Methimazole-disulfide as an Anti-thyroid Drug Metabolite Catalyzed the Highly Regioselective Conversion of Epoxides to Halohydrins with Elemental Halogens

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The regioselective ring opening of epoxides using elemental iodine and bromine in the presence of methimazole (MMI, a anti-thyroid drug) and its metabolite methimazole-disulfide as new catalysts are studied. MMI easily converted *in vitro* to MMI-disulfide without any double activation presented *in vivo*. FT-Raman and UV spectroscopies are used to study the interaction of iodine with these catalysts. The results indicate that both catalysts are efficient in polyiodide formation, but MMI-disulfide can catalyze this reaction in higher yield and regioselectivity. The complex $[(\text{MMI-disulfide})I]^+.I_3^-$ is considered to be formed initially which could be bulkier by addition of excess of iodine in the course of the reaction. These bulky nucleophiles have a fundamental role in the high regioselectivity by attacking the less sterically hindered epoxide carbon. In this study we suggest that MMI is readily converted to MMI-disulfide by interaction with iodine or activated iodine in thyroid gland, and this process is responsible for high anti-thyroid activity of MMI.

Key Words : Anti-thyroid drug, Methimazole, Ring opening, Polyiodide, Halohydrins

Introduction

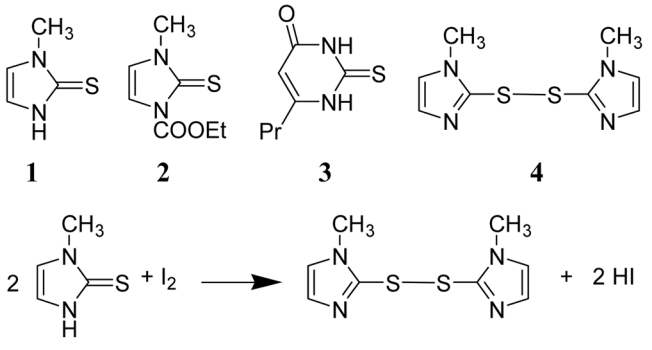
Methimazole (MMI, **1**), carbimazole (CBZ, **2**), and propyl-thiouracil (PTU, **3**) are currently the most commonly employed drugs in the treatment of hyperthyroidism.[1] They depress the formation of thyroid hormones 3,5,3'-triiodothyronine (T_3) and 3,5,3',5'-tetraiodothyronine (T_4) by inhibiting the first step of the hormonal biosynthesis which is the incorporation of oxidized iodides into tyrosine residues in the large thyroid hormone precursor molecule, thyroglobulin.[2,3]

These molecules contain the thiourea pharmacophore.[4-6] Because of a push-pull mechanism in which the nitrogen lone pairs donate electrons to the thiocarbonyl group; this pharmacophore must possess significant electron donor properties at the sulfur atom. In an initial proposed mechanism[7,8] of action of anti-thyroid agents by forming stable complexes with diiodine, they could divert it from the second oxidation step of iodides ($I_2 \rightarrow 2I^+ + 2e^-$) and consequently prevent the electrophilic substitution of I^+ on the tyrosine residues of thyroglobulin. Another mechanism[3] involves an enzyme containing selenocysteine in its active site, which is responsible for the monodeiodination of the prohormone thyroxine (T_4) to the biologically active hormone (T_3) in the first step in thyroid hormone action. In the deiodinase cycle, the selenol group of the enzyme (E-SeH) first reacts with T_4 to form selenenyl iodides (E-SeI) with a release of the T_3. Subsequent reaction of the (E-SeI) with a thiol of other cofactors releases I^- and regenerates the active site. The anti-thyroid drugs react with the (E-SeI) intermediate to inhibit the enzyme active site regeneration by formation of a stable selenenyl sulfide.

Moreover, the catalytic ring opening of epoxides with elemental halogens has been reported in the presence of thiourea and related crown ethers.[9,10] Anti-thyroid drugs **1**-**3** contain the thiourea pharmacophore and we decided to examine the catalytic behavior of these drugs in the ring opening reactions of epoxides in the presence of elemental halogens. PTU **3** is difficult to study because of insolubility in organic solvents. CBZ **2** *in vivo*, is rapidly and totally metabolized to MMI **1** and the anti-thyroid action of CBZ can be ascribed entirely to MMI.[11] So, we have selected MMI **1** as a catalyst in a regioselective conversion of epoxides to halohydrins in the presence of elemental iodine. In this study, we wish to report the results of the reactions of epoxides with elemental iodine and bromine in the presence of a catalytic amount of the inexpensive and readily available anti-thyroid drug, methimazole (MMI, **1**) and it's well-known metabolite methimazole-disulfide **4** (Scheme 1).

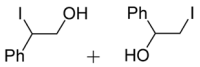
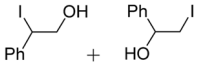
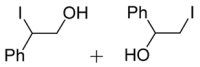
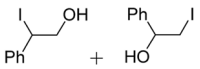
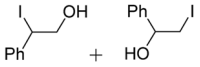
Results and Discussion

The results of the reactions of styrene oxide with elemental iodine in the presence of MMI, are summarized in Table 1. For comparison, the cleavage behavior of styrene



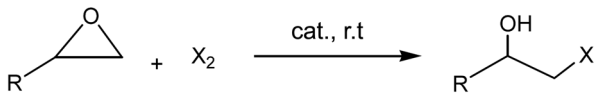
Scheme 1

Table 1. Reaction of styrene oxide (1 mmol) with elemental iodine (1 mmol) in the presence of representative catalysts

Entry	Catalyst	Conditions	Product (s)	Conversion %[a]	Ref.
1	–	I_2, r.t/acetone		83	12
2	–	I_2, r.t/CH_2Cl_2	No reaction	0	12
3	–	I_2, r.t /THF	 3 : 1	30	12
4	**1**	I_2, r./CH_2Cl_2	 2 : 1	40	
5	**1**	I_2, r.t/THF	 2 : 1	80	
6	**1**[b]	I_2, r.t/THF	 1 : 9	88	
7	**4**	I_2, r.t/THF	 1 : 8	>98	

[a]Relative yield according to GC. [b]Reaction was carried out with recovered catalytst

oxide with elemental iodine in the absence of catalyst is given in entries 1-3. As shown in Table 1, iodination of styrene oxide with an excess of elemental iodine in the absence of catalyst does not occur even under reflux and extension of reaction time to several days, and unreacted styrene oxide are completely recovered. As reported by Turos[12] and reexamined by us (Table 1, entry 3), iodination cleavage of styrene oxide with iodine in the absence of a catalyst, in THF solvent, proceed to only about 30% conversion with low regioselectivity. Whereas, MMI can catalyze this reaction to completion but the regioselectivity is not sufficient. Interestingly, we observed that the yields and regioselectivity are improved when the reaction is performed in the presence of the recovered catalyst (entry 6). Spectral analysis showed that the catalyst was converted to methimazole-disulfide. It is well known that the thiols can be converted to disulfide in the presence of bromine or iodine.[13] So, we prepared MMI-disulfide (**4**) easily from MMI in 90% yield, and used it as catalyst in the ring opening



Scheme 2

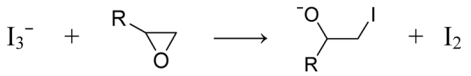
reactions. The results of the reactions of styrene oxide with elemental iodine in the presence of MMI-disulfide, showed that yield and regioselectivity of the ring opening reaction were increased and catalyst **4** is the most effective one (Table 1, entry 7). We suggest the low reverse-regioselectivity of this reaction in the presence of catalyst **1** (Table 1, entry 5) is due to the formation of hydroiodic acid and interference in the reaction mechanism course. So, MMI-disulfide **4** is the best choice because it's inexpensive and can readily be prepared with high conversion yield in short reaction times.

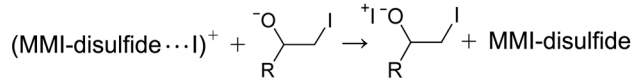
The results obtained with some representative epoxides in the presence of MMI-disulfide (**4**) as catalyst are summarized in Table 2 and are compared with some other methods. When epoxides were allowed to react in the presence of **4**, increases in yield and regioselectivities were observed in all of the reactions studied. Generally, the optimum amounts of the catalysts were found to be 10 mole % of epoxide and halogen. However, bromination is faster than iodination cleavage with similar high yields and regioselectivity.

The regioselectivity and rate of cleaving epoxides by elemental iodine in the presence of a catalyst can be explained in terms of the following suggested mechanisms:[9]

MMI-disulfide + 2 $I_2 \rightarrow$ (MMI-disulfide$\cdots$I)$^+I_3^-$

(MMI-disulfide$\cdots$I)$^+I_3^- \rightarrow$ (MMI-disulfide$\cdots$I)$^+ + I_3^-$

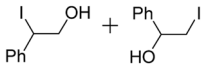
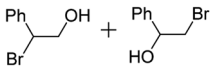
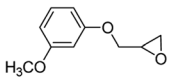
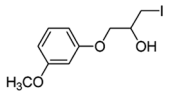
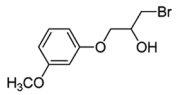
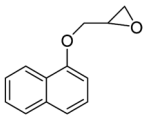
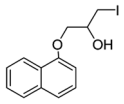
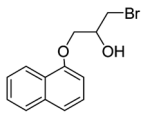
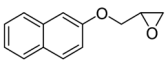
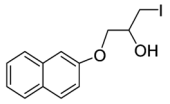
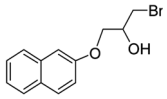
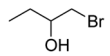




In support of this mechanism, the UV spectra of iodine, and complex formation between iodine and catalysts **1** and **4** are shown in Figure 1. None of the initial reactants show any measurable absorption in the 300-440 nm region, whereas the addition of the catalyst to iodine results in a strong absorption band at 360 nm, presumably due to the complex formation of iodine with catalyst. The intensity of the band at 360 nm, as evidence for the ease of formation of polyiodide ion, decreased in the case of MMI. However, in the case of MMI-disulfide this band appeared immediately and corroborated the much faster complexation of iodine with this catalyst.

The UV-Vis Spectra of iodine in the presence of increasing amounts of MMI-disulfide are shown in Figure 2. While none of the initial reactants show any measurable absorption in the 250-450 nm region, addition of the catalyst to iodine results in two strong absorption in 290 and 360 nm, due to the formation of iodine-catalyst complexes. It should be noted that the bands of 292 and 364 nm are characteristic for the formation of polyiodide ions such as I_3^- and I_5^-, in the process of complex formation between iodine and electron-pair-donating atoms.[14,15] It is well known that both ions absorb in the same region around 360 and 290 nm with little

Table 2. Reaction of Epoxides with Elemental Bromine and Iodine in the Presence of MMI-disulfide (**4**) as the Catalyst

Entry	Epoxide	Catalyst	Reaction conditions	Time / h	Yield / %[a]	Product (s)	Ref.
1		–	LiI, AcOH, THF, rt	1.3	87(2:1)		18
2	"	–	HI, rt, $CHCl_3$	0.25	> 99		19
3	"	**4**	I_2, rt, THF	2	85		
4	"	**4**	Br_2, rt, THF	1.5	89		
5	"	–	Br_2, rt, CH_2Cl_2	1	31		12
6	"	–	$nBu_4N^+Br^-/Mg(NO_3)_2$, $CHCl_3$, rt	5	78(1:5)		20
7	"	–	HBr, rt, $CHCl_3$	0.25	> 99		19
8		**4**	I_2, rt, THF	4.5	92		
9	"	**4**	Br_2, rt, THF	3	95		
10		**4**	I_2, rt, THF	5.25	92		
11	"	**4**	Br_2, rt, THF	4	95		
12		**4**	I_2, rt, THF	5	93		
13	"	**4**	Br_2, rt, THF	4.5	95		
14		**4**	I_2, rt, THF	2	96		
15	"	**4**	Br_2, rt, THF	1.25	97		
16		**4**	I_2, rt, THF	4	75		
17	"	**4**	Br_2, rt, THF	3	79		

[a]Isolated yield.

deviation in their absorbtivities.[14c,14e]

Complexation studies of MMI by iodine in a 1:1, 1:2 and 2:1 molar ratios, showed that in all of the cases a dark solid complex deposited. In each case, breakdown of the complex upon thiosulfate work up, the same colorless crystal of the MMI-disulfide was obtained and the structure of this product was confirmed by ^{1}H-NMR, IR and MS spectra. Since we believed that the MMI rapidly converted to the MMI-disulfide by a redox reaction with iodine.

The *Raman* spectra of the MMI: iodine complex which formed in a 1:2 molar ratio are shown in Figures 3. According to the mechanism and Scheme 1, one half equivalent of iodine consumed for generation of MMI-disulfide from MMI and residue of iodine in the presence of this *in situ*-

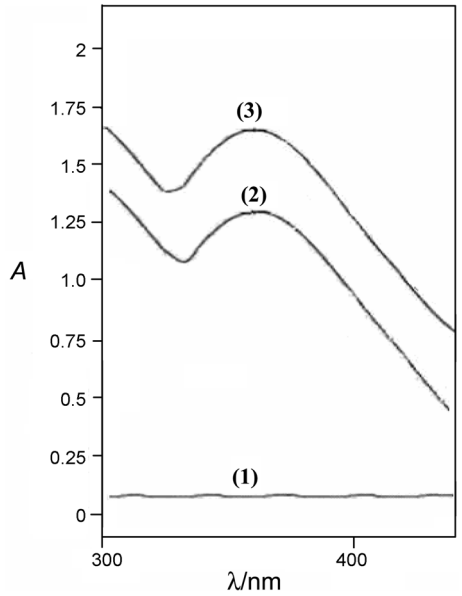


Figure 1. Absorption spectra of: (1) iodine; (2) and (3) complexes of MMI and MMI-disulfide with iodine in dichloromethane solution respectively.

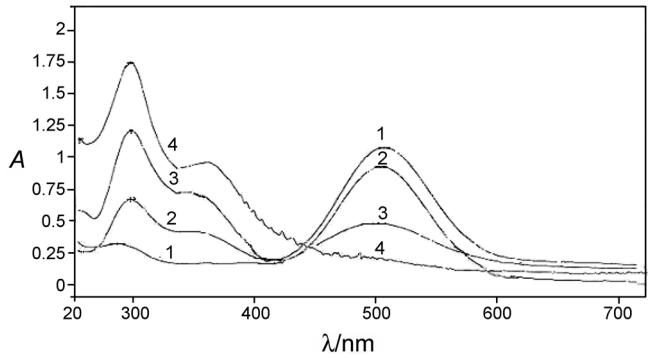


Figure 2. Absorption spectra of iodine in CH_2Cl_2 in the presence of various concentration of MMI-disulfide (**4**). The catalyst: I_2 mole ratios are: 1) 0.00, 2) 0.001, 3) 0.01 and 4) 0.1.

formed catalyst can be converted to I_3^- and higher polyiodides which showed a series bands at 110, 143, 165 cm^{-1} which intensity of the band at 165 cm^{-1} increased relative to the band at 110 cm^{-1}. This pattern confirmed the formation of other polyiodides such as I_5^-, and I_7^-. This band also shifts to higher wavenumbers until it reaches that of free iodine (approx. 180 cm^{-1}). Solid I_2 is known[16] to show a *Raman* active stretching frequency near 190 cm^{-1} which was not observed in our spectrum. The *Raman* spectra of the triiodide anions exhibit a sharp band at 110 and 140 cm^{-1} corresponding to the symmetrical and unsymmetrical stretching of iodine bonds (Fig. 4). Whereas in the case of MMI-disulfide: iodine complex (1:1), the *Raman* spectra of the complex showed conversion only up to I_3^-. evediently, in the case of MMI-disulfide or another catalyst which formed initially I_3^-, higher polyiodides such as I_5^-, I_7^-, etc were formed in the presence of excess of iodine which provided in catalytic reaction.

Thus we suggest that the major nucleophile at the first of

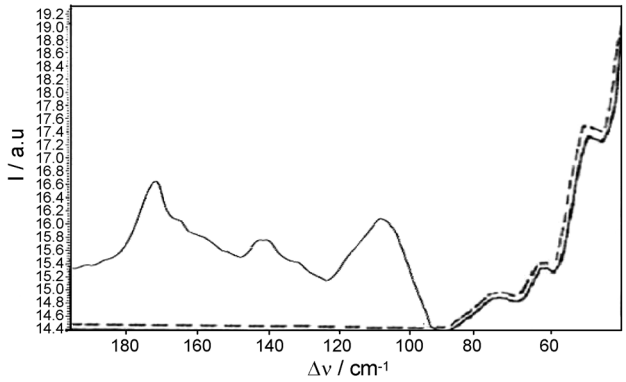


Figure 3. The Raman spectra of MMI (---) and MMI-iodine (1:2) Complex (—).

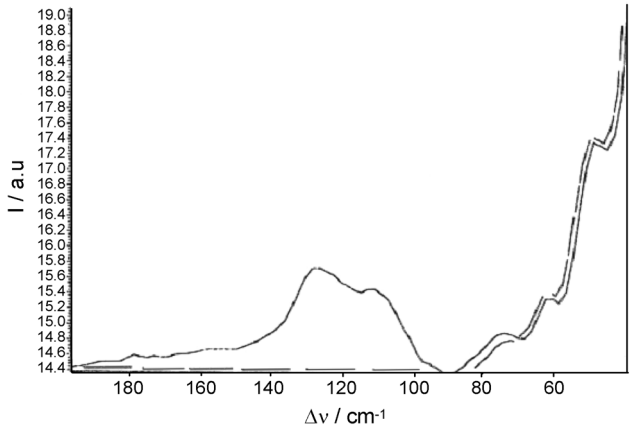


Figure 4. The Raman spectra of MMI-disulfide (---) and MMI-disulfide:iodine (1:1) complex, (MMI-disulfide)$I]^+.I_3^-$ (—).

the reaction is I_3^-, and this nucleophile is converted to higher bulky polyiodides such as I_5^- and I_7^- in the course of the reaction. These bulky nucleophiles have a fundamental role in the high regioselectivity observed attacking on the less sterically hindered epoxide carbon.

The electron donor properties of MMI **1** towards the Lewis acid I_2 have already received attention. The MMI-disulfide (**4**) is the earliest MMI metabolite detected in an *in vitro* interaction system containing MMI, TPO, I_2, and H_2O_2.[17] Whereas, Laurence *et al.*[4] was reported a charge transfer complex, the equilibrium reaction between MMI and iodine has recently been reinvestigated by Isaia *et al.*[18] FT-Raman spectra of complexes which formed from 1:1 and 1:2 molar ratio of MMI:I_2, were showed the formation of polyiodide ions such as I_3^- and I_8^{2-}. X-Ray crystallography was proved the formation of MMI-disulfide cations as counter ions of polyiodides. Our observation in MMI and iodine interaction showed that the MMI-disulfide formation is a fast reaction, without any double activation. A simple work up of products by thiosulfate solution, remove the polyiodides and the neutral MMI-disulfide **4** was obtained as colorless crystals in high yields. So, we suggested that MMI by interaction with I_2 or activated iodine in thyroid gland such as (E-SeI) readily converted to MMI-disulfide and this is responsible for high anti-thyriode activity of MMI.

In conclusion, we have found that MMI-disulfide which is readily prepared in situ from MMI, can be catalyze the regioselective ring opening of epoxides by elemental iodine and bromine under neutral conditions, as well as the convenience of this procedure, which makes this synthetic technique highly useful. UV-Vis and Resonance *Raman* spectroscopy indicated that the complex (MMI-disulfide$\cdots$ I)$^+I_3^-$ is formed. Accordingly, we suggest that the major nucleophile in the first of the reaction is the triiodide ion, I_3^- and can be bulkier in the presence of excess of iodine to I_5^- and I_7^-. These bulky nucleophiles play a fundamental role in the high regioselectivity observed. It is due to an attack on the less sterically hindered epoxide carbon. Finally, our results showed that MMI-disulfide is a powerful "iodine sponge" and readily converted it to I^-, I_3^-, etc. however, this is responsible for high anti-thyriode activity of MMI by depressing the formation of thyroid hormones

Experimental Section

All materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland). Melting points were determined in open capillary tubes in an Electrothermal IA 9700 melting point apparatus. ^{1}H-NMR spectra were recorded on a Bruker-100 MHz instrument using *TMS* as an internal standard. UV-Vis spectra were obtained with a Shimadzu-AA 670 spectrometer. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. The *Raman* spectrum was recorded employing a 180° back-scattering geometry and a Bomem MB-154 Fourier Transform *Raman* spectrometer. It was equipped with a ZnSe beam splitter and a TE cooled InGaAs detector. *Rayleigh* filtration was afforded by a set of two holographic technology filters. The spectrum was collected with a resolution of 4 cm^{-1} by coadding the results of 1000 scans. The purity determination of the substrates and reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-10A instrument with a flame ionization detector using a column of 15% carbowax 20 M chromosorb W acid-washed 60-80 mesh. Column chromatography was carried out on short columns of silica gel 60 (230-400 mesh) in glass columns (2-3 cm diameter) using 15-30 g silica gel per 1 g of crude mixture.

Preparation of Catalyst. A solution of iodine (0.254 g, 1 mmol) in CH_2Cl_2 (5 cm^3) was added dropwise to a stirred solution of methimazole (0.1 g, 1 mmol) in CH_2Cl_2 (10 cm^3) in 15 min at room temperature. The reaction mixture was stirred for 30 min and then was washed with 10% aqueous $Na_2S_2O_3$ (2 × 10 cm^3) and water (2 × 10 cm^3). The organic layer was dried over anhydrous $MgSO_4$ and evaporated. The colorless crystals of methimazole-disulfide were obtained in 90% yield. Mp. 138 ºC, δ_H (100 MHz; $CDCl_3$; Me_4Si) 3.57 (6H, s, Me), 6.70 (4H, m, MMI) ppm. IR ν_{max}/cm^{-1} (KBr): 754 (s), 832 (m), 845 (m), 908 (w), 1028 (m), 1180 (m), 1217 (m), 1262 (s), 1351 (m), 1390 (m), 1508 (w), 1593 (m), 1625 (s), 2920 (w), 2994 (w), 3053 (w); MS *m/z* 228 (M+2), 226 (M^+). Elemental analysis: (Found: C, 42.45; H, 4.45; N, 24.76; S, 28.34. Calc. for $C_8H_{10}N_4S_2$: C, 42.39; H, 4.50; N, 24.86; S, 28.39%).

General Procedure for Halogenative Cleavage of Epoxides. A solution of epoxide (1 mmol) in THF (5 cm^3) was added to a stirred solution of MMI-disulfide (0.023 g, 0.1 mmol) **4** in THF (5 cm^3) at room temperature. Next, a solution of 1 mmol elemental halogen in THF (10 cm^3) was added dropwise during 40 min. The progress of reaction was monitored by TLC and GLC. After complete disappearance of the starting material, the reaction mixture was washed with 10% aqueous $Na_2S_2O_3$ (2 × 10 cm^3) and H_2O (2 × 10 cm^3). The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 cm^3). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated. The crude was purified by chromatography on a column of silica gel. The halohydrins obtained throughout this procedure were identified by comparison with authentic samples prepared according to literature procedures.[9,10,19-24]

The product has been reported before but ^{1}H-NMR spectral data were not given.

1-Iodo-3-(naphthalen-1-yloxy)-propan-2-ol (entry 10). δ_H (100 MHz; $CDCl_3$; Me_4Si) 2.6 (1H, br, OH), 3.6 (2H, m, CH_2I), 4.0 (1H, m, CH), 4.3 (2H, m, CH_2O), 7.2-7.3 (2H, m, ArH), 7.3-7.6 (3H, m, ArH), 7.7-7.9 (2H, m, ArH).

1-Bromo-3-(naphthalen-1-yloxy)-propan-2-ol (entry 11). δ_H (100 MHz; $CDCl_3$; Me_4Si) 2.6 (1H, br, OH), 3.75 (2H, m, CH_2I), 4.1 (1H, m, CH), 4.4 (2H, m, CH_2O), 7.2-7.3 (2H, m, ArH), 7.3-7.5 (3H, m, ArH), 7.7-7.9 (2H, m, ArH).

1-Iodo-3-(naphthalen-2-yloxy)-propan-2-ol (entry 12). δ_H (100 MHz; $CDCl_3$; Me_4Si) 2.4 (1H, br, OH), 3.5 (2H, m, CH_2I), 4.0 (1H, m, CH), 4.3 (2H, m, CH_2O), 6.9 (2H, m, ArH), 7.5 (3H, m, ArH), 7.85 (1H, m, ArH), 8.35 (1H, m, ArH).

1-Bromo-3-(naphthalen-2-yloxy)-propan-2-ol (entry 13). δ_H (100 MHz; $CDCl_3$; Me_4Si) 2.6 (1H, br, OH), 3.68 (2H, m, CH_2I), 4.1 (1H, m, CH), 4.4 (2H, m, CH_2O), 6.9 (2H, m, ArH), 7.5 (3H, m, ArH), 7.85 (1H, m, ArH), 8.35 (1H, m, ArH).

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