NJC

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. B. Kamble, D. Devalankar and G. M. Suryavanshi, *New J. Chem.*, 2018, DOI: 10.1039/C8NJ01616J.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/njc

DOI: 10.1039/C8NJ01616J

Journal Name

COMMUNICATION

Two Stereocentered HKR of *anti-β,β'*-diphenylpropanoxirane and *anti*-3-phenylethyloxiranes Catalysed by Co(III)(salen)-OAc Complex : An Enantioselective Synthesis of (+)-Sertraline and (+)-Naproxen

avansReceived 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Rohit B. Kamble,[a,c] Dattatraya Devalankar [b] and Gurunath Suryavanshi [a]*

The Co$^{(III)}$(salen)OAc catalyzed two stereocentered hydrolytic kinetic resolution (HKR) of *anti-β,β'*-diphenylmethyloxirane and *anti*-3-phenylethyloxiranes affords corresponding *anti*-1,2-diols and oxiranes in high enantiomeric excess. The synthetic potential of this methodology has been shown by the enantioselec-tive synthesis of (+)-sertraline an antidepressant drug and (+)-naproxen an anti-inflammatory drug.

Introduction

The substituted diarylmethanes are present in variety of biological active pharmaceutical as well as natural products as a core unit which shows anti-inflammatory activity,[1] SERMs,[2] dopamine transport ligands,[3] NMDA receptor antagonist,[4] and anticancer activities[5] (Fig. 1).

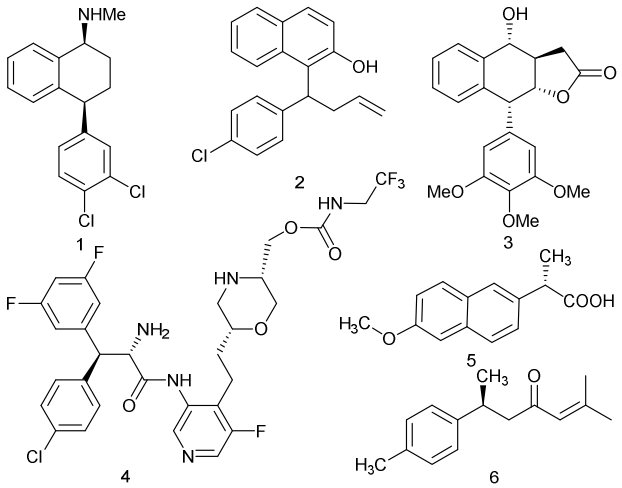
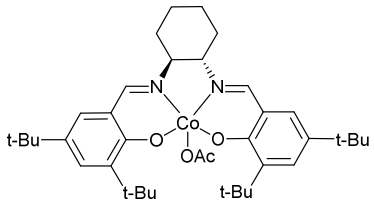


Fig 1: Bioactive and Natural Products containing substituted diarylmethanes and 3-phenylalkyl moieties

The exclusive examples contains, sertraline (1) acts as antidepressant,[6a] 2-naphthol derived (2)[6b] substituent used to treat breast cancer, natural product podophyllotoxin (3),[6c] and MK-8718 (4) an HIV protease inhibitor.[6d] Also these moieties were often used as basic unit in supramolecular structures such as macrocycles, catenanes, and rotaxanes.[6e] Whereas, optically active 3-phenyl alkyls moieties was used from long time as non-steroidal anti inflammatory drugs such as naproxen (5)[6f] and ibuprofen an analgesic drug. These motifs were present in number of natural products like turmerone (6) which shows an promising inductors of neural stem cell proliferation.[6g] Hence, keeping the importance of such moieties in mind, we applied our methodlogy to two stereocentered HKR to synthesize eantiopure diphenylmethane and 3-phenyl alkyl moieties.

Previously, enantiomerically pure *3,3'*-diarylsubstituted functionality were synthesized under asymmetric hydrogenation using transition metals such as Rh[8a], Cu[8b,c] and organometallic 1,4-addition on *α,β*-unsaturated compounds[8d,e]. Even though asymmetric hydrogenation has been used as powerful approach to synthesis of enantiopure *3,3'*-diarylsubstituted compounds but to achieve the high enantioselectivity these compounds required assistance of a coordinating group attached to C-C bond.



(*S,S*)-(salen)Co(III)OAc Complex , **7**

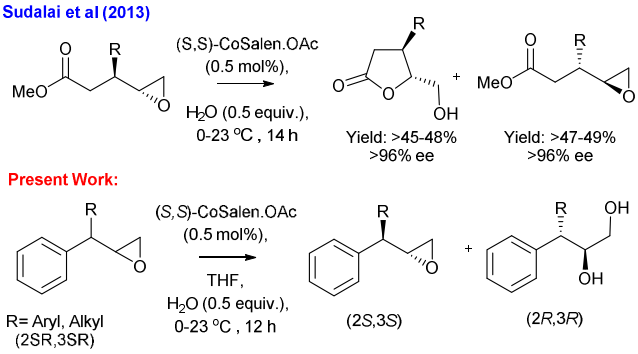
Fig 2: Jacobsen Catalyst for HKR

Jacobsen's hydrolytic and phenolic kinetic resolution (HKR & PKR) of terminal epoxides with one stereocenter catalyzed by Co(III)-salen complex **7** employ water and phenol as a nucleophile respectively [9,10] (Fig. 2). Even though having impressive scope for the HKR, it was extensively used for the resolution of terminal epoxide with one chiral centre.[11] The kinetic resolution has been studied comprehensively to understand its mechanistic and

[a] *Chemical Engineering and Process Development Division, National Chemical Laboratory, dr. Homi Bhabaha Road, Pune-411008*
[b] *Postdoctoral Fellow at Department of Radiology, UAB Hospital, Birmingham AL, United States.*
[c] *Academy of Scientific & Innovative Research, New Delhi, India- 110 001*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8NJ01616J

synthetic aspects, that include some recent studies relating to kinetic resolution of racemic terminal epoxides bearing adjacent C-O and C-N binding substituents to furnish enantiopure *syn*- or *anti*-alkoxy and azido epoxides and the corresponding 1,2-diols.[7a,12] In 2013, Sudalai *et. al.* applied two stereocentered HKR to synthesis enantiopure substituted *γ*-butyrolactones and epoxy esters from racemic epoxy esters bearing adjacent C-C binding substituents (Scheme 1).[13] Despite these impressive achievements HKR has only been applied to epoxyesters to offer optically active butyrolactone.



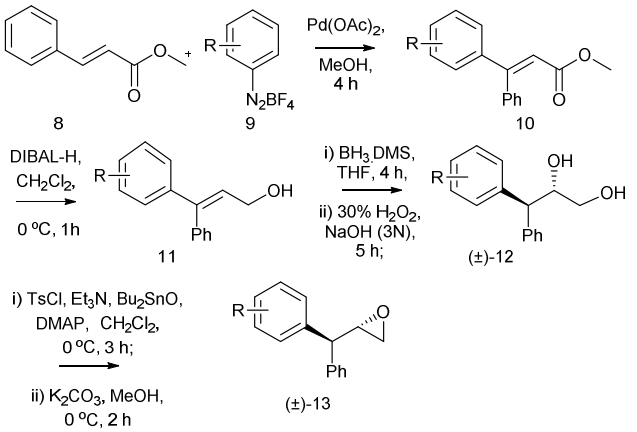
Scheme1: Two stereocentered HKR of epoxiester and *anti-β,β′*-diphenylpropanoxirane

In the present work it is of interest to extend its scope to include the terminal epoxides bearing C-C binding substituents with different aryl groups instead of ester functionality. The aim of such an investigation was to obtain enantioenriched aryl epoxides and aryl diols bearing C-C binding substitution by an unswerving method from the respective racemic materials, thus complementing other tedious routes.[14]

In this communication we wish to report a flexible, novel single step method that employs Co-catalyzed HKR of racemic 3-substituted epoxy aryls with two stereocenters to produce epoxy aryls bearing adjacent C-C binding substituents and corresponding diols in high optical purities (Scheme 1).

Result and Discussion

We anticipated that the extension of HKR to the two stereocentered racemic aryl epoxides bearing C-C binding substituents would enable us to procure both enantiomers of



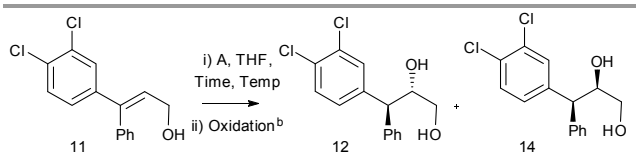
Scheme 2 : Synthesis of racemic *anti-β,β′*-diphenylpropanoxirane

aryl epoxides and aryl diols depending upon the chiral ligand chosen. Accordingly the racemic anti-aryl and alkyl epoxides the substrates for the HKR were efficiently prepared in a highly diastereoselective manner from the corresponding allylic alcohols *via* a simple sequential steps which mainly includes (i) Heck coupling of phenyl methyl cinnamate 8 with arenediazonium tetrafluoroborate 9 to obtain the *(E)-β,β′*- diphenylcinnamate 10. [15] (ii) The obtained *(E)-β,β′*-diphenylcinnamate 10 reduced to allylic alcohol 11 using DIBAL-H. (iii) The boranedimethylsulphide and H_2O_2 mediated hydroboration of 11 offered diphenylpropan-1,2-diol 12. (iv) Catalytic selective monotosylation and subsequent base mediated epoxidation of 12 gives desired racemic epoxide (±)-13 (Scheme 2).

Initially, hydroboration under reflux conditions using BH_3.DMS (1.5eq.) and 30% H_2O_2 (2eq.) resulted in the formation of 1:1 diastereomeric mixture of (±)-12 and 14. We have noticed that during hydroboration of allylic alcohol, epimerization at benzylic position takes place due to less sterric difference between two aryl substituents.

To overcome this difficulty we decided to control the reaction parameters of hydroboration such as concentration of BH_3.DMS, temperature and time of reaction. Firstly, we changed the temperature of reaction from reflux to ambient temperature but no change in the diastereomeric ratio were observed instead yield of the reaction decreased from 78 to 72% (Table1,entry b). Further we decreased the temperature of reaction from room temperature to 0 °C, to our delight the diastereomeric ration increases to 9:1 but reaction yield further decreases to 67% (Table1, entry c).

Table No.1: Co-catalysed HKR of racemic *anti-β,β′*-diphenylpropanoxirane



Entry	BH_3.DMS (A)(equi.)	H_2O_2 (equi.)	Temp. (°C)	Time (hr)	Yield (%)	dr[a] (12:14)
a	1	2	70	8	78	1:1
b	1	2	25	8	72	1:1
c	1.5	2	0	8	67	9:1
d	1.5	2.5	0	4	62	>20:1

From above observation it was confirmed that temperature and time are the key factors for determination diastereoselectivity. Hence, we added BH_3.DMS (1.5eq.) in allylic alcohol at 0 °C and increased slowly to room temperature & kept for 4 hr followed by addition of 30% H_2O_2 and NaOH (3N). To our delight this reaction condition gave diastereoselective diol 12 with >20:1 diastereoselectivity (Table1, entry d). Hence, having optimized reaction conditions for hydroboration reaction we synthesized various substituted racemic diols.

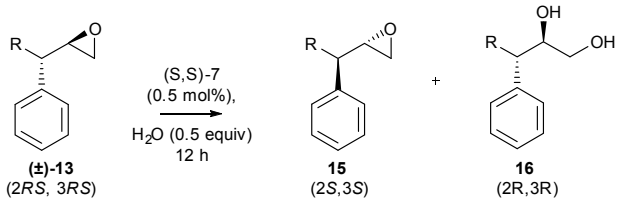
However, the Heck coupling of the aryl diazonium tetrafluoroborate bearing electron donating substituent like methoxy and methyl with methyl cinnamate 8 resulted in the

DOI: 10.1039/C8NJ01616J

inseperable mixture of diastereomers. In this scheme 2, the relative stereochemistry between the C-C binding substituent and the epoxide group is established prior to the HKR itself in the hydroboration reaction and in this way a simple asymmetric reaction can be used to obtain vital enantiomerically pure aryl epoxides and aryl diols respectively.

Thus, when HKR of the racemic *anti-β, β'*-diphenylpropanoxirane was performed with (*S,S*)-Co(III)(salen)- OAc complex (5 mol%) and water (0.5 equiv), the corresponding *anti-β, β'*-diphenylpropanoxirane 15 yield and ee (15a-e, Table 2) and anti-*β, β'*-diphenylpropan-1,2-diol 16 yield and ee (16a-e, Table 2) were obtained.

Table No.2: Co-catalysed HKR of racemic *anti-β,β'*- diphenylpropan -oxirane

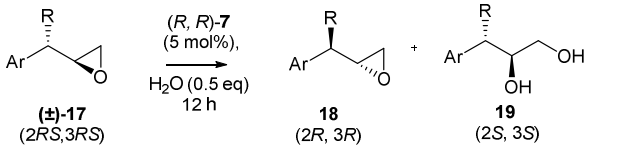


Entry	R (13)	*Epoxide* (15) Yield[a] (%)	*ee*[b] (%)	Diol (16) Yield[a] (%)	ee[b] (%)
a	3,4-diChlorophenyl	50	94	48	98
b	4-Bromophenyl	50	96	48	94
c	4-Chlorophenyl	47	94	50	98
d	4-Flurophenyl	50	98	49	91
e	2-Flurophenyl	49	90	48	92

[a]isolated yields, [b]Eantiomeric Excess determined by HPLC

A variety of substrates were screened for the HKR process that led to the isolated yields of product as shown in Table 2 with complete stereocontrol.

Table No.3: Co-catalysed HKR of racemic *anti*-3-phenylethyloxiranes -ne



Entry	Ar	R	*Epoxide* (18) Yield[a] (%)	*ee*[b] (%)	Diol (19) Yield[a] (%)	*ee*[b] (%)
a	Phenyl	Methyl	48	96	49	92
b	Phenyl	Isobutyl	49	93	50	95
c	6-MeO-Naphtahyl	methyl	48	95	48	97

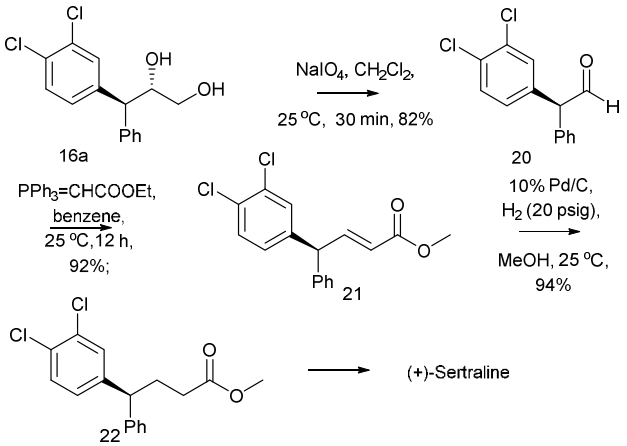
[a]isolated yields, [b]Eantiomeric Excess determined by HPLC

When the HKR of racemic 2-(1-phenylethyl)oxiranes carried out under standard reaction conditions, the corresponding enantiopure epoxides and diols was achieved in high optical purity and yield respectively (18a-c and 19a-c, Table 3).

The carbon at benzylic position next to epoxide bearing high bulky group such as isobutyl 17b gives the corresponding optically pure epoxide 18b and diol 19b (Table 3). The change in aromatic ring i.e. phenyl to naphthyl, there was no change in the either in optical purity or in yield (Entry c, Table 3).

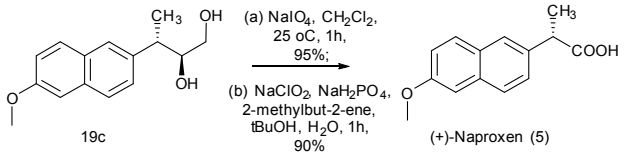
Among the various applications of this two stereocentered HKR, an enantioselective synthesis of (+)-Sertraline (1) and naproxen (5) attracted our attention due to their pharmaceutical importance.

(+)-Sertraline (1) is a selective serotonin reuptake inhibitor (SSRI), discovered by Pfizer chemist Reinhard Sarges in 1970.[16] For the synthesis of Sertraline chiral diol 16a was chosen as the starting material (Scheme 3). $NaIO_4$ mediated oxidative cleavage of 16a to aldehyde 20 followed by the two carbon Wittig extension afforded *α, β*- unsaturated ester 21. The Pd/C catalyzed reductive hydrogenation of unsaturated ester to 22 was achieved in 90% yield. Followed by known protocol affords the (+)-Sertraline.



Scheme 3. Synthesis of (+)-Sertraline

The synthesis of (+)-Naproxen (5) commences from the corresponding enantiopure diol 19c as shown in scheme 4. The diol was subjected for the oxidative cleavage using sodium periodate to give aldehyde in quantitative yield. The aldehyde was in situ oxidized to give (+)-naproxen (5) in 90% yield (Scheme 4).



Scheme 4: Synthesis of (+)-Naproxen

Conclusions

In conclusion, the (salen)Co(III)-catalyzed HKR of racemic *anti-β,β'*- diphenylpropanoxirane provides a highly practical route to the synthesis of enantiopure key intermediate *anti*-β,β'-diphenylpropanoxirane and *anti*-β,β'-diphenylpropandiol in single step. The key steps involved diastereoselective hydroboration of allylic alcohol and two stereocentered HKR. This method has been successfully applied to the enantioselective synthesis of (+)-sertraline and (+)-naproxen. The reaction is convenient to carry out under mild conditions, displaying a wide range of substrate scope. We think that this

View Article Online
DOI: 10.1039/C8NJ01616J

HKR strategy will find enormous scope as well as applications in the synthesis of bioactive molecules owing to the flexible nature of the synthesis of starting material and the ready availability of Co-catalysts in both enantiomeric forms.

Conflicts of interest

"There are no conflicts to declare".

Experimental Section

General Procedure for Hydrolytic kinetic resolution:

To a solution of (*S,S*)/(*R,R*)-Co-salen (0.5 mol%) in toluene (2 mL), AcOH (0.036 mmol) was added. It was allowed to stir at 25 °C in open air for 30 min. During this time the colour changed from orange-red to a dark brown, it was then dried under vacuum. To this racemic *anti-β,β '*-diphenylmethyloxirane (1 mmol) and H_2O (0.5 mmol) was added at 0 °C. Then the reaction was allowed to stir for 12 h at 25 °C. After completion of reaction (monitored by TLC), the crude product was purified by column chromatography over silica gel to give chiral *anti-β,β'*-diphenylmethyloxirane (15a-e) and *anti-β,β'*-diphenylpropane-1,2-diol (16a-e).

(±)-(3,4-dichlorophenyl)(phenyl)methyl) oxirane (13a)

Yield: 85%, colorless oil; IR ($CHCl_3$, cm^{-1}): υ_{max} 690, 810, 904, 1081, 1209, 1371, 1443, 3062, 3390, 756; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50-2.53 (m, 1H), 2.83-2.87, (m, 1H), 3.42-3.46 (m, 1H), 3.74-3.77 (m, 1H), 7.10-7.39 (m, 8H) ; ^{13}C NMR (50 MHz, $CDCl_3$): δ 46.3, 52.6, 54.4, 127.4, 128.0, 128.3, 128.8, 130.3, 130.5, 131.0, 132.6, 139.9, 141.3;

(2*S, 3S*)-3-(3,4-Dichlorophenyl)-3-(phenyl)methyl)oxirane (15a)

Yield: 50%, colourless oil; $[\alpha]_D^{25}$ = -23.6 (*c* 1, $CHCl_3$); Optical purity: 94% *ee* determined from HPLC analysis [OD-H column, *n*-hexane/ 2-propanol (97.5:2.5), 0.5 mL/min, 254 nm]; Retention time: t_{major} = 24.01 and t_{minor} = 29.13 min. Anal. Calcd for $C_{15}H_{12}OCl_2$ requires C, 64.54; H, 4.33; found C, 64.55; H, 4.35%; HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{12}Cl_2O$: 279.0331, found: 279.0338

(±)-3-(3,4-Dichlorophenyl)-3-phenylpropane-1,2-diol (12a)

Yield: 67%, colorless oil; IR (CHCl3, cm-1): υmax 749, 850, 1011, 1236, 1462, 1620, 2844, 3456; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.62 (br s, 1H), 2.28 (br s, 1H), 3.43 (dd, *J* = 6.3 Hz, 11.1 Hz, 1H), 3.61 (dd, *J* = 3.0, 11.1 Hz, 1H), 4.00 (d, *J* = 9.2 Hz, 1H), 4.40 (m, 1H), 7.19-7.47 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 54.1, 64.3, 73.3, 127.2, 128.0, 129.0, 130.4, 130.6, 130.7, 132.5, 140.5, 141.8;

(2*R*, 3*R*)-3-(3,4-dichlorophenyl)-3-phenylpropane-1,2-diol (16a)

Yield: 48%, colourless oil; $[\alpha]_D^{25}$ = -28.5 (*c* 1, $CHCl_3$); Optical purity: 98% *ee* determined from HPLC analysis [Chiral OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 254 nm]; Retention time: t_{minor} = 45.637 and t_{major} = 50.037 min.; IR ($CHCl_3$, cm^{-1}): υ_{max} 749, 850, 1011, 1236, 1462, 1620, 2844, 3456; Anal. Calcd for $C_{15}H_{14}O_2Cl_2$ requires C, 60.63; H, 4.75; found C, 60.75; H, 4.70%. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{14}Cl_2ONa$: 319.0264, found: 319.0263

(±)- (4-bromophenyl)(phenyl)methyl)oxirane (13b)

Yield: 92% (352 mg) , colorless gummy; ^{1}H NMR: (200 MHz, $CDCl_3$) δ 2.46-2.50 (q, 1H, *J*=4Hz), 3.40 (3.47 (m, 1H), 3.74-3.78 (d, 1H, *J* = 8Hz), 7.11-7.26 (m,6H), 7.30-7.35 (m, 1H), 7.38-7.45 (dt, *J* = 8Hz, 2H); ^{13}C NMR (50 MHz, CDCl3) δ 46.4, 52.9, 54.6, 120.9, 127.1, 128.4, 128.7, 131.4, 131.6, 140.1, 140.5; Anal. Calcd for $C_{15}H_{13}BrO$ requires C, 62.30; H, 4.53; Br, 27.63; O, 5.53; found C, 62.28; H, 4.52%.

(2*S, 3S*)-3-[(4-bromophenyl)-3-(phenyl)]methyloxirane: (15b)

Yield: 50%, $[\alpha]_D^{25}$ -22.18 (c 0.5, $CHCl_3$); Optical purity: 96% *ee* determined from HPLC analysis [Chiral OD-H column, *n*-hexane/ 2-propanol (97.5:2.5), 0.5 mL/min, 254 nm]; Retention time: t_{minor} = 13.92 and t_{major} = 15.83 min. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{14}BrO$: 289.0223, found: 289.0213

(±)- (4-bromophenyl)-3-phenylpropane-1,2-diol (12b):

Yield: 62% (409 mg) , colorless gummy, IR($CHCl_3$, cm^{-1})- 3351 (broad), 1488, 1453, 1009, 698; ^{1}H NMR: (200 MHz, $CDCl_3$) δ 3.21-3.46 (m, 4H), 3.83-3.87 (d, 1H, *J*=8Hz), 4.22-4.28 (t, 1H, *J* = 6Hz), 7.13-7.29 (m, 7H), 7.35-7.40 (d, 2H, *J* = 10Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54, 64.7, 73.6, 120.6, 126.9, 128.0, 128.8, 130.4, 131.6, 140.5, 141.$C_{15}H_{15}BrO_2$ requires: C, 58.65; H, 4.92; found C, 58.63; H, 4.89%.

(2*R, 3R*)-3-[(4-bromophenyl)-3-(phenyl)]propane-1,2-diol (16b)

Yield: 48%, colorless oil; $[\alpha]_D^{25}$ =+30.46 (c 1, $CHCl_3$); Optical purity: 94% *ee* determined from HPLC analysis [Chiral OD-H column, *n*-hexane/ 2-propanol (95:05), 0.5 mL/min, 254 nm]; Retention time: t_{major} = 40.837 and t_{major} = 66.29 min. IR($CHCl_3$, cm^{-1})- 3351 (broad), 1488, 1453, 1009, 698;

(±)- (4-chlorophenyl)(phenyl)methyl)oxirane (13c)

Yield: 93% (326 mg) ; colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.48-2.52 (q, 1H, *J* = 4Hz), 2.82-2.86 (q, 1H, *J* = 8Hz), 3.42-3.48 (m, 1H), 3.77-3.80 (d,1H, *J* = 6Hz), 7.14-7.22 (m, 5H), 7.25-7.35 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.4, 52.8, 54.7, 127.1, 128.4, 128.6, 128.7, 130.0, 132.8, 139.5, 140.6; $C_{15}H_{13}ClO$ requires : C, 73.62; H, 5.35; Cl, 14.49; O, 6.54 found C, 73.58; H, 5.29%;

(2*S, 3S*)-3-[(4-chlorophenyl)-3-(phenyl)]methyloxirane (15c)

Yield: 48%, $[\alpha]_D^{25}$=–16.14 (c 0.5, $CHCl_3$); Optical purity: 90% *ee* determined from HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (97.5:2.5), 0.5 mL/min, 254 nm); Retention time: t_{major} = 18.190 and t_{minor}= 20.97 min.; HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{14}ClO$: 245.0728, found: 245.0778

(±)- (4-chlorophenyl)-3-phenylpropane-1, 2-diol (12c)

Yield: 63% (351 mg); Colorless gummy; ^{1}H NMR: (200 MHz, $CDCl_3$) δ 3.21-3.48 (m, 4H), 3.80-3.84 (d, 1H, *J* = 8Hz), 4.20 (bs, 1H), 7.18 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.0, 64.7, 73.1, 127.0, 128.1, 128.7, 128.9, 130.1. 132.5, 140.0, 141.2; $C_{15}H_{15}ClO_2$ requires; C, 68.57; H, 5.75; Cl, 13.49; O, 12.18 found C, 68.51; H, 5.70%.;

(2*R, 3R*)-3-(4-chlorophenyl)-3-phenylpropane-1, 2-diol (16c)

Yield: 47%, $[\alpha]_D^{25}$=+ 19.23 (c 1, $CHCl_3$); Optical purity: 94% ee determined from HPLC analysis (Chiral OD-H column, *n*-hexane/ 2-propanol (95.5:5), 0.5 mL/min, 254 nm); Retention time: t_{minor} = 27.2 and t_{major} = 30.607 min. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{15}ClO_2Na$: 285.0653, found: 285.0645

(±)- (4-fluorophenyl)(phenyl)methyl)oxirane (13d)

Yield: 86% (245 mg) ; Colorless oil; ^{1}H NMR: (200 MHz, $CDCl_3$) δ 2.47-2.51 (q, 1H, *J* = 4Hz), 2.82-2.86 (q, 1H, *J* = 4Hz), 3.42-3.48 (m,1H), 3.78-3.82 (d,1H, *J* = 8Hz), 6.94-7.03 (t, 2H, *J* = 10Hz), 7.16-7.23 (m, 5H), 7.25-7.31 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 45.2,52.6, 63.0, 115.2-115.8 (d, *J* = 21 Hz), 126.6, 128.2, 129.4, 130.1-130.4 (d, *J* = 8Hz), 137.0, 141.2, 164.5; $C_{15}H_{13}FO$ requires C, 78.93; H, 5.74; F, 8.32; O, 7.01 found C, 78.87; H, 5.69;

(2*S , 3S*)-3-(4-fluorophenyl)(phenyl)methyl)oxirane (15d)

Yield: 50 %, colorless oil; $[\alpha]_D^{25}$=+2.82 (c 0.5, $CHCl_3$);Optical purity: 98% ee determined from HPLC analysis [Chiral OD-H column, *n*-hexane/ 2-propanol (97.5:2.5), 0.5 mL/min, 254 nm]; Retention time: t_{major} = 10.157 and t_{minor} = 11.353 min. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{13}FONa$: 251.0843, found: 251.0841

(±)- (4-fluorophenyl)-3-phenylpropane-1, 2-diol (12d)

Yield: 68% (308 mg); Colorless gummy; ^{1}H NMR: (200 MHz, $CDCl_3$) δ 3.01(bs, 2H), 3.26-3.52 (m,2H), 3.89-.394 (d,1H, *J* = 10Hz), 4.26-4.32

View Article Online
DOI: 10.1039/C8NJ01616J

(t, 1H, *J* = 6Hz), 6.91-6.99 (m. 4H), 7.16-7.29 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.9, 64.7, 74.0, 115.3-115.8 (d, *J* = 21Hz), 126.9, 128.1, 128.8, 130.1-130.2 (d, *J* = 8Hz), 136.9, 141.4, 164.1; $C_{15}H_{15}FO_2$ requires C, 73.15; H, 6.14; F, 7.71; O, 12.99 found C, 73.09; H, 6.11;

(2*R*, 3*R*)-3-(4-fluorophenyl)-3-phenylpropane-1, 2-diol (16d)

Yield: 49%, $[\alpha]^{25}_D$= –122.4 (c 1, $CHCl_3$);Optical purity: 91% *ee* determined from HPLC analysis [Chiral OD-H column, *n*-hexane/ 2-propanol (90:10), 0.5 mL/min, 220 nm]; Retention time: t_{minor} = 26.78 and t_{major} = 29.63 min.; HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{15}FO_2Na$: 269.0948, found: 269.0940

(±)- (2-fluorophenyl)(phenyl)methyl)oxirane (13e)

Yield: 89% (290 mg); Colorless Oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.52-2.56 (q, 1H, J= 2.66 Hz), 2.88-2.92 (q, 1H, *J* = 3.91 Hz), 3.56-3.63 (m, 1H), 4.25-4.28 (d, 1H, *J* = 6.4 Hz), 7.03-7.10 (m, 1H), 7.13-7.18 (m, 1H), 7.31-7.43 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.2, 46.6, 53.8, 115.4 (d, *J* = 23 Hz), 124.1 (d, *J* = 2.87 HZ), 127.0, 128.3, 128.5, 128.6, 129.9, (d, *J* = 3.83 Hz), 140.1; $C_{15}H_{13}FO$ requires C, 78.93; H, 5.74; F, 8.32; O, 7.01 found C, 78.88; H, 5.72;

(2*R*, *3R*)-3-(2-fluorophenyl)(phenyl)methyl)oxirane (15e)

Yield: 49%, colorless oil; $[\alpha]^{25}_D$ = –26.85 (c 0.5, $CHCl_3$), Optical purity 90% *ee* determined from HPLC analysis [Chiral OD-H column, *n*-hexane/ 2-propanol (97.5:2.5) Retention time: t_{minor} = 16.253 and t_{major} = 17.317 min. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{13}FONa$: 251.0843, found: 251.0840

(±)-(2-fluorophenyl)-3-phenylpropane-1, 2-diol (12e)

Yield: 65% (352 mg) ; Colorless gummy; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.88 (bs, 1H), 2.97 (bs, 1H), 3.28-3.33 (q, 1H, *J* = 6Hz), 3.46-3.49 (d, 1H, *J* = 11.4 Hz), 4.29-4.31 (d, 1H, *J* = 9 Hz), 4.35-4.39 (t, 1H, *J* = 7Hz), 6.93-6.96 (dt, 1H, *J* = 10 Hz), 7.02-7.08 (m, 1H), 7.11-7.23 (m, 5H), 7.27-7.33 (m, 1H), 7.41-7.45 (dt, 1H, *J* = 1.83, 7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 47.0, 64.8, 73.2, 115.6 (d, *J* = 23 Hz), 124.1 (d, *J* = 3.84 Hz), 126.9, 128.2, 128.3, 128.1, 128.9, 129.3 (d, *J* = 3.84), 140.6, 159.9, 162.4; $C_{15}H_{15}FO_2$ requires C, 73.15; H, 6.14; F, 7.71; O, 12.99 found C, 73.12; H, 6.09;

(2*S*, 3*S*)-3-(2-fluorophenyl)-3-phenylpropane-1, 2-diol (16e)

Yield: 48%, $[\alpha]^{25}_D$ = +6.25 (c 1, $CHCl_3$), Optical purity 92% *ee* determined from HPLC analysis (Chiral AD-H column, *n*-hexane/ 2-propanol (90:10); Retention time: t_{major} = 25.810 and t_{minor} = 30.13 min. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{15}FO_2Na$: 269.0948 found: 269.0940

(±)-1-phenylethyl oxirane (17a)

Yield: 89% (261 mg); Colorless Oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30-1.33 (d, 3H, *J* = 6 Hz), 2.52-2.56 (q, 1H, *J* = 2, 4Hz), 2.70-2.84 (m, 2H), 3.04-3.10 (m, 1H, *J* = 2 and 6Hz), 7.18-7.26 (m, 2Hz), 7.29-7.36 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0, 41.3, 45.7, 56.3, 126.7, 127.5, 128.5, 142.7; $C_{10}H_{12}O$ requires C, 81.04; H, 8.16; O, 10.80 found C, 81.05; H, 8.18;

(2*R*, 3*R*)-3-phenylethyl-2,3-oxirane (18a)

Yield: 49%, $[\alpha]^{25}_D$ = +10.07 (c 1, $CHCl_3$), Optical purity 96% *ee* determined from HPLC analysis (Chiral AD-H column, *n*-hexane/ 2-propanol (97.5:2.5)]; Retention time: t_{minor} = 10.23 and t_{major} = 11.79 min.; HRMS (ESI) calculated $[M+H]^+$ for $C_{10}H_{13}O$: 149.0961 found: 149.0961

(±)-3-phenylbutane-1, 2-diol (12f)

Yield: 82% (339 mg); Colorless Oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27-1.30 (d, 3H, *J* = 6Hz), 1.99 (bs, 2H), 2.79-2.94 (qui, 1H, *J* = 7Hz), 3.49-3.82 (m, 3H), 7.16-7.26 (m, 3H), 7.28-7.38 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.9, 42.9, 64.5, 76.3, 127.0, 128.0, 128.8, 143.1; $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49; O, 19.25 Found C, 72.24; H, 8.44;

(2*S*, 3*S*)-3-phenylbutane-1, 2-diol (19a)

Yield: 46%, $[\alpha]^{25}_D$ = –4.33 (c 1, $CHCl_3$), Optical purity 92% *ee* determined from HPLC analysis (Chiral AD-H column, *n*-hexane/ 2-propanol (90:10); Retention time: t_{minor} = 25.4 and t_{major} = 28.067 min HRMS (ESI) calculated $[M+]^+$ for $C_{10}H_{14}O_2Na$: 189.0886 found: 189.0887

(±)-3-methyl-1-phenylbutyloxirane (17b)

Yield: 89% (290 mg); Colorless Oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85-0.89 (dd, 6H, *J* = 2.53 and 4 Hz), 1.40-1.60 (m,1H), 1.70-1.82 (m, 2H),2.2-2.4 (q, 1H, *J* = 7.58 Hz),2.46-2.50 (q, 1H, *J* = 2.78 Hz), 2.63-2.67(q, 1H, *J* = 4Hz), 2.94-3.01 (m, 1H),7.5-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.8, 23..5, 25.2, 42.3, 46.5, 47.0, 56.8, 126.8, 127.9, 128.6 ; $C_{13}H_{18}O$ requires C, 82.06; H, 9.54; O, 8.41 found C, 82.10; H, 9.52

(*R*)-2-((*R*)-3-methyl-1-phenylbutyl)oxirane (18b)

Yield: 47%, $[\alpha]^{25}_D$ =+ 6.84 (c 1, $CHCl_3$), Optical purity 92% *ee* determined from HPLC analysis (Chiral AD-H column, *n*-hexane/ 2-propanol (90:10); Retention time: t_{major} = 9.673 and t_{minor} = 11.977 min;

(±)-5-methyl-3-phenylhexane-1,2-diol (12g)

Yield: 84% (363 mg); White solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81-0.85 (dd, 6H,*J* = 1.64 and 6.57 Hz), 1.17 -1.36 (m, 1H), 1.66-1.79(m, 2H), 1.98 (bs, 2H), 2.66-2.77 m, 1H), 3.21-3.41 (m, 2H), 3.60-3.75 (m,1H), 7.13-7.16(dd, 2H, *J* = 6Hz);^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 24.2, 25.1, 65.2, 76.3, 126.9, 128.2, 128.6, 141.6; $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68; O, 15.36 found C, 74.99; H, 9.67;

(2*S*, 3*S*)-5-methyl-3-phenylhexane-1,2-diol (19b)

Yield: 50%, $[\alpha]^{25}_D$= – 17.94 (c 1, $CHCl_3$); Optical purity 92% *ee* determined from HPLC analysis (Chiral AD-H column, *n*-hexane/ 2-propanol (90:10); Retention time: t_{minor} = 25.4 and t_{major} = 28.067 min.; HRMS (ESI) calculated $[M+H]^+$ for $C_{13}H_{20}O_2Na$: 231.1356 found: 231.1355

(±)-1-(6-methoxynaphthalen-2-yl) ethyl) oxirane (17c)

Yield: 86% (231 mg); Colorless Oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37-1.41 (d, 3H, *J* = 8Hz), 2.55-2.59 (q, 1H, *J* = 2Hz), 2.82 (q, 1H, *J* = 4Hz), 2.84-2.97 (q, 1H, *J* = 6Hz), 3.10-3.17 (m, 1H), 7.09-7.14 (m, 2H), 7.34-7.39 (dd, 1H, *J* = 6Hz), 7.60-7.70 (t, 3H, *J* = 8Hz, 12Hz) ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0, 41.3, 45.8, 55.2, 56.4, 105.5, 118.9, 125.7, 126.6, 126.9, 129.0, 129.2, 133.6, 137.8, 157.5; $C_{15}H_{16}O_2$ requires C, 78.92; H, 7.06; O, 14.02 found C, 78.89; H, 7.04 ;

(2*R*, 3*R*)-3-(6-methoxynaphthalen-2-yl) ethyl) oxirane (18c)

Yield: 50%, $[\alpha]^{25}_D$ = +8.42 (c 1, $CHCl_3$), Optical purity 93% *ee* determined from HPLC analysis (Chiral AD-H column, *n*-hexane/ 2-propanol (90:10) Retention time: t_{major} = 14.36 and t_{major} = 19.88 min. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{17}O_2$: 229.1223 found: 229.1223

(±)-3-(6-methoxynaphthalen-2-yl) butane-1, 2-diol (12h)

Yield: 82 % (291 mg); Colorless Oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31-1.34 (d, 3H, *J* = 6Hz), 2.06 (bs, 2H), 2.89-3.03 (m, 1H), 3.49-3.58 (q, 1H, *J* = 6Hz, 4Hz), 3.74-3.83 (dt, 2H, *J* = 10Hz, 4Hz), 3.91 (s, 3H), 7.09-7.154 (m, 2H), 7.29-7.34 (dd, 1H, *J* = 8Hz), 7.57 (s, 1H), 7.64-7.70 (dd, 2H, *J* = 4Hz, 8Hz); $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.37; O, 19.49 found C, 73.12; H, 7.38;

(2*S*, 3*S*)-3-(6-methoxynaphthalen-2-yl) butane-1, 2-diol (19c)

Yield: 48%, $[\alpha]^{25}_D$= –76.5 (c 1, $CHCl_3$), Optical purity 97% *ee* determined from HPLC analysis (Chiral AD-H column, *n*-hexane/ 2-propanol (90:10); Retention time: t_{minor} = 19.10 and t_{major} = 20.407 min. HRMS (ESI) calculated $[M+H]^+$ for $C_{15}H_{18}O_3Na$: 269.1148 found: 269.1148

Synthesis of Sertraline:

(*R*)-2-(3,4-Dichlorophenyl)-2-phenylacetaldehyde (20)

To stirred solution of diol (-)-15b (1 g, 3.3 mmol) in ethanol/H_2O (15 mL, 2:1) at 20 °C, $NaIO_4$ (0.863 g, 4.0 mmol) was added and the

View Article Online
DOI: 10.1039/C8NJ01616J

reaction mixture was stirred for 4 h. After completion of reaction (monitored by TLC), it was quenched with water (10 mL) and product was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude product 12 which was taken up for further reaction without purification.

Yield: 82%, colorless oil; $[\alpha]_D^{25}$ = +4.2 (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): υ_{max} 698, 1030, 1136, 1178, 1380, 1448, 1466, 1720, 2853, 2929 ; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.85 (d, *J* = 1.3 Hz, 1H), 7.24 -7.52 (m, 8H), 9.92 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 45.4, 126.7, 127.2, 128.9, 129.1, 129.4, 130.7, 132.9, 133.3, 138.8, 139.5, 197.2; Anal. Calcd for $C_{14}H_{10}OCl_2$ requires C, 63.42; H, 3.80; found C, 63.45; H, 3.81%.

Methyl (*R*, *E*)-4-(3,4-dichlorophenyl)-4-phenylbut-2-enoate (21)

To a solution of aldehyde 19 (0.9 g, 3.55 mmol) in dry benzene (25 mL), was added $Ph_3P{=}CHCO_2Me$ (1.42 g, 4.26 mmol) at 25 °C. The reaction mixture was refluxed for 10 h, and then quenched with water (5 mL). The product was extracted with EtOAc (3 x 20 mL) and washed with water (3 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to give the crude products which upon column chromatographic purification with silica gel using petroleum ether: ethyl acetate (8:2) as eluent gave pure 20 as colourless oil.

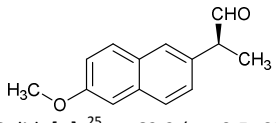
Yield: 92%, colourless oil; $[\alpha]_D^{25}$ = +1.2 (*c* 1, $CHCl_3$) {lit.[9] $[\alpha]_D^{20}$ +1.0 (*c* 1.12, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): υ_{max} 636, 700, 818, 918, 983, 1030, 1130, 1170, 1377, 1652, 1713, 2946; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.75 (s, 3H), 4.84 (d, *J* = 7.3 Hz, 1H), 5.75 (d, *J* = 15.6 Hz, 1H), 7.09 (m, 1H), 7.26-7.42 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 51.6, 52.3, 123.1, 127.2, 127.8, 128.4, 128.9, 130.3, 130.9, 133.3, 140.2, 141.6, 148.6, 165.2; Anal. Calcd for $C_{17}H_{14}O_2Cl_2$ requires C, 63.57; H, 4.39; found C, 63.60; H, 4.40%.

(*R*)-Methyl-4-(3,4-dichlorophenyl)-4-phenylbutanoate (22)

To a solution of ester 20 (0.85 g, 2.66 mmol) in methanol (20 mL), was added 10% Pd/C (60 mg) and stirred under hydrogen atmosphere (1 atm) at 25 °C. The reaction mixture was further stirred at 25 °C for 6 h, and the progress monitored by TLC. After completion of reaction, it was filtered through a Celite pad and washed with EtOAc (3 x 20 mL). The combined organic phase was concentrated under vacuum. The crude product thus obtained was purified by column chromatography on silica gel using using petroleum ether: ethyl acetate (8:2) as eluent to give pure 21 as colorless oil.

Yield: 94%, colorless oil; $[\alpha]_D^{25}$ = -6.0 (*c* 1, $CHCl_3$) {lit.[17] $[\alpha]_D^{20}$ -6.1 (*c* 1.12, CHCl3)}; IR ($CHCl_3$, cm^{-1}): υ_{max} 680, 2970, 1202, 1365, 1494, 1600, 1722, 2930; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.21-2.38 (m, 4H), 3.64 (s, 3H), 3.85-3.94 (m, 1H), 7.15-7.31 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 30.2, 32.0, 50.4, 51.4, 126.3, 127.1, 127.6, 127.8, 128.4, 128.7, 129.7, 130.4, 132.5, 142.6, 144.5, 173.0; Anal. Calcd for $C_{17}H_{16}O_2Cl_2$ requires C, 63.17; H, 4.99; found C, 63.21; H, 4.87 %.

(*S*)-2-(6-methoxynaphthalen-2-yl)propanal [18]



Yield: 95%, White Solid; $[\alpha]_D^{25}$ = +62.2 (c = 0.5, CH_2Cl_2), {$[\alpha]_D^{28}$ 64.42 (c = 0.55, CH_2Cl_2)}, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, 3H, *J* = 6.8 Hz), 3.77 (q, 1H, *J* = 7.0 Hz), 3.93 (s, 3H), 7.10 - 7.25 (m, 2H), 7.29 (dd, 1H, *J* = 8.3, 1.5 Hz), 7.61 (s, 1H), 7.77 (d, 1H, *J* = 8.3 Hz), 7.73 (d, 1H, J=8.8 Hz), 9.66 - 9.94 (m, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.6, 52.8, 55.2, 105.5, 119.2, 126.6, 126.9, 127.6, 129.0, 129.1, 132.6, 133.8, 157.8, 201.1.

(+)-Naproxen (5)

Yield: 90%; White amorpous solid; $[\alpha]_D^{25}$ = +61.1 (c = 0.50, CH_2Cl_2) {lit.[18] $[\alpha]_D^{25}$ = 60.09 (c = 0.56, CH_2Cl_2)}, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.62 (d, 3H, *J* = 7.2 Hz), 3.86 - 3.91 (m, 1H), 3.93 (s, 3H), 7.09 - 7.21 (m, 2H), 7.44 (dd, 1H, *J* = 8.6, 1.7 Hz), 7.65 - 7.81 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.1 , 45.3, 55.3 , 105.6, 119.0, 126.1, 126.2, 127.2, 128.9, 129.3, 133.8, 134.8, 157.7, 181.0. These spectroscopic data correspond to reported data.[12]

Notes and references

1 S. Cardinal, P-A. Paquet-Côté , J. Azelmat , C. Bouchard , D. Grenier , N. Voyer, Bioorganic & Medicinal Chemistry, 2017, **25**, 2043.

2 a) I. Shiina, Y. Sano, K. Nakata, M.Suzuki, T. Yokoyama, A. Sasaki, T. Orikasa, T. Miyamoto, M. Ikekita, Y. Nagahara, Y. Hasome, *Bioorg. Med. Chem.*, 2007, **15**, 7599, b) T. Kojima , T. Ogawa, S. Kitao , M. Sato , A. Oda , K. Ohta , Y. Endo, *Bioorganic & Medicinal Chemistry* , 2015, **23,** 6900.

3 a) P.S. Kharkar, A. M. Batman, J. Zhen, P. M. Beardsley, M. E. A. Reith, A. K. Dutta, *ChemMedChem*, 2009, **4**, 1075, b) L-W. Hsin, C. M. Dersch, M. H. Baumann, D. Stafford, J.R. Glowa, R. B. Rothman, A. E. Jacobson, K. C. Rice, *J. Med. Chem.* 2002, **45**, 1321, (c) S.P. Runyon, F. I.Carroll, *Current Topics in Medicinal Chemistry,* 2006, ***6,*** 1825-1843 (d) J. Cao, R. D. Slack, O. M. Bakare, C. Burzynski,R. Rais, B. S. Slusher, T. Kopajtic, A. Bonifazi, M. P. Ellenberger, H. Yano, Y. He, G-H. Bi,Z.-X. Xi, C. J. Loland, A. H. Newman, *J. Med. Chem.* 2016, **59,** 10676, e) J. Lee, S. U. Kang, J. O. Lim, H. K. Choi, M. K. Jin, A. Toth, L. V. Pearce, R. Tran, Y. Wang, T. Szabo, P. M. Blumberg, *Bioorg. Med. Chem*., 2004, **12**, 371, f) J. G. Cumming, A. E.Cooper, K. Grime, C. J. Logan, S. McLaughlin, J. Oldfield, J. S. Shaw, H. Tucker, J. Winter, D. Whittaker, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 5012;

4 (a) S. T. Moe, D. L. Smith, E. G. DelMar, S. M. Shimizu, B. C. Van Wagenen, M. F. Balandrin, Y. Chien, J. L. Razkiewicz, L. D. Artman, H. S. White, A. L. Mueller, *Bioorg. Med. Chem. Lett*., 2000, **10**, 2411;

5 a) V. Srivastava, A. S. Negi, J. K. Kumar, M. M. Gupta and S. P. S. Khanuja, *Bioorg. Med. Chem.*, 2005, **13**, 5892, b) D. E. Schteingart, J. E. Sinsheimer, R. S. Benitez, D. F. Homan, T. D. Johnson and R. E. Counsell, *Anticancer Res*., 2012, **32**, 2711,c) Q. Hu, L. Yin, C. Jagusch, U. E. Hille, R. W. Hartmann, *J. Med. Chem*. 2010, **53**, 5049.

6 a) Welch, W. M. *Adv. Med. Chem*. 1995, **3**, 113; b) B. Das, C. R. Reddy, J.Kashanna, S. K.Mamidyala, C. G.Kumar, *Med Chem Res*, 2012, **21,** 3321, (c) A. L. Eyberger, R. Dondapati, J. R.Porter, *J. Nat. Prod*., 2006, **69**, 1121; d) C. J. Bungard, P.D. Williams, J. E. Ballard, et al., *ACS Med.Chem.Lett.*, 2016, **7**, 702; For more specific biological activities of diphenylmethyl moiety please see ref. D. Ameen, T. J. Snape, *Med. Chem. Comm.,* 2013, **4**, 893; e) J. C. Ma, D. A. Dougherty, *Chem. Rev.* 1997, **97**, 1303, f) Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. Naproxen Up to Date: a Review of Its Pharmacological Properties and Therapeutic Efficacy and Use in Rheumatic Diseases and Pain States. *Drugs*, 1979, **18**, 241. g) J. Hucklenbroich, R. Klein, B.Neumaier, R. Graf, G. R.Fink, M. Schroeter, M. A. Rueger, *Stem Cell Research & Therapy* ,2014, **5**, 100

7 (a) R. S. Reddy, P. V. Chouthaiwale, G. Suryavanshi, V. B. Chavan and A. Sudalai, Chem. Commun., 2010, **46**, 5012; (b) D. A. Devalankar, P. V.Chouthaiwale, A. Sudalai, *Tetrahedron: Asymmetry*. 2012, **23**, 240; (c) R. B. Kamble, S. H. Gadre, G.Suryavanshi, *Tetrahedron Lett.* 2015, **56**, 1263; (d) Rohit B. Kamble & Gurunath Suryavanshi (2018): Synthesis of key intermediate for (+)-tofacitinib through CoIII(salen)-catalyzed two stereocentered hydrolytic kinetic resolution of (±)-

View Article Online
DOI: 10.1039/C8NJ01616J

methyl-3-(oxiran-2-yl)butanoate, Synthetic Communications, *DOI: 10.1080/00397911.2018.1434204*

8 (a) Q. Yan, D. Kong, M. Li, G. Hou, G. Zi, *J. Am. Chem. Soc.,* 2015, **137**, 10177; (b) K. Yoo, H. Kim, J. Yun, *Chem. Eur. J.* 2009, **15**, 11134; (c) D. Lee, Y. Yang, J.Yun, *Org.Lett*., 2007, **9**, 2749; (d) K. Takatsu, R. Shintani,T. Hayashi, Angew. Chem. Int. Ed,. 2011, **50**, 5548; (e) S. Sörgel, N. Tokunaga, K. Sasaki, K. Okamoto, T. Hayashi, *Org. Lett*., 2008, **10**, 589.

9 (a) S. E. Schaus, B. E. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307; (b) J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.*, 1999, **121**, 6086.

10 M. Tokunaga; J. F. Larrow; F. Kakiuchi, E. N. Jacobsen, *Science*, 1997, **277**, 936.

11 P.Kumar, P. Gupta, *Synlett,* 2009, **9**, 1367

12 (a) D. A. Devalankar, P. V. Chouthaiwale, A. Sudalai, *Synlett*, 2014, **25**, 102; (b) P. U Karabal, D. A. Kamble, A. Sudalai, *Org. Biomol. Chem*., 2014, **12**, 2349.

13 D. A. Devalankar, P. U. Karabal, A. Sudalai, *Org. Biomol. Chem.*, 2013, **11**, 1280.

14 S. Takano, M. Yanase, K. Ogsawara, *Heterocycles*, 1989, **29**, 249.

15 J. C. Pastrea, C. R. D. Correia, *Adv. Synth. Catal.*, 2009, **351**, 1217.

16 R. Sarges, J. R. Tretter, S. S. Tenen, A. Weissman, *J. Med. Chem.,* 1973, **16**, 1003.

17 A. Alexakis, S. E. Hajjaji, D. Polet, X. Rathgeb, *Org. Lett.,* 2007, **9**, 3393.

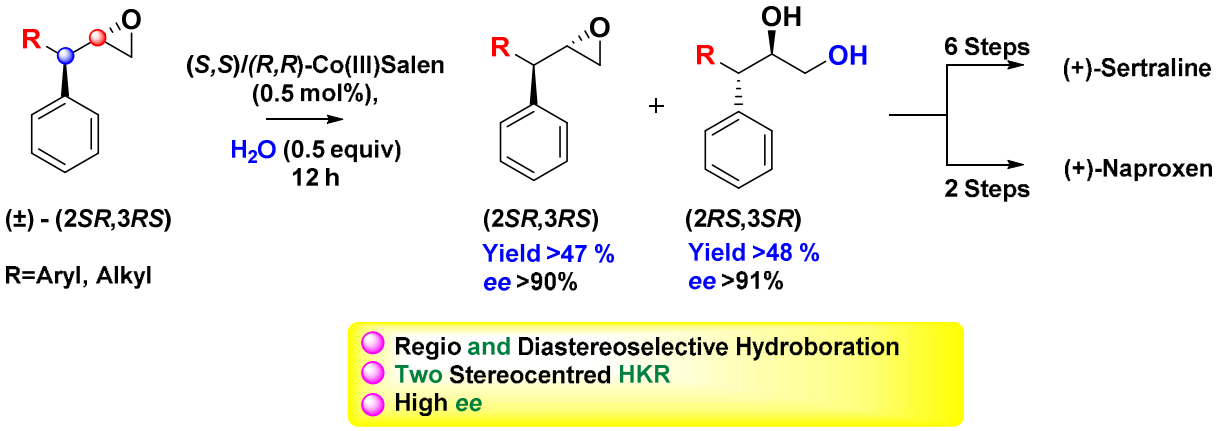
18 L. Zhang, , Z. Zuo, X. Wan, Z. Huang , *J .Am.Chem.Soc.,* 2014, **136**, 15501.

View Article Online
DOI: 10.1039/C8NJ01616J

Two Stereocentered HKR of *anti-β,β'*-diphenylpropanoxirane and *anti*-3-phenylethyloxiranes Catalysed by Co(III)(salen)-OAc Complex : An Enantioselective Synthesis of (+)-Sertraline and (+)-Naproxen

Rohit B. Kamble, Dattatray Devalankar and Gurunath Suryavanshi*

The Co(III)(salen)OAc catalyzed two stereocentered hydrolytic kinetic resolution (HKR) of *anti-β,β'*-diphenylmethyloxirane and *anti*-3-phenylethyloxiranes affords corresponding *anti*-1,2-diols and oxiranes in high enantiomeric excess. The synthetic potential of this methodology has been shown by the enantioselective synthesis of (+)-sertraline an antidepressant drug and (+)-naproxen an anti-inflammatory drug.



- Regio and Diastereoselective Hydroboration
- Two Stereocentred HKR
- High *ee*