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Highly facile biomimetic regioselective ring opening of epoxides to halohydrins in the presence of β-cyclodextrin☆

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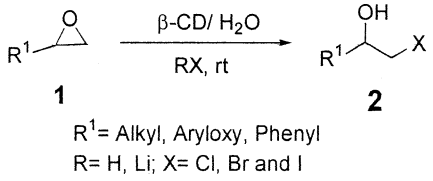
Abstract—Highly regioselective ring opening of epoxides to halohydrins has been carried out in impressive yields with hydrogen and lithium halides in presence of β-cyclodextrin using water as solvent.

1. Introduction

There is continued interest in the regioselective ring opening of oxiranes to vicinal halohydrins due to their significance[1] especially in the synthesis of halogenated marine natural products[2] and in various organic synthetic transformations.[3] But the most general method of preparing these *vic*-halohydrins by the ring opening of epoxides with hydrogen halides suffers from various disadvantages such as pharmacologically inactive halohydrins, unwanted byproducts and low regioselectivity.[4] This has spurred research in different directions ranging from elemental halogens,[5] metal halides such as LiX,[6] $TiCl_4$–LiX,[7] $CeCl_3$ $7H_2O$–NaI,[8] to chlorosilanes,[9] haloboranes[10] etc. However, these reagents also suffer from various disadvantages such as in situ preparation of reagents, longer reaction times (up to several days in some cases), reflux temperatures, hygroscopic nature of catalysts etc. In view of these limitations, there is still the need for a widely applicable and alternate approach, preferably using water as solvent which is gaining increasing importance in the present day organic synthesis. Amongst various approaches, the most attractive methodology with wide applicability and industrial potential appeared to be from the easily accessible epoxides and inexpensive hydrogen halides if the disadvantages associated with this method such as unwanted byproduct formation and low regioselectivities can be overcome. The best choice appeared to be through supramolecular catalysis involving cyclodextrins and using water as solvent. Such reactions do not generate any toxic waste products either (Scheme 1).



Scheme 1.

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host–guest complexes by non-covalent bonding as seen in enzymes. Complexation depends on the size, shape and hydrophobicity of the guest molecule. Thus mimicking of biochemical selectivity that shows shape and substrate selectivity will be superior to chemical selectivity. Our earlier expertise in the field of biomimetic modeling of organic chemical reactions[11] prompted us to attempt the regioselective ring opening of epoxides with hydrogen halides in the presence of β-cyclodextrin (β-CD) as this is one of the most useful synthetic transformations with a variety of applications.

2. Results and discussion

The reaction was carried out by the in situ formation of the β-CD complex of the epoxide (**1**) in water followed by the addition of hydrogen halide or lithium halide and stirring at room temperature to give the corresponding halohydrins (**2**) in impressive yields (Tables 1 and 2). The reaction goes smoothly at room temperature without the formation of any side products or rearrangements. The catalyst can be easily recovered and reused. β-CD has been chosen as the catalyst since it is inexpensive and easily accessible. However, these reactions do take place with α-CD. Though inclusion complexation takes place in situ during the

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Keywords: epoxides; hydrogen halides and lithium halides; cyclodextrin; supramolecular catalysis; water.

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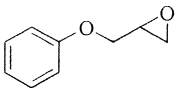
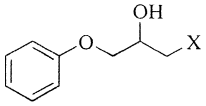
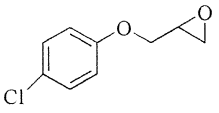
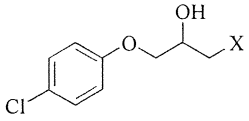
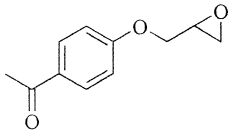
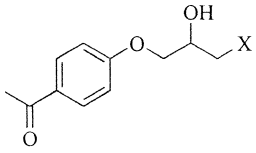
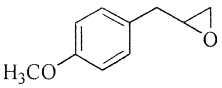
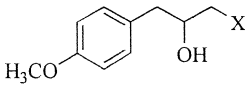
Table 1. Biomimetic synthesis of halohydrins from oxiranes and hydrogen halides

Entry	Epoxide (**1**)	Reagent	Product[a] (**2**)	Yield[b] (%)
				
1		HCl	**2a**. X=Cl	96
2		HBr	**2b**. X=Br	90
3		HI	**2c**. X=I	89
				
4		HCl	**2d**. X=Cl	94
5		HBr	**2e**. X=Br	88
6		HI	**2f**. X=I	90
				
7		HCl	**2g**. X=Cl	92
8		HBr	**2h**. X=Br	94
9		HI	**2i**. X=I	89
				
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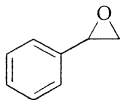
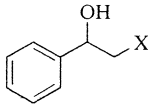
11		HBr	**2k**. X=Br	92
12		HI	**2l**. X=I	90
				
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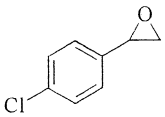
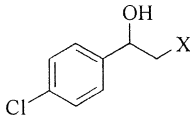
14		HBr	**2n**. X=Br	90
15		HI	**2o**. X=I	95
				
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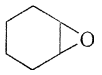
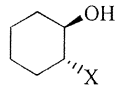
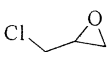
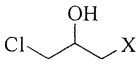
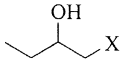
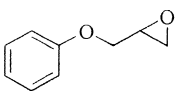
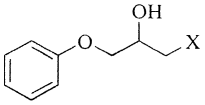
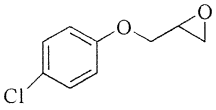
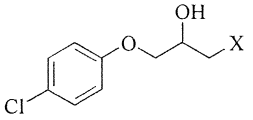
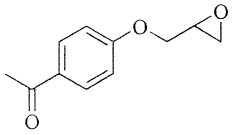
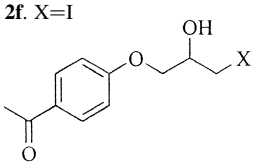
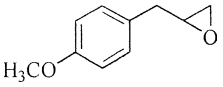
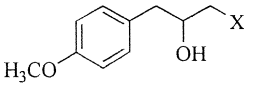
17		HBr	**2q**. X=Br	88
18		HI	**2r**. X=I	87
				
19		HCl	**2s**. X=Cl	88
20		HBr	**2t**. X=Br	90
21		HI	**2u**. X=I	84
				
22		HCl	**2v**. X=Cl	92
23		HBr	**2w**. X=Br	90
24		HI	**2x**. X=I	87
				
25		HCl	**2y**. X=Cl	89
26		HBr	**2z**. X=Br	91
27		HI	**2z′**. X=I	95

[a] All products were characterized by ^{1}H NMR, Mass and IR spectra data.
[b] Isolated yields.

Table 2. Biomimetic synthesis of halohydrins from oxiranes and lithium halides

Entry	Epoxide (**1**)	Reagent	Product[a] (**2**)	Yield[b] (%)
				
1		LiCl	**2a**. X=Cl	89
2		LiBr	**2b**. X=Br	85
3		LiI	**2c**. X=I	82
				
4		LiCl	**2d**. X=Cl	90
5		LiBr	**2e**. X=Br	81
6		LiI	**2f**. X=I	85
				
7		LiCl	**2g**. X=Cl	85
8		LiBr	**2h**. X=Br	90
9		LiI	**2i**. X=I	87
				
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	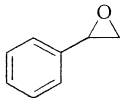		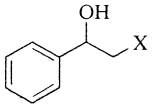	
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	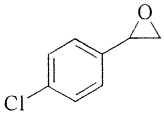		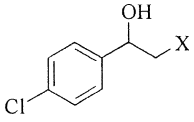	
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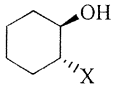
17		LiBr	**2q**. X=Br	81
18		LiI	**2r**. X=I	85
				
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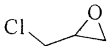
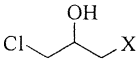
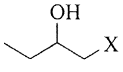
				
22		LiCl	**2v**. X=Cl	85
23		LiBr	**2w**. X=Br	82
24		LiI	**2x**. X=I	79
				
25		LiCl	**2y**. X=Cl	83
26		LiBr	**2z**. X=Br	80
27		LiI	**2z′**. X=I	77

[a] All products were characterized by ^{1}H NMR, Mass and IR spectra data.
[b] Isolated yields.

reaction, the complexes have been isolated and characterized by powder X-ray[12] and ^{1}H NMR studies.[13] Here, the role of CD appears to be not only to activate the epoxides but also to promote highly regioselective ring opening due to inclusion complex formation. Thus, in this new biomimetic methodology, chloro, bromo and iodohydrins can be obtained in high yields. Since these reactions are taking place in the microenvironment of cyclodextrin, high selectivities are obtained without any side product formation. Especially notable is the selectivity obtained with styrene epoxides (entries 13–18) where the halide ion attacked the terminal carbon whereas in the procedures reported so far, either the halide ion attacked the benzylic carbon or mixtures were obtained. In this methodology even the acid sensitive ether linkages in **2a**–**2i** are left intact due to microenvironmental effect in spite of the epoxides being opened with hydrogen halides. Though these reactions can also be carried out using lithium halides, the yields obtained were comparatively lower. However, other metal halides such as NaX, KX did not work out.

3. Conclusion

Thus, it has been shown for the first time that halohydrins with high synthetic potential can be made in a biomimetic fashion with high regioselectivity from the easily accessible epoxides and inexpensive hydrogen halides in the presence of β-CD. Thus, this high selectivity, which was not possible with earlier methods could be achieved due to the inclusion complex formation of epoxides with β-cyclodextrin which then reacted with hydrogen halides. Further potential applications of this reaction are under study.

4. Experimental

4.1. General

All reagents were purchased from Fluka or SD Fine Chemicals and were used with out further purification. Silica gel (100–200 mesh) for chromatography was purchased from SD Fine Chemicals and compounds were visualized on analytical thin layer chromatograms (TLC) by UV light (254 nm). Optical rotations were measured in chloroform. ^{1}H NMR spectra were recorded at 200, 300 or 400 MHz. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which is used as internal standard and coupling constants (J) are reported in Hz. IR absorptions (in cm^{-1}) and the molecular ions and/or base peaks in MS are given.

4.2. General procedure for the preparation of halohydrins from the corresponding epoxides

β-Cyclodextrin (1 mmol) was dissolved in water (25 mL) at 60°C, epoxide (1 mmol) dissolved in methanol/acetone (1 mL) was added slowly with stirring and cooled to room temperature. Then 1.5 mmol of hydrogenhalide or lithium halide was added and stirring at room temperature was continued (12 h in case of hydrogenhalide or 24 h for lithium halide). It was extracted with ethyl acetate (3×25 mL) and filtered. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed in vacuum. The crude product was purified by silica gel column chromatography using ethyl acetate: hexane (2:8) as eluent. All the products were characterized by ^{1}H NMR, IR, and Mass spectral data and compared with the data reported in the literature for the authentic samples.

4.2.1. 1-Chloro-3-phenoxy-2-propanol (2a).[8] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.50 (d, 1H, J=3.2 Hz), 3.70–3.85 (m, 2H), 4.10–4.15 (m, 2H), 4.18–4.25 (m, 1H), 6.90–7.0 (m, 3H), 7.30–7.40 (m, 2H); MS (EI) m/z: 186 (M^+); IR (KBr) 3450 cm^{-1}.

4.2.2. 1-Bromo-3-phenoxy-2-propanol (2b).[14] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.45 (d, 1H, J=3.0 Hz), 3.75–3.80 (m, 2H), 4.05–4.10 (m, 2H), 4.15–4.20 (m, 1H), 6.90–7.05 (m, 3H), 7.30–7.35 (m, 2H); MS (EI) m/z: 230 (M^+); IR (KBr) 3500 cm^{-1}.

4.2.3. 1-Iodo-3-phenoxy-2-propanol (2c).[14] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.40 (brs, 1H), 3.30–3.55 (m, 2H), 3.80–4.10 (m, 3H), 6.75–7.0 (m, 3H), 7.15–7.35 (m, 2H); MS (EI) m/z: 278 (M^+); IR (KBr) 3500 cm^{-1}.

4.2.4. 1-Chloro-3-(4-chlorophenoxy)-2-propanol (2d).[17] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.40 (d, 1H, J=3.2 Hz), 3.70–3.80 (m, 2H), 4.05–4.15 (m, 2H), 4.19–4.25 (m, 1H), 6.85 (d, 2H, J=9.2 Hz), 7.25 (d, 2H, J=9.2 Hz); MS (EI) m/z: 220 (M^+); IR (KBr) 3510 cm^{-1}.

4.2.5. 1-Bromo-3-(4-chlorophenoxy)-2-propanol (2e).[17] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05 (d, 1H, J=3.2 Hz), 3.45–3.60 (m, 2H), 3.95–4.05 (m, 2H), 4.10–4.20 (m, 1H), 6.75 (d, 2H, J=8.2 Hz), 7.20 (d, 2H, J=8.2 Hz); MS (EI) m/z: 264 (M^+); IR (KBr) 3515 cm^{-1}.

4.2.6. 1-Iodo-3-(4-chlorophenoxy)-2-propanol (2f).[17] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.40 (brs, 1H), 3.35–3.40 (m, 1H), 3.45–3.50 (m, 1H), 3.95–4.0 (m, 1H), 4.05–4.10 (m, 2H), 6.85 (d, 2H, J=8.2 Hz), 7.25 (d, 2H, J=8.2 Hz); MS (EI) m/z: 312 (M^+); IR (KBr) 3540 cm^{-1}.

4.2.7. 1-Chloro-3-(4-acetylphenoxy)-2-propanol (2g). Pale yellow liquid, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.55 (s, 3H), 3.0 (brs, 1H), 3.75–3.80 (m, 2H), 4.0–4.40 (m, 3H), 6.90 (d, 2H, J=7.6 Hz), 7.95 (d, 2H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.21, 45.69, 68.78, 69.61, 114.25, 130.65, 162.31, 197.47; MS (EI) m/z 228 (M^+). Anal. calcd for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73. Found: C, 57.80; H, 5.68.

4.2.8. 1-Bromo-3-(4-acetylphenoxy)-2-propanol (2h). White Solid, mp 64–66°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.55 (s, 3H), 3.45–3.65 (m, 2H), 4.10–4.20 (m, 3H), 6.90 (d, 2H, J=7.6 Hz), 7.90 (d, 2H, J=7.6 Hz), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.11, 34.53, 69.05, 69.33, 114.09, 130.46, 162.08, 197.12; MS (EI) m/z 273 (M^+). Anal. calcd for $C_{11}H_{13}BrO_3$: C, 48.37, H, 4.80. Found: C, 48.45; H, 4.75.

4.2.9. 1-Iodo-3-(4-acetylphenoxy)-2-propanol (2i). Yellow solid, mp 68–70°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.55 (s, 3H), 3.30–3.50 (m, 2H), 3.90–4.10 (m, 3H), 6.90 (d, 2H, J=7.8 Hz), 7.90 (d, 2H, J=7.8 Hz), ^{13}C NMR

($CDCl_3$, 50 MHz) δ 8.84, 26.21, 69.12, 70.57, 114.66, 130.64, 162.75, 196.96; MS (EI) *m/z* 320 (M^+). Anal. calcd for $C_{11}H_{13}IO_3$: C, 41.27; H, 4.09. Found: C, 41.34; H, 4.10.

4.2.10. 1-Chloro-3-(4-methoxyphenyl)-2-propanol (2j). Pale yellow liquid, ^1H NMR ($CDCl_3$, 200 MHz) δ 2.80 (d, 2H, *J*=7.8 Hz), 3.50 (dd, 1H, *J*=5.2, 9.6 Hz), 3.60 (dd, 1H, *J*=4.4, 9.6 Hz), 3.80 (s, 3H), 3.90–4.0 (m, 1H), 6.80 (d, 2H, *J*=8.0 Hz), 7.12 (d, 2H, *J*=8.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.20, 47.80, 55.10, 72.10, 116.50, 130.10, 131.22, 158.32; MS (EI) *m/z*: 200 (M^+); IR (KBr) 3485 cm^{-1}. Anal. calcd for $C_{10}H_{13}ClO_2$: C, 59.86; H, 6.53. Found: C, 59.72; H, 6.44.

4.2.11. 1-Bromo-3-(4-methoxyphenyl)-2-propanol (2k). Pale yellow liquid, ^1H NMR ($CDCl_3$, 200 MHz) δ 2.05 (brs, 1H), 2.85 (d, 2H, *J*=6.2 Hz), 3.35 (dd, 1H, *J*=4.8, 9.6 Hz), 3.55 (dd, 1H, *J*=3.8, 9.6 Hz), 3.80 (s, 3H), 3.95–4.0 (m, 1H). 6.85 (d, 2H, *J*=8.6 Hz), 7.15 (d, 2H, *J*=8.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 39.10, 41.42, 55.10, 70.05, 116.22, 130.10, 131.05, 158.10; MS (EI) *m/z*: 244 (M^+); IR (KBr) 3480 cm^{-1}. Anal. calcd for $C_{10}H_{13}BrO_2$: C, 49.00, H, 5.35, Found. C, 48.88; H, 5.18.

4.2.12. 1-Iodo-3-(4-methoxyphenyl)-2-propanol (2l). Pale yellow liquid, ^1H NMR ($CDCl_3$, 200 MHz) δ 1.90 (brs, 1H), 2.85 (d, 2H, *J*=6.2, 9.2 Hz), 3.25 (dd, 1H, *J*=4.6, 9.2 Hz), 3.35 (dd, 1H, *J*=3.8, 9.2 Hz), 3.60–3.75 (m, 1H), 3.80 (s, 3H), 6.85 (d, 2H, *J*=8.2 Hz), 7.15 (d, 2H, *J*=8.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.67, 41.66, 55.10, 71.62, 113.92, 128.98, 130.12, 158.25; MS (EI) *m/z*: 292 (M^+); IR (KBr) 3560 cm^{-1}. Anal. calcd for $C_{10}H_{13}IO_2$: C, 41.12; H, 4.49. Found: C, 41.18, H, 4.42.

4.2.13. 2-Chloro-1-phenylethanol (2m).[8] ^1H NMR ($CDCl_3$, 200 MHz) δ 2.50 (brs, 1H), 3.45–3.60 (m, 2H), 4.98 (dd, 1H, *J*=3.6, 9.6 Hz), 7.25–7.45 (m, 5H); MS (EI) *m/z*: 156 (M^+); IR (KBr) 3460, 2935 cm^{-1}.

4.2.14. 2-Bromo-1-phenylethanol (2n).[14] ^1H NMR ($CDCl_3$, 200 MHz) δ 2.80 (brs, 1H), 3.45–3.65 (m, 2H), 4.90 (dd, 1H, *J*=3.2, 9.4 Hz), 7.25–7.40 (m, 5H); MS (EI) *m/z*: 200 (M^+); IR (KBr) 3415, 2940 cm^{-1}.

4.2.15. 2-Iodo-1-phenylethanol (2o).[14] ^1H NMR ($CDCl_3$, 200 MHz) δ 2.50 (brs, 1H), 3.39–3.50 (m, 2H), 4.75 (m, 1H), 7.25–7.40 (m, 5H); MS (EI) *m/z*: 248 (M^+); IR (KBr) 3398, 2930 cm^{-1}.

4.2.16. 2-Chloro-1-(4-chlorophenyl) ethanol (2p).[15] ^1H NMR ($CDCl_3$, 200 MHz) δ 3.40–3.65 (m, 2H), 4.98 (m, 1H), 7.25–7.40 (m, 4H); MS (EI) *m/z*: 190 (M^+); IR (KBr) 3382, 2933 cm^{-1}.

4.2.17. 2-Bromo-1-(4-chlorophenyl) ethanol (2q).[15] ^1H NMR ($CDCl_3$, 200 MHz) δ 2.50 (brs, 1H), 3.50–3.60 (m, 2H), 4.85 (m, 1H), 7.25–7.40 (m, 4H); MS (EI) *m/z*: 234 (M^+); IR (KBr) 3450, 2960 cm^{-1}.

4.2.18. 2-Iodo-1-(4-chlorophenyl)ethanol (2r).[16] ^1H NMR ($CDCl_3$, 200 MHz) δ 2.45 (brs, 1H), 3.45–3.50 (m, 2H), 4.80–4.88 (m, 1H), 7.20–7.40 (m, 4H); MS (EI) *m/z*: 282 (M^+); IR (KBr) 3460, 2960 cm^{-1}.

4.2.19. 2-Chloro cyclohexanol (2s).[8] ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20–1.40 (m, 3H), 1.60–1.85 (m, 3H), 2.10–2.20 (m, 1H), 2.30–2.40 (m, 1H), 3.50–3.60 (m, 1H), 3.90–4.00 (m, 1H); MS (EI) *m/z*: 134 (M^+); IR (KBr) 3430, 2960 cm^{-1}.

4.2.20. 2-Bromo cyclohexanol (2t).[14] ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20–1.45 (m, 3H), 1.60–1.80 (m, 3H), 2.10–2.25 (m, 1H), 2.30–2.40 (m, 1H), 3.55–3.65 (m, 1H), 3.80–3.95 (m, 1H); MS (EI) *m/z*: 178 (M^+); IR (KBr) 3432, 2965 cm^{-1}.

4.2.21. 2-Iodo cyclohexanol (2u).[14] ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20–1.60 (m, 4H), 1.80–1.90 (m, 1H), 2.0–2.20 (m, 2H), 2.40–2.50 (m, 1H), 3.50–3.65 (m, 1H), 3.95–4.05 (m, 1H); MS (EI) *m/z*: 226 (M^+); IR (KBr) 3425, 2960 cm^{-1}.

4.2.22. 1,3-Dichloro-2-propanol (2v).[8] ^1H NMR ($CDCl_3$, 200 MHz) δ 2.50 (brs, 1H), 3.60–3.80 (m, 4H), 4.0–4.10 (m, 1H); MS (EI) *m/z* 128 (M^+).

4.2.23. 1-Bromo-3-chloro-2-propanol (2w).[6b] ^1H NMR ($CDCl_3$, 200 MHz) δ 2.70 (brs, 1H), 3.55 (d, 2H, *J*=4.2 Hz), 3.65–3.75 (m, 2H), 3.95–4.05 (m, 1H); MS (EI) *m/z* 171 (M^+).

4.2.24. 1-Chloro-3-iodo-2-propanol (2x).[8] ^1H NMR ($CDCl_3$, 200 MHz) δ 2.45 (brs, 1H), 3.30–3.45 (m, 2H), 3.60–3.70 (m, 2H), 3.72–3.85 (m, 1H); MS (EI) *m/z* 220 (M^+).

4.2.25. 1-Chloro-2-butanol (2y).[8] ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, 3H, *J*=7.1 Hz), 1.50–1.65 (m, 2H), 2.20 (brs, 1H), 3.35 (dd, 1H, *J*=6.0, 7.1 Hz), 3.55 (dd, 1H, *J*=3.6, 7.1 Hz), 4.10–4.20 (m, 1H); MS (EI) *m/z* 108 (M^+).

4.2.26. 1-Bromo-2-butanol (2z).[6a] ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, 3H, *J*=7.4 Hz), 1.50–1.60 (m, 2H), 2.20 (brs, 1H), 3.30–3.40 (m, 1H), 3.45–3.55 (m, 1H), 4.0–4.10 (m, 1H); MS (EI) *m/z* 153 (M^+).

4.2.27. 1-Iodo-2-butanol (2z′).[8] ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (t, 3H, *J*=7.2 Hz), 1.55–1.70 (m, 2H), 3.05–3.25 (m, 1H), 3.30–3.50 (m, 1H), 3.75–3.80 (m, 1H); MS (EI) *m/z* 200 (M^+).

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