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A Concise Stereoselective Total Synthesis of Methoxyl Citreochlorols and Their Structural Revisions

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A concise, stereoselective and protecting group free approaches for the total synthesis of (−)-(2*S*,4*R*)- and (+)-(2*R*,4*S*)-3′-methoxyl citreochlorols and their stereoisomers are demonstrated. All four stereoisomers were synthesized to establish the absolute stereochemistry of the reported structures and the structures were revised accordingly. The approach involves chelation controlled regioselective reduction of a diester, silyl iodide promoted ring-opening iodo esterification of lactones, highly chemo- and regioselective ring-opening of an epoxy ester, dichloromethylation of a carboxyl group, and *syn*- and *anti*-selective reduction of the resulted β-hydroxy ketone as key steps.

Introduction

Halogen-containing small molecules are continually being isolated from nature and becoming very attractive day by day. These small molecules possess fascinating architectures and show exceptionally diverse biological activities.[1] Especially, chlorinated secondary metabolites display a range of biological activities like anticancer, antibiotic, antimalarial, anti-HIV, etc.[2] *Pencillium* based fungal metabolites are an excellent source of halogenated compounds, especially for chlorinated compounds. Exceptional class of organohalogens having *gem*-dichloromethyl and trichloromethyl functional groups have been isolated from several fungal sources.[3] Citreovirone[4] and citreochlorol[5] are a class of polyketides with geminal dichloromethyl moiety isolated from *Penicillium Citreoviride* B. In 2017, Yong's group isolated several aromatic polyketide moieties having *dichloromethide* functional group, namely 3′-methoxyl citreochlorol and their analogs from a fungal species *Penicillium Sp.* that grows on *Pinellia Ternata*.[6] Structures of citreochlorols (Figure 1) were established based on exhaustive NMR and mass spectral studies. The absolute stereochemistry was determined by $[Rh_2(OCOCF_3)_4]$-induced ECD experiments and NMR spectral analysis of their MTPA esters. Citreochlorols are moderately active against several human pathogenic microorganisms like *E.coli* and *S-aureus* (MIC 62.6 and 76.6 μg/ml).

We recently reported the first stereoselective total synthesis of (2*S*,4*R*)-3′-methoxyl citreochlorol **1** and its stereoisomer **3** using an auxiliary assisted aldol reaction strategy.[7] Careful analysis of Yong's report[6] illustrates that compounds **1** and **2** were isolated from the ethyl acetate extract of *Penicillium* species by a preparative HPLC technique on an achiral column. The reported structures of compounds **1** and **2** suggest that

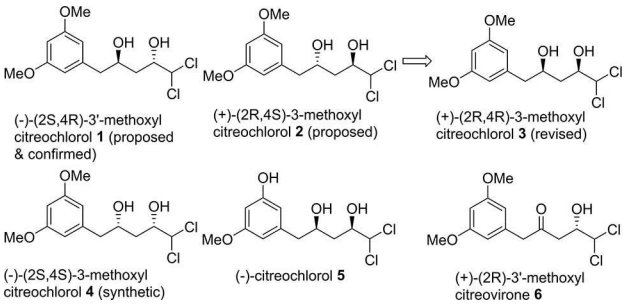

Figure 1. Representative structures of methoxyl citreochlorol and its analogs.

they are enantiomers and should possess identical spectral characteristics with opposite optical rotation signs. But the NMR spectral data and specific rotations of both the isomers show small variations and are not identical. Moreover, the absolute stereochemistry of **1** was confirmed by us using X-ray analysis, and it was identical with the reported structure **1** (Figure 2).[7] Whereas, the synthetic *syn*-diol[7] **3** showed identical spectral and optical rotation data as for the reported compound **2** which was proposed as an *anti*-diol. To gain more insights on the absolute stereochemistry of proposed structure **2**, we had decided to synthesize all the four stereoisomers of methoxyl citreochlorols (**1**, **2**, **3**, and **4**) to establish their absolute configuration.

In this article, we present a new synthetic approach that uses both *D*- and *L*-malic acids as chiral reagents to synthesize

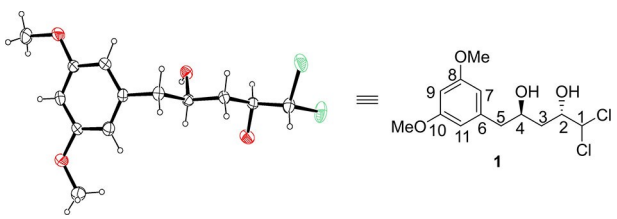

Figure 2. ORTEP structure of (2*S*, 4*R*)-3′-methoxy citreochlorol **1**.

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all the four isomers of compound **1**. Enantiomerically pure malic acids are commercial, economically viable, and are excellent chiral sources in total syntheses.[8] Accordingly, two identical synthetic routes were established, one from *L*-malic acid for the synthesis of compounds **1** and **3**, and the second from *D*-malic acid for the synthesis of **2** and **4**.

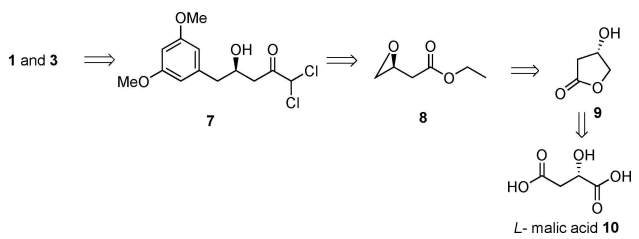
Results and Discussion

The retrosynthetic analysis of compounds **1** and **3** is given in Scheme 1. We hypothesized that both *syn*- and *anti*-diols of methoxyl citreochlorols could be obtained from a common key intermediate ketone **7** by selective reduction methods. Ketone **7** can be synthesized from epoxide **8** in two steps using regioselective ring opening of epoxide, with 3,5-dimethoxy phenylmagnesium bromide followed by dichloromethyl addition to the carboxyl group. Epoxide **8** in turn can be prepared from lactone **9** by ring-opening, haloesterification, and epoxidation methods. The lactone **9** can be easily prepared from commercial *L*-malic acid in three steps using esterification, regioselective reduction of the ester moiety followed by lactonization.

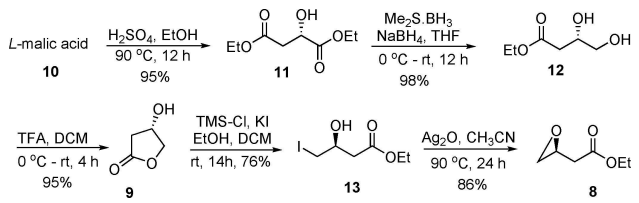
We started the synthesis aiming at the natural product **1** and its synthetic isomer **3** starting from *L*-malic acid (Scheme 2). *L*–Malic acid was first converted to its diester by refluxing it in ethanol in the presence of H_2SO_4 to provide **11** in 95% yield. Subsequently, diester **11** was subjected to chelation controlled regioselective reduction using borane in the presence of catalytic $NaBH_4$ to give diol **12** in 98% yield.[9] The diol was immediately treated with trifluoroacitic acid to obtain the lactone **9** as the sole product in 95% yield. The lactone was then subjected to a selective ring-opening reaction by the nucleophilic substitution and esterification method using a modified protocol.[10] When lactone **9** was treated with 2 equivalents of TMSCl, KI, and 2 equivalents of ethanol in dichloromethane it provided iodohydrin **13** in 76% yield.[11] The iodohydrin was then reacted with silver (I) oxide which gave the epoxide **8** in 86% yield.[12]

The epoxide **8** was then subjected to a chemoselective and regioselective ring-opening reaction with aryl magnesium bromide. A freshly generated 3,5-dimethoxyphenyl magnesium bromide reacted with epoxide **8** in the presence of copper(I) iodide to provide a highly regioselective ring-opening product **14** in 81% yield.[13] The ester **14** was then directly treated with dichloromethyl lithium, which is generated *in situ* from dichloromethane and a base (Table 1, entry 3) to provide dichloromethyl ketone **7** in 54% along with recovered ester (20%).[14,15] To improve the yield, ester **14** was converted to Weinreb amide **15** in 93% yield[7] which upon reaction with dichloromethyl lithium produced compound **7** in 58% yield along with recovered amide (24%) (Table 1, entry 6). Overall, the alternative method that uses two steps provided only 53% yield. Several other conditions to improve the yields were unsuccessful; hence we further proceeded with ester **14** to procure the intermediate **7** (Scheme 3).

The key intermediate **7** is equipped with the required carbon skeleton, including the dichloromethide group. The stereoselective reduction β-hydroxy ketone was conducted using both *syn*- and *anti*-selective protocols. At first, the ketone was subjected to *anti*-selective reduction using tetramethylammonium triacetoxyborohydride to provide the desired *anti*-diol, *i.e.* (2*S*,4*R*)-3′-methoxyl citreochlorol **1** in 96% yield along with its *syn*-diastereomer in 3%.[16] The synthetic compound **1** was found to be identical with the natural product **1**. The NMR spectral data and specific rotation are in good agreement with the reported values (Table 2). Also, the absolute configuration of synthetic compound **1** was established based on X-ray analysis (Figure 2).[7,17]



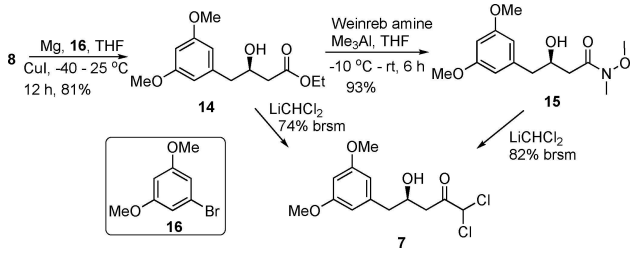
Scheme 1. Retrosynthetic analysis of methoxyl citreochlorols.



Scheme 2. Preparation of epoxy ester **8** from *L*-malic acid.

Table 1. Conditions for the addition of dichloromethyl lithium to ester and amide.

S. No.	Compound	Conditions	Yield [%]
1.	**14**	*n*-BuLi, CH_2Cl_2, THF : Hexane (1 : 1), −94 to −78 °C, 1 h	–
2.	**14**	LDA, CH_2Cl_2,THF,−78 °C, 1 h	41%
3.	**14**	Cy_2NLi, CH_2Cl_2, THF, −78 °C, 2 h	54%
4.	**15**	*n*-BuLi, CH_2Cl_2, THF, −78 °C, 2 h	–
5.	**15**	*n*-BuLi, CH_2Cl_2, THF: Et_2O : Hexane (4 : 1 : 1), −110 °C, 2 h	–
6.	**15**	Cy_2NLi, CH_2Cl_2, THF, −78 °C, 2 h	58%



Scheme 3. Preparation of key intermediate **7** from epoxide **8**.

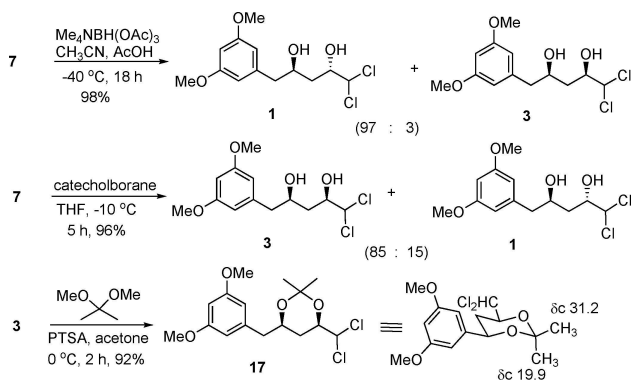
Similarly, a *syn*-selective reduction of ketone **7** in the presence of catechol borane provided a mixture of isomeric diols in 96% yield (Scheme 4).[18] The less polar diastereomer **3** was isolated in 82% yield showing lower chemical shift ($\delta_H = 5.69$ ppm) value for C_1-H proton and the more polar *anti*-isomer **1** was isolated in 14% with a higher chemical shift ($\delta_H = 5.76$ ppm) for C_1-H proton.[19] The *syn*-diol has identical δ_H-values (4.16 ppm) and *anti*-diol has different δ_H-values (4.16 and 4.27) for C_2 and C_4 methines. Similarly, two diastereotropic methylene protons at C_3 were clearly distinguishable in H-NMR, *syn*-diol showing two signals at 1.80 and 2.06 ppm and *anti*-diol gives a single multiplet at 1.88 ppm. Also, ^{13}C-NMR spectra of both *syn*- and *anti*-diols were differentiated only from the chemical shift values of C_2 and C_4 positions. While the *syn*-diol showed signals at δ_c 75.5 and 72.2, the *anti*-diol produced signals at δ_c 73.7 and 69.3 for C_2 and C_4. Though the absolute stereochemistry of *anti*-isomer **1** was confirmed using X-ray analysis, the stereochemistry of its corresponding *syn*-diastereomer **3** was further established by standard NMR methods. For that, the diol **3** was protected with acetonide group to obtain compound **17**. The ^{13}C-NMR of compound **17** showed well resolved signals for two methyl groups of acetonide which appeared at δ_c 19.9 and 31.2 ppm, clearly confirming the *syn*-relation of diol in compound **3**.[20] Unfortunately, selective deprotection of methoxy group of *syn*-diol **3** for the synthesis of citreochlorol **5** was unsuccessful under several reaction conditions.[7]

After careful analysis, it was confirmed that the spectral data of synthetic **3**, is completely matching with the reported natural product[6] (see Table 2). Hence, the stereochemistry of proposed structure **2** was reassigned as *syn*-diol **3**. To gain more insight regarding the absolute stereochemistry of the *anti*-isomer **2**, we decided to synthesize both the enantiomers of compounds **1** and **3** namely *anti*-isomer **2** and its corresponding diastereomer **4** from *D*-malic acid (Scheme 5).

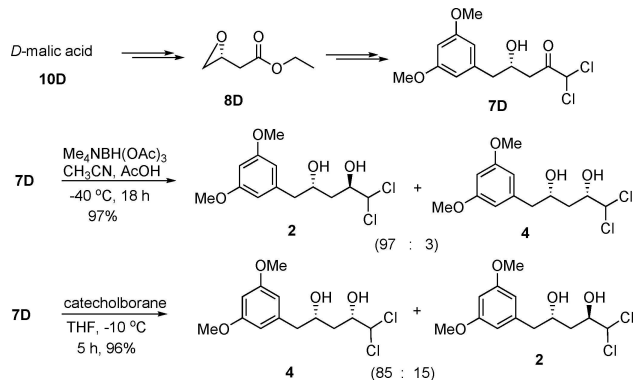
Our synthesis began with the conversion of *D*-malic acid **10D** to the key intermediate **7D** following similar synthetic protocols used for the preparation of compound **7**. Then compound **7D** was selectively reduced to diol **2** by treating it with tetramethylammonium triacetoxyborohydride to provide the desired *anti*-diol, i.e. (2*R*,4*S*)-3′-methoxyl citreochlorol **2** in 94% as the major isomer. The spectral data of compound **2** was not matching with the reported data for the natural product **2** but it exactly matched with the data of compound **1**, also showed opposite optical rotation. This clearly confirmed that compound **2** is an enantiomer of compound **1** and does not match with the isolated natural product. Likewise, the *syn*-selective reduction of **7D** with catecholborane provided *syn*-diol **4** in 82% yield along with *anti*-diol **2** in 14% yield. The NMR

Table 2. H-NMR and specific rotation of reported and synthetic methoxyl citreochlorols.

S. No	Reported **1** (−)-isomer (δ_H ppm)	Reported and revised (+)-isomer **3** (δ_H ppm)	Synthetic **1** (δ_H ppm)	Synthetic **3** (δ_H ppm)	Synthetic **2** (δ_H ppm)	Synthetic **4** (δ_H ppm)
C1	5.75 (d, 4.4)	5.72 (d, 4.0)	5.76 (d, 4.3)	5.69 (d, 4.2)	5.76 (d, 4.3)	5.69 (d, 4.2)
C2	4.25 (m)	4.17 (m)	4.26 (dd,5, 11.1)	4.15 (m)	4.26 (dd, 5, 11.1)	4.15 (m)
C3a	1.88 (m)	1.80 (m)	1.9 (m)	1.82 (m)	1.9 (m)	1.82 (m)
C3b	1.89 (m)	2.04 (m)	1.9 (m)	2.06 (m)	1.9 (m)	2.06 (m)
C4	4.17 (m)	4.12 (m)	4.18 (m)	4.15 (m)	4.18 (m)	4.15 (m)
C5a	2.67 (dd, 8.9, 13.4)	2.69 (dd, 4.4, 13.5),	2.67 (dd, 5, 11.1)	2.70 (dd, 9, 13.3)	2.67 (dd, 5, 11.1)	2.70 (dd, 9, 13.3)
C5b	2.81 (dd, 4.1, 13.4)	2.82 (dd, 8.5, 13.5)	2.80 (dd, 4, 13.4)	2.81 (dd, 3.9, 13.4)	2.80 (dd, 4, 13.4)	2.81 (dd, 3.9, 13.4)
C7	6.37 (br s)	6.36 (br s)	6.37 (br s)	6.37 (br s)	6.37 (br s)	6.37 (br s)
C8(OMe)	3.78 (s)	3.78 (s)	3.79 (s)	3.79 (s)	3.79 (s)	3.79 (s)
C9	6.36 (br s)	6.36 (br s)	6.37 (br s)	6.37 (br s)	6.37 (br s)	6.37 (br s)
C10(OMe)	3.78 (s)	3.78 (s)	3.79 (s)	3.79 (s)	3.79 (s)	3.79 (s)
C11	6.37 (br s)	6.36 (br s)	6.37 (br s)	6.37 (br s)	6.37 (br s)	6.37 (br s)
Specific Rotation:	$[\alpha]^{25}_D = -2.3$ (c 0.16, MeOH)	$[\alpha]^{25}_D = +4.6$ (c 0.13, MeOH)	$[\alpha]^{22}_D = -5.6$ (c 0.05, MeOH)	$[\alpha]^{22}_D = +4.6$ (c 0.16, MeOH)	$[\alpha]^{22}_D = +4.3$ (c 0.16, MeOH)	$[\alpha]^{22}_D = -6.0$ (c 0.05, MeOH)



Scheme 4. Preparation of methoxyl citreochlorols **1** and **3** from *L*-malic acid.



Scheme 5. Preparation of methoxyl citreochlorols **2** and **4** from *D*-malic acid.

spectral data of **4** was found to be in good agreement with compound **3** except for the opposite optical rotation.

From Table 2, it is clear that the spectral data of natural product **1** was identical to synthetic **1**, and natural product **3** (previously proposed as *anti*-isomer **2**)[6] was identical to synthetic *syn*-isomer **3**. The remaining two isomers obtained from *D*-malic acid, i.e., synthetic compounds **2** and **4**, are non-natural stereoisomers, and they are epimers of natural compounds **1** and **3**.

Conclusion

In conclusion, we have synthesized all the four stereoisomers of methoxyl citreochlorols from *L*- and *D*-malic acids. The absolute configuration of isolated compounds was established by comparing the spectral and optical rotation data of synthesized compounds. The structures of isolated natural products i.e. the (−)-methoxyl citreochlorol was confirmed as *anti*-diol **1**, and (+)-methoxyl citreochlorol was confirmed as *syn*-diol **3**. Both the compounds **1** and **3** (similarly **2** and **4**) were synthesized in a concise, and protecting group free manner from a chiral pool starting material. Lactone opening by halo esterification, chemo- and regioselective ring opening of epoxide, the addition of dichloromethyl lithium to amide, and *syn*- and *anti*-selective reduction of β-hydroxy ketone were used as crucial steps. The final product's overall yields after eight-step synthesis are obtained as 24.2% and 21.5% from commercially available malic acids.

Experimental Section

General Techniques: All the reactions utilizing air- or moisture-sensitive reagents were performed under an atmosphere of argon or nitrogen. Tetrahydrofuran (THF) and diethyl ether were double distilled from LAH, and dichloromethane (DCM) was distilled from CaH_2 before use. Pyridine and i-Pr_2NH were distilled from CaH_2 and dried over 4 Å molecular sieves. Commercially available reagents were used as received. Reactions using heating conditions were conducted in an oil bath. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel glass plates (60-F254) that were analyzed by fluorescence upon 254 nm irradiation or by staining with p-anisaldeyde/AcOH/H_2SO_4/EtOH, $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$/$H_2SO_4$. The products were purified by open chromatography on a silica gel (spherical, neutral, 100–230 μm) column. NMR spectra were recorded with an Avance III-500 (Bruker) (^{1}H: 500 MHz, ^{13}C{1H}: 125 MHz) or a 700 MHz (1H: 700 MHz, 13 C{1H}: 175 MHz) spectrometer and referenced to the solvent peak at 7.26 ppm (1H) and 77.00 ppm (13 C{1H}) for $CDCl_3$. Infrared spectra were recorded with a Bruker-Alpha (ATR-ZnSe) spectrometer and are reported as wavenumber (cm^{-1}). Single-crystal X-ray intensity data were collected on a Bruker KAPPA APEX-II diffractometer in omega and phi scan mode, Mo Kα = 0.71073 Å at 298 K. A Q-Exactive benchtop HRMS was used for the high-resolution mass analysis.

Preparation of diethyl (*S*)-2-hydroxysuccinate(11): To a stirred solution of *L*-malic acid (5 g, 37.2 mmol) in 40 mL ethanol was added concentrated sulphuric acid (4.38 g and 44.64 mmol) dropwise. The reaction mixture was stirred at reflux for 12 hours. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was diluted with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$, water and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum to give ester **11** (6.7 g, 95%) as colourless oil. $[\alpha]^D_{22} = -6.2$ (c 3, $CHCl_3$) $R_f = 0.6$ (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (t, J = 5,1H), 4.29 (q, J = 5, 2 H), 4.25 (q, J = 5, 2H), 2.87–2.76 (m, 2H), 2.47 (bs, 1 H), 1.31 (t, J = 5, 3H), 1.27 (t, J = 5, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 170.5, 67.3, 62.1, 61.0, 38.7, 14.1; IR (neat, cm^{-1}): 3396, 2971, 1779, 1450, 1378, 1296, 1179, 1050; HRMS (ESI-quadrupole) m/z: $[M+Na]^+$ Calcd for $C_8H_{14}O_5Na$ 213.1829; Found 213.0734.

Compound **11D** obtained in 95% yield as a colorless oil. $[\alpha]^D_{22} = +5.9$ (c 3, $CHCl_3$)

Preparation of ethyl (*R*)-3,4-dihydroxybutanoate (12): To a stirred solution of malate ester **11** (5.8 g, 35.8 mmol) in THF (40 mL) was added borane dimethyl sulfide (3.4 mL, 35.8 mmol) drop wise. After 1 hour the reaction mixture was cooled to 0 °C and added $NaBH_4$ (0.135 g, 3.58 mmol). The reaction mixture was continued to stir at room temperature for 12 hours. Completion of the reaction was confirmed by TLC analysis. The reaction mixture was carefully treated with MeOH at 0 °C. The solvents were evaporated under vacuum and the residue was purified by column chromatography (Silica gel, EtOAc:hexane 1.5:1) to afford the product **12** (5.2 g, 98%) as colorless oil. $[\alpha]^D_{22} = -22.3$ (c 2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (q, J = 5 Hz, 2H), 4.13–4.10 (m, 1H), 3.66 (dd, J = 5, 15 Hz, 1 H), 3.52 (dd, J = 5, 10 Hz, 1H), 2.87 (bs, 2H), 2.60–2.46 (m, 2H) 1.26 (t, J = 10 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 68.6, 65.7, 60.9, 37.6, 14.1; IR (neat, cm^{-1}): 3346, 2972, 1745, 1447, 1375, 1282, 1177, 1052. HRMS (ESI-quadrupole) m/z: $[M+Na]^+$ Calcd for $C_6H_{12}O_4Na$ 171.0736; Found 171.0628.

Compound **12d** obtained in 98% as colourless oil: $[\alpha]^D_{22} = +28.4$ (c 1.2, $CHCl_3$).

Preparation of 3-(*S*)-hydroxy-4-butanolide (9): To a stirred solution of diol **12** (3 g, 20.2 mmol) in CH_2Cl_2 (30 mL) was added trifluoroacetic acid (0.6 mL, 7.08 mmol) at 0 °C. The reaction mixture was stirred at 25 °C and the reaction progress was closely monitored by TLC. Once the starting material disappeared, solvents were removed under reduced pressure and the residue was purified by column chromatography (Silica gel, EtOAc: hexane 1:1) to afford the product **9** (1.95 g, 95%) as colorless oil. $[\alpha]^D_{22} = -66.6$ (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68–4.66 (m, 1H), 4.43–4.39 (m, 1H), 4.29 (d, J = 10 Hz, 1H), 2.77–2.72(m, 1H), 2.52 (d, 15 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 76.1, 67.5, 37.8; IR (neat, cm^{-1}): 3363, 2980, 1786, 1379, 1191, 1093, 998; HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_4H_7O_3$ 103.0317; Found 103.0392.

Compound **9d** obtained in 98% yield as colourless oil: $[\alpha]^D_{22} = +63.2$ (c 1, $CHCl_3$).

Prepration of ethyl 3-(*S*)-hydroxy-4-iodobutanoate (13)[22]: To a stirred suspension of potassium iodide (9.76 g, 58.8 mmol) in DCM (20 ml) was added TMS-Cl (7.5 ml, 58.8 mmol) drop wise at 0 °C. The suspension was warmed to 25 °C for 30 minutes until a dark brown colour solution formed. Lactone **9** (3 g, 29.4 mmol) and absolute EtOH (5.12 ml, 88.2 mmol) in CH_2Cl_2 (20 ml) was added to reaction mixture drop wise manner. The reaction was continued overnight at 25 °C and the completion of the reaction was confirmed by TLC. The solvents were removed under reduced pressure and the residue was dissolved in diethyl ether (30 mL). The organic layer was washed with 5% aqueous $Na_2S_2O_3$ solution (3×10 mL), water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc = 5:1 to 3:1) to afford the product **13** (5.5 g, 76%) as pale yellow oil. $[\alpha]^D_{22} = -10.5$ (c 1, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.18 (q, J = 8.0 Hz, 2H), 4.02–3.97 (m, 1H), 3.35–3.27 (m, 2H), 3.22–3.19 (m, 1H), 2.69–2.57 (m, 2H), 1.27 (t, J = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6, 67.4, 60.9, 40.7, 14.0, 12.1; IR (neat, cm^{-1}): 3346, 2974, 1740, 1424, 1381, 1306, 1200,

1085; HRMS (ESI-quadrupole) m/z: $[M+Na]^+$ Calcd for $C_6H_{11}IO_3Na$ 280.9753; Found 280.9644.

Compound **13D** obtained in 76% as pale yellow colour: $[\alpha]^D_{22} = +10.2$ (c 1, $CHC1_3$).

Preparation of ethyl (*S*)-3,4-epoxybutanoate (8): To a stirred solution of iodo compound **13** (700 mg, 2.86 mmol) in acetonitrile (15 ml) was added Ag_2O (800 mg, 3.44 mmol) at 25 °C. The reaction was continued for 24 h and the completion of the reaction was confirmed by TLC analysis. The solids were filtered off though a pad of celite, the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (Silica gel, hexane/ether = 5:1 to 4:1) to afford epoxy ester **8** (320 mg, 86%) as colorless oil. $[\alpha]^D_{22} = -8.4$ (c 0.5, $CHC1_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.19 (q, *J* = 10 Hz, 2H), 3.30–3.27 (m, 1H), 2.84 (t, *J* = 5 Hz, 1H), 2.57–2.54 (m, 3H), 1.28 (t, *J* = 10 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ: 170.4, 60.9, 48.0, 46.7, 38.1, 14.2; IR (neat, cm^{-1}): 2941, 1746, 1467, 1380, 1270, 1193, 1042, 974; HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_6H_{11}O_3$ 131.1630; Found 131.0702.

Compound **8D** obtained in 76% as colourless oil: $[\alpha]^D_{22} = +9.1$ (c 1, $CHC1_3$).

Praparation of ethyl (*R*)-4-(3,5-dimethoxyphenyl)-3-hydroxybutanoate (14): To a stirred suspension of Mg (923 mg, 38 mmol) in Et_2O (10 ml) under N_2 atmosphere was added dimethoxy bromobenzene (4.16 g, 19.21 mmol) in Et_2O (10 ml) dropwise manner at 40 °C. After 2 h the reaction mixture was allowed cool to room temperature. The Grignard solution was then added to a stirred suspension of CuI (724 mg, 3.8 mmol) in THF at −40 °C. After 30 min a solution of epoxide **8** (500 mg, 3.8 mmol) was added in THF (5 ml) dropwise over 1 h using syringe pump at same temperature. The reaction mixture was slowly warmed to room temperature and stirred for 12 h. Completion of the reaction was confirmed by TLC analysis. The reaction mixture was carefully treated with saturated ammonium chloride solution at 0 °C. The residue was extracted with EtOAC (20 ml × 3), the combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude compound was purified by column chromatography (silica gel; petroleum ether/ethyl acetate (8:2) to afford the ester **14** (825 mg, 81%). $[\alpha]^D_{20}$ −4.6 (c 0.5, $CHCl_3$), ^{1}H NMR(500 MHz, $CDCl_3$) δ: 6.33 (d, *J* = 2.2 Hz, 2H) 6.29 (t, *J* = 4.3 Hz,1H), 4.25–4.20 (m, 1H), 4.18–4.14 (m, 1H), 3.77 (s, 6H), 2.80 (dd, *J* = 7.15, 13.5 Hz, 1H), 2.68 (dd, *J* = 6.15, 13.5 Hz, 1H), 2.49 (dd, *J* = 3.55, 16.35 Hz, 1H), 2.41 (dd, *J* = 8.7, 16.4 Hz, 1H), 1.28 (t, J = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.7, 160.9, 139.9, 107.4, 98.6, 68.9, 60.7, 55.2, 43.2, 40.5, 14.1; IR (neat, cm^{-1}): 3433, 2940, 1723, 1595, 1460, 1295, 1149, 1058, 834: HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{14}H_{21}O_5$ 269.1389; Found 269.1375.

Compound **14D** obtained in 81% as pale yellow colour oil: $[\alpha]^D_{22} = +5.2$ (c 1, $CHC1_3$).

Preparatio of (*R*)-4-(3,5-Dimethoxyphenyl)-3-hydroxy-*N*-methoxy-*N*-methylbutanamide (15): To a stirred suspension of MeONH-Me·HCl (180 mg, 1.85 mmol) in THF (5 mL) at −10 °C was added a solution of $AlMe_3$ (2 M solution, 0.93 mL, 1.85 mmol) over a 15 min period. The reaction mixture was stirred at room temperature for 45 min, then a solution of ester **14** (200 mg, 0.74 mmol) in THF (10 mL) was added, and the resulting mixture was stirred at room temperature for 2 h. Completion of the reaction was confirmed by TLC, and the reaction was treated carefully with saturated NH_4Cl solution (5 mL) followed by addition of EtOAc (10 mL) and saturated solution of Rochelle salt (5 mL). The resulting mixture was stirred until formation clear solution (3 h). The organic layer was separated, and the aqueous phase was extracted with EtOAc (2× 10 mL). The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude compound was purified by column chromatography to obtain the amide **15** (195 mg, 93%) as a light yellow oil. $[\alpha]^D_{22}$ −29 (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (d, J = 1.45 Hz, 2H), 6.31 (d, J = 2.1 Hz, 1H), 4.30–4.25 (m, 1H), 3.75 (s, 6H), 3.6 (s, 3H), 3.15 (s, 3H), 2.84 (dd, J = 7.1, 13.5 Hz, 1H), 2.71–2.55 (m, 2H), 2.51 (dd, J = 8.8, 16.4 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 173.5, 160.8, 140.5, 107.3, 98.5, 68.9, 61.2, 55.2, 43.2, 37.4, 31.8; IR (neat, cm − 1): 2926, 2853, 1644, 1599, 1464, 1389, 1294, 1205, 1153, 1067, 995. HRMS (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{14}H_{22}NO_5$ 284.1497; Found 284.1492.

Compound **15D** obtained in 93% yield as pale yellow colour oil: $[\alpha]^D_{22} = +23.7$ (c 0.5, $CHC1_3$).

Preparation of (*R*)-1,1-Dichloro-5-(3,5-dimethoxyphenyl)-4-hydroxypentan-2-one (7): To a stirred solution of ester **14** (400 mg, 1.49 mmol) in CH_2Cl_2 (0.5 mL) and THF (10 mL) at −78 °C under a N_2 atmosphere was added lithium dicyclohexylamide in THF (generated by treating *n*-BuLi (21 mL, 0.7 M, 14.9 mmol) and dicyclohexylamine (3 mL, 14.9 mmol) in THF at 0 °C for 15 min) slowly over 1 h using a syringe pump. The reaction mixture was stirred for additional 1 h, and completion of the reaction was confirmed by TLC. The reaction mixture was treated with saturated NH_4Cl solution. The organic layer was separated, the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water, 2 N oxalic acid, brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, 10% EtOAc/hexane) to give **7** (251 mg, 54%) as a colorless oil along with recovery of the starting ester (53 mg, 13%). $R_f = 0.6$ (30% EtOAc in petroleum ether); $[\alpha]^D_{20}$ −7.0 (c 0.1, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.39–6.36 (m, 3H), 5.88 (s, 1H), 4.39–4.33 (m, 1H), 3.78 (s, 6H), 3.05–2.96 (m, 2H), 2.77 (d, *J* = 6.3 Hz, 2H). ^{13}C{1H} NMR (175 MHz, $CDCl_3$) δ 196.4, 161.0, 139.5, 107.4, 98.8 70.0, 68.6, 55.3, 43.4, 41.8, ; IR (neat): 2926, 2853, 1734, 1653, 1597, 1449, 1205, 1152, 1070, 994 cm^{-1}. (ESI-quadrupole) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}O_4C_{l2}$ 307.0503; Found 307.0498.

Compound **7D** obtained in 58% as colourless oil: $[\alpha]^D_{20}$ +5.88 (c 1.02, $CHCl_3$)

Preparation of (2*S*,4*R*)-1,1-Dichloro-5-(3,5-dimethoxyphenyl) pentane-2,4-diol (1): To a stirred solution of tetramethylammonium triacetoxyborohydride (40 mg, 0.15 mmol) in acetonitrile (0.3 mL) and anhydrous acetic acid (0.3 mL) at −40 °C was added ketone **7** (10 mg, 0.0326 mmol) in acetonitrile (0.2 mL). The reaction mixture was stirred for 18 h, and completion of the reaction was confirmed by TLC. The reaction mixture was treated carefully with 0.5 N aqueous sodium potassium tartrate solution (1 mL). The product was extracted with DCM (3 × 5 mL), and the combined organic layers were washed with H_2O, sat. $NaHCO_3$ solution, and brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to give 3′-methoxyl citreochlorol **1** (9.6 mg, 96%) as white needles along with the syn-isomer **3** (0.3 mg, 2%) (1H NMR of crude shows dr = 97:3). $R_f = 0.4$ (30% EtOAc in petroleum ether); $[\alpha]^D_{25}$ −5.6 (c 0.05, MeOH); ^{1}H NMR(500 MHz, $CDCl_3$) δ 6.37 (s, 3H), 5.76 (d, *J* = 4.3 Hz, 1H), 4.26 (dd, J = 5, 11.1 Hz, 1H), 4.21–4.16 (m, 1H), 3.79 (s, 6H), 2.82 (dd, *J* = 4, 13.4 Hz, 1H), 2.67 (dd, *J* = 9, 13.4 Hz, 1H), 2.19 (bs, 2H), 1.9 (t, *J* = 5 Hz, 2H). ^{13}C{1H} NMR (125 MHz, $CDCl_3 + CCl_4$) δ 161.1, 139.9, 107.3, 98.8, 76.5, 73.7, 69.3, 55.3, 44.4, 38.2; IR (neat): 3424, 2926, 1601, 1463, 1295, 1204, 1155, 1071, 837, 780; HRMS (ESI-quadrupole) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{18}O_4C_{l2}Na$ 331.0479; Found 331.0471.

Compound **2** obtained in 85% yield (9.9 mg) as colorless oil.: $[\alpha]^D_{22}$ +4.6 (0.16, MeOH)

Preparation of (2*S*,4*S*)-1,1-Dichloro-5-(3,5-dimethoxyphenyl) pentane-2,4-diol 3: To a stirred solution of **7** (10 mg, 0.033 mmol) in THF (0.5 mL) at −10 °C was added catecholborane (0.021 mL, 0.195 mmol). The reaction mixture was stirred for 5 h, and

completion of the reaction was confirmed by TLC. The reaction mixture was treated carefully with MeOH (0.2 mL) and 0.5 N aqueous sodium potassium tartrate solution (0.2 mL). The product was extracted with EtOAc (3×5 mL), and the combined organic layers were washed with 2 N NaOH (2 mL×3), water, brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum to give 3′-methoxyl citreochlorol **3** (8.6 mg, 85%) as a colorless oil with along with the anti-isomer **1** (1 mg, 9.7%) dr. R_f=0.4 (30% EtOAc in petroleum ether); $[\alpha]^{D}_{22}$+4.3 (c 0.16, MeOH); ^{1}H NMR (500 MHz,$CDCl_3$) δ 6.37 (bs, 1H), 5.71 (d, *J*=4.2 Hz, 1H), 4.17−4.14 (m, 1H), 3.79 (s, 6H), 2.81 (dd, *J*=3.9, 13.4 Hz, 1H), 2.70 (dd, *J*=9, 13.3 Hz, 1H), 2.66−2.45 (bm, 2H), 2.06 (d, *J*=14.5 Hz, 1H), 1.86–1.79 (m, 1H); ^{13}C{1H} NMR (125 MHz, $CDCl_3+CCl_4$) δ 161.1, 139.5, 107.4, 98.8, 76.3, 75.5, 72.2, 55.3, 44.7, 37.1; IR (neat): 3424, 2926, 1601, 1464, 1296, 1204, 1155, 1071, 837, 780: HRMS (ESI-quadrupole) m/z: $[M+Na]^+$ Calcd for $C_{13}H_{18}O_4C_{l2}Na$ 331.0479; Found 331.0471.

Compound **4** obtained in 85% yield (9 mg) as yellow oil. $[\alpha]^{D}_{22}$-6.00 (c 0.05, MeOH).

Preparation of (2*S*,4*S*)-1,1-Dichloro-6-(3,5-dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane 17: To a stirred solution of **3** (50 mg, 0.16) in acetone (2 mL) at 0 °C was added PTSA (5 mg) and 2,2-Dimethoxy propane (0.5 mL). The reaction mixture was stirred for 1 h at rt, and completion of the reaction was confirmed by TLC. Solid K_2CO_3 (0.5 g) was added and the solids were removed by filtration and washed with ethyl acetate (2×5 mL). The filtrate was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography to give **17** (48 mg, 81%) a light yellow color oil. R_f=0.8 (30% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3+CCl_4$) δ 6.35 (d, 5 Hz, 2H), 6.31 (s, 1H), 5.53 (d, *J*=5 Hz, 1H), 4.07–4.03 (m, 2H), 3.78 (s, 6H), 2.89 (dd, *J*=5, 10 Hz, 1H), 2.61 (dd, *J*=5, 10 Hz, 1H), 1.80–1.86 (m, 1H), 1.45 (s, 6H), 1.43−1.35 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3+CCl_4$) δ 160.7, 139.7, 107.5, 99.6, 98.4, 73.9, 73.7, 69.5, 55.2, 43.1, 31.2, 29.9, 19.9; IR (neat): 2950, 1606, 1470, 1210, 1118, 1075, 839, 766: HRMS (ESI-quadrupole) m/z: 349.0973 $[M+H]^+$ Calcd for $C_{16}H_{23}O_4Cl_2$; Found 349.0969.

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Conflict of Interest

The authors declare no conflict of interest.

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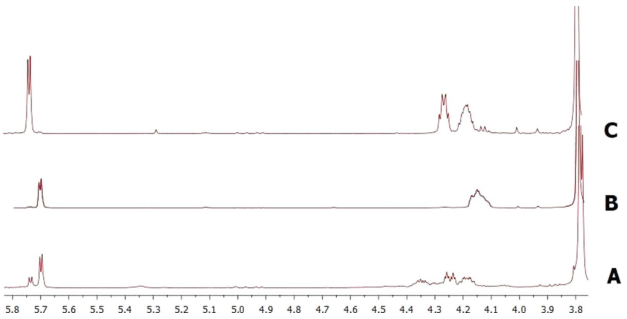

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