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The first total synthesis of neohelmanticins A–D, amino derivatives of the 1,2-dihydroxypropane core and biological evaluation

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ABSTRACT

A concise total synthesis of neohelmanticins A–D has been accomplished in 15 steps starting from commercially available gallic acid. Swern oxidation conditions, a Grignard reaction, Sharpless kinetic resolution, and regioselective ring opening of an epoxide with lithium aluminum hydride (LAH) are the key features to install the basic core, dihydroxy phenyl propane **2**. One hydroxyl group of this core was esterified with tiglic acid followed by the oxidation and esterification with corresponding acids to yield neohelmanticins A–D.

1. Introduction

Bioactive natural products continue to be a source of inspiration for chemical biology and medicinal chemistry research.[1] Neohelmanticins A–D (Fig. 1) are an architecturally novel group of highly oxygenated phenyl propanoid class of compounds isolated from the European medicinal plant *Tapsia garganica* (umbelliferaceae) by Liu et al. in 2006 (Fig. 1).[2] The structure and absolute configuration of the neohelmanticins were established on the basis of spectroscopic data as well as on degradation experiments. These compounds have shown significant cytotoxic activity against leukemia (EL_4), carcinoma (S180), and MCF_7 cell lines, respectively. Neohelmanticins share a common phenyl propanoid core attached to different esters; the common phenyl propanoid core contains two stereogenic centers, a phenyl ring, and an angelate moiety. Due to their remarkable anticancer activity and scarce availability from the natural sources, the neohelmanticins have become attractive synthetic targets. As a part of our synthetic studies on biologically important natural products,[3] we were attracted to the neohelmanticins on the basis of their cytotoxic activity and as potential small molecule leads for the development of new therapeutics. Herein, we report efficient total synthesis of neohelmanticins A–D by utilizing the Swern oxidation, a Grignard reaction, and Sharpless kinetic resolution as key steps. In addition, we also prepared a series of dihydroxy phenyl propanoid analogues by introducing the various amines and assessed them for their cytotoxic activity. To the best of our knowledge this is the first report on the synthesis of neohelmanticins.

2. Results and discussion

2.1. Chemistry

2.1.1. Retrosynthetic analysis of neohelmanticins A–D

As outlined in Scheme 1, we envisioned retrosynthetically that all the neohelmanticins can be obtained via esterification of the corresponding acids (angelic acid for **1a**, octanoic acid for **1b**, hexanoic acid for **1c,** and butanoic acid for **1d**) with alcohol **3**. Compound **3** could in turn be obtained from the epoxide **4** via the regioselective ring opening of an epoxide, esterification with tiglic acid followed by asymmetric dihydroxylation. Further disconnection of epoxide **4** led to secondary alcohol **5**, which itself could be constructed via the addition of vinyl Grignard to the aldehyde **11**. The aldehyde **11** (Scheme 2) may be accessible from commercially available gallic acid **6** in a five-step sequence.

2.1.2. Synthesis of basic core of the neohelmanticins A–D

According to this retrosynthetic analysis, the preliminary experiments for the synthesis of the phenyl propanoid core are depicted in Scheme 2. The synthesis began with gallic acid **6**, which was converted to its methyl ester **7** in 90% yield through reaction with thionyl chloride ($SOCl_2$) refluxing in MeOH. Methylenation[4] of **7** in the presence of CuO furnished **8**, which was further converted into methyl ether **9** in the presence of dimethyl sulfate.[5] Reduction of **9** with lithium aluminum hydride, followed by Swern oxidation[6] afforded aldehyde **11**. The Grignard reaction of **11** by the addition of vinyl magnesium bromide in THF afforded secondary alcohol **5** as a racemic mixture in excellent yield (98%). The Sharpless kinetic

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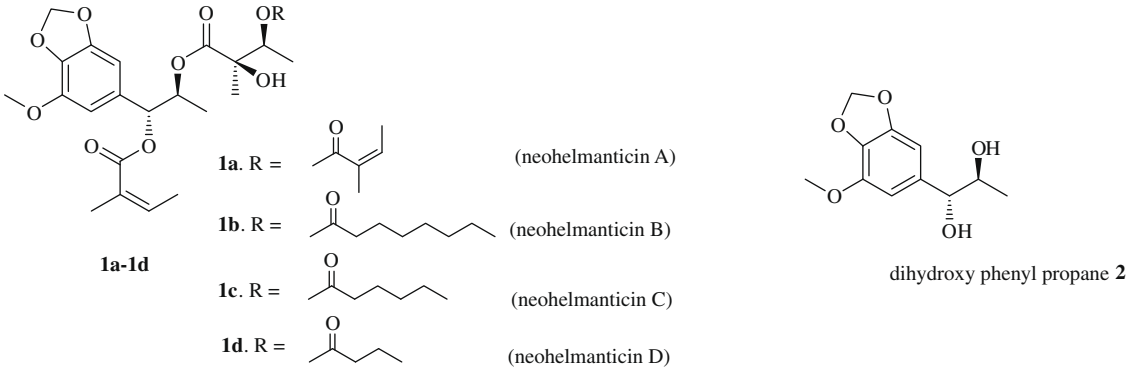


Figure 1. Chemical structures of neohelmanticins A–D and dihydroxyphenyl propane.

resolution[7] of this racemic mixture of secondary alcohol **5** with cumene hydroperoxide in the presence of titanium isopropoxide and (−)-DIPT in DCM at −20 °C furnished **12** (48%) and epoxide **4** (47%) with 99% ee. The stereochemistry of the compounds **12** and **4** was established by 2D NMR spectroscopy. Finally, ring opening of epoxide **4** with LAH[8] in THF afforded the basic phenylpropanoid core **2** (dihydroxyphenyl propane) of the neohelmanticins.

2.1.3. Synthesis of neohelmanticins A–D

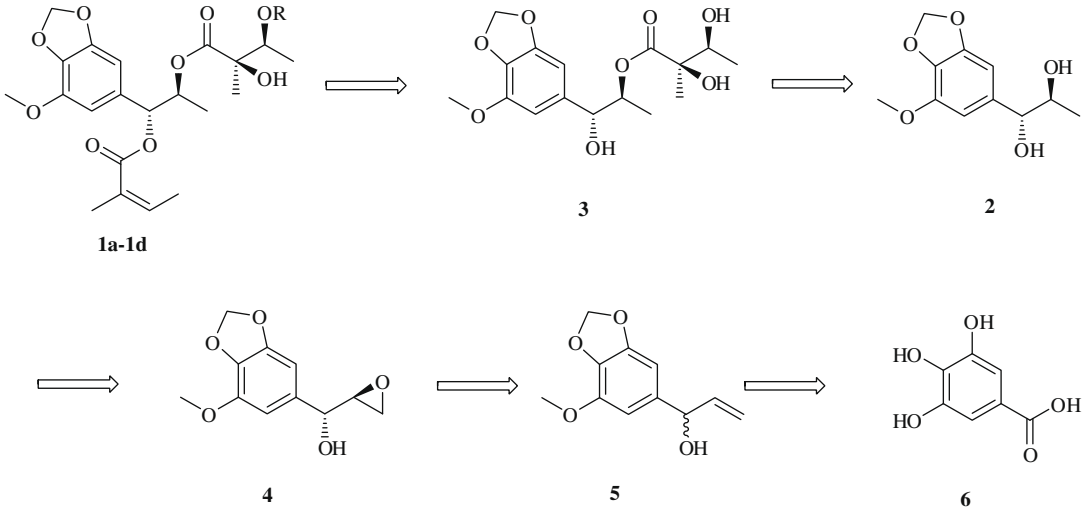
The synthesis of neohelmanticins A–D commenced from epoxide **4**, in which the hydroxyl group was protected as a THP ether,[9] and the resultant epoxy THP ether **13** was subjected to ring opening with LAH[8] to furnish **14**, in an overall yield of 91% (Scheme 3). Compound **14** was converted to tiglate ester **15** through reaction with tiglic acid in the presence of EDCI and DMAP in pyridine[10] in 90% yield. Upon treatment of **15** with AD-mix-α in (1:1) aqueous *t*-BuOH at 2–5 °C, highly stereoselective dihydroxylation[2] occurred to give the *threo* isomer diol **16** in 97% yield, which was further esterified with the corresponding acid derivatives in the presence of EDCI and DMAP in pyridine[10] to afford **17a–17d** in quantitative yield. Finally, deprotection of the THP group,[11] followed by the esterification with angelic acid afforded the neohelmanticins A–D, **1a–1d**.[12]

2.1.4. Synthesis of 1,2-dihydroxyphenyl propanoid derivatives

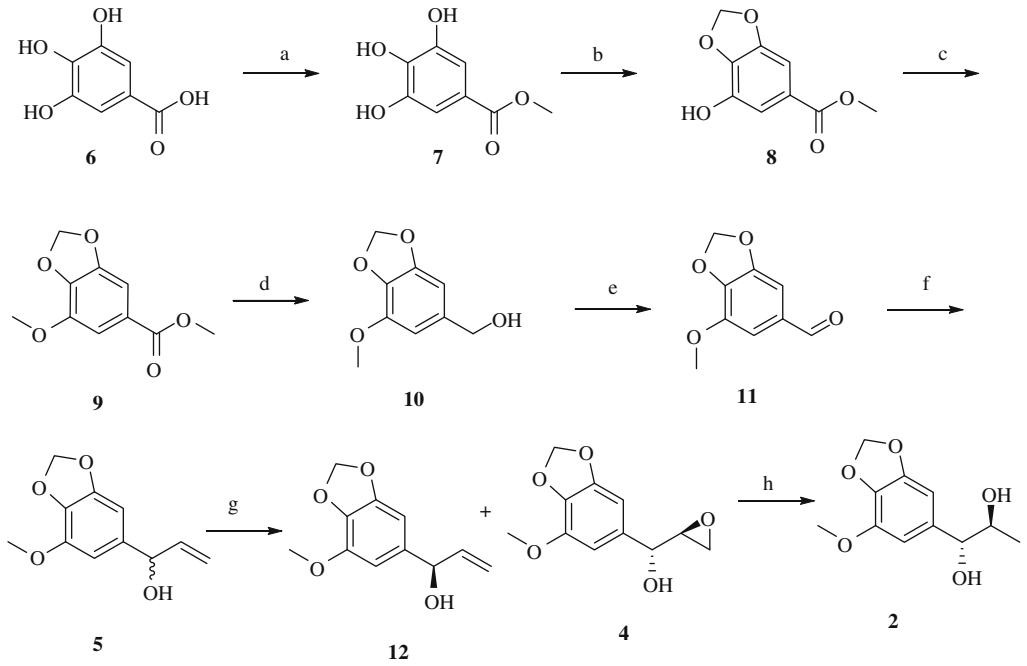
In prior studies, it has been reported that the neohelmanticins could increase their cytotoxic activity in comparison with their biogenetic precursor, 1,2-dihydroxy propane derivative **2**. However, except for neohelmanticin A, other compounds are equal or less potent than **2**[2] (di hydroxyl phenyl propane). Further, in order to improve the activity of 1,2-dihydroxy propane, we planned for the synthesis of 1,2-dihydroxy propane derivatives and for an investigation of their structure activity relationships (SARs). Therefore, we initially focused our attention to introduce the amine functionality and synthesis of the derivatives as illustrated in Scheme 4. It is well known that introduction of NH functionality into organic molecules can often dramatically change their physical and chemical properties.[13] In addition, extension and branching of the hydrocarbon chain may affect their bioactivity. Thus, we synthesized a series of (1*R*,2*S*)-3-(substituted amino)-1-(4-methoxybenzo[*a*][1,3]dioxol-6-yl) propan-1,2-diol[14] derivatives **19–27** by introducing the aliphatic amines, aromatic amines, and heteroaromatic amines, respectively.

3. Biological activity

All of the synthesized derivatives were tested in vitro against a panel of cancer cell lines. The cell lines used for this study are the colon cancer (colo-205), skin cancer (A-431), breast cancer (MCF-7), and lung cancer (A-549).[15] To our disappointment, introduction of the amine moiety at C-9 was not a good site to modify since none of the derivatives showed any activity. The lack of activity of synthetic derivatives cannot be explained simply by reaction mechanism. The binding affinity or selectivity of the structures of



Scheme 1. Retrosynthetic analysis of neohelmanticins A–D.



Scheme 2. Reagents and conditions: (a) $SOCl_2$, CH_3OH, reflux, 2–4 h, 90%; (b) K_2CO_3, CuO, CH_2I_2, DMF, 130 °C, 5 h, 60%; (c) $(CH_3)_2SO_4$, NaOH, EtOH, reflux, 5 h, 87%; (d) LAH, THF, 0 °C to 30 °C, 30 min, 96%; (e) $(CO)_2Cl_2$, DMSO, TEA, DCM, −78 °C, 1 h, 96%; (f) $CH_2CHMgBr$, THF, 0 °C to rt, 15 min, 98%; (g) (−)-DIPT 0.6 equiv, $Ti(OiPr)_4$ 0.5 equiv, cumene hydroperoxide, 0.6 equiv, DCM, −20 °C, 12 h, **4** (47%), **12** (48%); (h) LAH, THF, 0 °C to rt, 3 h, 92%.

the compounds to the reactive site of the target (enzyme) must play a key role. At this point, it may be that the esterification of the hydroxyl groups remains the optimum functional group to exhibit activity. These early conclusions point the way for further more focused studies aiming at the design and synthesis of the more potent and selective analogues as biological tools and potential drug candidates.

4. Conclusion

In conclusion, we have described first total synthesis of neohelmanticins A–D comprising the construction of the dihydroxyphenyl propane core **2** and esterification with the appropriate acids of the core skeleton of the neohelmanticins. In addition, we also demonstrated the synthesis and biological evaluation of dihydroxy phenyl propane derivatives **19–27**. Although compounds with improved cytotoxic activity have not yet been found, this laid a solid foundation for the further lead optimization of the derivatives by the systematic modifications. Efforts aimed to prepare the potent analogues are underway in our group.

5. Experimental

5.1. General

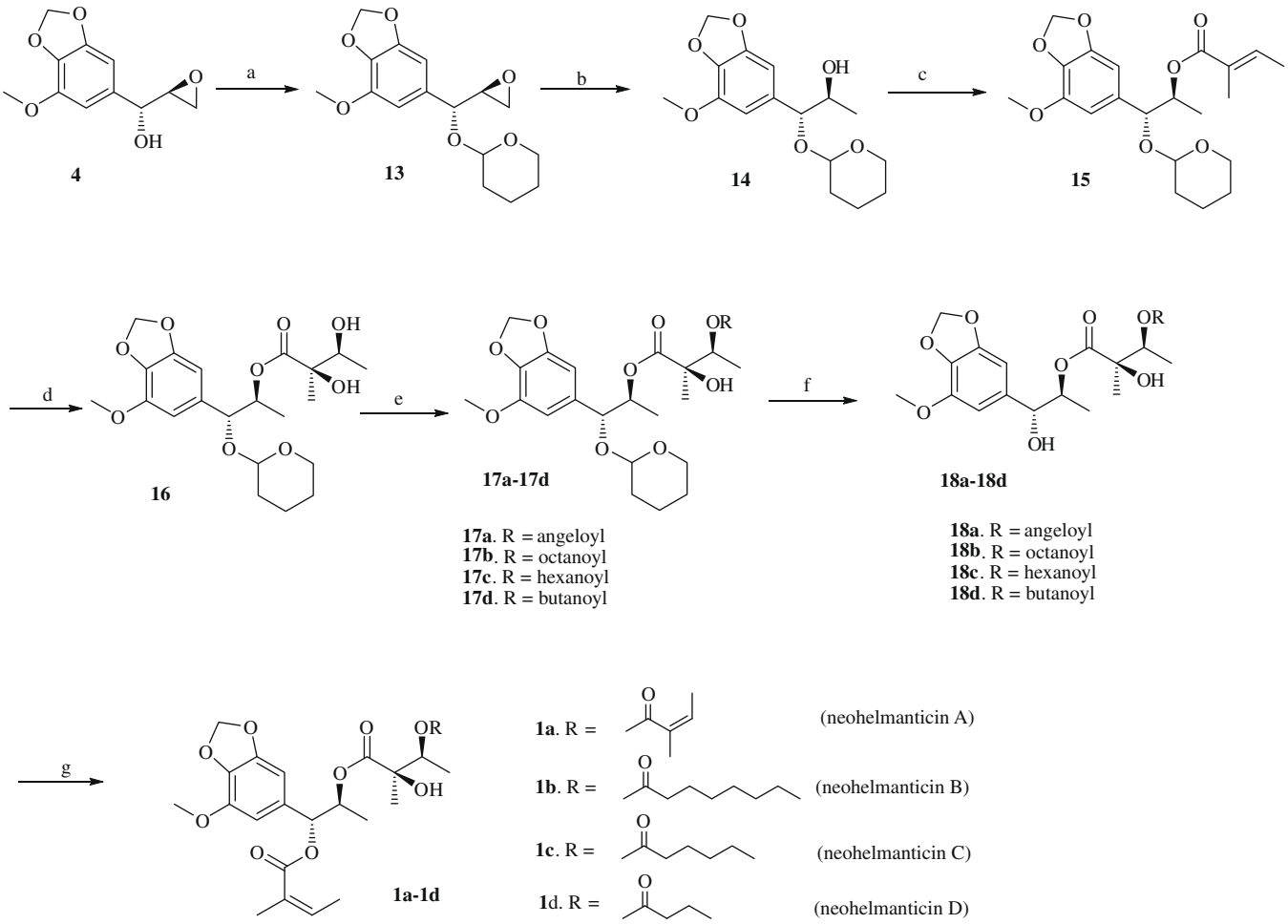
All commercially available reagents were used without further purification unless otherwise stated. The solvents used were all of AR grade and were distilled under a positive pressure of dry nitrogen atmosphere where necessary. All reactions were performed in pre-dried apparatus under an atmosphere of nitrogen unless otherwise stated. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) performed on Merck Silica Gel 60 F_{254} plates. Visualization was performed with 5% methanolic H_2SO_4 solution followed by heating. Column chromatography was carried out using silica gel 60–120 mesh (Qingdao Marine Chemical, China). High-resolution spectra were obtained on LC-MSD-Trap-SL instrument. NMR spectra were recorded on Bruker 300 MHz spectrometers, with tetramethylsilane as an internal standard, using $CDCl_3$. The chemical shifts are expressed as δ values in parts per million (ppm) and the coupling constants (J) are given in hertz (Hz). Yields were of purified compounds and were not optimized. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C.

5.1.1. Methyl 3,4,5-trihydroxybenzoate 7

To a solution of the gallic acid **6** (4.000 g, 23.53 mmol) in MeOH (30 mL) at room temperature was slowly added thionyl chloride (2 mL) dropwise at 0 °C. The mixture was refluxed at 65 °C for 4 h. The mixture was cooled to room temperature and solvent was evaporated to dryness. The resulting residue was dissolved in DCM, washed with saturated $NaHCO_3$ solution, and dried (Na_2SO_4). Removal of the solvent afforded the crude product, which was purified by silica gel column chromatography eluting with $CHCl_3$–acetone (80:20) to give **7** (90%) as a colorless syrupy oil. ^{1}H NMR (300 MHz, acetone-d_6): δ 3.88 (s, 3H), 7.15 (d, 1H, J = 1.5 Hz), 7.32 (d, 1H, J = 1.5 Hz); HREIMS: m/z $[M]^+$ found 184.0351; calcd 184.0372 for $C_8H_8O_5$.

5.1.2. Methyl 3,4-methylenedioxy,5-hydroxy benzoate 8

To a solution of **7** (3.000 g, 16.30 mmol) in dry DMF (25 mL) were added sequentially CH_2I_2 (5.460 g, 20.40 mmol), CuO (0.340 g, 4.27 mmol), and K_2CO_3 (4.750 g, 34.36 mmol). The reaction mixture was stirred at 130 °C for 5 h. After completion of the reaction, the mixture was cooled to room temperature, K_2CO_3 was removed by filtration, and DMF was removed by vacuum distillation. Then, water (30 mL) was added to the residue and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with aqueous HCl, saturated $NaHCO_3$ solution, brine, dried over Na_2SO_4, and evaporated under vacuum. The crude product was purified by silica gel column chromatography using hexane–EtOAc (85:15) as eluent to give **8** (60%) as a pale yellow colored liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H), 6.06 (s, 2H), 7.15 (d, 1H, J = 1.5 Hz), 7.32 (d, 1H, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 150.4, 143.4, 136.7, 134.6, 102.8, 101.6,

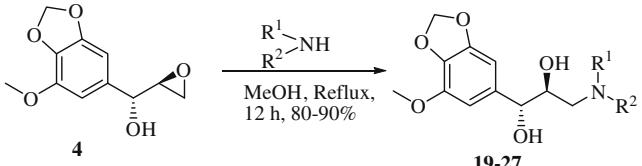


Scheme 3. Reagents and conditions: (a) CSA, DHP, DCM, rt, 5 h, 96%; (b) LAH, THF, 0 °C to rt, 3 h, 91%; (c) tiglic acid, EDCI, DMAP, Py, rt, 16 h, 90%; (d) AD-mix-α, $CH_3SO_2NH_2$, $(CH_3)_3COH$–H_2O; 1:1, 2–5 °C, 24 h, 97%; (e) angelic acid for a, octanoic acid for b, hexanoic acid for c, *n*-butyric acid for d, EDCI, DMAP, Py, rt, 16 h, 90% for **17a**, 95% for **17b**, 92% for **17c**, 92% for **17d**, 16 h;(f) CSA, CH_3OH, rt, 12 h, 90% for **18a**, 92% for **18b**, 90% for **18c**, 90% for **18d**; (g) angelic acid, EDCI, DMAP, Py, rt, 16 h, 90% for **1a**, 92% for **1b**, 85% for **1c**, 80% for **1d**.

101.6, 52.1; HREIMS *m/z* $[M]^+$ found 196.0384; calcd 196.0372 for $C_9H_8O_5$.

5.1.3. Methyl 3,4-methylenedioxy,5-methoxy benzoate 9

To a solution of **8** (0.913 g, 4.66 mmol) in ethanol (15 mL) at 0 °C temperature under nitrogen was slowly added a solution of NaOH (0.373 g, 9.33 mmol) in EtOH. After being stirred for 15 min at room temperature, dimethyl sulfate (1.175 g, 9.33 mmol) was added dropwise and reaction mixture was allowed to reflux for 5 h. After completion of the reaction, ethanol was concentrated to dryness. Then water (30 mL) was added and extracted with EtOAc (2 × 30 mL). The combined organic layers were dried and evaporated. The product was purified by column chromatography using 10% ethyl acetate in hexane as eluent to give **9** (87%) as



19. $R^1 = R^2$ = Ethyl
20. R^1 = H, R^2 = *n*-Propyl
21. R^1 = H, R^2 = Isobutyl
22. R^1 = H, R^2 = *p*-Methoxy benzyl
23. R^1 = H, R^2 = *m*-Triflouromethyl benzyl
24. R^1 = H, R^2 = *p*-Triflouromethyl benzyl
25. R^1 = H, R^2 = Mercaptobenzamidazolyl
26. R^1 = H, R^2 = 3-Amino-5-mercapto-1,2,4,-triazolyl
27. R^1 = H, R^2 = 2-Amino-5-mercapto1,3,4-thia-diazolyl

Scheme 4. Synthesis of dihydroxy phenyl propane derivatives.

an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.94 (s, 3H), 6.06 (s, 2H), 7.21 (d, 1H, J = 1.5 Hz), 7.33 (d, 1H, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 149.8, 143.2, 135.8, 134.6, 105.6, 102.6, 101.6, 58.8, 52.1; HREIMS m/z $[M]^+$ found 210.0562; calcd 210.0528 for $C_{10}H_{10}O_5$.

5.1.4. 3,4-Methylenedioxy,5-methoxy benzyl alcohol 10

To a solution of lithium aluminum hydride (0.070 g, 1.90 mmol) in dry THF (5 mL) was slowly added a solution of **9** (0.200 g, 0.95 mmol) in dry THF at 0 °C. The reaction mixture was allowed to stir at room temperature for 30 min. After completion of the reaction (TLC), aqueous saturated NH_4Cl solution (5 mL) was added at 0 °C and stirred for additional 15 min. The reaction mixture was filtered through Celite and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford crude product, which was purified by silica gel column chromatography using hexane–EtOAc (80:20) as eluent to give **10** (96%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 3H), 4.59 (d, 2H, J = 5.4 Hz), 5.97 (s, 2H), 6.56 (s, 1H), 6.57 (s, 1H); HREIMS m/z $[M]^+$ found 182.0621; calcd 182.0579 for $C_9H_{10}O_4$.

5.1.5. Preparation of myristicinaldehyde 11

To a solution of oxalyl chloride (2.013 g, 15.85 mmol) in dry DCM (15 mL) at −78 °C under inert atmosphere was added dimethylsulfoxide (2.474 g, 31.71 mmol) dropwise. After being stirred at −78 °C for 15 min, a solution of **10** (1.924 g, 10.57 mmol) in dry DCM (5 mL) was added dropwise and allowed to stir for 30 min. Then, triethylamine (7.474 g, 74.00 mmol) was added and allowed to stir for 15 min, the reaction mixture was brought to room temperature and the reaction was quenched with water (40 mL). The organic layer was washed with brine, dried over sodium sulfate, and solvent was evaporated to dryness. The crude product was purified by silica gel column chromatography using hexane–EtOAc (90:10) as eluent to give **11** (96%) as an amorphous solid. IR (KBr), 3430, 2922, 1694, 1627, 1508 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (s, 3H), 6.11 (s, 2H), 7.05 (d, 1H, J = 1.5 Hz), 7.14 (d, 1H, J = 1.5 Hz), 9.79 (s, 1H); HREIMS m/z $[M]^+$ found 180.0460; calcd 180.0423 for $C_9H_8O_4$.

5.1.6. 1-(3,4-Methylenedioxy,5-methoxy phenyl) prop-2-en-1-ol 5

To a solution of myristicinaldehyde **11** (2.736 g, 15.20 mmol) in dry THF (30 mL) under nitrogen atmosphere at 0 °C was added vinyl magnesium bromide (6.72 mL of 1 M solution in THF) dropwise. The reaction mixture was allowed to stir for 15 min at room temperature. After completion (TLC), the reaction was quenched with saturated NH_4Cl solution at 0 °C and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and solvent was evaporated to dryness. The crude product was purified by column chromatography using hexane–EtOAc (90:10) as eluent to give **5** (98%) as a gummy liquid. IR (KBr), 3417, 2978, 1892, 2780, 1634, 1507, 1130, 1195 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 5.10 (d, 1H, J = 6.0 Hz), 5.18–5.20 (m, 1H), 5.34 (dd, 1H, J = 12 Hz, J = 8 Hz), 5.94–6.10 (m, 1H,), 5.96 (s, 2H), 6.56 (d, 1H, J = 1.2 Hz), 6.57 (d, 1H, J = 1.2 Hz).

5.1.7. (*R*)-(3,4-Methylenedioxy,5-methoxy phenyl)((*S*)-oxiran-2-yl) methanol 4 and (*R*)-1-(4-methoxybenzo[*d*][1,3]dioxol-6-yl)prop-2-en-1-ol 12

To a stirred solution of evacuated flame dried powdered 4 Å molecular sieves (5 g) and (−)-DIPT (1.091 g, 4.66 mmol) in DCM (25 mL) was added slowly Ti(*i*OPr)$_4$ (1.103 g, 3.88 mmol) at −20 °C. Subsequently, the mixture was allowed to stir for 20 min then cumene hydroperoxide (0.717 g, 4.65 mmol) was added at the same temperature. After being stirred for 20 min, a solution of compound **5** (1.615 g, 7.76 mmol) in DCM (5 mL) was added dropwise. The reaction mixture was allowed to stir for 12 h. The reaction was quenched by a solution containing 1.7 g of NaOH dissolved in 17 mL of saturated NaCl at 0 °C and continued to stir for 3 hours at rt. Then, 17 g of Na_2SO_4 and 2 g of Celite were added and stirring was continued for 15 min, and this mixture was filtered through Celite. The filtrate was concentrated. The product was purified by silica gel column chromatography using hexane–EtOAc (90:10) as eluent to give **12** (48%) and using hexane–EtOAc (75:25) as eluent to give **4** (47%) as a syrupy liquid. $[\alpha]_D^{25} = -25.6$ (c 3.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76–2.79 (m, 1H), 2.95 (q, 1H, J = 2.7 Hz), 3.18–3.21 (m, 1H), 3.92 (s, 3H), 4.83 (d, 1H, J = 2.7 Hz), 5.98 (s, 2H), 6.59 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 149.0, 143.4, 134.8, 132.6, 107.6, 102.1, 101.6, 77.6, 66.2, 63.4, 58.0; HREIMS m/z $[M]^+$ found 224.0664; calcd 224.0685 for $C_{11}H_{12}O_5$.

5.1.8. (1*R*,2*S*)-1-(3,4-Methylenedioxy,5-methoxy phenyl)propane 1,2-diol 2

To a solution of lithium aluminum hydride (0.969 g, 0.002 mmol) in dry THF (5 mL) under nitrogen atmosphere at 0 °C was slowly added a solution of **4** (0.05 g, 0.22 mmol) in dry THF. The reaction mixture was allowed to stir for 3 h at room temperature. After completion, the reaction was quenched with saturated NH_4Cl solution and allowed to stir for an additional 15 min. The reaction mixture was filtered through Celite and the filtrate was extracted with EtOAc (2x20 mL). The combined organic layer was dried and evaporated to get crude product, which was purified by silica gel column chromatography using hexane–EtOAc (80:20) as eluent to give **2** (92%) as an oil. $[\alpha]_D^{25} = -16.6$ (c 0.16, $CHCl_3$), (reported $[\alpha]_D^{25} = -23$ (c 0.62, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (d, 3H, J = 6.6 Hz), 3.90 (s, 3H), 3.95 (dq, 1H, J = 6.6, 4.5 Hz), 4.55 (d, 1H, J = 4.5 Hz), 5.97 (s, 2H), 6.56 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 143.7, 135.3, 134.9, 106.0, 101.5, 101.0, 77.5, 72.2, 56.8, 17.6; HREIMS m/z $[M]^+$ found 226.0824; calcd 226.0841 for $C_{11}H_{14}O_5$.

5.1.9. 4-Methoxy-6-((*R*)-((*S*)-oxiran-2-yl)(tetrahydro-2*H*-pyran-2-yloxy)methyl) benzo[*d*][1,3]dioxole 13

To a solution of **4** (0.050 g, 0.22 mmol) in dry DCM (2 mL) at 0 °C was added camphorsulfonic acid (0.005 g, 0.002 mmol). After being stirred for 5 min, dihydropyran (DHP) (0.022 g, 0.27 mmol) was added and the reaction mixture was allowed to stir for 5 h at room temperature. The reaction was quenched with aqueous saturated $NaHCO_3$ solution (20 mL) and stirred for an additional 10 min. and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were dried over sodium sulfate and evaporated to give **13** (96%) as a colorless liquid. $[\alpha]_D^{25} = -26.2$ (c 0.70, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6–1.80 (m, 6H), 2.70–2.81 (m, 2H), 3.06–3.12 (m,1H), 3.6–3.7 (m, 1H), 3.90 (s, 1H), 3.92 (s, 3H), 4.50–4.53 (m, 1H), 4.73–4.76 (m, 1H), 5.96 (s, 2H), 6.52–6.54 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ150.0, 142.6, 134.6, 131.9, 106.9, 104.0,102.0, 101.6, 78.4, 76.2, 74.4, 58.0, 58.0, 31.0, 25.8, 21.5; HRESIMS m/z $[M]^+$ found 308.1256; calcd 308.1260 for $C_{16}H_{20}O_6$.

5.1.10. (1*R*,2*S*)-1-(4-Methoxybenzo[*d*][1,3]dioxol-6-yl)-1-(tetrahydro-2H-pyran-2-yloxy)propan-2-ol 14

To a solution of lithium aluminum hydride (0.034 g, 0.92 mmol) in dry THF (3 mL) at 0 °C was slowly added a solution of **13** (0.950 g, 0.30 mmol) in THF (0.5 mL) dropwise. After being stirred for 3 h at room temperature, reaction was quenched with aqueous saturated NH_4Cl solution at 0 °C and allowed to stir for an additional 15 min. The reaction mixture was filtered through Celite and extracted with EtOAc (2 × 20 mL). The combined organic layers were dried and evaporated to dryness. The product was purified by column chromatography using hexane–EtOAc (75:25) as

eluent to give **14** (91%) as **a** colorless oil. $[\alpha]_D^{25} = -32.6$ (*c* 0.9, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, 3H, *J* = 6.7 Hz), 1.58–1.60 (m, 6H), 3.49–3.58 (m, 1H), 3.92 (s, 3H), 3.93–3.96 (m, 2H), 4.48–4.51 (m, 2H), 5.98 (s, 2H), 6.48 (d, 1H, *J* = 1.5 Hz), 6.52 (d, 1H, *J* = 1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 142.0, 133.9, 132.0, 107.0, 104.6, 102.0, 101.6, 78.1, 77.6, 57.9, 57.8, 30.9, 25.9, 21.6, 16.9; HRESIMS *m/z* $[M]^+$ found 310.1424; calcd 310.1416 for $C_{16}H_{22}O_6$.

5.1.11. (*E*)-(1*R*,2*S*)-1-(4-Methoxybenzo[*d*][1,3]dioxol-6-yl)-1-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yl 2-methylbut-2-enoate 15

To a solution of tiglic acid (0.050 g, 0.50 mmol) in pyridine (5 mL) were added EDCI (0.099 g, 0.33 mmol) and DMAP (0.004 g, 0.03 mmol) at 0 °C. The resultant white cloudy suspension was brought to room temperature and stirred until EDCI completely dissolved. Then, a solution of **14** (0.052 g, 0.17 mmol) in pyridine was added dropwise. After being stirred for 16 h, the reaction mixture was concentrated to remove pyridine, aqueous 1 N HCl was added and extracted with DCM (2 × 10 mL). The combined organic layers were washed with brine, dried, and evaporated. The product was purified by column chromatography using hexane–EtOAc (85:15) as eluent to give **15** (90%) as a colorless oil. $[\alpha]_D^{25} = -8.8$ (*c* 1.1, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (d, 3H, *J* = 6.4 Hz), 1.31 (d, 3H, *J* = 6.4 Hz), 1.42–1.69 (m, 6 H), 1.82 (d, 3H, *J* = 6.4 Hz), 3.31–3.40, 3.44–3.53 (m, 1H), 3.88 (s, 1H) 3.90 (s, 3H), 4.51, 4.92 (t, 1H, *J* = 3.02 Hz), 4.65 (dd, 1H, *J* = 5.2 Hz), 5.16–5.00 (m,1H), 5.95 (s, 2H), 6.49 (d, 1H, *J* = 1.3 Hz), 6.52 (d, 1H, *J* =1.3 Hz), 6.57–6.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 148.3, 143.8, 138.4, 136.2, 133.0, 125.6, 105.0, 103.8, 102.6, 101.0, 78.5, 72.1, 62.8, 57.6, 30.9, 25.80, 21.7, 21.0, 16.8, 15.8; HRESIMS *m/z* $[M]^+$ found 392.1827; calcd 392.1835 for $C_{21}H_8O_7$.

5.1.12. (2*R*,3*S*)-(1*R*,2*S*)-1-(4-Methoxybenzo[*d*][1,3]dioxol-6-yl)-1-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yl 2,3-dihydroxy-2-methylbutanoate 16

To a solution of compound **15** (0.038 g, 0.09 mmol) in 2 mL of *tert*-butyl alcohol–water (1:1) were added AD-mix-α (0.136 g) and $CH_3SO_2NH_2$ (0.09 mmol) at room temperature. The mixture was allowed to stir for 24 h at 2–5 °C. The reaction was quenched with sodium sulfite (0.14 g) and the mixture was continued to stir for additional 30 min. The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried and concentrated to afford the crude product. The product was purified by column chromatography over silica gel using hexane–EtOAc (65:35) as an eluent to give **16** (97%) as an oil. IR (KBr), 3455, 2941, 1731, 1635, 1508, 1258, 1025 cm^{-1}; $[\alpha]_D^{25} = -28.5$ (*c* 7.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, 3H, *J* = 5.2 Hz), 1.20 (d, 3H, *J* = 5.2 Hz), 1.22 (s, 3H), 1.57–1.62 (m, 6H), 3.49–3.51 (m, 1H), 3.89 (s, 2H), 3.91 (s, 3H), 4.67–4.72 (m, 1H), 4.91–4.93 (m, 1H), 5.15–5.18 (m, 1H), 5.95 (s, 2H), 6.49 (d, 1H, *J* = 3.7 Hz), 6.57 (d, 1H, *J* = 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 149.3, 143.8, 135.4, 132.9, 107.8, 104.0, 102.0, 101.9, 78.5, 76.9, 75.3, 72.0, 62.8, 57.0, 30.9, 25.8, 21.7, 16.9, 16.0, 14.5; ESIMS: *m/z* 427 (M^++1); HRESIMS *m/z* $[M]^+$ found 426.1862; calcd 426.189 for $C_{21}H_{30}O_9$.

5.2. General procedure for the preparation of compounds 17a–17d

To a solution of the acid (0.21 mmol) in pyridine were added EDCI (0.068 g, 0.35 mmol) and DMAP (0.003 g, 0.03 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature until EDCI had completely dissolved in the reaction mixture. Then immediately a solution of compound **16** (0.06 g, 0.14 mmol) in pyridine was added. After being stirred for 16 h, the reaction mixture was concentrated to remove pyridine. The reaction was quenched with aqueous 1 N HCl and was extracted with DCM (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to dryness. The product was purified by column chromatography using hexane–EtOAc (85:15) as eluent to give **17a–17d**.

5.2.1. (*Z*)-(2*S*,3*R*)-3-(((1*R*,2*S*)-1-(4-Methoxybenzo[*d*][1,3]dioxol-6-yl)-1-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yloxy)carbonyl)-3-hydroxybutan-2-yl2-methylbut-2-enoate 17a

Syrupy liquid, yield 90%; IR (KBr): 3450, 2941, 1733, 1644, 1526, 1258, 1025 cm^{-1}; $[\alpha]_D^{25} = -12.0$ (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, 3H, *J* = 6.4 Hz), 1.40–1.30 (m, 8H), 1.60–1.50 (m, 4H), 1.88 (q, 3H, *J* = 4 Hz), 3.27–3.37 (m, 1H), 3.45–3.56 (m, 1H), 3.88 (s,1H), 3.90 (s, 3H), 4.45, 4.53 (t, 1H, *J* = 2.8 Hz), 4.58 (dd, 1H, *J* = 4.7 Hz, 2.8 Hz), 4.99–5.10 (m, 2H), 5.94 (s, 2H), 6.45 (d, 1H, *J* = 1.1 Hz), 6.47 (d, 1H, *J* = 1.1 Hz), 6.51 (d, 1H, *J* = 1.1 Hz), 6.55 (d, 1H, *J* = 1.13 Hz), 6.82–6.93 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 168.4, 147.6, 144.3, 137.4, 134.6, 134.6, 126. 8, 107.6, 102.9, 101.6, 101.4, 82.6, 74.6, 74.8, 72.8, 64.4, 56.8, 32.8, 25.4, 21.6, 21.0, 18.4, 16.1, 16.4, 15.9; HRESIMS *m/z* $[M]^+$ found 508.2342; calcd 508.2308 for $C_{26}H_{36}O_{10}$.

5.2.2. (2*S*,3*R*)-3-(((1*R*,2*S*)-1-(4-Methoxybenzo[*d*][1,3]dioxol-6-yl)-1-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yloxy)carbonyl)-3-hydroxybutan-2-yl octanoate 17b

Liquid, yield 95%; IR (KBr), 3464, 2926, 1734, 1642, 1546, 1250, 1124 cm^{-1}; $[\alpha]_D^{25} = -10.15$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.4 Hz), 1.11 (s, 3H), 1.17 (d, 3H, *J* = 6.4 Hz), 1.20 (d, 3H, *J* = 6.8 Hz), 1.28–1.40 (m, 6H), 1.60–1.80 (m, 8H), 1.8–2.0 (m, 2H), 2.0–2.3 (m, 2H), 3.20 (br s, 1H), 3.30–3.38, 3.48–3.57 (m, 1H), 3.94 (s, 3H), 4.48 (t, 1H, *J* = 2.8 Hz), 4.60 (dd, 1H, *J* = 6 Hz, 4 Hz), 5.10–5.18 (m, 2H), 5.94 (s, 2H), 6.54 (d, 1H, *J* = 1.8 Hz), 6.48 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 172.3, 148.7, 143.3, 135.2, 132.4, 107.6, 103.6, 102.0, 101.3, 81.6, 74.8, 73.9, 73.6, 62.9, 56.2, 35.6, 32.0, 25.6, 21.5, 18.5, 19.0, 16.5, 16.2, 16.1, 15.9, 14.3; HRESIMS *m/z* $[M]^+$ found 552.2890; calcd 552.2934 for $C_{29}H_{44}O_{10}$.

5.2.3. (2*S*,3*R*)-3-(((1*R*,2*S*)-1-(4-Methoxybenzo[*d*][1,3]dioxol-6-yl)-1-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yloxy)carbonyl)-3-hydroxybutan-2-yl hexanoate 17c

Liquid, yield 92%; IR (KBr), 3456, 2921, 1730, 1642, 1528, 1236, 1026 cm^{-1}; $[\alpha]_D^{25} = -13.3$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.4 Hz), 1.14 (s, 3H), 1.18 (d, 3H, *J* = 6.6 Hz), 1.20 (d, 3H, *J* = 6.8 Hz), 1.30–1.48 (m, 4H), 1.74–1.86 (m, 4H), 2.10–2.20 (m, 2H), 3.20 (br s,1H), 3.28–3.30, 3.48–3.60 (m, 1H), 3.94 (s, 3H), 4.48 (t, 1H, *J* = 2.8 Hz), 4.58 (dd, 1H, *J* = 6.4 Hz, 4 Hz), 5.08–5.23 (m, 2H), 5.90 (s, 2H), 6.56 (d, 1H, *J* = 1.8 Hz), 6.48 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 167.9, 147.7, 144.5, 138.0, 134.8, 134.7, 126.9, 108.0, 102.8, 101.6, 101.8, 82.6, 74.7, 74.9, 72.9, 64.6, 56.9, 32.8, 25.4, 21.8, 21.2, 18.6, 16.2,16.6, 16.0,16.1, 15.8, 14.2. HRESIMS *m/z* $[M]^+$ found 524.2610; calcd 524.2621 for $C_{27}H_{40}O_{10}$.

5.2.4. (2*S*,3*R*)-3-(((1*R*,2*S*)-1-(4-Methoxybenzo[*d*][1,3]dioxol-6-yl)-1-(tetrahydro-2*H*-pyran-2-yloxy)propan-2-yloxy)carbonyl)-3-hydroxybutan-2-yl-butanoate 17d

Syrupy liquid, yield 92%; IR (KBr), 3500, 3041, 1736, 1638, 1524, 1268, 1084 cm^{-1}; $[\alpha]_D^{25} = -11.1$ (*c* 0.4, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.6 Hz), 1.11 (s, 3H), 1.22 (d, 3H, *J* = 6.7 Hz), 1.26 (d, 3H, *J* = 6.7 Hz), 1.20–1.38 (m, 2H), 1.50–1.70 (m, 8H), 2.18–2.30 (m, 2H), 3.22 (br s, 1H), 3.30–3.40, 3.36–3.50 (m,1H), 3.90 (s, 1H), 4.60 (dd, 1H, *J* = 6.4 Hz), 4.90 (t, 1H, *J* = 2.4 Hz), 5.24–5.00 (m, 2H), 5.98 (s, 2H), 6.56 (d, 1H, *J* =1.91 Hz), 6.48 (d, 1H, *J* = 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 172.3, 148.9, 143.3, 135.0, 132.6, 107.6, 103.5, 101.6,

101.4, 81.9, 74.8, 73.8, 73.6, 62.3, 56.6, 36.1, 31.9, 25.4, 21.4, 18.4, 18.3, 16.1, 15.7, 14.0; HRESIMS *m/z* $[M]^+$ found 496.2362; calcd 496.2308 for $C_{25}H_{36}O_{10}$.

5.3. General procedure for the preparation of compounds 18a–18d

To a solution of compounds **17a–17d** (0.10 mmol) in MeOH (2 mL) at 0 °C was added slowly CSA (0.005 g, 0.002 mmol). After addition, the ice bath was removed and the reaction mixture was allowed to stir for 12 h at room temperature. The reaction mixture was concentrated to remove MeOH; aqueous saturated $NaHCO_3$ solution (20 mL) was added and stirred for an additional 10 min. The aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were washed with water, dried, and concentrated to afford compounds **18a–18d**.

5.3.1. (*Z*)-(2*S*,3*R*)-3-(((1*R*,2*S*)-1-Hydroxy-1-(4-methoxybenzo[*d*]-[1,3]dioxol-6-yl)propan-2-yloxy)carbonyl)-3-hydroxybutan-2-yl 2-methylbut-2-enoate 18a

Oil, yield 90%; $[\alpha]_D = -23.1$ (*c* 1.5, $CHCl_3$), IR (KBr), 3450, 2940, 1736, 1635, 1508, 1256, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (d, 3H, *J* = 6.2 Hz), 1.22 (s, 3H), 1.27 (d, 3H, *J* = 6.4 Hz), 3.20 (br s, 1H), 3.90 (s, 3H), 4.64 (d, 1H, *J* = 5.0 Hz), 4.92–5.02 (m, 1H), 5.13 (q, 1H, *J* = 6.4 Hz), 5.95 (s, 2H), 6.51 (s, 2H), 6.84–6.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 168.4, 164.5, 150.0, 144.0, 135.6, 133.1, 124.8, 108.0, 103.0, 101.9, 76.2, 75.6, 73.8, 72.4, 71.1, 57.1, 20.2,18.4, 16.2, 15.8, 14.5; HRESIMS *m/z* $[M]^+$ found 424.1730; calcd 424.1733 for $C_{21}H_{28}O_9$.

5.3.2. (2*S*,3*R*)-3-(((1*R*,2*S*)-1-Hydroxy-1-(4-methoxybenzo[*d*][1,3]-dioxol-6-yl)propan-2-yloxy)carbonyl)-3-hydroxybutan-2-yl octanoate 18b

Syrupy liquid, yield 92%; $[\alpha]_D = -22.1$ (*c* 1.2, $CHCl_3$), IR (KBr), 3436, 2656, 1738, 1642, 1564, 1265, 1084 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.15 (d, 3H, *J* = 6.4 Hz), 1.20 (s, 3H), 1.26 (d, 3H, *J* = 6.4 Hz), 1.33–1.40 (m, 2H), 1.48–1.60 (m, 4H), 1.70–2.21 (m, 4H), 2.36 (br s, 1H), 3.17 (br s, 1H), 3.94 (s, 3H), 4.60 (d, 1H, *J* = 4.8 Hz), 4.80–4.99 (m, 1H), 5.16 (q, 1H, *J* = 6.4 Hz), 5.98 (s, 2H), 6.52 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 171.9, 148.9, 143.4, 136.0, 132.6, 107.5, 101.4, 102.8, 74.7, 74.8, 73.8, 57.0, 36.1, 18.6, 18.1, 16.2, 16.1, 16.0, 14.1; HRESIMS *m/z* $[M]^+$ found 468.2341; calcd 468.2359 for $C_{24}H_{36}O_9$.

5.3.3. (2*S*,3*R*)-3-(((1*R*,2*S*)-1-Hydroxy-1-(4-methoxybenzo[*d*][1,3]-dioxol-6-yl)propan-2-yloxy)carbonyl)-3-hydroxybutan-2-yl hexanoate 18c

Liquid, yield 90%; $[\alpha]_D = -28.2$ (*c* 1.5, $CHCl_3$), IR (KBr), 3506, 2984, 1738, 1626, 1584, 1286, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.13 (d, 3H, *J* = 6.4 Hz), 1.24 (s, 3H), 1.26 (d, 3H, *J* = 6.42 Hz), 1.36–1.38 (m, 2H), 1.40–1.50 (m, 2H), 1.78–2.18 (m, 2H), 2.33 (br s, 1H), 3.20 (br s, 1H), 3.94 (s, 3H), 4.68 (d, 1H, *J* = 4.6 Hz), 4.88–5.0 (m, 1H), 5.14 (q, 1H, *J* = 6.42 Hz), 5.98 (s, 2H), 6.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 172.0, 148.7, 143.4, 136.1, 132.5, 107.4, 101.4, 103.0, 74.8, 74.7, 73.8, 57.1, 36.1, 18.5, 18.1, 16.1, 16.1, 16.1, 15.8, 14.1; HRESIMS *m/z* $[M]^+$ found 440.2024; calcd 440.2046 for $C_{22}H_{32}O_9$.

5.3.4. (2*S*,3*R*)-3-(((1*R*,2*S*)-1-Hydroxy-1-(4-methoxybenzo[*d*][1,3]-dioxol-6-yl)propan-2-yloxy)carbonyl)-3-hydroxybutan-2-yl butanoate 18d

Oil, yield 90%; $[\alpha]_D = -29.1$ (*c* 1.0, $CHCl_3$), IR (KBr), 3484, 2946, 1736, 1636, 1526, 1284, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.17 (d, 3H, *J* = 6.4 Hz), 1.21 (s, 3H), 1.24 (d, 3H, *J* = 6.4 Hz), 1.58–1.70 (m, 2H), 2.20–2.30 (m, 2H), 2.36 (br s, 1H), 3.17 (br s, 1H), 3.90 (s, 3H), 4.66 (d, 1H, *J* = 4.8 Hz), 4.95–5.08 (m, 1H), 5.10 (q, 1H, *J* = 6.4 Hz), 5.95 (s, 2H), 6.52 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 172.3, 148.9, 143.3, 135.0, 132.6, 107.6, 101.6, 101.5, 103.5, 74.8, 73.7, 74.8, 57.0, 21.5, 18.3, 16.4, 15.5, 14.0; HRESIMS *m/z* $[M]^+$ found 412.1704; calcd 412.1733 for $C_{20}H_{28}O_9$.

5.4. General procedure for the preparation of neohelmanthacins A–D, 1a–1d

To a solution of angelic acid (0.029 g, 0.29 mmol) in pyridine at 0 °C was added a mixture of EDCI (0.028 g, 0.15 mmol) and DMAP (0.002 g, 0.01 mmol). After addition, the ice bath was removed and the reaction mixture was allowed to stir at room temperature until EDCI completely dissolved. Then, a solution of compounds **18a–18d** (0.06 mmol) in pyridine was added. After being stirred for 16 h, the reaction mixture was concentrated to remove pyridine. The reaction was quenched with aqueous 1 N HCl and aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were washed with brine, dried, and evaporated to dryness. The product was purified by column chromatography using hexane–EtOAc as eluent to give **1a–1d** (80–92%). All the data matched exactly with the literature.[2]

5.4.1. Neohelmanticin A 1a

Oil, yield 90%; $[\alpha]_D = -25.5$ (*c* 1.65, $CHCl_3$), (reported $[\alpha]_D = -25$ (*c* 0.37, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (d, 3H, *J* = 6.2 Hz), 1.22 (s, 3H), 1.27 (d, 3H, *J* = 6.4 Hz), 1.82 (q, 3H, *J* = 1.8 Hz), 1.85 (s, 3H), 3.20 (br s, OH), 3.90 (s, 3H), 4.64 (d, 1H, *J* = 5.0 Hz), 5.08 (q, 1H, *J* = 6.4 Hz), 5.12–5.20 (m, 1H), 5.86 (d, 1H, *J* = 4.8 Hz), 5.98 (q, 1H, *J* = 7.0, 1.5 Hz), 5.95 (s, 2H), 6.21 (q, 1H, *J* = 7.6 Hz), 6.51 (s, 2H), 6.1–6.3 (m, 1H); HRESIMS *m/z* $[M]^+$ found 506.2146; calcd 506.2152 for $C_{26}H_{34}O_{10}$.

5.4.2. Neohelmanticin B 1b

Oil, yield 92%; $[\alpha]_D = -22.0$ (*c* 0.1, $CHCl_3$), (reported $[\alpha]_D = -21$ (*c* 0.096, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.5 Hz), 1.18 (d, 3H, *J* = 6.4 Hz), 1.24 (s, 3H), 1.22 (d, 3H, *J* = 6.4 Hz), 1.33–1.38 (m, 2H), 1.48–1.60 (m, 4H), 1.92 (q, 3H, *J* = 1.5 Hz), 1.76–2.24 (m, 6H), 2.36 (br s, 1H), 3.17 (br s, 1H), 3.94 (s, 3H), 4.60 (d, 1H, *J* = 4.8 Hz), 4.98–5.02 (m, 1H), 5.16 (q, 1H, *J* = 6.4 Hz), 5.88 (d, 1H, *J* = 4.6 Hz), 5.98 (s, 2H), 6.12 (q, 1H, *J* = 7.4 Hz), 6.52 (s, 2H); HRESIMS *m/z* $[M]^+$ found 550.2764; calcd 550.2778 for $C_{29}H_{42}O_{10}$.

5.4.3. Neohelmanticin C 1c

Liquid, yield 85%; $[\alpha]_D = -31.1$ (*c* 0.2, $CHCl_3$), (reported $[\alpha]_D = -32$ (*c* 0.23, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.5 Hz), 1.17 (d, 3H, *J* = 6.4 Hz), 1.26 (s, 3H), 1.20 (d, 3H, *J* = 6.4 Hz), 1.33–1.38 (m, 2H), 1.56–1.58 (m, 4H), 1.91 (q, 3H, *J* = 1.5 Hz), 1.76–2.24 (m, 2H), 2.36 (br s, 1H), 3.17 (br s, 1H), 3.94 (s, 3H), 4.60 (d, 1H, *J* = 4.8 Hz), 5.08–5.12 (m, 1H), 5.16 (q, 1H, *J* = 6.42 Hz, 1H), 5.88 (d, 1H, *J* = 4.6 Hz), 5.98 (s, 2H), 6.16 (q, 1H, *J* = 7.4 Hz), 6.53 (s, 2H); HRESIMS *m/z* $[M]^+$ found 522.2450; calcd 522.2465 for $C_{27}H_{38}O_{10}$.

5.4.4. Neohelmanticin D 1d

Oil, yield 80%; $[\alpha]_D = -32.0$ (*c* 0.2, $CHCl_3$), (reported $[\alpha]_D = -33$ (*c* 0.5, $CHCl_3$)); ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.5 Hz), 1.17 (d, 3H, *J* = 6.4 Hz), 1.21 (s, 3H), 1.24 (d, 3H, *J* = 6.4 Hz), 1.58–1.70 (m, 2H), 1.94(q, 3H, *J* = 1.5 Hz), 1.98 (q, 1H, *J* = 1.5 Hz), 2.08–2.10 (m, 1H), 2.18–2.20 (m, 2H), 2.36 (br s, 1H), 3.17 (br s,1H), 3.90 (s, 3H), 5.05–5.10 (m, 1H), 5.10 (q, 1H, *J* = 6.4 Hz), 5.95 (s, 2H), 6.16 (q, 1H, *J* = 7.5 Hz), 6.52 (s, 2H); HRESIMS *m/z* $[M]^+$ found 494.2100; calcd 494.2152 for $C_{25}H_{34}O_{10}$.

5.5. General procedures for preparation of compounds 19–27

To a solution of epoxide **4** (0.005 g, 0.22 mmol) in MeOH under N_2 atmosphere was added corresponding amine (0.24 mmol) at room temperature. Subsequently, the reaction mixture was allowed to reflux for 12 h. After completion of reaction (monitored by TLC), reaction mixture was cooled to room temperature and solvent was evaporated to dryness. The crude product was purified by silica gel column chromatography using hexane–EtOAc as eluent to give the compounds **19–27** in good yields (80–90%).

5.5.1. (1*R*,2*S*)-3-(Diethylamino)-1-(4-methoxybenzo[*a*][1,3]dioxol-6-yl)propane-1,2-diol 19

Pale yellow liquid, yield 85%; $[\alpha]_D = -9.0$ (*c* 0.66, acetone); IR (KBr), 3330, 2261, 1642, 1614, 1520, 1234, 1022 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 1.07 (t, 6H, *J* = 7.2 Hz), 2.57–2.70 (m, 6H), 3.67 (q, 1H, *J* = 6.9 Hz), 3.86 (s, 3H), 4.49 (d, 1H, *J* = 6.9 Hz), 5.94 (s, 2H) 6.62 (d, 1H, *J* = 1.5 Hz), 6.68 (d, 1H, *J* =1.5 Hz); ^{13}C NMR (75 MHz, acetone-d_6): δ 149.4, 144.1, 138.6, 135.0, 107.7, 101.9, 101.7, 78.4, 71.1, 58.1, 56.8, 48.2, 11.8; HRESIMS *m/z* $[M]^+$ found 297.1646; calcd 297.1600 for $C_{15}H_{23}NO_5$.

5.5.2. (1*R*,2*S*)-1-(4-Methoxybenzo[*a*][1,3]dioxol-6-yl)-3-(propylamino)propane-1,2-diol 20

Yellow oil, yield 82%; $[\alpha]_D = -37.7$ (*c* 0.2, $CHCl_3$); IR (KBr), 3300, 2264, 1622, 1610, 1526, 1244, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, *J* = 7.2 Hz), 1.57–1.50 (sextet, 2H, *J* = 7.2 Hz), 2.64–2.58–2.60 (m, 2H), 2.78–2.81 (m, 2H), 3.76–3.78 (m,1H), 3.90 (s, 3H,OMe), 4.77 (d, 1H, *J* = 4.8 Hz), 5.97 (s, 2H), 6.57 (s, 1H), 6.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 143.8, 135.7, 134.7, 105.8, 101.6, 100.4, 77.7, 71.9, 56.8, 51.2, 50.1, 21.8, 11.6; HRESIMS *m/z* $[M]^+$ found 283.1366; calcd 283.1420 for $C_{14}H_{21}NO_5$.

5.5.3. (1*R*,2*S*)-3-(Isobutylamino)-1-(4-methoxybenzo[*a*][1,3]-dioxol-6-yl)propane-1,2-diol 21

Oil, yield 90%; $[\alpha]_D = -17.25$ (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, 6H, *J* = 6.6 Hz), 1.94–1.83 (m, 1H), 2.46–2.59 (m, 2H), 2.87 (d, 2H, *J* = 4.8 Hz), 3.90 (s, 3H), 3.93–4.0 (m,1H), 4.83 (d, 1H, *J* = 4.2 Hz), 5.96 (s, 2H), 6.62 (s, 1H), 6.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.2, 143.8, 134.0, 134.6, 105.7, 101.6, 100.4, 76.8, 76.8, 71.6, 57.0, 56.7, 50.4, 27.6, 20.5; HRESIMS *m/z* $[M]^+$ found 297.3446; calcd 297.3468 for $C_{15}H_{23}NO_5$.

5.5.4. (1*R*,2*S*)-3-(4-Methoxyphenylamino)-1-(4-methoxybenzo-[*a*][1,3]dioxol-6-yl)propane-1,2-diol 22

Oil, yield 88%; $[\alpha]_D = -22.9$ (*c* 0.56, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.48 (d, 1H, *J* = 12.0 Hz), 2.66–2.73 (m, 1H), 3.57 (q, 1H, *J* = 13.2 Hz), 3.79 (s, 3H), 3.70–3.79 (m, 2H), 3.87 (s, 3H), 4.68 (d, 1H, *J* = 4.4 Hz), 5.95 (s, 2H), 6.49 (s, 1H), 6.50 (s, 1H), 6.79 (d, 2H, *J* = 8.1 Hz), 7.05 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 149.1, 143.7, 143.7,135.0, 134.7, 130.8, 114.0, 105.9, 101.6, 100.5, 75.0, 72.0, 59.6, 56.8, 55.3; HRESIMS *m/z* $[M]^+$ found 361.1576; calcd 361. 1525 for $C_{19}H_{23}NO_6$.

5.5.5. (1*R*,2*S*)-3-(3-(Trifluoromethyl)benzylamino)-1-(4-methoxybenzo[*a*][1,3]dioxol-6-yl)propane-1,2-diol 23

Oil, yield 82%; $[\alpha]_D = -21.1$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.08 (d, 1H, *J* = 12 Hz, 1H), 2.80–2.89 (m,1H), 3.78–3.84 (m, 3H), 3.87 (s, 3H), 4.71–4.72 (m, 1H), 5.95 (s, 2H), 6.50 (d, 1H, *J* = 3.0 Hz), 6.52 (s, 1H), 7.47–7.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.0, 56.6, 59.6, 71.8, 75.5, 100.1, 101.5, 105.6, 124.8, 125.4, 125.7, 129.2, 132.1, 134.7, 135.0, 143.6, 149.0; HRESIMS *m/z* $[M]^+$ found 399.1227; calcd 399.1294 for $C_{19}H_{20}F_3NO_5$.

5.5.6. (1*R*,2*S*)-3-(4-(Trifluoromethyl)benzylamino)-1-(4-methoxybenzo[*a*][1,3]dioxol-6-yl)propane-1,2-diol 24

Yellow oil, yield 80%; $[\alpha]_D = -23.1$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 2.63–2.57 (m, 1H), 2.84–2.91 (m, 1H), 3.85–3.93 (m, 1H), 3.85 (s, 3H), 3.83–3.88 (m, 2H), 4.75 (br s, 1H), 5.93 (s, 2H), 6.50 (d, 2H, *J* = 3.6 Hz), 7.28 (d, 2H, *J* = 9.9 Hz), 7.51 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.2, 143.8, 134.9, 134.6, 130.1, 125.5, 105.9, 101.5, 100.2, 75. 3, 71.2, 59.0, 56.7, 54.9; HRESIMS *m/z* $[M]^+$ found 399.1263; calcd 399.1294 for $C_{19}H_{20}F_3NO_5$.

5.5.7. 1-(2-Mercapto-1*H*-benzo[d]imidazol-1-yl)-2-(4-methoxybenzo[*d*]dioxol-6-yl)ethane-1,2-diol 25

Oil, yield 70%; $[\alpha]_D = -7.1$ (*c* 0.8, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$): δ 3.49–3.38 (m, 1H), 3.69–3.72 (m, 1H), 3.89 (s, 3H), 4.02–4.06 (m, 1H), 4.57 (d, 1H, *J* = 7.2 Hz), 5.94 (s, 2H), 6.68 (s, 2H), 7.12–7.16 (m, 2H), 7.41–7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 153.1, 147.8, 142.7, 138.8, 134.7, 126.5, 125.5, 106.25, 106.0, 80.1, 79.3, 61.3, 41.0; HRESIMS *m/z* $[M]^+$ found 374.0929; calcd 374.0936 for $C_{18}H_{18}N_2O_5S$.

5.5.8. 1-(5-Mercapto-1*H*-1,2,4-triazol-3-ylamino)-2-(4-methoxybenzo[*d*][1,3]dioxol-6-yl)ethane-1,2-diol 26

Oil, yield 83%; $[\alpha]_D = -15.3$ (*c* 0.76, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD): δ 3.02–3.08 (m, 1H), 3.18–3.30 (m, 1H), 3.77 (s, 3H), 3.70–3.80 (m, 1H), 4.42 (d, 2H, *J* = 6.6 Hz), 5.81 (s, 2H), 6.49 (d,1H, *J* = 1.2 Hz), 6.54 (d, 1H, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, CD_3OD): δ 150.1, 144.7, 137.6, 135.9, 108.9, 102.5, 102.3, 76.8, 75.8, 57.2, 36.6; HRESIMS *m/z* $[M]^+$ found 340.0834; calcd 340.0841 for $C_{13}H_{16}N_4O_5S$.

5.5.9. 1-(2,5-Dihydro-5-mercapto-1,3,4-thiazol-2-ylamino)-2-(4-ethoxybenzo [*d*][1,3]dioxol-6-yl)ethane-1,2-diol 27

Oil, yield 90%; $[\alpha]_D = -13.1$ (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, acetone-d_6): δ 3.20–3.30 (m, 1H), 3.48–3.38 (m,1H), 3.86 (s, 3H), 3.90–3.98 (m, 1H), 4.59 (d, 1H, *J* = 6.0 Hz), 5.94 (s, 2H), 6.63 (d, 1H, *J* = 1.2 Hz), 6.69 (d, 1H, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, acetone-d_6): δ 148.1, 142.8, 138.4, 136.4, 133.7, 113.2, 106.2, 100.5, 100.3, 75.0, 73.9, 55.4, 37.6; HRESIMS *m/z* $[M]^+$ found 357.0402; calcd 357.0453 for $C_{13}H_{15}N_3O_5S_2$.

5.6. Cytotoxicity evaluation

All the derivatives were tested for in vitro cytotoxicity on different cancer cell lines by MTT assay. The cell lines used in this study were Colo-205 (Colon-cancer), A-431 (Skin cancer), and MCF-7 (breast cancer). All the cells were obtained from National Center for cellular Sciences (NCCS)-Pune, India. DMEM (Dulbeccos Modified eagles medium), MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide], trypsin, and EDTA were purchased from sigma chemicals Co (St. Louis, MO), and Fetal bovine serum was purchased from Gibco.

Cells in 96 well plates were incubated with compounds tested for 48 h at 37 °C in DMEM with 10% FBS medium. Then, the above media were replaced with 90 μl of fresh serum-free DMEM and 10 μl of MTT reagent (5 mg/mL), and plates were incubated at 37 °C for 4 h, thereafter above media were replaced with 200 μl of DMSO and incubated at 37 °C for 15 min. The absorbance at 570 nm was measured on a spectrophotometer (Spectra max, Molecular devices). The values for each point were calculated from the triplicate wells.

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