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Enantiomerically pure α-methoxyaryl acetaldehydes as versatile precursors: a facile chemo-enzymatic methodology for their preparation

Buddh Singh [a], Pankaj Gupta [a], Asha Chaubey [a], Rajinder Parshad [a], Shiromani Sharma [b], Subhash C. Taneja [a,*]

[a] *Indian Institute of Integrative Medicine (CSIR), Canal Road, Jammu Tawi 180 001, India*
[b] *D.N. College, Chaudhary Charan Singh University, Meerut 250 001, India*

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ABSTRACT

A facile and efficient synthesis of optically active α-methoxyaryl acetic acids (up to 95% ee), α-methoxyaryl ethanols (up to 93% ee) and α-methoxyaryl acetonitriles (up to 93% ee) was achieved via *Arthrobacter* sp. lipase-catalyzed kinetic resolution of masked aldehydes as the key synthons, that is, α-hydroxyaryl acetaldehyde acetals.

1. Introduction

Enantiomerically pure α-alkoxy/hydroxyl aryl acetaldehydes are very versatile chiral synthons for the preparation of natural products, such as rhodinose,[1] rocellaric acid,[2] lipoxine A,[3] brevicomin,[4] goniodiol analogues[5] and amino sugars.[6] These molecules are the precursors of α-alkoxy arylacetic acids, which are also used as chiral auxiliaries in Diels–Alder reactions[7] and for chiral recognition by NMR in the method known as 'Mosher's method'.[8] Moreover, MPA (methoxyphenyl acetic acid) and MTPA (methoxytrifluoromethyl phenylacetic acid) have been the most widely used reagents for the determination of absolute configuration of secondary alcohols, amines and sulfoxides by ^{1}H NMR,[9,10] even though some novel auxiliaries and reagents based on α-alkoxy aryl acetic acids are also reported.[11] α-Alkoxyphenyl acetic acids are extremely useful in the resolution of amines via diastereoisomer formation; as a consequence of differentiation in the physio-chemical properties of these diastereoisomers they can easily be crystallized and separated.[12] Analogues of mandelic acid and α-methoxyphenyl acetic acid have been reported to behave as plant growth regulators,[13] calcium antagonists,[14] and also as apoptosis inhibitors.[15]

Due to numerous biological and pharmacological properties of these molecules, a number of routes for the synthesis of α-methoxyaryl acetaldehydes and α-methoxy aryl acetic acids are available in the literature; for example, (a) from (*S*)-(+)-*p*-tolyl-thiomethylsulfoxide;[16] (b) by asymmetric microbial reduction of α-keto acetals[17] and α-keto thioacetals;[18] (c) by Sharpless asymmetric dihydroxylation as a key step[19] and (d) from tartaric acid.[20] However, most of these synthetic routes suffer from low overall yields utilizing uneconomical protection–deprotection methodologies and low enantiomeric purity of the final products.

The absence of any simple and general methodology for the preparation of optically active α-methoxyaryl acetaldehyde precursors capable of producing downstream products, such as nitriles, alcohols and carboxylic acids, prompted us to look for an alternative synthesis. Herein, we report a facile chemo-enzymatic methodology, wherein the formation of masked aldehyde is the key step. The aldehyde synthon can easily be converted into other important downstream products, such as nitriles, alcohols and carboxylic acids in both the enantiomeric forms with high enantiomeric purity.

2. Results and discussion

Substituted β-bromostyrenes (prepared by known methods[21,22]) were used as the starting material for the preparation of racemic acetals as described in Scheme 1. Our strategy initiated with the synthesis of racemic 2,2-dimethoxy-1-aryl ethanol (masked aldehyde) **3** via a simple and novel route involving hydrohalogenation of substituted β-bromostyrene **1** followed by a nucleophilic substitution reaction in **2**, providing **3a–d** in ~80% overall isolated yields (Scheme 1).

For the synthesis of the target molecules, acetyl derivatives of 2,2-dimethoxy-1-aryl ethanols **4a–d** were subjected to enzymatic hydrolysis in biphasic systems, since in the lipase-catalyzed hydrolysis of acylates, biphasic reaction media have been found to provide rapid conversion and improved enantioselectivity.[23] A number of lipases from the institutes microbial repository were screened for enantioselective hydrolysis and out of these, a native strain *Arthrobacter* sp.[24] lipase designated as ABL (MTCC No. 5125) in a biphasic system (buffer/ACN = 4:1) was identified to be the best, in terms of both rate of hydrolysis and enantioselectivity, as depicted in Scheme 2 and Table 1. The kinetic resolution reactions

* Corresponding author. Tel.: +91 191 2569111/2569011; fax +91 191 2569222/2569333.
E-mail address: sc_taneja@yahoo.co.in (S.C. Taneja).

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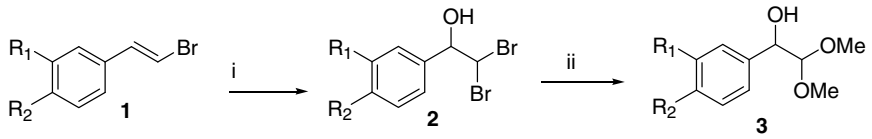
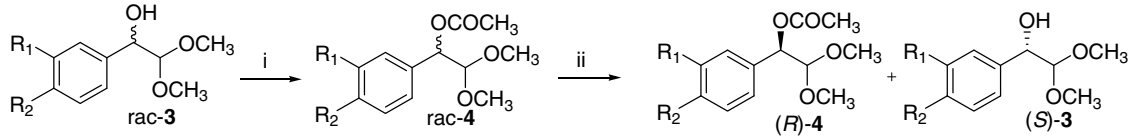


a, $R_1 = R_2 = H$; b, $R_1 = H$, $R_2 = OMe$; c, $R_1 = R_2 = OMe$; d, $R_1 + R_2 = -OCH_2O-$.

Scheme 1. Synthesis of racemic 2,2-dimethoxy-1-aryl ethanol. Reagents and conditions: (i) NBS, acetonitrile/water (1:1); (ii) methanol/KOH.



a, $R_1 = R_2 = H$; b, $R_1 = H$, $R_2 = OMe$; c, $R_1 = R_2 = OMe$; d, $R_1 + R_2 = -OCH_2O-$.

Scheme 2. Enzymatic hydrolysis of **4a**, **4b**, **4c** and **4d**. Reagents and conditions: (i) Ac_2O, Py, CH_2Cl_2; (ii) lipase, 0.1 M-phosphate buffer, pH 7.1.

Table 1
Enzymatic hydrolysis of **4a**, **4b**, **4c** and **4d** in a biphasic system using 20% co-solvent with respect to the buffer[a]

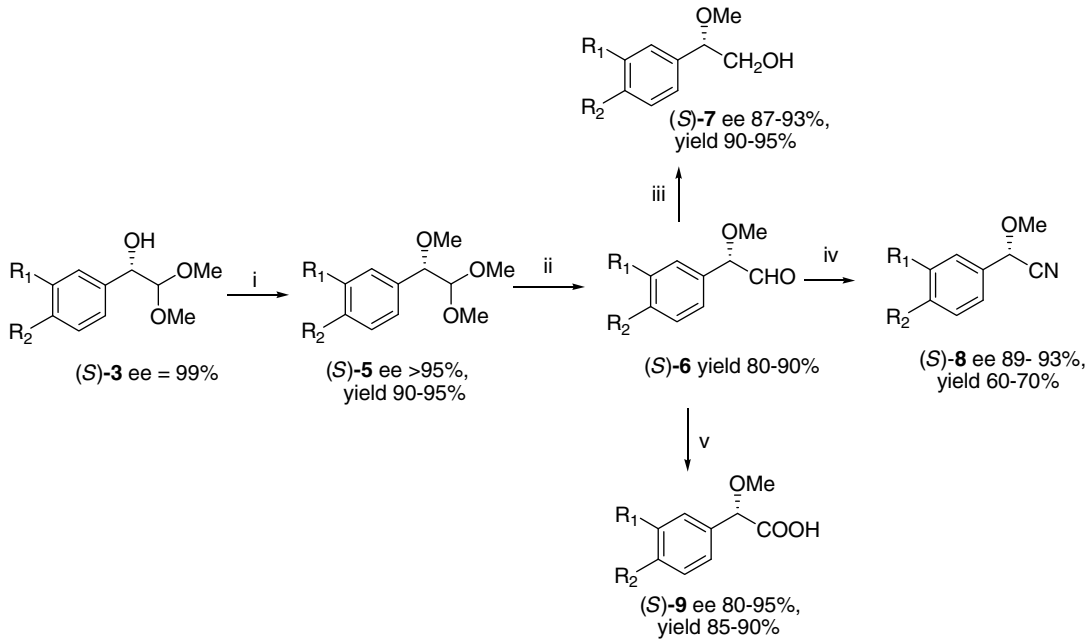
R_1	R_2	Co-solvent	Convn. (%)	Time (h)	ee_p (%) {Abs conf.}	ee_s (%) {Abs conf.}	*E*
H	H	ACN	50	2	99 (*S*)	99 (*R*)	1059
H	OCH_3	ACN	50	2	99 (*S*)	99 (*R*)	1059
OCH_3	OCH_3	Tol	50	12	99 (*S*)	99 (*R*)	1059
$R_1 + R_2 = -OCH_2O-$		ACN	50	3	99 (*S*)	99 (*R*)	1059

[a] All the reactions were performed at 25 °C using *Arthrobacter simplex* lipase (enzyme/substrate; 1.5:1) at 20 g/L concentration.

of **4a**–**d** were carried out in an aqueous phosphate buffer (0.1 M, pH 7.0), using 20% co-solvent such as acetonitrile/toluene. It was observed that the pH of the reaction mixture had a profound effect on rate as well as on enantioselectivity. Thus, in order to maintain the pH at 7.1, a 0.1 M solution of disodium hydrogen phosphate was added at regular intervals during the hydrolysis with ABL.

The conversion and enantiomeric excess (ee%) of enzyme (ABL)-catalyzed hydrolysis of **4a**, **4b**, **4c** and **4d** was measured by HPLC using a chiral stationary phase (*R*,*R*)-whelk-01 column.

After the synthesis of enantiomerically pure α-hydroxyaryl acetaldehydes in masked form, our next aim was to synthesize the downstream products such as α-methoxyaryl acetic acids,



a, $R_1 = R_2 = H$; b, $R_1 = H$, $R_2 = OMe$; c, $R_1 = R_2 = OMe$; d, $R_1 + R_2 = -OCH_2O-$.

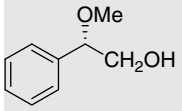
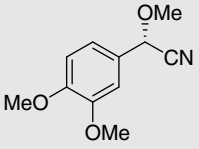
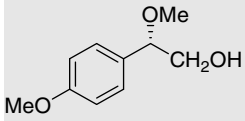
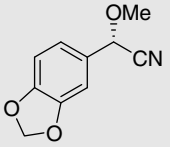
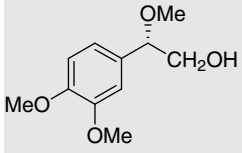
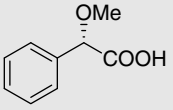
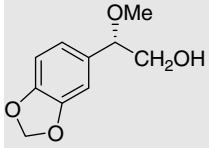
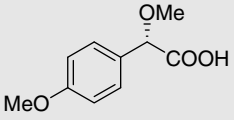
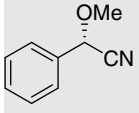
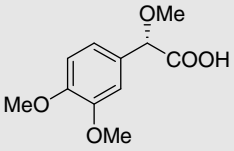
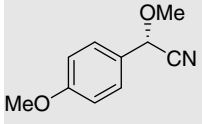
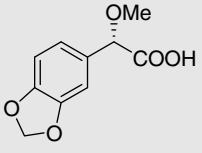
Scheme 3. Synthetic scheme for the preparation of downstream products. Reagents and conditions: (i) sodium hydride/methyl iodide in dry THF; (ii) dilute HCl in acetone; (iii) sodium borohydride in methanol; (iv) (a) hydroxylamine hydrochloride/NaOH; (b) acetic anhydride, 80 °C; (v) ammonical silver nitrate in toluene.

α-methoxyaryl ethanols and α-methoxyaryl acetonitriles in enantiomerically enriched form. To achieve this, the methyl ether of optically active (*S*)-α-hydroxyaryl acetaldehyde acetals (prepared after methylation of (*S*)-α-hydroxyaryl acetaldehyde acetals with methyl iodide) was subjected to acid hydrolysis to obtain (*S*)-α-methoxy aryl acetaldehyde in >95% ee, which on oxidation with Tollen's reagent afforded (*S*)-α-methoxyaryl acetic acids (~95% ee) in good yields without any significant loss in enantioselectivity. On reduction with $NaBH_4$, (*S*)-**6a**–**d** provided optically active (*S*)-α-methoxyaryl ethanols in quantitative yields (up to 93% ee). However, no attempts were made to optimize the conditions for improving the enantiomeric excess in these transformations.

During the synthesis of enantiomerically pure α-methoxyaryl acetonitriles from enantiomerically pure α-methoxyaryl acetaldehydes, it was observed that after the formation of an oxime with hydroxylamine hydrochloride, heating with acetic anhydride at a temperature higher than 100 °C would result in a significant loss of enantiomeric purity of the product; therefore, the reaction was carried out under controlled reaction conditions (70–80 °C) to avoid racemization (Scheme 3, Table 2). Herein, it was recognized that electron-donating substituents on the benzene ring did not have any significant effect on the rate as well as on enantioselectivity.

The enantiomeric purities of all of the optically active compounds were determined by using chiral stationary phased ODH,

Table 2
Synthesized downstream products from α-methoxyaryl acetaldehydes

Product	Yield[a] (%)	ee (%)	$[\alpha]_D^{25}$	Product	Yield[a] (%)	ee (%)	$[\alpha]_D^{25}$
 (*S*)-**7a**	90	>95	+104	 (*S*)-**8c**	64	93	−43
 (*S*)-**7b**	94	87	+92.4	 (*S*)-**8d**	70	89	−54
 (*S*)-**7c**	93	93	+98	 (*S*)-**9a**	82	80	+105
 (*S*)-**7d**	92	87	+87.5	 (*S*)-**9b**	85	90	+108
 (*S*)-**8a**	60	93	−67	 (*S*)-**9c**	86	91	+93.2
 (*S*)-**8b**	68	89	−57	 (*S*)-**9d**	90	89	+106

[a] Isolated yield.

OJH and (*R*,*R*)-whelk-01 columns. The absolute configurations of optically active compounds, such as **7a**, **7b**, **7c**, **9a**, **9b** and **9c**, were assigned on the basis of comparison the sign of specific rotation with that reported in the literature,[17,20] whereas for unknown compounds, a correlation was made with the absolute configurations of the resolved alcohols and esters and similar types of compounds based on the selectivity profile of *Arthrobacter* sp. lipase.

3. Conclusion

In conclusion, a series of enantiomerically pure masked α-methoxyaryl acetaldehydes, key synthons and their optically enriched downstream products, such as nitriles, alcohols and carboxylic acids (ee up to 95%), were prepared by a simple and efficient synthetic methodology via an ABL-catalyzed kinetic resolution step.

4. Experimental

4.1. General

^{1}H NMR spectra in $CDCl_3$ were recorded on Bruker 200 MHz spectrometers with TMS as the internal standard. Chemical shifts were expressed in parts per million (δ ppm). Reagents and solvents used were mostly of LR grade. Silica gel coated aluminium plates coated on alumina from M/s Merck were used for TLC. MS were recorded on Jeol MSD-300 and Bruker Esquire 3000 GC-Mass spectrometer. IR was recorded on a FT-IR Bruker (270-30) spectrophotometer. Optical rotations were measured on Perkin–Elmer 241 polarimeter at 25 °C using sodium D light. Enantiomeric excess (ee) was determined on a chiral stationary phase HPLC column.

4.2. General method for the preparation of substituted α-(dibromomethyl)aryl methanols 2a–d

Freshly prepared NBS (12 mmol) was added in small installments to a solution of substituted β-bromostyrenes **1a**–**d** (10 mmol) in 50 mL acetonitrile/water (1:1) in a reaction vessel, and the mixture was stirred at ambient temperature. After completion of the reaction as indicated by TLC, acetonitrile was removed at reduced pressure and the residue was extracted twice with ethyl acetate. The combined organic layers were washed with water and concentrated under reduced pressure to give α-(dibromomethyl)aryl methanols **2a**–**d** in quantitative yield.

4.3. General method for the preparation of 2,2-dimethoxy-1-aryl ethanols 3a–d

A solution of KOH (12 mmol) in methanol (50 mL) was added dropwise to a stirred solution of α-(dibromomethyl)-arylmethanol **2a**–**d** (10 mmol) in dry methanol (100 mL) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, potassium bromide was filtered off and methanol was evaporated at reduced pressure. The residue was purified by column chromatography using a gradient of ethyl acetate in hexane as eluent to give 2,2-dimethoxy-1-aryl ethanols **3a**–**d** in 75–80% yields.

4.4. General method for the preparation of acetic acid-2,2-dimethoxy-1-arylethyl esters 4a–d

Acetic anhydride (12 mmol) and a catalytic amount of DMAP were added to a solution of racemic 2,2-dimethoxy-1-aryl ethanols **3a**–**d** (10 mmol) in dry dichloromethane, and the reaction mixture was kept overnight at room temperature. The contents of the reaction mixture were poured into ice-cold water and extracted with dichloromethane. The organic layer was washed, dried and evaporated to get crude acetic acid-2,2-dimethoxy-1-arylethyl esters **4a**–**d**, which were purified by CC using a gradient of ethylacetate and hexane as eluent (90–95% yields).

4.5. General method for the preparation of 1-(aryl)-1,2,2-trimethoxy ethanes 5a–d

Sodium hydride (15 mmol) was added to a solution of 2,2-dimethoxy-1-arylethanols **3a**–**d** (10 mmol) in dry THF at 0–5 °C. After stirring for 5 min, methyl iodide was added to the reaction mixture. The reaction, after completion (as indicated by TLC), was worked up by quenching the excess of NaH with ethyl acetate, the contents were diluted with water and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate, and combined organic layers were washed with water, dried over sodium sulfate and concentrated under vacuo to give a crude product, which on column chromatography over silica gel gave1-(aryl)-1,2,2-trimethoxy ethanes **5a**–**d** in 90–95% yields.

4.6. General method for the preparation of α-methoxyaryl acetaldehydes 6a–d

Hydrochloric acid (100 mL of 1 M) was added to a solution of 1-aryl-1,2,2-trimethoxy ethanes **5a**–**d** (10 mmol) in 100 mL acetone. The solution was stirred at 80–90 °C and after completion of the reaction as indicated by TLC (benzene/ethyl acetate; 95:5), acetone was removed under vacuo and residue was extracted with ethyl acetate. The pH was made neutral by sodium bicarbonate solution, washed with water and concentrated in vacuo to give crude α-methoxyaryl acetaldehydes **6a**–**d** in 80–90% yields.

4.7. General method for the preparation of α-methoxyaryl acetic acids 9a–d

To a solution of α-methoxyaryl acetaldehyde (3 mmol) in 100 mL toluene was added Tollen's reagent (prepared from 1 g $AgNO_3$) dropwise, and the solution was stirred at room temperature. After completion of the reaction as indicated by TLC, the solution was diluted with distilled water and the toluene layer containing unwanted impurities was removed. The aqueous layer after washing with ethyl acetate was separated and acidified to pH 6.0. It was then extracted with ethylacetate (2×30 mL). The combined organic layer was dried and concentrated under reduced pressure to give α-methoxyaryl acetic acids **9a**–**d** (85–90% yields).

4.8. General method for the preparation of α-methoxyaryl acetonitriles 8a–d

Hydroxylamine hydrochloride (150 mg) was added to a stirred solution of α-methoxyaryl acetaldehyde (1 mmol) in 50 mL ethanol/water (1:1), and the solution was made slightly basic by the addition of 10% aq NaOH solution. After stirring for 0.5–1 h at room temperature, the progress of the reaction was monitored by TLC. The pH was adjusted to 6.5 by the addition of more hydroxylamine hydrochloride. The solution was concentrated under vacuo, and the residue was extracted with ethyl acetate. The organic layer was dried and concentrated under reduced pressure to give a crude oxime, which was heated with acetic anhydride in dry conditions at 70–80 °C until completion of the reaction. The acetic anhydride was removed under vacuo at low temperature to give crude α-methoxy arylacetonitriles **8a**–**d**, which were purified by column chromatography (pet. ether/ethyl acetate; 96:4) (60–70% yields).

4.9. General method for the preparation of α-methoxyaryl ethanols 7a–d

$NaBH_4$ (2 mmol) in small installments was added at 0–5 °C to a solution of α-methoxyaryl acetaldehyde (1 mmol) in 20 mL methanol. After completion of the reaction as indicated by TLC, the pH was made neutral by the addition of dil HCl and the contents were concentrated under reduced pressure. The residue was extracted with diethyl ether. The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was purified on a silica gel column to give α-methoxyaryl ethanols **7a**–**d** (90–95% yields).

4.10. Kinetic resolution of acetic acid-2,2-dimethoxy-1-phenylethyl ester 4a

Racemic acetic acid-2,2-dimethoxy-1-phenylethyl ester **4a** (1 g), aqueous phosphate buffer (75 mL, 0.1 M, pH 7.0), acetonitrile (15 mL) and whole cells of *Arthrobacter* sp. lipase (1.35 g) were stirred continuously at 25 ± 1 °C. The pH of the reaction mixture was adjusted at 7.1 with aqueous solution of disodium hydrogen phosphate. After a certain degree of conversion (~50%) as indicated by thin layer chromatography (TLC) and chiral high performance liquid chromatography (HPLC), the reaction was terminated by adding ethyl acetate and centrifuging the mixture at 10,000–15,000*g* to remove the enzyme and the suspended particles. The clear solution was decanted, and the centrifuged mass was extracted separately with ethyl acetate (3 × 25 mL). The organic layer was combined and washed with water. The combined organic layer was then dried and evaporated under reduced pressure to furnish a mixture comprising hydrolyzed alcohol and unhydrolyzed ester, which was separated by column chromatography (60–120 mesh) using a gradient of ethyl acetate and hexane as eluent to give (*R*)-(−)-**4a**, (432 mg), ee = 99%, $[\alpha]_D^{25} = -45.0$ (*c* 0.5, $CHCl_3$) and (*S*)-(+)-**3a**, (386 mg), ee = 99%, $[\alpha]_D^{25} = +10.5$ (*c* 1.0 $CHCl_3$), lit.;[17] (*S*)-(+)-**3a**, ee = 46%, $[\alpha]_D^{25} = +4.7$ (*c* 5, $CHCl_3$,), HPLC conditions: (*R*,*R*)-Whelk-01, chiral column, eluent 2-propanol/hexane (0.5:99.5), flow rate: 0.8 mL/min.

4.11. Preparation of optically active (*S*)-(+)-1-(phenyl)-1,2,2-trimethoxy ethane 5a

Compound **5a** was prepared using the same procedure as applied for the synthesis of racemic 1-(phenyl)-1,2,2-trimethoxy ethane **5a**: $[\alpha]_D^{25} = +55.2$ (*c* 1, $CHCl_3$), ee = 95%, HPLC conditions: ODH chiral column, eluent 2-propanol/hexane (0.5:99.5), flow rate: 0.8 mL/min.

4.12. Preparation of optically active (*S*)-(+)-α-methoxyphenyl acetaldehyde 6a

The compound was prepared using the method described for racemic **6a**, $[\alpha]_D^{25} = +52$ (*c* 0.5, $CHCl_3$) for crude (*S*)-**6a**.

4.13. Preparation of optically active (*S*)-(+)-2-methoxy-2-phenyl ethanol 7a

The compound was prepared using the same procedure as applied for racemic **7a**; Ee 95%, $[\alpha]_D^{25} = +104$ (*c* 1.0, acetone); HPLC conditions: OJH chiral column, eluent 2-propanol/hexane (0.5:99.5), flow rate: 0.8 mL/min; (lit.[19]; (*S*)-**7a**, $[\alpha]_D^{25} = +108.5$ (*c* 0.11 $CHCl_3$).

4.14. Preparation of optically active (*S*)-(−)-2-methoxy-2-phenyl acetonitrile 8a

The compound was prepared using the same procedure as applied for racemic **8a**, ee 93%, $[\alpha]_D^{25} = -67$ (*c* 1.0, $CHCl_3$); HPLC conditions: OJH chiral column, eluent 2-propanol/hexane (1.0:99), flow rate: 0.8 mL/min.

4.15. Preparation of optically active (*S*)-(+)-α-methoxy phenyl acetic acid 9a

The compound was prepared using the same procedure as applied for racemic **9a**, (*S*)-**9a**, ee 80%, $[\alpha]_D^{25} = +105$ (*c* 0.5, EtOH); (lit.[19] (*S*)-isomer, $[\alpha]_D^{25} = +146.0$ (*c* 1.04, EtOH), HPLC conditions for its methyl ester: (*R*,*R*)-whelk-01, chiral column, eluent 2-propanol/hexane (2.0:98.0), flow rate: 0.8 mL/min.

4.16. Kinetic resolution of acetic acid-2,2-dimethoxy-1-(4-methoxyphenyl)ethyl ester 4b

Racemic acetic acid-2,2-dimethoxy-1-(4-methoxyphenyl)ethyl ester **4b** (1 g), aqueous phosphate buffer (75 mL, 0.1 M, pH 7.0), acetonitrile (15 mL) and whole cells of *Arthrobacter* sp. lipase (1.5 g) were stirred continuously at 25 ± 1 °C. The pH of the reaction mixture was adjusted at 7.1 with aqueous solution of disodium hydrogen phosphate. After a certain degree of conversion (~50%) as indicated by thin layer chromatography (TLC) and chiral high performance liquid chromatography (HPLC), the reaction was terminated by adding ethyl acetate and centrifuging the mixture at 10,000–15,000*g* to remove the enzyme and the suspended particles. The clear solution was decanted, and the centrifuged mass was extracted separately with ethyl acetate (3 × 25 mL). The organic layer was combined and washed with water. The combined organic layer was then dried and evaporated under reduced pressure to furnish a mixture comprising hydrolyzed alcohol and unhydrolyzed ester, which was separated by column chromatography (60–120 mesh) using a gradient of ethyl acetate and hexane as eluent to give *R*-(−)-**4b**, (480 mg), ee = 99%, $[\alpha]_D^{25} = -61.0$ (*c* 0.5, $CHCl_3$) and (*S*)-(+)-**3b**, (410 mg), ee = 99%, $[\alpha]_D^{25} = +14.5$ (*c* 1.0 $CHCl_3$), HPLC conditions: (*R*,*R*)-whelk-01, chiral column, eluent 2-propanol/hexane (5:95), flow rate: 0.8 mL/min.

4.17. Preparation of optically active (*S*)-(+)-1-(4-methoxyphenyl)-1,2,2-trimethoxy ethane 5b

The compound was prepared from (*S*)-(+)-**3b** using the same procedure as applied for racemic **5b**. Ee = 95%, $[\alpha]_D^{25} = +52$ (*c* 0.5, $CHCl_3$), HPLC conditions: Chiralcel OJH chiral column, eluent 2-propanol/hexane (1.5:98.5), flow rate: 0.8 mL/min.

4.18. Preparation of optically active (*S*)-(+)-α-methoxy-2-(4-methoxyphenyl)acetaldehyde 6b

The compound was prepared from (*S*)-(+)-**5b** using the same procedure as applied for racemic **6b**. $[\alpha]_D^{25} = +68.1$ (*c* 1.0, $CHCl_3$) for crude (*S*)-(+)-**6b**.

4.19. Preparation of optically active (*S*)-(+)-2-methoxy-2-(4-methoxyphenyl)ethanol 7b

It was prepared from (*S*)-(+)-**6b** using the same procedure as applied for racemic **7b**. Ee = 87%, $[\alpha]_D^{25} = +92.4$ (*c* 1.0, $CHCl_3$), HPLC conditions for its acetyl derivative: Chiralcel OJH chiral column, eluent 2-propanol/hexane (0.5:99.5), flow rate: 0.8 mL/min.

4.20. Preparation of optically active (*S*)-(−)-2-methoxy-2-(4-methoxyphenyl)acetonitrile 8b

The compound was prepared from (*S*)-(+)-**6b** using the same procedure as applied for racemic **8b**. Ee = 89%, $[\alpha]_D^{25} = -57$ (*c* 1.0, $CHCl_3$), HPLC conditions: Chiralcel OJH chiral column, eluent, 2-propanol/hexane (2.0:98.0), flow rate: 0.8 mL/min.

4.21. Preparation of optically active *S*-(+)-α-methoxy-2-(4-methoxyphenyl)acetic acid 9b

The compound was prepared from (*S*)-(+)-**6b** using the same procedure as applied for racemic **9b**. Ee = 90%, $[\alpha]_D^{25} = +108$ (*c* 0.5, EtOH). HPLC conditions for its methyl ester: (*R*,*R*)-whelk-01, chiral column, eluent, 2-propanol/hexane (2.0:98.0), flow rate: 0.8 mL/min.

4.22. Kinetic resolution of acetic acid-2,2-dimethoxy-1-(3,4-dimethoxyphenyl)ethyl ester 4c

Racemic acetic acid-2,2-dimethoxy-1-(3,4-dimethoxyphenyl)-ethyl ester **4c** (1 g), aqueous phosphate buffer (75 mL, 0.1 M, pH 7.0), acetonitrile (15 mL) and whole cells of *Arthrobacter* sp. lipase (1.5 g) were stirred continuously at 25 ± 1 °C. The pH of the reaction mixture was adjusted at 7.1 with an aqueous solution of disodium hydrogen phosphate. After a certain degree of conversion (∼50%) as indicated by thin layer chromatography (TLC) and chiral high performance liquid chromatography (HPLC), the reaction was terminated by adding ethyl acetate and centrifuging the mixture at 10,000–15,000*g* to remove enzyme and the suspended particles. The clear solution was decanted, and the centrifuged mass was extracted separately with ethyl acetate (3 × 25 mL). The organic layer was combined and washed with water. The combined organic layer was then dried and evaporated under reduced pressure to furnish a mixture comprising hydrolyzed alcohol and unhydrolyzed ester, which was separated by column chromatography (60–120 mesh) using a gradient of ethyl acetate and hexane as eluent to give (*R*)-(−)-**4c**, (470 mg), ee = 99%, $[\alpha]_D^{25} = -52.2$ (*c* 1.0, $CHCl_3$) and (*S*)-(+)-**3c**, (400 mg), ee = 99%, $[\alpha]_D^{25} = +8.2$ (*c* 1.0 $CHCl_3$), HPLC conditions: (*R*,*R*)-whelk-01, chiral column, eluent 2-propanol/hexane (5:95), flow rate: 0.8 mL/min.

4.23. Preparation of optically active (*S*)-(+)-1-(3,4-dimethoxyphenyl)-1,2,2-trimethoxy ethane 5c

The compound was prepared from (*S*)-(+)-**3c** using the same procedure as applied for racemic **5c**. Ee = 95%, $[\alpha]_D^{25} = +40.4$ (*c* 0.5, $CHCl_3$), HPLC conditions: Chiralcel ODH chiral column, eluent 2-propanol/hexane (1.5:98.5), flow rate: 0.8 mL/min.

4.24. Preparation of optically active (*S*)-(+)-α-methoxy-2-(3,4-dimethoxyphenyl)acetaldehyde 6c

The compound was prepared from (*S*)-(+)-**5c** using the same procedure as applied for racemic **6c**. $[\alpha]_D^{25} = +54.5$ (c 1.0, $CHCl_3$) for crude (*S*)-(+)-**6c**.

4.25. Preparation of optically active (*S*)-(+)-2-methoxy-2-(3,4-dimethoxyphenyl)ethanol 7c

The compound was prepared from (*S*)-(+)-**6c** using the same procedure as applied for racemic **7c**. Ee ∼93%, $[\alpha]_D^{25} = +98$ (*c* 0.5, $CHCl_3$). HPLC conditions: Chiralcel OJH chiral column, eluent 2-propanol/hexane (5:95), flow rate: 0.8 mL/min.

4.26. Preparation of optically active (*S*)-(−)-2-methoxy-2-(3,4-dimethoxyphenyl)acetonitrile 8c

The compound was prepared from (*S*)-(+)-**6c** using the same procedure as applied for racemic **8c**. Ee ∼93%, $[\alpha]_D^{25} = -43$ (*c* 1.0, $CHCl_3$), HPLC conditions: Chiralcel OJH chiral column, eluent 2-propanol/hexane (0.5:99.5), flow rate: 0.8 mL/min.

4.27. Preparation of optically active (*S*)-(+)-2-methoxy-2-(3,4-dimethoxyphenyl)acetic acid 9c

The compound was prepared from (*S*)-(+)-**6c** using the same procedure as applied for racemic **9c**. Ee = 91%, $[\alpha]_D^{25} = +93.2$ (*c* 0.5, EtOH); HPLC conditions for its methyl ester: (*R*,*R*)-whelk-01, chiral column, eluent 2-propanol/hexane (5:95), flow rate: 0.8 mL/min.

4.28. Kinetic resolution of acetic acid-2,2-dimethoxy-1-(3,4-methylenedioxyphenyl)ethyl ester 3d

Racemic acetic acid-2,2-dimethoxy-1-(3,4-methylenedioxyphenyl)ethyl ester **4d** (1 g), aqueous phosphate buffer (75 mL, 0.1 M, pH 7.0), acetonitrile (15 mL) and whole cells of *Arthrobacter* sp. lipase (1.5 g) were stirred continuously at 25 ± 1 °C. The pH of the reaction mixture was adjusted at 7.1 with an aqueous solution of disodium hydrogen phosphate. After a certain degree of conversion (∼50%) as indicated by thin layer chromatography (TLC) and chiral high performance liquid chromatography (HPLC), the reaction was terminated by adding ethyl acetate and centrifuging the mixture at 10,000–15,000*g* to remove enzyme and the suspended particles. The clear solution was decanted, and the centrifuged mass was extracted separately with ethyl acetate (3 × 25 mL). The organic layer was combined and washed with water. The combined organic layer was then dried and evaporated under reduced pressure to furnish a mixture comprising hydrolyzed alcohol and unhydrolyzed ester, which was separated by column chromatography (60–120 mesh) using a gradient of ethyl acetate and hexane as eluent to give (*R*)-(−)-**4d**, (503 mg), ee = 99%, $[\alpha]_D^{25} = -62$ (*c* 1.0, $CHCl_3$) and (*S*)-(+)-**3d**, (455 mg), ee = 99%, $[\alpha]_D^{25} = +5.7$ (*c* 1.0 $CHCl_3$), HPLC conditions: (*R*,*R*)-whelk-01, chiral column, eluent 2-propanol/hexane (5:95), flow rate: 0.8 mL/min.

4.29. Preparation of optically active (*S*)-(+)-1-(3,4-methylenedioxyphenyl)-1,2,2-trimethoxy ethane 5d

The compound was prepared from (*S*)-(+)-**3d** using the same procedure as applied for racemic **5d**, ee = 95%, $[\alpha]_D^{25} = +51$ (*c* 1.0, $CHCl_3$). HPLC conditions: Chiralcel ODH chiral column, eluent 2-propanol/hexane (0.5:99.5), flow rate: 0.8 mL/min.

4.30. Preparation of optically active *S*-(+)-α-methoxy-2-(3,4-methylenedioxyphenyl)acetaldehyde 6d

The compound was prepared from (*S*)-(+)-**5d** using the same procedure as applied for racemic **6d**. $[\alpha]_D^{25} = +52.3$ (*c* 1.0, $CHCl_3$) for crude (*S*)-(+)-**6d**.

4.31. Preparation of optically active (*S*)-(+)-2-methoxy-2-(3,4-methylenedioxyphenyl)-ethanol 7d

The compound was prepared from (*S*)-(+)-**6d** using the same procedure as applied for racemic **7d**, ee = 87%, $[\alpha]_D^{25} = +87.5$ (*c* 0.5, $CHCl_3$), HPLC conditions for its acetyl derivative: Chiralcel OJH chiral column, eluent 2-propanol/hexane (0.5:99.5), flow rate: 0.8 mL/min.

4.32. Preparation of optically active *S*-(−)-2-methoxy-2-(3,4-methylenedioxyphenyl)acetonitrile 8d

The compound was prepared from (*S*)-(+)-**6d** using the same procedure as applied for racemic **8d**, ee = 89%, $[\alpha]_D^{25} = -54.0$ (*c* 1.0, $CHCl_3$), HPLC conditions: Chiralcel OJH chiral column, eluent 2-propanol/hexane (5:95), flow rate: 0.8 mL/min.

4.33. Preparation of optically active (*S*)-(+)-α-methoxy-2-(3,4-methylenedioxyphenyl)acetic-acid 9d

The compound was prepared from (*S*)-(+)-**6d** using the same procedure as applied for racemic **9d**, ee = 89%, $[\alpha]_D^{25} = +106.0$ (*c* 0.5, EtOH), HPLC conditions for its methyl ester: (*R*,*R*)-whelk-01, chiral column, eluent 2-propanol/hexane (2:98), flow rate: 0.8 mL/min.

4.34. Spectral data of synthesized compounds

4.34.1. α-(Dibromomethyl)benzene methanol $C_8H_8OBr_2$ 2a

Colourless viscous liquid, ^{1}H NMR (500 MHz): δ; 5.38 (1H, d, *J* = 7.4 Hz, C*H*Br_2), 6.0 (1H, d, *J* = 7.4 Hz, C*H*OH), 7.35–7.37 (3H, m, Ar*H*), 7.45–7.47 (2H, m, Ar*H*); ^{13}CNMR: δ; 45.6, 58.7, 128.6, 128.6, 129.5, 137.5; IR (neat) NaCl: 3406.2, 3029.1, 1584, 1494.7, 1141.5, 769.5, 693, 601.7 cm^{-1}; MS (*m*/*z*) (%); 280 (2.0), 263 (100), 261 (49.8), 184 (65.9), 182 (70.2), 171 (9.1), 169 (10.5),103 (73.2), 102 (34.6),77 (21.6).

4.34.2. 2,2-Dimethoxy-1-(phenyl)ethanol $C_{10}H_{14}O_3$ 3a

Colourless viscous liquid, ^{1}H NMR (200 MHz): δ; 3.25 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 4.28 (1H, d, *J* = 6.4 Hz, C*H*$(OMe)_2$), 4.61 (1H, d, *J* = 6.4 Hz, C*H*OH), 7.25–7.44 (5H, m, Ar*H*); ^{13}C NMR: δ; 55.0, 56.0, 74.1, 107.7, 127.2, 127.9, 128.3, 139.5; IR (neat) NaCl: 3446.1, 3032.5, 2932.4, 2833.8, 1691.2, 1453.4, 1190.9, 1125.8, 1068.9, 976.7, 762.4, 701 cm^{-1}; MS (*m*/*z*) (%); 165 (17.10) (M^+−OH), 151 (27.1).

4.34.3. 1-(Phenyl)-1,2,2-trimethoxy ethane $C_{11}H_{16}O_3$ 5a

Colourless viscous liquid, ^{1}H NMR (500 MHz): δ; 3.18 (3H, s, OCH_3), 3.23 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 4.16 (1H, d, *J* = 6.2 Hz, C*H*$(OMe)_2$), 4.36 (1H, d, *J* = 6.2 Hz, C*H*OMe), 7.25–7.35 (m, 5H, Ar*H*); ^{13}C NMR: δ; 54.4, 55.7, 56.9, 83.9, 106.5, 128.1, 128.3, 128.5, 138.0; IR (neat) NaCl: 2934.8, 2801, 1722.8, 1493.6, 1453.5, 1189.1, 1111.2, 701 cm^{-1}; MS (*m*/*z*) (%): 165 (M^+−OMe) (39.5), 121 (17.6), 77 (11.9), 75 (100).

4.34.4. α-Methoxyphenyl acetaldehyde $C_9H_{10}O_2$ 6a

Colourless viscous liquid, ^{1}H NMR (500 MHz): δ; 3.46 (3H, s, OCH_3), 4.64 (1H, d, *J* = 1.2 Hz, C*H*OCH_3), 7.1–7.4 (5H, m, Ar*H*), 9.6 (1H, d, *J* = 1.6 Hz, CHO); ^{13}C NMR: δ; 57.3, 88.3, 125.4, 127.5, 129.0, 129.1, 198.3; IR (neat) NaCl: 3439.1, 2925.8, 2853.8, 1735, 1454, 1108, 700 cm^{-1}; MS (*m*/*z*) (%); 151 (5.8) (M^++1), 134 (6.3), 167.3 (13), 121 (100), 92 (7.1).

4.34.5. 2-Methoxy-2-phenyl ethanol $C_9H_{12}O_2$ 7a

Colourless viscous liquid, ^{1}H NMR (500 MHz): δ; 3.31 (3H, s, OCH_3), 3.56–3.68 (2H, m, CH_2OH), 4.31 (1H, dd, *J* = 4.4 Hz, 7.83 Hz, C*H*OMe), 7.34 (5H, Ar*H*); ^{13}C NMR: δ; 56.9, 67.4, 84.7, 126.9, 127.8, 128.2, 138.3; IR (neat) NaCl: 3425.6, 2933.1, 1454.3, 1112.0, 1065.1, 759.3, 702.2 cm^{-1}; MS (*m*/*z*) (%); 121 (100) (M^+−OMe), 91 (19.9), 77 (7.1).

4.34.6. α-Methoxyphenyl acetic acid $C_9H_{10}O_3$ 9a

Colourless viscous liquid, ^{1}H NMR (200 MHz): δ; 3.41 (3H, s, OCH_3), 4.78 (1H, s, C*H*OCH_3), 7.26–7.45 (m, 5H, Ar*H*); ^{13}C NMR: δ; 57.7, 82.4, 127.7, 129.2, 129.4, 135.7, 175.7; IR (neat) NaCl: 3064.9, 3033.2, 2936.9, 1726, 1197.1, 1105.5, 722 cm^{-1}; MS (*m*/*z*): 164.6, 148.7, 120.7, 92.7.

4.34.7. 2-Methoxy-2-phenyl acetonitrile C_9H_9ON 8a

Colourless viscous liquid, ^{1}H NMR (500 MHz): δ; 3.52 (3H, s, OCH_3), 5.18 (1H, s, C*H*), 7.25–7.89 (5H, m, Ar*H*); ^{13}C NMR: δ; 56.8, 72.3, 117.0, 127.1, 127.3, 129.9, 133.5; IR (neat) NaCl: 3390.1, 3001.0, 1454.2, 1193.8, 1088.1, 758.5, 698.2 cm^{-1}; MS (*m*/*z*) (%); 147 (27.3), 146 (9.9), 132 (10.8), 121 (100), 116 (59.3).

4.34.8. Acetic acid-2,2-dimethoxy-1-phenylethyl ester $C_{12}H_{16}O_4$ 4a

Colourless viscous liquid, ^{1}H NMR (200 MHz): δ; 2.11 (3H, s, OC(O)CH_3), 3.29 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 4.54 (1H, d, *J* = 6.3 Hz, C*H*$(OCH_3)_2$), 5.83 (1H, d, *J* = 6.3 Hz, *CH*OAc), 7.32–7.42 (5H, m, Ar*H*); ^{13}C NMR: δ; 21.5, 55.1, 55.9, 74.7, 105.5, 128.1, 128.6, 129.2, 137.2; IR (neat) NaCl: 2939.1, 2835.2, 1741.7, 1372.0, 1077.9, 700.5 cm^{-1}; MS (*m*/*z*) (%); 224, 193 (40.6), 165 (24.1), 75 (100).

4.34.9. α,α-Dibromomethyl-(4-methoxyphenyl)methanol $C_9H_{10}O_2Br_2$ 2b

Light yellow viscous liquid, ^{1}H NMR (200 MHz): δ; 3.91 (1H, O*H*), 3.81 (3H, s OCH_3), 4.99 (1H, d, *J* = 5.3 Hz, C*H*Br_2), 5.74 (1H, d, *J* = 5.2 Hz, C*H*OH), 6.90 (2H, d, *J* = 8.6 Hz, Ar*H*), 7.34 (2H, d, *J* = 8.6 Hz, Ar*H*), ^{13}C NMR: δ; 52.4, 55.3, 78.5, 113.8, 130.0, 131.5, 159.9; IR (neat) NaCl: 3446.2, 3002.9, 2836.9, 1611.2, 1513.0, 1252.8, 1030.6, 833.4 cm^{-1}; MS (*m*/*z*) (%); 310 (1.9), 150 (1.8), 149 (2.9), 138 (9.7), 137 (100), 135 (6), 122 (1.5), 109 (15.3), 108 (1.5), 94 (14.5), 77 (22.9).

4.34.10. 2,2-Dimethoxy-1-(4-methoxyphenyl)ethanol $C_{11}H_{16}O_4$ 3b

Colourless viscous liquid, ^{1}H NMR (200 MHz): δ; 3.26 (3H, s, OCH_3), 3.47 (3H, s, OCH_3), 3.8 (3H, s, OCH_3), 4.27 (1H, d, *J* = 6.5 Hz, C*H*$(OCH_3)_2$), 4.56 (1H, d, *J* = 6.5 Hz, C*H*OCH_3), 6.89 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.33 (2H, d, *J* = 8.5 Hz, Ar*H*); ^{13}C NMR: δ; 54.7, 55.1, 55.7, 73.4, 107.6, 113.5, 128.2, 131.6, 159.1; IR (neat) NaCl, 3457.9, 2936.6, 2835.3, 1613, 1515.1, 832.0, 574.5 cm^{-1}; MS (*m*/*z*) (%); 212 (1.4), 152 (2.1), 149 (10.9), 137 (13.5), 135 (39.7), 121 (16.6), 105 (1.2), 94 (11), 77 (31.4), 75 (100), 66 (8.9).

4.34.11. 1-(4-Methoxyphenyl)-1,2,2-trimethoxyethane $C_{12}H_{18}O_4$ 5b

Colourless viscous liquid,^{1}H NMR (200 MHz): δ; 3.20 (3H, s, OCH_3), 3.23 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.14 (1H, d, *J* = 5.6 Hz, C*H*$(OCH_3)_2$), 4.37 (1H, d, *J* = 5.6 Hz, C*H*OCH_3), 6.91 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.28 (2H, d, *J* = 7.3 Hz, Ar*H*); ^{13}C NMR: δ; 55.4, 55.7, 56.0, 56.5, 83.2, 106.3, 113.5, 129.0, 129.8, 159.3; IR (neat) NaCl, 2936.2, 2832.7, 1612.4, 1513.0, 1302.1, 1246.7, 1108.7, 831.5, 637.4 cm^{-1}; MS (*m*/*z*) (%); 226 (2), 195 (4.3), 164 (1.6), 135 (29), 121 (15), 108 (5), 92 (5), 91 (6), 78 (7), 75 (100), 49 (23).

4.34.12. α-Methoxy-2-(4-methoxyphenyl)acetaldehyde $C_{10}H_{12}O_3$ 6b

Colourless liquid, ^{1}H NMR (200 MHz): δ; 3.40 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.59 (1H, d, *J* = 1.5 Hz, C*H*OMe), 6.93 (2H, d, *J* = 2.1 Hz, Ar*H*), 7.25 (2H, d, *J* = 1.9 Hz, Ar*H*), 9.55 (1H, d, *J* = 1.6 Hz, C*H*O); ^{13}C NMR: δ; 54.9, 56.9, 87.5, 114.2, 125.2, 128.68, 159.0, 199.1; IR (neat) NaCl, 3449.5, 2963.2, 2836.4, 1735.5, 1610.1, 1511.0, 1250.9, 1106.4, 831.9 cm^{-1}; MS (*m*/*z*) (%); 180 (0.3), 164 (1.8), 151 (100), 150 (0.4).

4.34.13. 2-Methoxy-2-(4-methoxyphenyl)ethanol $C_{10}H_{14}O_3$ 7b

Colourless liquid, ^{1}H NMR (200 MHz): δ; 3.28 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.61–3.73 (2H, m, CH_2OH), 4.26 (1H, dd, J = 4.1 Hz, 8.2 Hz, CHOMe), 6.91(2H, d, J = 8.6 Hz, ArH), 7.24 (2H, d, J = 8.6 Hz, ArH); ^{13}C NMR: δ; 54.2, 54.7, 66.4, 83.1, 86.6, 112.9, 127.1, 159.6; IR (neat) NaCl: 3422.5, 2934.9, 1611.6, 1513.2, 1247.7, 1108.7, 1033.9, 832 cm^{-1}; MS (m/z) (%), 182 (1.4), 183 (1.5), 152 (100), 135 (20.4), 122 (3.6), 108 (6.2), 91 (6), 77 (7), 66 (3.6), 52 (4).

4.34.14. α-Methoxy-2-(4-methoxyphenyl)acetic acid $C_{10}H_{12}O_4$ 9b

White solid, mp 64 °C, ^{1}H NMR (200 MHz): δ; 3.39 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.72 (1H, s, CHOMe), 6.90 (2H, d, J = 8.2 Hz, ArH), 7.34 (2H, d, J = 8.3 Hz, ArH); ^{13}C NMR: δ; 54.3, 56.0, 80.5, 113.4, 126.9, 127.6, 167.8, 180.4; IR (neat) NaCl; 3423.1, 2936.3, 2837.2, 1734.5, 1610.4, 1512.7, 1249.9, 1176.0, 1101.1, 1031.2, 988.5, 830.7 cm^{-1}; MS (m/z) (%); 195 (M$^+$−1), 181, 165, 134.

4.34.15. 2-Methoxy-2-(4-methoxyphenyl)acetonitrile $C_{10}H_{11}O_2N$ 8b

Colourless liquid, ^{1}H NMR (200 MHz): δ; 3.50 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 5.15 (1H, s, CHOMe), 6.94 (2H, d, J = 8.6 Hz, ArH), 7.41 (2H, d, J = 8.7 Hz, ArH); ^{13}C NMR: δ; 55.3, 56.8, 73.3, 115.8, 118.5, 126.8, 130.3, 162.1; IR (neat) NaCl; 2936.0, 2838.2, 2558.3, 2037.4, 1612.0, 1513.9, 1463.5, 1253.8, 1178.4, 1082.8, 829.5 cm^{-1}; MS (m/z) (%); 177 (23), 151 (5.9), 147 (13), 146 (100), 135 (9.5), 103 (12.7), 91 (14.4), 77 (15.3), 76 (16.4), 64 (11.3), 53 (12.6), 45 (22.3).

4.34.16. Acetic acid-2,2-dimethoxy-1-(4-methoxyphenyl)ethyl ester $C_{13}H_{18}O_5$ 4b

Colourless liquid, ^{1}H NMR (200 MHz): δ; 2.10 (3H, s, OCOCH_3), 3.3 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.52 (1H, d, J = 6.3 Hz, CH(OCH$_3$)$_2$), 5.78 (1H, d, J = 6.28 Hz, CHOAc), 6.88 (2H, d, J = 4.8 Hz, ArH), 7.33 (2H, d, J = 4.8 Hz, ArH); ^{13}C NMR: δ; 20.8, 54.3, 55.3, 56.1, 74.0, 105.0, 114.5, 128.3, 128.6, 159.5, 169.8; IR (neat) NaCl, 3450.2, 2938.4, 2836.8, 1740.8, 1613.3, 1516.2, 1238.8, 1072.7, 1032.0, 831.6 cm^{-1}; MS (m/z) (%); 254 (.3), 223 (.2), 195 (.3), 181 (.5), 149 (1.7), 137 (3), 135 (1.9), 121 (3.7), 91 (.8), 77 (2.4), 75 (100), 49 (7.7).

4.34.17. α,α-Dibromomethyl-(3,4-dimethoxyphenyl)methanol $C_{10}H_{12}O_3Br_2$ 2c

White crystalline solid, mp 97 °C, ^{1}H NMR (200 MHz): δ; 3.04 (1H, d, J = 3.70 Hz, OH), 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.94–4.98 (1H, m, CHBr$_2$), 5.75 (1H, d, J = 5.3 Hz, CHOH), 6.82–6.96 (3H, m, ArH); ^{13}C NMR: δ; 52.3, 55.8, 78.7, 109.8, 110.8, 119.6, 130.4, 148.9, 149.4; IR (neat) NaCl; 3467.3, 3078.4, 2979.4, 2913.3, 1592.4, 1325.0, 1102.3, 814.3 cm^{-1}; MS (m/z) (%); 340 (4.8), 180 (2.9), 167 (100), 165 (4.2), 151 (3.8), 139 (33.3), 107 (3.5), 77 (10.2).

4.34.18. 2,2-Dimethoxy-1-(3,4-dimethoxyphenyl)ethanol $C_{12}H_{18}O_5$ 3c

White solid, mp 48 °C, ^{1}H NMR (200 MHz): δ; 3.26 (3H, s, OCH_3), 3.46 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.26 (1H, d, J = 6.5 Hz, CH(OCH$_3$)$_2$), 4.54 (1H, d, J = 6.5 Hz, CHOH), 6.8 (1H, d, J = 8.8 Hz, ArH), 6.90 (2H, d, J = 8.9 Hz, ArH); ^{13}C NMR: δ; 54.9, 55.8, 56.0, 73.8, 107.7, 110.1, 110.8, 119.5, 131.9, 148.6, 148.8; IR (KBr); 3380.2, 3081.7, 2993.6, 2966.5, 2835.3, 1594.4, 1514.6, 1464.6, 1263.9, 812.0, 747.9 cm^{-1}; MS (m/z) (%); 242 (3.2), 179 (5.5), 167 (4.7), 165 (1.66), 151 (5.3), 139 (8.2), 124 (3.3), 121 (1.3), 108 (3), 79 (2.2), 75 (100), 65 (2.9), 49 (17.7), 47 (3.6).

4.34.19. 1-(3,4-Dimethoxyphenyl)-1,2,2-trimethoxy ethane $C_{13}H_{20}O_5$ 5c

White solid, mp 43 °C, ^{1}H NMR (200 MHz): δ; 3.22 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.88 (6H, s, OCH_3), 4.1 (1H, s, J = 6.1 Hz, CH(OCH$_3$)$_2$), 4.35 (1H, s, J = 6.1 Hz, CHOCH$_3$), 6.8–6.9 (3H, m, ArH); ^{13}C NMR: δ; 54.4, 55.6, 55.8, 55.9, 56.8, 83.5, 106.4, 110.4, 110.6, 120.6, 130.3, 148.7, 148.9; IR(KBr), 3529.3, 2936.7, 2832.5, 1594, 1516, 1464, 1261, 1108.5, 1028, 812.5, 752 cm^{-1}; MS (m/z) (%); 257 (1.70) (M$^+$+1), 226 (1.5), 182 (32.5), 181 (32), 166 (7.2), 165 (6.2), 151 (6.2), 135 (1.2), 121 (1.1), 107 (1.3), 95 (1.8), 75 (100).

4.34.20. α-Methoxy-2-(3,4-dimethoxyphenyl)acetaldehyde $C_{11}H_{14}O_4$ 6c

colourless liquid, ^{1}H NMR (200 MHz): δ; 3.43 (3H, s, OCH_3), 3.89 (6H, s, 2 × OCH_3), 4.60 (1H, d, J = 1.5 Hz, CHOCH$_3$), 6.85–6.97 (3H, m, ArH), 9.57 (1H, d, J = 1.6 Hz, CHO); ^{13}C NMR: δ; 55.2, 55.5, 56.9, 87.5, 110.3, 111.3, 120.1, 126.5, 148.9, 149.2, 197.5; IR (neat) NaCl; 3449.8, 2935.8, 2835.7, 1733, 1594.0, 1515.1, 1265.4, 1026.4, 811.5 cm^{-1}; MS (m/z) (%); 210 (2.3), 182 (9.2), 181 (100), 166 (31.7), 165 (21.1), 151 (14.3), 137 (5), 121 (2.5), 77 (7.9).

4.34.21. 2-Methoxy-2-(3,4-dimethoxyphenyl)ethanol $C_{11}H_{16}O_4$ 7c

White solid, mp 45 °C, ^{1}H NMR (200 MHz): δ; 3.30 (3H, s, OCH_3), 3.80 (6H, s, 2 × OCH_3), 3.63–3.71 (2H, m, CH_2OH), 4.25 (1H, dd, J = 4.2 Hz, 8.0 Hz, CHOMe), 6.84–6.86 (3H, m, ArH); ^{13}C NMR: δ; 54.1, 54.5, 55.1, 65.1, 82.1, 107.3, 108.8, 117.3, 128.6, 144.3, 146.9; IR (neat) NaCl; 3423.0, 2934.9, 2835.5, 1594.1, 1517.1, 1464.7, 1262.5, 1110.6, 1027.2, 812.6 cm^{-1}; MS (m/z) (%); 213 (4) (M$^+$+1), 212 (3.2), 183 (11.4), 182 (100), 167 (22), 166 (10.9), 151 (8.3), 137 (3.4), 95 (3.2).

4.34.22. α-Methoxy-2-(3,4-dimethoxyphenyl)acetic acid $C_{11}H_{14}O_5$ 9c

White solid, mp 92 °C, ^{1}H NMR (200 MHz): δ; 3.40 (3H, s, OCH_3), 3.87 (6H, s, OCH_3), 4.70 (1H, s, CHOCH$_3$), 6.85 (1H, d, J = 8.1 Hz, ArH), 6.90 (1H, d, J = 8.2 Hz, ArH), 7.01 (1H, s, ArH); ^{13}C NMR: δ; 56.3, 56.5, 57.6, 82.2, 110.1, 111.4, 120.6, 125.5, 146.4, 147.6, 177.2; IR (neat) NaCl, 3488.8, 2952.0, 2853.5, 1735.9, 1599.1, 1496.3, 1467.7, 1418.4, 1259.6, 1097.1, 803.0 cm^{-1}; MS (m/z); 226, 224, 194.8, 164.9.

4.34.23. 2-Methoxy-2-(3,4-dimethoxyphenyl)acetonitrile $C_{11}H_{13}O_3N$ 8c

Colourless liquid, ^{1}H NMR (200 MHz): δ; 3.52 (3H, s, OCH_3), 3.92 (6H, s, 2 × OCH_3), 5.14 (1H, s, CHOMe), 6.85 (1H, d, J = 8.2 Hz, ArH), 6.99–7.07 (2H, m, ArH); ^{13}C NMR: δ; 56.3, 56.4, 57.4, 72.5, 110.4, 111.4, 115.3, 120.6, 123.3, 149.2, 150.5; IR (neat) NaCl; 3081.0, 3003.7, 2605.7, 2226.2, 2863.7, 1751.6, 1715.4, 1596.4, 1518.0, 1464.4, 1420.8, 1262.1, 1082.9, 1052.0, 813.1, 783.2, 746.5 cm^{-1}; MS (m/z) (%); 208 (3.6) (M$^+$+1), 207 (27), 177 (13), 176 (100), 131 (6.9), 103 (5), 90 (8.1), 79 (6.8), 64 (15.4).

4.34.24. Acetic acid-2,2-dimethoxy-1-(3,4-dimethoxyphenyl)ethylester $C_{14}H_{20}O_6$ 4c

White solid, mp 98 °C, ^{1}H NMR (200 MHz): δ; 2.13 (3H, s, C(O)CH_3), 3.32 (3H, s, OCH_3), 3.44 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.54 (1H, d, J = 6.2 Hz, CH(OMe)$_2$), 5.78 (1H, d, J = 6.2 Hz, CHOAc), 6.86 (1H, d, J = 8.1 Hz, ArH), 6.90 (1H, d, J = 8.2 Hz, ArH), 7.0 (1H, s, ArH); ^{13}C NMR: δ; 21.3, 54.8, 55.5, 56.3, 56.8, 74.9, 104.9, 110.7, 110.9, 120.2, 129.2, 148.6, 148.9, 169.8; IR (KBr); 3082.7, 1734.1, 1593.2, 1519.4, 1192.9, 1237.1 cm^{-1}; MS (m/z) (%); 284 (1.1), 195 (.5), 180 (.3), 166 (.8), 165 (1.2), 151 (2.4), 125 (4), 121 (.5), 107 (.5), 75 (100).

4.34.25. α,α-Dibromomethyl-(3,4-methylenedioxyphenyl)-methanol $C_9H_8O_3Br_2$ 2d

Colourless liquid, ^{1}H NMR (200 MHz): δ; 2.94 (1H, d, *J* = 3.6 Hz, O*H*), 4.94 (1H, d, *J* = 5.2 Hz, C*H*Br$_2$), 5.7 (1H, d, *J* = 5.2 Hz, C*H*OH), 5.97 (2H, s, OC*H*$_2$O), 6.71–6.92 (3H, m, Ar*H*); ^{13}C NMR: δ; 52.6, 79.2, 101.7, 107.6, 108.6, 121.3, 131.7, 147.7, 147.9; IR (neat) NaCl; 3513.8, 3004.9, 2829.1, 1503.4, 1444.7, 1247.6, 1038.3, 932.6 cm^{-1}; MS (*m*/*z*) (%); 326 (15.4), 324 (30), 322 (14.9), 164 (16.4), 152 (100), 149 (15.4), 135 (34), 123 (31), 122 (12.8), 121 (22.9), 93 (100), 77 (38), 65 (100).

4.34.26. 2,2-Dimethoxy-1-(3,4-methylenedioxyphenyl)ethanol $C_{11}H_{14}O_5$ 3d

White solid, mp 55 °C, ^{1}H NMR (200 MHz): δ; 2.67 (1H, br s, O*H*), 3.29 (3H, s, OC*H*$_3$), 3.47 (3H, s, OC*H*$_3$), 4.25 (1H, d, *J* = 6.4 Hz, C*H*(OCH$_3$)$_2$), 4.52 (1H, d, *J* = 6.4 Hz, C*H*OH), 5.95 (2H, s, OC*H*$_2$O), 6.78 (1H, d, *J* = 7.9 Hz, Ar*H*), 6.88 (1H, d, *J* = 8.0 Hz, Ar*H*), 6.92 (1H, s, Ar*H*); ^{13}C NMR: δ; 55.3, 56.3, 74.2, 101.3, 107.9, 108.0, 108.4, 121.1, 133.7, 148.0, 148.5; IR (neat) NaCl; 3451.2, 2902.3, 2781.2, 1489.7, 1443.7, 1249.3, 1077.0, 929.0 cm^{-1}; MS (*m*/*z*) (%); 226 (15.5), 165 (4.7), 151 (15.2), 150 (8.7), 135 (28.3), 123 (5.3), 105 (5.3), 91 (4), 76 (100), 49 (100).

4.34.27. 1-(3,4-Methylenedioxyphenyl)-1,2,2-trimethoxy ethane $C_{12}H_{16}O_5$ 5d

Semi solid, ^{1}H NMR (200 MHz): δ; 3.24 (3H, s, OC*H*$_3$), 3.25 (3H, s, OC*H*$_3$), 3.45 (3H, s, OC*H*$_3$), 4.09 (1H, d, *J* = 6.1 Hz, C*H*(OMe)$_2$), 4.34 (1H, d, *J* = 6.1 Hz, C*H*OMe), 5.96 (2H, s, OC*H*$_2$O), 6.79–6.86 (3H, m, Ar*H*); ^{13}C NMR: δ; 54.8, 56.0, 57.1, 84.0, 101.4, 106.7, 108.3, 108.4, 122.1, 132.2, 148.2, 148.9; IR (neat) NaCl; 2934.0, 2900.1, 2830.7, 1488.6, 1442.6, 1243.1, 1108.3, 943.9 cm^{-1}; MS (*m*/*z*) (%); 240 (2.7), 209 (5), 178 (2.1), 165 (35.1), 166 (23.1), 121 (2.9), 75 (100), 77 (10).

4.34.28. α-Methoxy-(3,4-methylenedioxyphenyl)acetaldehyde $C_{10}H_{10}O_4$ 6d

Semisolid, ^{1}H NMR (200 MHz): δ; 3.42 (3H, s, OC*H*3), 4.54 (1H, s, C*H*OMe), 5.98 (2H, s, OC*H*$_2$O), 6.78–6.81 (3H, m, Ar*H*), 9.55 (1H, d, *J* = 1.0 Hz, C*H*O); ^{13}C NMR: δ; 57.4, 88.2, 101.7, 107.9, 108.7, 121.9, 127.8, 148.4, 148.8, 198.3; IR (neat) NaCl; 3448.3, 2901.9, 1735.0, 1487.8, 1246.7, 1037.9, 812.1 cm^{-1}; MS (*m*/*z*) (%); 194 (2.7), 167 (1.2), 166 (11), 165 (100), 150 (27.5), 149 (24.8), 133 (2.6), 121 (32), 119 (4.6), 79 (5.4), 77 (9.4), 64 (8.2).

4.34.29. 2-Methoxy-2-(3,4-methylenedioxyphenyl)ethanol $C_{10}H_{12}O_4$ 7d

White solid, mp 38 °C, ^{1}H NMR (200 MHz): δ; 2.33 (1H, br s, O*H*), 3.28 (3H, s, OC*H*$_3$), 3.41–3.60 (2H, m, C*H*$_2$OH), 4.21 (1H, dd, *J* = 4.4 Hz, 7.8 Hz, C*H*OMe), 5.90 (2H, s, OC*H*$_2$O), 6.72–6.81 (3H, m, Ar*H*); ^{13}C NMR: δ; 56.9, 67.5, 84.5, 101.3, 107.2, 108.5, 120.7, 132.4, 147.7, 148.1; IR (neat) NaCl; 3423.2, 2931.7, 2902.1, 1487.3, 1439.9, 1246.1, 1109.4, 1038.7, 930.0, 843.2 cm^{-1}; MS (*m*/*z*) (%); 196 (6.6), 166 (10.2), 165 (100), 150 (24), 149 (18.6), 119 (3.6), 107 (4.8), 77 (10.2), 64 (7.5), 55 (4.4), 46 (13.8), 45 (8.7).

4.34.30. α-Methoxy-(3,4-methylenedioxyphenyl)acetic acid $C_{10}H_{10}O_5$ 9d

White solid, mp 74 °C, ^{1}H NMR (200 MHz): δ; 3.40 (3H, s, OC*H*$_3$), 4.69 (1H, s, C*H*OMe), 5.97 (2H, s, OC*H*$_2$O), 6.78–6.93 (3H, m, Ar*H*); ^{13}C NMR: δ; 57.1, 81.7, 101.3, 107.4, 108.4, 121.4, 129.1, 148.1, 148.2, 174.2; IR (neat) NaCl; 3394.1, 2923.0, 1731.8, 1503.8, 1245.0, 1101.9, 1038.1 cm^{-1}; MS (*m*/*z*) (%); 208.6, 176.9, 121.

4.34.31. 2-Methoxy-2-(3,4-methylenedioxyphenyl)acetonitrile $C_{10}H_9O_3N$ 8d

Colourless liquid, ^{1}H NMR (200 MHz): δ; 3.50 (3H, s, OC*H*$_3$), 5.0 (1H, s, C*H*OMe), 6.01 (2H, s, OC*H*$_2$O), 6.81–6.98 (3H, m, Ar*H*); ^{13}C NMR: δ; 57.2, 72.2, 101.4, 107.9, 108.6, 117.2, 121.7, 127.2, 148.5, 149.1; IR (neat) NaCl; 3077.5, 3001.4, 2933.6, 2617.7, 2237.6, 504.6, 1489.2, 1446.9, 1253.5, 1080.9, 833.0, 810.2 cm^{-1}; MS (*m*/*z*) (%); 191 (32.6), 165 (16.6), 160 (99.5), 104 (10.4), 102 (15.5), 87 (23.7), 77 (13.8), 76 (14.8), 75 (27.9), 74 (45.2), 64 (18.8), 57 (19.5), 46 (100), 45 (95).

4.34.32. Acetic acid-2,2-dimethoxy-1-(3,4-methylenedioxyphenyl)ethyl ester $C_{13}H_{16}O_6$ 4d

White solid, mp 63 °C, ^{1}H NMR (200 MHz): δ; 2.03 (3H, s, OCOC*H*$_3$), 3.20 (3H, s, OC*H*$_3$), 3.31 (3H, s, OC*H*$_3$), 5.61 (1H, d, *J* = 6.1 Hz, C*H*OAc), 5.80 (2H, s, OC*H*$_2$O), 6.61–90 (3H, m, Ar*H*); ^{13}C NMR: δ; 21.5, 54.8, 55.8, 74.6, 101.5, 105.3, 109.4, 112.9, 122.1, 130.8, 147.4, 147.9, 170.1; IR (neat) NaCl; 2914.7, 2835.7, 1742.0, 1480.5, 1233.6, 1037.2 cm^{-1}; MS (*m*/*z*) (%); 268 (3.4), 209 (2.2), 178 (3.2), 147 (7.2), 133 (9.3), 121 (3.1), 77 (11.4), 76(100).

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24. (a) *Arthrobacter* sp. cell biomass was prepared in shake flasks and in 10 L fermentor-containing medium (1% peptone, and 0.5% NaCl and 0.5% beef

extract, pH 7.0). The medium was inoculated with an overnight preculture prepared in the same broth. The culture was grown at 30 °C for 16–18 h at 200 rpm. The cell pellet was separated from the broth by centrifugation at 10,000*g* for 15 min at 4 °C, and was preserved at −20 °C till further use. *Arthrobacter* sp. microbial culture (ABL, MTCC No. 5125), isolated at institute has been deposited in MTCC culture collection under Budapest Treaty (2004);

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