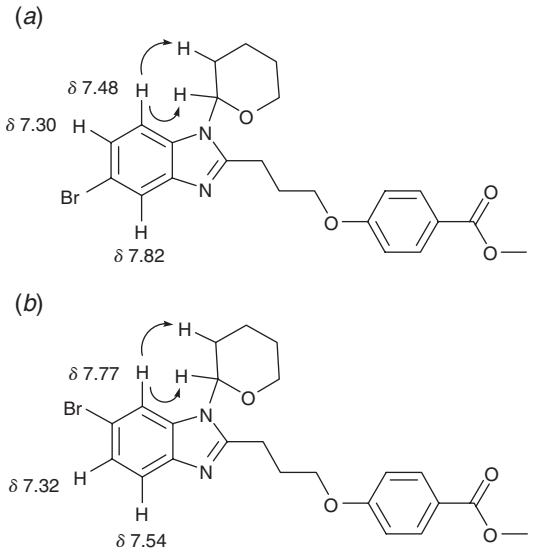


Diagram 7.

this compound was assigned as the bromo derivative (34). NOESY correlations were observed instead between signals due to the *ortho* proton and the protons on C2 and C3 of the tetrahydropyranyl ring (Diagram 7*a*).

A 2D NOESY experiment on the more-polar compound showed a strong correlation between the signal at δ 7.77 and the signals from the protons at C2 and C3 in the tetrahydropyranyl ring, and so this compound was assigned as the bromo derivative (33). NOESY correlations were not observed between the other protons on the benzimidazole ring and those in the tetrahydropyranyl ring (Diagram 7*b*).

Finally, it is noted that the desired 1*H*-benzimidazolylpropyl aryl ether (35) may exist in tautomeric forms. However, analysis of the compound by ^{1}H NMR spectroscopy indicated that the tautomeric forms, if present, were rapidly interconverting at room temperature.

Conclusion

Selective protection of nitrogen and oxygen in aminoalcohols can normally be accomplished by acylation, and the different reactivities of amides and esters can then be exploited. However, when the nitrogen is part of an imidazole, the leaving group ability of this group makes the reactivity of acylimidazoles and esters comparable. Further complications can occur since acylimidazoles in turn are acylating agents and so free hydroxyls in the neighbourhood can react.

We have overcome the issues for a series of hydroxypropylbenzimidazoles and the methodology should be applicable to related substances.

Experimental

All reactions were performed under an atmosphere of anhydrous nitrogen, unless stated otherwise. Anhydrous diethyl ether and tetrahydrofuran (THF) were obtained by distillation over sodium benzophenone ketyl immediately prior to use. Anhydrous dichloromethane was obtained by distillation over calcium hydride or P_2O_5 immediately prior to use. Anhydrous *N*,*N*-dimethylformamide (DMF) was obtained by stirring over calcium hydride for 24 h and distilling under reduced pressure

immediately prior to use. Anhydrous triethylamine was obtained by storing analytical grade reagent (Merck) over KOH pellets.

Purifications were achieved by flash chromatography on silica gel (0.040–0.063 mm) unless stated otherwise. Thin-layer chromatography was performed using Merck 60 F_{254} plates with samples visualized by means of iodine vapour, phosphomolybdic acid (5% in ethanol), and vanillin (1% in ethanol) with heating, or under ultraviolet (254 nm) light.

Products were obtained analytically pure direct from chromatography and generally did not need recrystallization.

^{1}H NMR spectra were recorded on Bruker AC-200F (200 MHz), DPX-300 (300 MHz) and AMX-400 (400 MHz) spectrometers. All samples were dissolved in $CDCl_3$ or CD_3OD and referenced to residual protonated solvent ($CHCl_3$, 7.26 ppm) or (CH_3OH, 3.31 ppm). ^{13}C NMR spectra were recorded on Bruker AC-200F (50 MHz), DPX-300 (75 MHz), and AMX-400 (100 MHz) spectrometers. All samples were dissolved in $CDCl_3$ or CD_3OD and referenced to residual protonated solvent ($CHCl_3$, 77.00 ppm) or (CH_3OH, 49.00). Infrared spectra were acquired on a Perkin–Elmer 1600 series spectrometer and the spectra for oils were recorded on the neat compounds between NaCl plates. Electron ionization (EI) mass spectra were recorded on a modified Kratos mass spectrometer calibrated with perfluorokerosene (PFK). Microanalyses were performed by the Campbell Microanalytical Laboratory, Department of Chemistry, University of Otago, Dunedin, New Zealand.

*3-(1′*H*-Benzimidazol-2′-yl)propan-1-ol (4)*

A mixture of *o*-phenylenediamine (3.01 g, 27.8 mmol), γ-butyrolactone (2.63 g, 30.5 mmol), and hydrochloric acid (15 mL, 4 M) was refluxed for 2 h. The mixture was cooled and was made alkaline with saturated sodium carbonate solution. The crude precipitate was collected and was triturated with dichloromethane to give (4) as a solid (4.11 g, 84%). Mp 145–146°C. (Found: $M^{+\bullet}$ 176.0947. $C_{10}H_{12}N_2O$ requires $M^{+\bullet}$ 176.0949). ν_{max} (neat)/cm^{-1} 3048, 2937, 1534, 1420, 1273, 1060, 743. δ_H (200 MHz, CD_3OD) 1.87 (2 H, tt, *J* 7.4 and 6.4, $CH_2CH_2CH_2$), 2.78 (2 H, t, *J* 7.4, CCH_2), 3.46 (2 H, t, *J* 6.4, CH_2OH), 6.90–7.10 (2 H, m, ArH), 7.20–7.40 (2 H, m, ArH). δ_C (50 MHz) 26.3, 32.0, 62.0, 115.3, 123.2, 139.4, 156.5. Mass spectrum *m*/*z* 176 (30%, $M^{+\bullet}$), 157 (10), 145 (48), 132 (100), 131 (36), 118 (10), 104 (8), 92 (17), 77 (14), 65 (15).

*2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (3)*

Methyl 4-hydroxybenzoate (0.078 g, 0.515 mmol) and triphenylphosphine (0.148 g, 0.567 mmol) were dissolved in anhydrous THF (2 mL) and DMF (1 mL). To this stirred solution was added, dropwise, a solution of (4) (0.100 g, 0.567 mmol) and diethyl azodicarboxylate (DEAD) (0.089 mL, 0.567 mmol) in THF (1 mL). The reaction was monitored by thin-layer chromatography (TLC). After 2 h, water (25 mL) was added and the product was extracted into dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/methanol) to give the *pyrrolobenzimidazole* (3) as a white solid (0.040 g, 44%). Mp 103–105°C (lit.[19] 105–107°C).

When the above reaction was repeated in the absence of methyl 4-hydroxybenzoate the cyclized product (3) was obtained in 68% yield.

*Reaction of 3-(1′*H*-Benzimidazol-2′-yl)propan-1-ol (4) with di-*tert*-Butyl Dicarbonate*

To a stirred mixture of (4) (0.10 g, 0.57 mmol) in triethylamine (6 mL) was added di-*tert*-butyl dicarbonate (0.14 g, 0.62 mmol) and a catalytic amount of DMAP. The reaction was monitored by TLC. Once the reaction was complete (2 h) water (20 mL) was added and the product was extracted into dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; 3 : 2 ethyl acetate/hexanes) to give tert-*butyl 2-(3′*-tert-*butoxycarbonyloxypropyl)-1*H-*benzimidazole-1-carboxylate* (8) as a white solid (0.09 g, 43%). Mp 124–125°C. (Found: C, 63.9; H, 7.5; N, 7.4%. $C_{20}H_{28}N_2O_5$ requires C, 63.8; H, 7.5; N, 7.4%). ν_{max} (neat)/cm^{-1} 2978, 1742, 1542, 1372, 1319, 1255, 1161, 1119. δ_H (200 MHz, $CDCl_3$) 1.26 (9 H, s, Bu^t), 1.71 (9 H, s, Bu^t), 2.28 (2 H, tt, *J* 7.3 and 6.5, $CH_2CH_2CH_2$), 3.30 (2 H, t, *J* 7.3, CCH_2), 4.25 (2 H, t, *J* 6.5, OCH_2), 7.25–7.35 (2 H, m, ArH), 7.63–7.73 (1 H, m, ArH), 7.85–7.95 (1 H, m, ArH). δ_C (50 MHz) 26.3, 27.6, 27.7, 28.0, 66.2, 81.7, 85.4, 114.8, 119.4, 123.0, 124.1, 133.0, 142.1, 148.8, 153.5, 155.5. Mass spectrum *m*/*z* 376 (13%, $M^{+\bullet}$), 276 (10), 220 (33), 203 (19), 176 (5), 159 (14), 145 (73), 132 (62), 52 (100).

*Reaction of 3-(1′*H*-Benzimidazol-2′-yl)propan-1-ol (4) with Acetic Anhydride*

To a stirred solution of (4) (0.50 g, 2.8 mmol) in dichloromethane (10 mL) and triethylamine (13 mL) was added a catalytic amount of DMAP, and the mixture was cooled to 0°C. Acetic anhydride (0.3 mL, 3.12 mmol) was added dropwise, and the reaction was monitored by TLC. Once the reaction was complete (1 h) water (30 mL) was added, and the product was extracted into dichloromethane (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/hexanes).

The less-polar product was *3-(1′-acetyl-1′*H*-benzimidazol-2′-yl)propyl acetate* (10) which was obtained as an off-white solid (0.20 g, 27%). Mp 110–113°C. (Found: $M^{+\bullet}$ 260.1156. $C_{14}H_{16}N_2O_3$ requires $M^{+\bullet}$ 260.1161). ν_{max} (neat)/cm^{-1} 2966, 1719, 1542, 1454, 1360, 1237, 1178, 1031, 743. δ_H (200 MHz, $CDCl_3$) 2.01 (3 H, s, $OCOCH_3$), 2.22 (2 H, tt, *J* 7.5 and 6.6, $CH_2CH_2CH_2$), 2.75 (3 H, s, $NCOCH_3$), 3.21 (2 H, t, *J* 7.5, CCH_2), 4.21 (2 H, t, *J* 6.6, OCH_2), 7.20–7.34 (2 H, m, ArH), 7.55–7.72 (2 H, m, ArH). δ_C (50 MHz) 20.5, 25.8, 26.6, 28.2, 63.4, 113.3, 119.7, 124.0, 124.0, 132.1, 142.3, 155.7, 168.7, 170.7. Mass spectrum *m*/*z* 260 (45%, $M^{+\bullet}$), 218 (35), 200(8), 187 (30), 175 (35), 157 (39), 145 (100), 132 (85), 92 (15).

The more-polar product was *3-(1′-acetyl-1′*H*-benzimidazol-2′-yl)propyl acetate* (9) which was obtained as a white solid (0.41 g, 67%). Mp 117–118°C (lit.[20] 134–134.5°C) (Found: C, 65.7; H, 6.5; N, 13.0%. $C_{12}H_{14}N_2O_2$ requires C, 66.0; H, 6.5; N, 12.8%). ν_{max} (neat)/cm^{-1} 2961, 1724, 1590, 1458, 1417, 1231, 1042, 1002, 948, 739. δ_H (200 MHz, $CDCl_3$) 1.92 (3 H, s, $COCH_3$), 2.13 (2 H, tt, *J* 7.2 and 6.4, $CH_2CH_2CH_2$), 2.97 (2 H, t, *J* 7.2, CCH_2), 4.09 (2 H, t, *J* 6.4, OCH_2), 7.10–7.30 (2 H, m, ArH), 7.45–7.60 (2 H, m, ArH). δ_C NMR (50 MHz) 20.6, 25.6, 27.3, 63.3, 114.5, 122.2, 138.5, 154.2, 171.4. Mass spectrum *m*/*z* 218 (33%, $M^{+\bullet}$), 175 (18), 157 (16), 145 (100), 132 (90), 118 (5), 77 (7).

*Reaction of 3-(1′*H*-Benzimidazol-2′-yl)propan-1-ol (4) with Trityl Chloride*

To a solution of (4) (0.05 g, 0.28 mmol) in dichloromethane (2 mL) and triethylamine (2 mL) was added trityl chloride (0.09 g, 0.31 mmol), and the reaction was monitored by TLC. When the reaction was complete (2 h) water (15 mL) was added and the product was extracted into ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; 4 : 1 ethyl acetate/hexanes) to give *2-(3′-trityloxypropyl)-1*H*-benzimidazole* (11) as a white solid (0.08 g, 75%). Mp 161–163°C (Found: $M^{+\bullet}$ 418.1969. $C_{29}H_{26}N_2O$ requires $M^{+\bullet}$ 418.1967). ν_{max} (neat)/cm^{-1} 3048, 1537, 1490, 1419, 1266, 1219, 743, 696 cm^{-1}. δ_H (300 MHz, CD_3OD) 2.05–2.25 (2 H, m, $CH_2CH_2CH_2$), 3.02 (2 H, t, *J* 7.5, CCH_2), 3.22 (2 H, t, *J* 5.9, OCH_2), 7.15–7.55 (19 H, m, ArH). δ_C (50 MHz) 27.0, 29.3, 63.6, 87.8, 115.2, 123.0, 127.8, 128.6, 129.1, 129.6, 145.4, 156.3. Mass spectrum *m*/*z* 418 (10%, $M^{+\bullet}$), 260 (18), 243 (100), 175 (60), 145 (9), 132 (13), 105 (14).

*Reaction of 3-(1′*H*-benzimidazol-2′-yl)propan-1-ol (4) with Benzyl Bromide*

To a stirred suspension of (4) (1.0 g, 5.7 mmol) and anhydrous potassium carbonate (1.5 g, 11.3 mmol) in anhydrous acetonitrile (15 mL) was added, dropwise, benzyl bromide (0.7 mL, 6.2 mmol) and the mixture heated to reflux. The reaction was monitored by TLC and was stopped after 1.5 h by adding water (40 mL). The product was

extracted into dichloromethane (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/methanol) to give *3-(1′-benzyl-1′*H*-benzimidazol-2′-yl)propan-1-ol* (12) as a pale brown oil (0.7 g, 46%). (Found: $M^{+\bullet}$ 266.1423. $C_{17}H_{18}N_2O$ requires $M^{+\bullet}$ 266.1419). ν_{max} (NaCl)/cm^{-1} 3258, 2933, 1614, 1510, 1462, 1413, 1156, 1060, 744. δ_H (200 MHz, $CDCl_3$) 2.09 (2 H, tt, *J* 6.6 and 5.8, $CH_2CH_2CH_2$), 2.99 (2 H, t, *J* 6.6, CCH_2), 3.76 (2 H, t, *J* 5.8, OCH_2), 5.33 (2 H, s, NCH_2Ph), 6.95–7.10 (2 H, m, ArH), 7.10–7.35 (6 H, m, ArH), 7.60–7.80 (1 H, m, ArH). δ_C (50 MHz) 25.1, 29.5, 46.8, 61.9, 109.4, 119.1, 122.1, 122.5, 126.1, 127.9, 128.9, 135.3, 135.8, 142.4, 155.1. Mass spectrum *m*/*z* 266 (13%, $M^{+\bullet}$), 236 (20), 222 (100), 207 (14), 145 (23), 91 (100), 65 (19).

*Reaction of 3-(1′*H*-benzimidazol-2′-yl)propan-1-ol (4) with 3,4-dihydropyran*

To a stirred solution of (4) (0.20 g, 1.13 mmol) in dichloromethane/dioxane (9 mL, 5 : 4) was added 3,4-dihydropyran (0.207 mL, 2.27 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). The reaction mixture was heated under reflux and was monitored by TLC. After 3 days the reaction was stopped by the addition of water (30 mL). The products were extracted into dichloromethane (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to give the crude product mixture, which was purified by flash chromatography (silica; ethyl acetate).

The least-polar product, a colourless viscous oil (0.020 g, 5%), was *1-(tetrahydropyran-2′-yl)-2-[3′-(tetrahydropyran-2″-yloxy)propyl]-1*H*-benzimidazole* (15). (Found $M^{+\bullet}$ 344.2102. $C_{20}H_{28}N_2O_3$ requires $M^{+\bullet}$ 344.2100). ν_{max} (NaCl)/cm^{-1} 2940, 2863, 1723, 1613, 1517, 1455, 1280, 1207, 1083, 1002, 899, 813, 744. δ_H (200 MHz, $CDCl_3$) 1.25–1.90 (10 H, m, 6 × tetrahydropyranyl CH_2 and 3 × $CH_2CH_2CH_2O$), 1.90–2.60 (4 H, m, 6 × tetrahydropyranyl CH_2 and 3 × $CH_2CH_2CH_2O$), 2.90–3.20 (2 H, m, CCH_2), 3.4–4.0 (5 H, m, OCHO, NCHO and CH_2OCHO), 4.10–4.40 (1 H, m, OCHO, NCHO and CH_2OCHO), 4.50–4.70 (1 H, m, OCHO, NCHO and CH_2OCHO), 5.50 (1 H, dd, *J* 11.1 and 2.2, OCHO, NCHO and CH_2OCHO), 7.10–7.30 (2 H, m, ArH), 7.50–7.80 (2 H, m, ArH). δ_C (50 MHz) 19.7, 23.2, 25.0, 25.3, 28.0, 30.4, 30.6, 30.7, 62.6, 66.5, 69.1, 84.1, 99.0, 112.2, 119.1, 121.8, 122.0, 133.4, 142.8, 153.5. Mass spectrum *m*/*z* 344 (6%, $M^{+\bullet}$), 259 (24), 216 (31), 201 (17), 175 (66), 159 (49), 145 (32), 132 (100), 85 (72).

The next polar compound to elute was *2-[3′-(tetrahydropyran-2′-yloxy)propyl]-1*H*-benzimidazole* (14) which was obtained as a white solid (0.075 g, 25%). Mp 80–81°C. (Found: C, 69.4; H, 7.9; N, 10.8%. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.7; N, 10.8%). ν_{max} (neat)/cm^{-1} 3054, 2941, 2868, 1622, 1540, 1455, 1272, 1200, 1120, 1034, 986, 903, 743. δ_H (200 MHz, $CDCl_3$) 1.42–1.83 (6 H, m, 3 × tetrahydropyranyl CH_2), 2.0–2.27 (2 H, m, $CH_2CH_2CH_2O$), 3.10 (2 H, t, *J* 7.2, CCH_2), 3.43–3.70 (2 H, m, OCH_2), 3.76–3.97 (2 H, m, OCH_2), 4.55 (1 H, t, *J* 2.6, OCHO), 7.14–7.24 (2 H, m, ArH), 7.49–7.56 (2 H, m, ArH). δ_C (50 MHz) 20.1, 25.2, 26.1, 27.8, 30.7, 63.3, 66.6, 99.7, 114.5, 121.8, 141.0, 154.9. Mass spectrum *m*/*z* 260 (39%, $M^{+\bullet}$), 232 (11), 201 (6), 187 (17), 175 (93), 159 (100), 132 (100), 85 (39), 57 (14).

The third compound to elute was further purified by flash chromatography (silica; 9 : 1 ethyl acetate/methanol) to give *3-[1′-(tetrahydropyran-2′-yl)-1*H*-benzimidazole-2-yl]propan-1-ol* (13) as a white solid (0.015 g, 5%). Mp 111–113°C. (Found: C, 69.5; H, 7.6; N, 10.7%. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.7; N, 10.8%). ν_{max} (neat)/cm^{-1} 3250, 2940, 2859, 1516, 1458, 1414, 1084, 1043, 745. δ_H (200 MHz, $CDCl_3$) 1.50–2.50 (8 H, m, 3 × tetrahydropyranyl CH_2 and $CH_2CH_2CH_2O$), 3.10 (2 H, t, *J* 6.9, CCH_2), 3.50–3.80 (1 H, m, tetrahydropyranyl CH_2O), 4.20–4.27 (1 H, m, tetrahydropyranyl CH_2O), 3.77 (2 H, t, *J* 5.6, CH_2OH), 5.49 (1 H, dd, *J* 8.6, 2.4, OCHO), 7.0–7.35 (2 H, m, ArH), 7.60–7.90 (2 H, m, ArH). δ_C (50 MHz) 23.2, 25.0, 25.6, 29.9, 30.6, 61.7, 69.2, 84.2, 112.0, 119.0, 122.1, 122.3, 133.3, 141.2, 153.0. Mass spectrum *m*/*z* 260 (22%, $M^{+\bullet}$), 230 (5), 216 (30), 201 (9), 175 (23), 157 (13), 146 (41), 132 (100), 85 (48).

*Reactions of 2-[3′-(Tetrahydropyran-2′-yloxy)propyl]-1*H*-benzimidazole (14)*

To a solution of (14) (0.06 g, 0.021 mmol) in dichloromethane (2 mL) and triethylamine (3 mL) was added Boc-anhydride (0.05 g, 0.02 mmol) and a catalytic amount of DMAP. The reaction was monitored by TLC and once the reaction was complete (after 0.5 h) water (10 mL) was added. The product was extracted into dichloromethane (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/hexanes) to give tert-*butyl 2-[3′-(tetrahydropyran-2′-yloxy)propyl]-1*H*-benzimidazol-1-ylcarbamate* (16) as a colourless oil (0.06 g, 79%). (Found: $M^{+\bullet}$ 360.2048. $C_{20}H_{28}N_2O_4$ requires $M^{+\bullet}$ 360.2049). ν_{max} (NaCl)/cm^{-1} 2939, 1746, 1542, 1454, 1290, 1255, 1155, 1031, 767. δ_H (200 MHz, $CDCl_3$) 1.30–1.90 (6 H, m, 3 × tetrahydropyranyl CH_2), 1.71 (9 H, s, Bu^t), 2.10–2.30 (2 H, m, $CH_2CH_2CH_2O$), 3.30 (2 H, t, *J* 7.6, CCH_2), 3.40–3.62 (2 H, m, 2 × CH_2O), 3.79–4.0 (2 H, m, 2 × CH_2O), 4.61 (1 H, t, *J* 3.2, OCHO), 7.22–7.35 (2 H, m, ArH), 7.62–7.73 (1 H, m, ArH), 7.86–7.95 (1 H, m, ArH). δ_C (50 MHz) 19.3, 25.3, 27.5, 27.9, 28.2, 30.5, 62.0, 66.6, 85.2, 98.6, 114.7, 119.2, 123.8, 123.9, 133.0, 142.0, 148.8, 156.2. Mass spectrum *m*/*z* 360 (25%, $M^{+\bullet}$), 304 (5), 276 (9), 232 (39), 219 (23), 203 (52), 176 (80), 159 (55), 145 (42), 132 (88), 57 (100).

To a solution of the carbamate (16) (0.04 g, 0.11 mmol) in methanol (2 mL) was added a catalytic amount of PPTS. The reaction mixture was heated under reflux and the reaction monitored by TLC. Once the reaction was complete (15 h), water (10 mL) was added and the product was extracted into dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/methanol) to give (4), which had spectroscopic data identical to that of an authentic sample.

*Derivatives from 3-(1′-Acetyl-1′*H*-benzimidazol-2′-yl)propyl Acetate (9)*

Reaction with Boc-Anhydride. To a solution of (9) (0.04 g, 0.02 mmol) in dichloromethane (2 mL) and triethylamine (1 mL) was added Boc-anhydride (0.04 g, 0.02 mmol) and a catalytic amount of DMAP. The reaction was monitored by TLC. Once the reaction was complete (0.3 h), water (15 mL) was added, and the product was extracted into dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/hexanes) to give tert-*butyl 2-(3′-acetoxypropyl)-1′*H*-benzimidazole-1-carboxylate* (17) as a pale brown solid (0.05 g, 98%). Mp 74–75°C. (Found: C, 64.1; H, 7.0; N, 8.7%. $C_{17}H_{22}N_2O_4$ requires C, 64.1; H, 7.0; N, 8.8%). ν_{max} (neat)/cm^{-1} 2978, 1742, 1537, 1448, 1243, 1149, 1037, 843, 755. δ_H (200 MHz, $CDCl_3$) 1.71 (9 H, s, Bu^t), 2.02 (3 H, s, $COCH_3$), 2.25 (2 H, tt, *J* 7.8 and 6.4, $CH_2CH_2CH_2$), 3.29 (2 H, t, *J* 7.8, CCH_2), 4.24 (2 H, t, *J* 6.4, OCH_2), 7.20–7.40 (2 H, m, ArH), 7.60–7.75 (1 H, m, ArH), 7.80–7.95 (1 H, m, ArH). δ_C (50 MHz) 20.8, 26.3, 27.8, 28.0, 63.7, 85.4, 114.8, 119.4, 124.0, 124.2, 132.9, 142.0, 148.8, 155.5, 170.9. Mass spectrum *m*/*z* 318 (17%, $M^{+\bullet}$), 262 (20), 245 (16), 203 (17), 175 (23), 158 (27), 145 (100), 132 (67).

Reaction of tert-*Butyl 2-(3′-acetoxypropyl)-1′*H*-benzimidazole-1-carboxylate (17).* To a cooled (0°C) solution of the *N*-Boc-protected acetate (17) (0.04 g, 0.13 mmol) in methanol (2 mL) was added, dropwise, cold sodium hydroxide (0.5 mL, 0.5 M), and the reaction was monitored by TLC. After 15 min, water (10 mL) was added, and the product was extracted into dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/hexanes) to give tert-*butyl 3-(1′*H*-benzimidazol-2′-yl)propyl carbonate* (18) as a white solid (0.014 g, 40%). Mp 132–133°C. (Found: C, 65.4; H, 7.1; N, 10.2%. $C_{15}H_{20}N_2O_3$ requires C, 65.2; H, 7.3; N, 10.1%). ν_{max} (neat)/cm^{-1} 2919, 1740, 1423, 1364, 1284, 1161, 1033, 850.

δ_H (200 MHz, $CDCl_3$) 1.50 (9 H, s, Bu^t), 2.23 (2 H, tt, *J* 6.8, and 6.4, $CH_2CH_2CH_2$), 3.01 (2 H, t, *J* 6.8, CCH_2), 3.21 (2 H, t, *J* 6.4, OCH_2), 7.35–8.0 (2 H, m, ArH), 7.10–7.35 (2 H, m, ArH). δ_C (50 MHz) 25.6, 27.4, 27.7, 65.8, 82.5, 114.8, 122.2, 138.4, 153.5, 153.9. Mass spectrum *m*/*z* 276 (35%, $M^{+\bullet}$), 261 (4), 220 (21), 203 (10), 159 (47), 145 (100), 132 (92).

Reaction with Dihydropyran. To a stirred solution of the acetate (9) (1.7 g, 7.6 mmol) in chloroform (25 mL) was added 3,4-dihydropyran (1.4 mL, 15.0 mmol) and a catalytic amount of PPTS. The reaction mixture was heated under reflux and was monitored by TLC. After 2 days, more 3,4-dihydropyran (1.4 mL, 15.0 mmol) and a further catalytic amount of PPTS were added. The reaction was stopped after 5 days by the addition of water (50 mL). The product was extracted into dichloromethane (3 × 40 mL), and the combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica; 17 : 3 ethyl acetate/hexanes) to give the *3-[1′-(tetrahydropyran-2′-yl)-1′*H*-benzimidazol-2′-yl]propyl acetate* (19) as a colourless, viscous oil (1.6 g, 70%). (Found $M^{+\bullet}$ 302.1631. $C_{17}H_{22}N_2O_3$ requires $M^{+\bullet}$ 302.1630). ν_{max} (NaCl)/cm^{-1} 2942, 2854, 1737, 1613, 1517, 1456, 1243, 1042, 898, 745. δ_H (200 MHz, $CDCl_3$) 1.50–2.20 (6 H, m, 3 × tetrahydropyranyl CH_2), 2.04 (3 H, s, $COCH_3$), 2.26 (2 H, tt, *J* 7.7 and 6.3, $CH_2CH_2CH_2$), 3.01 (2 H, t, *J* 7.7, CH_2), 3.60–3.80 (1 H, m, CH_2O), 4.10–4.40 (1 H, m, CH_2O), 4.23 (2 H, t, *J* 6.3, CH_2OCO), 5.48 (1 H, dd, *J* 11.0 and 2.4, NCHO), 7.10–7.26 (2 H, m, ArH), 7.50–7.75 (2 H, m, ArH). δ_C (50 MHz) 20.9, 23.2, 24.9, 25.0, 26.7, 30.6, 63.6, 69.2, 84.1, 111.9, 119.3, 121.9, 122.2, 133.5, 142.8, 152.7, 171.0. Mass spectrum *m*/*z* 302 (27%, $M^{+\bullet}$), 218 (26), 175 (13), 157 (14), 145 (100), 132 (83), 85 (87), 67 (13).

*3-[1′-(Tetrahydropyran-2′-yl)-1′*H*-benzimidazol-2′-yl]-propan-1-ol (13)*

To a solution of the *N*-THP acetate (19) (0.13 g, 0.50 mmol) in methanol (3 mL) at 0°C was added cold sodium hydroxide (1.2 mL, 0.5 M), dropwise. TLC was used to monitor the reaction. Once the reaction was complete (0.75 h) water (20 mL) was added, and the product was extracted into ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified using flash chromatography (silica; 4 : 1 ethyl acetate/methanol) to give (13) as a white solid (0.1 g, 88%). This compound was identical with that reported above.

*Mitsunobu Coupling with 3-(1-Benzyl-1*H*-benzimidazol-2-yl)propan-1-ol (12)*

To a stirred solution of methyl 4-hydroxybenzoate (0.04 g, 0.25 mmol) and triphenylphosphine (0.13 g, 0.5 mmol) in anhydrous THF (2 mL) was added, dropwise, a solution of the *N*-benzyl alcohol (12) (0.10 g, 0.4 mmol) and DEAD (0.08 mL, 0.5 mmol) in THF (1 mL). After 1 h, further DEAD (0.03 mL) was added and the reaction was stirred for an additional 1 h. Water (25 mL) was added and the product was extracted into dichloromethane (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica; 9 : 1 ether/hexanes) to give methyl *4-[3′-(1′-benzyl-1′*H*-benzimidazol-2′-yl)propyloxy]benzoate* (20) as pale yellow solid (0.06 g, 60%). Mp 101–102°C. (Found: C, 74.7; H, 6.0; N, 7.2%. $C_{25}H_{24}N_2O_3$ requires C, 75.0; H, 6.0; N, 7.0%). ν_{max} (neat)/cm^{-1} 2948, 1713, 1605, 1578, 1509, 1454, 1412, 1316, 1281, 1254, 1168, 1105, 1044, 769, 697. δ_H (400 MHz, $CDCl_3$) 2.40 (2 H, tt, *J* 7.3 and 6.6, $CH_2CH_2CH_2$), 3.03 (2 H, t, *J* 7.3, CCH_2), 3.86 (3 H, s, OCH_3), 4.10 (2 H, t, *J* 5.9, CH_2O), 5.31 (2 H, s, $PhCH_2N$), 6.83 (2 H, d (broad), *J* 8.9, ArH), 6.90–7.10 (2 H, m, ArH), 7.15–7.35 (6 H, m, ArH), 7.77 (1 H, d, *J* 7.7, ArH), 7.95 (2 H, d (broad), *J* 8.9, ArH). δ_C (100 MHz) 23.7, 26.7, 46.7, 51.7, 66.7, 109.4, 114.0, 119.2, 122.0, 122.4, 122.5, 126.1, 127.8, 128.9, 131.5, 135.4, 135.8, 142.6, 154.1, 162.5, 166.7. Mass spectrum *m*/*z* 400 (10%, $M^{+\bullet}$), 277 (5), 249 (24), 222 (100), 207 (10), 157 (12), 131 (27), 91 (86), 65 (12).

*Mitsunobu Coupling with 3-[1′-(Tetrahydropyran-2′-yl)-1′*H*-benzimidazol-2′-yl]propan-1-ol (13)*

To a stirred solution of methyl 4-hydroxybenzoate (0.06 g, 0.38 mmol) and triphenylphosphine (0.20 g, 0.77 mmol) in anhydrous THF (3 mL) was added, dropwise, a solution of the alcohol (13) (0.2 g, 0.6 mmol) and DEAD (0.12 mL, 0.77 mmol) in THF (1 mL). The reaction was monitored using TLC. After 1 h, further DEAD (0.1 mL) was added, and the reaction was stirred for an additional 1 h. The reaction was stopped by the addition of water (25 mL), the product was extracted into dichloromethane (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; ether) to give *methyl 4-[3′-(1′-(tetrahydropyran-2″-yl)-1′*H*-benzimidazol-2′-yl)propyloxy]benzoate* (21) as a pale yellow viscous oil (0.08 g, 55%). (Found $M^{+\bullet}$ 394.1893. $C_{23}H_{26}N_2O_4$ requires $M^{+\bullet}$ 394.1893). ν_{max} (NaCl)/cm^{-1} 2947, 2856, 1711, 1605, 1511, 1283, 1255, 1166, 1042, 847. δ_H (300 MHz, $CDCl_3$) 1.55–1.85 (4 H, m, 2 × tetrahydropyranyl CH_2), 1.95–2.10 (1 H, m, tetrahydropyranyl CH_2), 2.25–2.40 (1 H, m, tetrahydropyranyl CH_2), 2.43 (2 H, tt, *J* 7.0, 6.2, $CH_2CH_2CH_2$), 3.14 (2 H, t, *J* 7.0, CCH_2), 3.61 (1 H, m, tetrahydropyranyl OCH_2), 4.12–4.25 (1 H, m, tetrahydropyranyl OCH_2), 3.88 (3 H, s, OCH_3), 4.16 (2 H, t, *J* 5.9Hz, OCH_2), 5.48 (1 H, dd, *J* 11.0 and 2.3, tetrahydropyranyl $OCHN$), 6.92 (2 H, d (broad), *J* 8.9, ArH), 7.17–7.25 (2 H, m, ArH), 7.55–7.73 (2 H, m, ArH), 7.98 (2 H, d (broad) *J* 8.9, ArH). δ_C (75 MHz) 23.2, 24.6, 25.0, 27.3, 30.6, 51.8, 66.9, 69.1, 84.2, 112.1, 114.1, 119.3, 121.9, 122.2, 122.6, 131.6, 133.5, 142.9, 152.8, 162.6, 166.8. Mass spectrum *m*/*z* 394 (10%, $M^{+\bullet}$), 309 (10), 216 (20), 149 (40), 132 (100), 85 (34).

*3-(6′-Bromo-1′*H*-benzimidazol-2′-yl)propan-1-ol (23)*

4-Bromo-1,2-phenylenediamine (22)[21] (3.6 g, 19 mmol), γ-butyrolactone (2.6 g, 30.5 mmol), and hydrochloric acid (15 mL, 4 M) were heated under reflux for 2.5 h. The mixture was cooled and was made alkaline with saturated sodium carbonate solution. The product was extracted with ethyl acetate (4 × 30 mL), and the combined organic layers were dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to give the crude product which was triturated with dichloromethane to yield *alcohol* (23) as an orange brown solid (4.4 g, 89%). Mp 148–150°C. (Found: $M^{+\bullet}$ 254.0051. $C_{10}H_{11}{}^{79}BrN_2O$ requires $M^{+\bullet}$ 254.0054. Found: $[M+2]^{+\bullet}$ 256.0030. $C_{10}H_{11}{}^{81}BrN_2O$ $[M+2]^{+\bullet}$ requires 256.0034). ν_{max} (neat)/cm^{-1} 3130, 2931, 1531, 1443, 1407, 1266, 1037, 796. δ_H (200 MHz, CD_3OD) 2.02 (2 H, tt, *J* 7.7 and 6.5, $CH_2CH_2CH_2$), 2.94 (2 H, t, *J* 7.7, CCH_2), 3.62 (2 H, t, *J* 6.5, OCH_2), 7.20–7.40 (2 H, m, ArH), 7.50–7.70 (1 H, m, ArH). δ_C (50 MHz) 26.3, 31.8, 62.0, 115.9, 116.5, 118.4, 126.2, 136.9, 141.2, 158.0. Mass spectrum *m*/*z* 256 (24% $[M+2]^{+\bullet}$), 254 (24%, $M^{+\bullet}$), 224 (34), 222 (34), 209 (100), 207 (100), 144 (24), 131 (38), 90 (19), 63 (42).

*Benzylation of 3-(6′-Bromo-1′*H*-benzimidazol-2′-yl)propan-1-ol (23)*

Alcohol (23) (1.0 g, 3.9 mmol) was dissolved in anhydrous acetonitrile (15 mL) and then anhydrous potassium carbonate (1.0 g, 7.8 mmol) was added. The suspension was heated to reflux and then benzyl bromide (0.5 mL, 4.3 mmol) was added dropwise. The reaction was monitored by TLC and was stopped when complete (ca. 3 h) by the addition of water (40 mL). The product was extracted into dichloromethane (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/methanol). A mixture of *3-(1′-benzyl-6′-bromo-1′*H*-benzimidazol-2′-yl)propan-1-ol* (24) and *3-(1′-benzyl-5′-bromo-1′*H*-benzimidazol-2′-yl)propan-1-ol* (25) was obtained as an oil (0.7 g, 53%, 1 : 1 isomeric ratio). (Found: $M^{+\bullet}$ 344.0522. $C_{17}H_{17}{}^{79}BrN_2O$ requires $M^{+\bullet}$ 344.0524. Found: $[M+2]^{+\bullet}$ 346.0494. $C_{17}H_{17}{}^{81}BrN_2O$ requires $(M+2)^{+\bullet}$ 346.0490). ν_{max} (NaCl)/cm^{-1} 3280, 2933, 1609, 1509, 1462, 1408, 1272, 1059, 908, 810, 731, 696. Mass spectrum *m*/*z* 346 (12% $[M+2]^{+\bullet}$) 344 (12%, $M^{+\bullet}$), 316 (15), 314 (15), 302 (58), 300 (58), 287 (7), 285 (7), 222 (15), 211 (21), 209 (22), 91 (100).

Separation of small amounts of the regioisomers was achieved by further chromatography to give firstly the less-polar compound, an oil (25): δ_H (400 MHz, $CDCl_3$) 2.07 (2 H, tt, *J* 6.9 and 5.8, $CH_2CH_2CH_2$), 2.96 (2 H, t, *J* 6.9, CCH_2), 3.73 (2 H, t, *J* 5.8, CH_2OH), 5.29 (2 H, s, CH_2Ph), 6.95–7.30 (5 H, m, ArH), 7.05 (1 H, d, *J* 8.6, ArH), 7.29 (1 H, dd, *J* 8.6 and 1.8, ArH), 7.84 (1 H, d, *J* 1.8, ArH). δ_C (100 MHz) 24.7, 29.6, 47.0, 61.6, 110.8, 115.1, 121.9, 125.5, 126.0, 128.1, 129.1, 134.2, 135.3, 143.3, 156.3.

Next was obtained the more-polar compound, an oil (24): δ_H (400 MHz, $CDCl_3$) 2.06 (2 H, tt, *J* 7.0 and 5.9, $CH_2CH_2CH_2$), 2.94 (2 H, t, *J* 7.0, CCH_2), 3.73 (2 H, t, *J* 5.9, CH_2OH), 5.26 (2 H, s, CH_2Ph), 6.95–7.01 (2 H, m, ArH), 7.25–7.30 (3 H, m, ArH), 7.32 (1 H, dd, *J* 8.6 and 1.8, ArH), 7.35 (1 H, d, *J* 1.6, ArH), 7.57 (1 H, d, *J* 8.6, ArH). δ_C (100 MHz) 24.7, 29.5, 46.9, 61.6, 112.6, 115.7, 120.3, 125.4, 125.9, 128.0, 129.0, 135.2, 136.4, 140.9, 156.0.

Mitsunobu Coupling of the N-*Benzylbromobenzimidazoles (24) and (25)*

Methyl 4-hydroxybenzoate (0.06 g, 0.38 mmol) and triphenylphosphine (0.20 g, 0.77 mmol) were dissolved in anhydrous THF (3 mL). To this stirred solution, a solution of (24), (25) (0.2 g, 0.6 mmol), and diethyl azodicarboxylate (0.12 mL, 0.77 mmol) in THF (1 mL) was added dropwise. The reaction was monitored using TLC. After 1 h, further DEAD (0.1 mL) was added and the reaction was stirred for an additional 1 h. Water (25 mL) was added and the product was extracted into dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; 17 : 3 ether/hexanes) to give *methyl 4-[3′-(1′-benzyl-6′-bromo-1′*H*-benzimidazol-2′-yl)propyloxy]benzoate* (26) and *methyl 4-[3′-(1′-benzyl-5′-bromo-1′*H*-benzimidazol-2′-yl)propyloxy]benzoate* (27).

The less-polar compound (27) (0.05 g, 27%) had mp 149–150°C. (Found: $M^{+\bullet}$ 478.0889. $C_{25}H_{23}{}^{79}BrN_2O_3$ requires $M^{+\bullet}$ 478.0869. Found: $[M+2]^{+\bullet}$ 480.0875. $C_{25}H_{23}{}^{81}BrN_2O_3$ requires $[M+2]^{+\bullet}$ 480.0872). ν_{max} (neat)/cm^{-1} 2933, 1715, 1605, 1505, 1455, 1277, 1256, 1166, 1105, 772. δ_H (300 MHz, $CDCl_3$) 2.38 (2 H, tt, *J* 7.1 and 6.0, $CH_2CH_2CH_2$), 3.03 (2 H, t, *J* 7.1, CCH_2), 3.87 (3 H, s, OCH_3), 4.10 (2 H, t, *J* 6.0, CH_2O), 5.30 (2 H, s, CH_2Ph), 6.83 (2 H, d (broad), *J* 8.9, ArH), 6.95–7.02 (2 H, m, ArH), 7.07 (1 H, d, *J* 8.5, ArH), 7.21–7.28 (3 H, m, ArH), 7.29 (1 H, dd, *J* 8.5 and 1.8, ArH), 7.89 (1 H, d, *J* 1.8, ArH), 7.95 (2 H, d (broad), *J* 8.9, ArH). δ_C (75 MHz) 23.7, 26.6, 46.9, 51.8, 66.6, 110.7, 114.0, 115.0, 122.2, 122.6, 125.4, 126.0, 128.1, 129.1, 131.5, 134.4, 135.4, 143.9, 155.4, 162.4, 166.8. Mass spectrum *m*/*z* 480 (4% $[M+2]^{+\bullet}$), 478 (4%, $M^{+\bullet}$), 329 (11), 327 (11), 302 (70), 300 (70), 210 (10), 208 (10), 91 (100).

The more-polar compound (26) (0.05 g, 26%) had mp 116–117°C. (Found: $M^{+\bullet}$ 478.0908. $C_{25}H_{23}{}^{79}BrN_2O_3$ requires $M^{+\bullet}$ 478.0905. Found: $(M+2)^{+\bullet}$ 480.0890. $C_{25}H_{23}{}^{81}BrN_2O_3$ requires $(M+2)^{+\bullet}$ 480.0872). ν_{max} (neat)/cm^{-1} 2953, 1712, 1600, 1509, 1280, 1252, 1169, 1105, 770. δ_H (300 MHz, $CDCl_3$) 2.39 (2 H, tt, *J* 7.0 and 6.1, $CH_2CH_2CH_2$), 3.02 (2 H, t, *J* 7.2, CCH_2), 3.87 (3 H, s, OCH_3), 4.11 (2 H, t, *J* 6.0, OCH_2), 5.28 (2 H, s, CH_2Ph), 6.83 (2 H, d (broad), *J* 8.9, ArH), 6.97–7.05 (2 H, m, ArH), 7.23–7.28 (3 H, m, ArH), 7.34 (1 H, dd, *J* 8.4 and 1.5, ArH), 7.36 (1 H, d, *J* 1.5, ArH), 7.61 (1 H, d, *J* 8.4, ArH), 7.95 (2 H, d (broad), *J* 8.9, ArH). δ_C (75 MHz) 23.7, 26.5, 46.9, 51.8, 66.7, 112.5, 113.9, 115.6, 120.5, 122.6, 125.4, 126.0, 128.1, 129.1, 131.5, 135.3, 136.5, 141.6, 155.1, 162.4, 166.7. Mass spectrum *m*/*z* 480 (4% $[M+2]^{+\bullet}$), 478 (4%, $M^{+\bullet}$), 329 (11), 327 (11), 302 (78), 300 (79), 287 (4), 285 (4), 210 (11), 208 (10), 91 (100).

Hydrogenolysis of N-*Benzyl Bromoethers (26) and (27)*

To a solution of the mixture of *N*-benzyl bromoethers (26) and (27) (0.01 g, 0.02 mmol) in 95% ethanol/ethyl acetate (2 mL) was added 10% Pd/charcoal (0.003 g), and 2–3 drops of concentrated sulfuric acid. The reaction mixture was placed under a hydrogen atmosphere at 1 atm. The reaction was monitored by TLC. After 22 h, the catalyst was filtered off and the solvent was removed under reduced pressure. The resulting oil was dissolved in water (5 mL) and made basic with saturated sodium hydrogen carbonate solution. The basic solution was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/hexanes) to give (21) (4.7 mg, 57%). This compound was identical (^{1}H NMR spectrum) to that obtained previously.

*Acetylation of 3-(6′-Bromo-1′*H*-benzimidazol-2′-yl)propan-1-ol (23)*

To a stirred solution of the bromobenzimidazole (23) (0.5 g, 1.9 mmol) in dichloromethane (5 mL) and triethylamine (5 mL) at 0°C was added a catalytic amount of DMAP, and then acetic anhydride (0.2 mL, 2.1 mmol). The reaction was monitored by TLC. When the reaction was complete (2 h), water (30 mL) was added, and the product was extracted into dichloromethane (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (90% ethyl acetate/hexanes) to give *3-(6′-bromo-1′*H*-benzimidazol-2′-yl)propyl acetate* (28) as a dark brown solid (0.51 g, 88%). Mp 93–96°C. (Found: $M^{+\bullet}$ 296.0160. $C_{12}H_{13}{}^{79}BrN_2O_2$ requires $M^{+\bullet}$ 296.0160. Found: $[M+2]^{+\bullet}$ 298.0144. $C_{12}H_{13}{}^{81}BrN_2O_2$ requires $[M+2]^{+\bullet}$ 298.0140). ν_{max} (neat)/cm^{-1} 2959, 1739, 1622, 1538, 1444, 1233, 1044, 911. δ_H (200 MHz, $CDCl_3$) 2.07 (3 H, s, $COCH_3$), 2.20 (2 H, tt, *J* 7.1 and 6.5, $CH_2CH_2CH_2$), 3.02 (2 H, t, *J* 7.1, CCH_2), 4.16 (2 H, t, *J* 6.5, OCH_2), 7.31 (1 H, dd, *J* 8.4, 1.6Hz, ArH), 7.40 (1 H, d, *J* 8.4, ArH), 7.68 (1 H, d, *J* 1.6, ArH). δ_C NMR (50 MHz) 20.7, 25.6, 27.1, 63.2, 115.2, 115.9, 117.6, 125.4, 136.9, 139.7, 155.2, 177.3. Mass spectrum *m*/*z* 298 (30% $[M+2]^{+\bullet}$), 296 (31%, $M^{+\bullet}$), 255 (13), 253 (14), 225 (96), 223 (100), 212 (78). 210 (75), 144 (29).

Reaction of the Bromoacetate (28) with Dihydropyran

To a stirred solution of the bromoacetate (28) (1.2 g, 4.0 mmol) in chloroform (25 mL) was added 3,4-dihydropyran (0.7 mL, 8.0 mmol) and a catalytic amount of PPTS. The reaction mixture was heated under reflux, and was monitored by TLC. After 2 days more 3,4-dihydropyran (0.7 mL, 8.0 mmol) and a catalytic amount of PPTS were added. The reaction was stopped after 5 days by the addition of water (50 mL). The product was extracted into dichloromethane (3 × 40 mL), and the combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; 17 : 3 ethyl acetate/hexanes) to give a mixture of *3-[6′-bromo-1′-(tetrahydropyran-2′-yl)-1′*H*-benzimidazol-2′-yl]propyl acetate* (29) and *3-[5′-bromo-1′-(tetrahydropyran-2′-yl)-1′*H*-benzimidazol-2′-yl]propyl acetate* (30) as a colourless viscous oil (1.28 g, 84%).

The mixture was separated by further chromatography. The less-polar compound (30) was obtained as an oil. (Found: C, 53.4; H, 5.7; N, 7.4%. $C_{17}H_{21}BrN_2O_3$ requires C, 53.5; H, 5.5; N, 7.3%). ν_{max} (NaCl)/cm^{-1} 2946, 2863, 1733, 1507, 1453, 1242, 1040, 1001, 907, 800. δ_H (200 MHz, $CDCl_3$) 1.60–1.90 (4 H, m, 3 × tetrahydropyranyl CH_2), 2.01–2.40 (2 H, m, 3 × tetrahydropyranyl CH_2), 2.05 (3 H, s, $COCH_3$), 2.24 (2 H, tt, *J* 7.2, 6.2, $CH_2CH_2CH_2$), 2.99 (3 H, t, *J* 7.2, CCH_2), 3.70 (1 H, m, tetrahydropyranyl OCH_2), 4.21–4.29 (1 H, m, tetrahydropyranyl OCH_2), 4.22 (2 H, t, *J* 6.2, OCH_2), 5.43 (1 H, dd, *J* 11.1 and 2.3, $NCHO$), 7.30 (1 H, dd, *J* 8.7 and 1.7, ArH), 7.49 (1 H, d, *J* 8.6, ArH), 7.81 (1 H, d, *J* 1.6, ArH). δ_C (50 MHz) 20.9, 23.1, 24.8, 24.9, 26.6, 30.7, 63.5, 69.2, 84.2, 113.3, 114.9, 122.0, 125.1, 132.4, 144.2, 153.8, 170.9. Mass spectrum *m*/*z* 382 (16% $[M+2]^{+\bullet}$), 380 (16%, $M^{+\bullet}$), 298 (29), 296 (33), 225 (50), 223(51), 212 (36), 210 (37), 144 (10), 85 (100).

The more-polar compound (29) was obtained as an oil. (Found: $M^{+\bullet}$ 380.0738. $C_{17}H_{21}{}^{79}BrN_2O_3$ requires $M^{+\bullet}$ 380.0715. Found: $[M+2]^{+\bullet}$ 382.0713. $C_{17}H_{21}{}^{81}BrN_2O_3$ requires $[M+2]^{+\bullet}$ 380.0715). ν_{max} (NaCl)/cm^{-1} 2944, 2857, 1737, 1512, 1455, 1431, 1241, 1084, 1042, 908. δ_H (200 MHz, $CDCl_3$) 1.60–1.90 (4 H, m, 2 × tetrahydropyranyl CH_2), 2.04 (3 H, s, CH_3CO_2), 2.00–2.40 (2 H, m, tetrahydropyranyl CH_2), 2.24 (2 H, tt, *J* 7.3 and 6.3, $CH_2CH_2CH_2$), 2.98 (2 H, t, *J* 7.3, CCH_2), 3.70 (1 H, m, tetrahydropyranyl OCH_2), 4.15–4.30 (1 H, m, tetrahydropyranyl OCH_2), 4.22 (2 H, t, *J* 6.1, CH_2O), 5.41 (1 H, dd, *J* 11.0, 2.2, $NCHO$), 7.31 (1 H, dd, *J* 8.7 and 1.3, ArH),

7.53 (1 H, d, *J* 8.6, ArH), 7.77 (1 H, d, *J* 1.5, ArH). δ_C (50 MHz) 20.8, 23.0, 24.7, 24.8, 26.4, 30.6, 63.5, 69.2, 84.1, 115.0, 115.4, 120.4, 125.2, 134.4, 141.8, 153.3, 170.7. Mass spectrum *m/z* 382 (4%, $[M+2]^{+\bullet}$), 380 (5%, $M^{+\bullet}$), 298 (38), 296 (43), 238 (24), 236 (25), 225 (97), 223 (100), 212 (37), 210 (37), 149 (17), 147 (21), 121 (30), 119 (26), 107 (28), 105 (25).

Hydrolysis of the Acetates (29) and (30)

To a mixture of acetates (29) and (30) (1.1 g, 2.9 mmol) in methanol (15 mL) at 0°C, was slowly added sodium hydroxide (4.5 mL, 0.5 M), and the reaction was monitored by TLC. Once the reaction was complete (1 h), water (50 mL) was added and the product was extracted into ethyl acetate (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography (silica; 9 : 1 ethyl acetate/methanol) to give a mixture of *3-[6′-bromo-1′-(tetrahydropyran-2′-yl)-1′*H*-benzimidazol-2′-yl]propan-1-ol* (31) and *3-[5′-bromo-1′-(tetrahydropyran-2′-yl)-1′*H*-benzimidazol-2′-yl]propan-1-ol* (32) as an off-white solid (0.95 g, 97%). The mixture was separated by further chromatography.

The less-polar compound (32) had mp 126–128°C. (Found: $M^{+\bullet}$ 338.0634. $C_{15}H_{19}{}^{79}BrN_2O_2$ requires $M^{+\bullet}$ 338.0630. Found: $[M+2]^{+\bullet}$ 340.0609. $C_{15}H_{19}{}^{81}BrN_2O_2$ requires $[M+2]^{+\bullet}$ 340.0609). ν_{max} (neat)/cm^{-1} 3285, 2940, 2857, 1512, 1453, 1207, 1084, 1042, 907. δ_H (200 MHz, $CDCl_3$) 1.55–1.85 (4 H, m, 3 × tetrahydropyranyl CH_2), 2.0–2.35 (2 H, m, 3 × tetrahydropyranyl CH_2), 2.09 (2 H, tt, *J* 6.9 and 5.8, $CH_2CH_2CH_2$), 3.05 (2 H, t, *J* 6.9, N=CCH_2CH$_2$CH$_2$), 3.61–3.71 (1 H, m, tetrahydropyranyl OCH_2), 4.16–4.26 (1 H, m, tetrahydropyranyl OCH_2), 3.74 (2 H, t, *J* 5.8, OCH_2), 4.82 (1 H, s (broad), OH), 5.46 (1 H, dd, *J* 10.8 and 2.2, NCHO), 7.28 (1 H, dd, *J* 8.6 and 1.8, ArH), 7.49 (1 H, d, *J* 8.6, ArH), 7.78 (1 H, d, *J* 1.8, ArH). δ_C (50 MHz) 22.8, 24.7, 24.9, 30.0, 30.5, 61.0, 69.0, 84.1, 113.4, 114.9, 121.5, 125.0, 132.1, 143.5, 154.7. Mass spectrum *m/z* 340 (13% $[M+2]^{+\bullet}$), 338 (13%, $M^{+\bullet}$), 296 (15), 294 (15), 226 (20), 224 (21), 210 (86), 209 (88), 85 (100).

The more-polar compound (31) had mp 131–133°C. (Found: $M^{+\bullet}$ 338.0634. $C_{15}H_{19}{}^{79}BrN_2O_2$ requires $M^{+\bullet}$ 338.0630. Found: $[M+2]^{+\bullet}$ 340.0604. $C_{15}H_{19}{}^{81}BrN_2O_2$ requires $[M+2]^{+\bullet}$ 340.0609). ν_{max} (neat)/cm^{-1} 3307, 2938, 2856, 1443, 1407, 1376, 1043, 900, 808. δ_H (200 MHz, $CDCl_3$) 1.50–1.90 (4 H, m, 3 × tetrahydropyranyl CH_2), 1.95–2.40 (2 H, m, 3 × tetrahydropyranyl CH_2), 2.10 (2 H, tt, *J* 7.0 and 5.9, $CH_2CH_2CH_2$), 3.03 (2 H, t, *J* 7.0, CCH_2), 3.59–3.75 (1 H, m, tetrahydropyranyl OCH_2), 4.15–4.25 (1 H, m, tetrahydropyranyl OCH_2), 3.74 (2 H, t, *J* 5.8, CH_2OH), 4.89 (1 H, s (broad), OH), 5.44 (1 H, dd, *J* 11.0 and 2.2, NC*H*O), 7.29 (1 H, dd, *J* 8.4 and 1.6, ArH), 7.49 (1 H, d, *J* 8.6, ArH), 7.77 (1 H, d, *J* 1.8, ArH). δ_C (50 MHz) 22.8, 24.7, 24.9, 29.9, 30.5, 61.0, 69.1, 84.1, 115.2, 115.4, 119.9, 125.2, 134.1, 141.1, 154.3. Mass spectrum *m/z* 340 (40%, $[M+2]^{+\bullet}$), 338 (40%, $M^{+\bullet}$), 310 (5), 308 (5), 296 (26), 294 (28), 281 (8), 279 (8), 226 (35), 224 (36), 212 (100), 210 (100), 85 (66).

Mitsunobu Coupling of the THP-Protected Bromobenzimidazoles (31) and (32)

To a stirred solution of methyl 4-hydroxybenzoate (0.09 g, 0.59 mmol) and triphenylphosphine (0.31 g, 1.2 mmol) in anhydrous THF (3 mL) was slowly added a solution of the THP-protected bromobenzimidazoles (31) and (32) (0.3 g, 0.89 mmol) and DEAD (0.19 mL, 1.2 mmol) in THF (1 mL). The reaction was monitored by TLC. After 1 h, further DEAD (0.15 mL) was added and the reaction was stirred for an additional 1 h. The reaction was stopped by addition of water (25 mL), and the product was extracted into dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica; 3 : 1 ether/hexanes).

The less-polar compound, *methyl 4-{3′-[5′-bromo-1′-(tetrahydropyran-2″-yl)-1′*H*-benzimidazol-2′-yl]propyloxy}benzoate* (34) was obtained as a white solid (0.07 g, 25%). Mp 118–121°C. (Found: $M^{+\bullet}$ 472.1006 $C_{23}H_{25}{}^{79}BrN_2O_4$ requires $M^{+\bullet}$ 472.1010. Found: $[M+2]^{+\bullet}$ 474.0994. $C_{23}H_{25}{}^{81}BrN_2O_4$ requires $[M+2]^{+\bullet}$ 474.0977). ν_{max} (neat)/cm^{-1} 2947, 2855, 1713, 1605, 1510, 1433, 1281, 1253, 1168, 1042, 906, 770. δ_H (300 MHz, $CDCl_3$) 1.59–1.81 (4 H, m, 3 × tetrahydropyranyl CH_2), 1.95–2.31 (2 H, m, 3 × tetrahydropyranyl CH_2), 2.40 (2 H, tt, *J* 7.0, 6.1, $CH_2CH_2CH_2$), 3.12 (2 H, m, CCH_2), 3.59 (1 H, m, tetrahydropyranyl OCH_2), 4.10–4.20 (1 H, m, tetrahydropyranyl OCH_2), 3.88 (3 H, s, OCH_3), 4.14 (2 H, t, *J* 5.9, OCH_2), 5.45 (1 H, dd, *J* 11.0, 2.3, NC*H*O), 6.91 (2 H, d (broad), *J* 8.9, ArH), 7.30 (1 H, dd, *J* 8.7 and 1.8, ArH), 7.48 (1 H, d, *J* 8.7, ArH), 7.82 (1 H, d, *J* 1.8, ArH), 7.98 (2 H, d (broad), *J* 9, ArH). δ_C (75 MHz) 23.0, 24.5, 24.9, 27.1, 30.7, 51.8, 66.7, 69.1, 84.2, 113.4, 114.0, 114.9, 122.0, 122.7, 125.1, 131.5, 132.4, 144.3, 153.9, 162.4, 166.7. Mass spectrum *m/z* 474 (12% $[M+2]^{+\bullet}$), 472 (12%, $M^{+\bullet}$), 411 (10), 409 (9), 323 (11), 321 (12), 296 (22), 294 (23), 238 (22), 236 (27), 211 (73), 209 (73), 85 (100).

The more-polar compound, *methyl 4-{3′-[6′-bromo-1′-(tetrahydropyran-2″-yl)-1′*H*-benzimidazol-2′-yl]propyloxy}benzoate* (33) was obtained as an oily solid (0.07 g, 25%). (Found: $M^{+\bullet}$ 472.1002. $C_{23}H_{25}{}^{79}BrN_2O_4$ requires $M^{+\bullet}$ 472.0998. Found: $[M+2]^{+\bullet}$ 474.0976. $C_{23}H_{25}{}^{81}BrN_2O_4$ requires $[M+2]^{+\bullet}$ 474.0977). ν_{max} (NaCl)/cm^{-1} 2946, 2856, 1713, 1605, 1578, 1510, 1435, 1407, 1378, 1279, 1253, 1168, 1043, 770. δ_H (300 MHz, $CDCl_3$) 1.58–1.90 (4 H, m, 3 × tetrahydropyranyl CH_2), 1.98–2.32 (2 H, m, 3 × tetrahydropyranyl CH_2), 2.41 (2 H, tt, *J* 6.9, 6.0, $CH_2CH_2CH_2$), 3.11 (2 H, m, CCH_2), 3.60 (1 H, m, tetrahydropyranyl OCH_2), 4.12–4.21 (1 H, m, tetrahydropyranyl OCH_2), 3.88 (3 H, s, OCH_3), 4.15 (2 H, t, *J* 5.9, OCH_2), 6.91 (2 H, d (broad), *J* 9.0, ArH), 7.32 (1 H, dd, *J* 8.5 and 1.8, ArH), 7.54 (1 H, d, *J* 8.4, ArH), 7.77 (1 H, d, *J* 1.8, ArH), 7.98 (2 H, d (broad), *J* 9.0, ArH). δ_C (75 MHz) 23.1, 24.5, 24.9, 27.1, 30.7, 51.8, 66.7, 69.2, 84.2, 114.1, 115.2, 115.5, 120.4, 122.7, 125.3, 131.6, 134.5, 141.9, 153.6, 162.5, 166.8. Mass spectrum *m/z* 474 (27% $[M+2]^{+\bullet}$), 475 (26%, $M^{+\bullet}$), 443 (5), 441 (4), 323 (13), 321 (15), 296 (30), 294 (33), 239 (27), 237 (35), 211 (86), 209 (86), 149(27), 85 (100).

Removal of the THP Group from the Bromoethers (33) and (34)

To a solution of the THP-protected bromoethers (33) and (34) (0.07 g, 0.15 mmol) in methanol (5 mL) was added a catalytic amount of PPTS. The reaction mixture was heated under reflux and the reaction was monitored by TLC. Once the reaction was complete (3 h) water (20 mL) was added, and the reaction mixture was made alkaline using saturated sodium hydrogen carbonate solution. The product was extracted into ethyl acetate (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4) and finally filtered. The solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography (silica; 4 : 1 ethyl acetate/hexanes) to give *methyl 4-[3′-(5′-bromo-1′*H*-benzimidazol-2′-yl)propyloxy]benzoate* (35) as a white solid (0.045 g, 78%); mp 162–165°C. (Found: $M^{+\bullet}$ 388.0426. $C_{18}H_{17}{}^{79}BrN_2O_3$ requires $M^{+\bullet}$ 388.0423. Found: $[M+2]^{+\bullet}$ 390.0406. $C_{18}H_{17}{}^{81}BrN_2O_3$ requires $[M+2]^{+\bullet}$ 390.0402). ν_{max} (neat)/cm^{-1} 2943, 1706, 1603, 1507, 1432, 1254. δ_H (300 MHz, $CDCl_3$) 2.37 (2 H, tt, *J* 7.3 and 5.8, $CH_2CH_2CH_2$), 3.11 (2 H, t, *J* 7.3, CCH_2), 3.89 (3 H, s, OCH_3), 4.09 (2 H, t, *J* 5.8, OCH_2), 6.83 (2 H, d, *J* 8.9, ArH), 7.32 (1 H, dd, *J* 8.2 and 1.6, ArH), 7.53 (1 H, s (broad), ArH), 7.94 (2 H, d, *J* 8.9, ArH), 9.97 (1 H, s (broad), NH). δ_C (75 MHz) 25.6, 27.3, 51.9, 66.9, 113.9, 115.7, 117.5, 122.8, 125.6, 131.6, 136.7, 138.9, 140.1, 154.8, 162.4, 166.9. Mass spectrum *m/z* 390 (12% $[M+2]^{+\bullet}$), 388 (11%, $M^{+\bullet}$), 359 (4), 357 (5), 239 (29), 237 (34), 212 (95), 210 (100), 180 (2), 178 (2), 158 (13), 156 (9), 132 (15), 130 (14).

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