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Synthetic studies on Ecteinascidin-743: synthesis of building blocks through Sharpless asymmetric dihydroxylation and aza-Michael reactions☆

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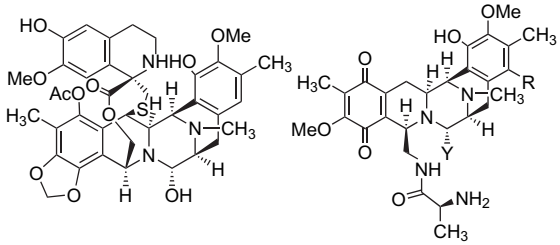
Abstract—A practical and an efficient synthesis of three building blocks of tetrahydroisoquinoline alkaloid Ecteinascidin-743 was accomplished, starting from readily available piperonal, 2-methyl anisole, and veratraldehyde. A combination of Vilsmeier–Haack reaction and Sharpless asymmetric dihydroxylation was employed for the synthesis of building blocks **A** and **B** whereas a Heck reaction in PEG-2000 and aza-Michael reactions were employed for the synthesis of building block **C**.

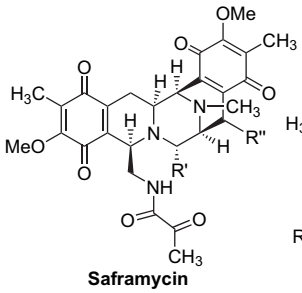
1. Introduction

The chemistry of tetrahydroisoquinoline alkaloids has attracted considerable interest over the years due to their potent biological properties.[1] Ecteinascidin-743 (ET-743) is a marine tetrahydroisoquinoline natural product isolated from *Ecteinascidia turbinata* by Rinehart et al.,[2] in 1990, which has been demonstrated to be a highly promising, exceedingly potent anti-tumor agent currently in phase II/III clinical trials and also attracting considerable attention owing to its unique mechanism of action.[3] The novel structure of ET-743 combined with the natural scarcity and remarkable biological activities make it an attractive and important synthetic target. ET-743 is structurally related to Safracin,[4] Saframycin,[5] and Reniaramycins,[6] which are also potent anti-tumor antibiotics that contain densely functionalized tetrahydroisoquinoline ring systems constituted from similar amino acid components.[7]

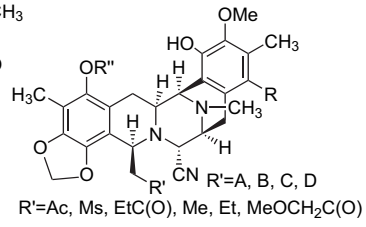


Ecteinascidin-*743*

safracin A : R=Y=H; R=Br, Y=H
B : R=H, Y=OH; R=H, Y=CN



Saframycin



R'=A, B, C, D
R'=Ac, Ms, EtC(O), Me, Et, MeOCH$_2$C(O)

Phthalascidin analogs

The first total synthesis was achieved by Corey[8] and later Fukuyama[9] and Zhu[10] have achieved two total syntheses. Cuevas and co-workers at pharmaMar have developed a semi-synthesis of ET-743 from Cyanosafracin B.[11] Corey and co-workers prepared a similar synthetic analogue of ET-743 (Phthlascidin, Pt-650) that exhibited virtually the same cytotoxicity as the natural product.[12] Other synthetic approaches have been reported from a number of research groups including those of Kubo,[13] Danishefsky,[14] Williams,[15] Liu,[16] and Magnus.[17]

2. Results and discussion

Our continued interest in the development of new protocols for the synthesis of nitrogen containing heterocycles[18] and hybrid natural products[19] related to anti-tumor compounds prompted us to adopt a convergent strategy for the synthesis of ET-743 and identify the three building blocks **A**–**C**. The retrosynthetic analysis revealed that the fully functionalized

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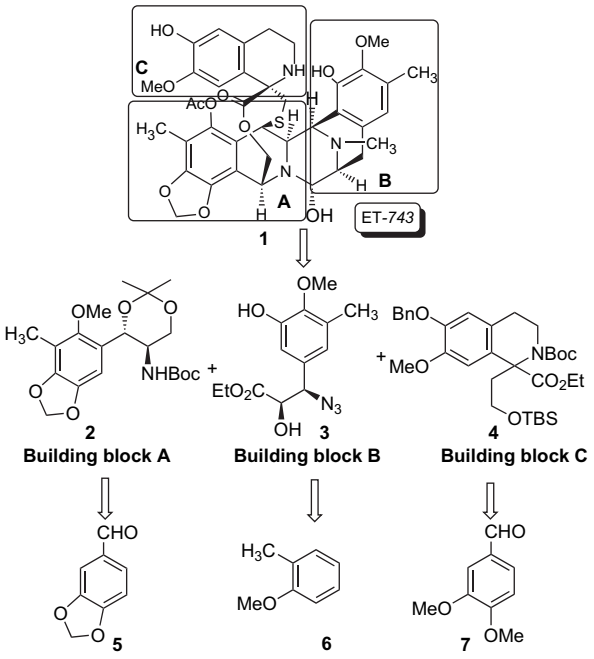
dihydroxy cinnamate esters could be useful chiral materials, which should furnish the desired stereochemistry at C-2 and C-3 in the target building blocks **A** and **B**. Building block **C** could be obtained from a Heck reaction, aza-Michael reaction, and carboxylation of a phenyl ethylamine derivative. Synthesis of these building blocks commenced with inexpensive and readily available starting materials piperonal, 2-methyl anisole, and veratraldehyde (Scheme 1), respectively.

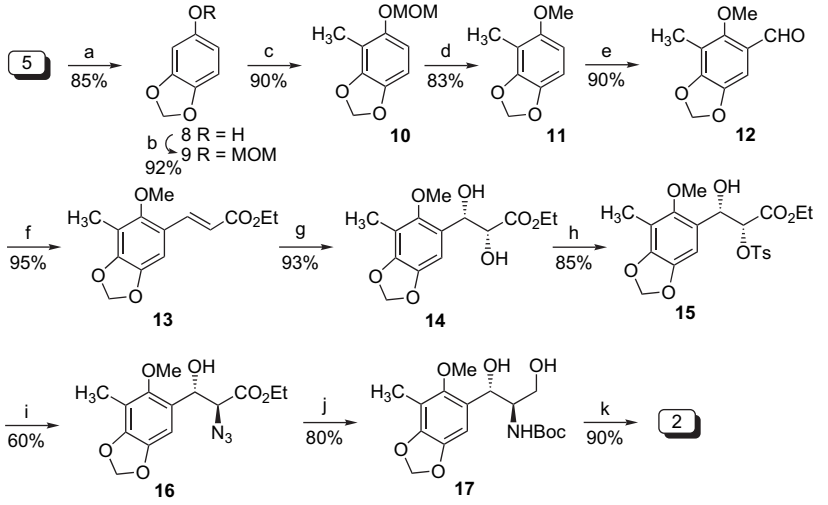


Scheme 1.

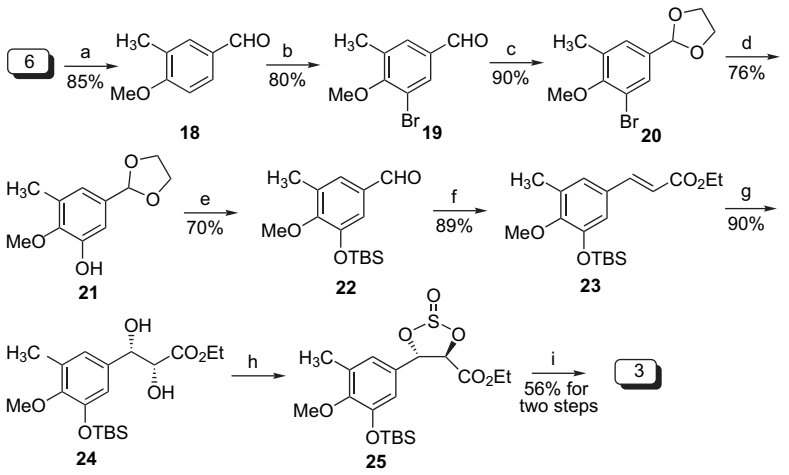
The chemical route for the synthesis of building block **A** (**2**) is shown in Scheme 2. The Baeyer–Villiger oxidation[20] of piperonal **5** using *m*-chloroperoxybenzoic acid followed by base hydrolysis gave the phenol **8**, which was protected as its MOM ether **9** using diisopropylethylamine (DIPEA) and methoxymethyl chloride (MOMCl). Selective monomethylation of compound **9** carried out at −78 °C using ^{n}BuLi, tetramethylethylenediamine (TMEDA) followed by methyl iodide gave the compound **10**. The MOM ether group in **10** was converted to methyl ether **11** by two-step sequence viz., deprotection of MOM group of the compound **5** using concd HCl in refluxing ethanol[21] followed by methylation using K_2CO_3 and methyl iodide in acetone. The Vilsmeier–Haack formylation[22,20b] of compound **11** using $POCl_3$/dimethylformamide gave the aldehyde **12**. Two-carbon homologation of aldehyde **12** using ethoxycarbonylmethylene triphenylphosphine in benzene at room temperature gave the unsaturated ester **13**.

The Sharpless asymmetric dihydroxylation[23] of unsaturated ester **13** using AD mix-α in ^{t}BuOH–H_2O (1:1) for 12 h gave the diol **14** with 97% ee. The aim of selective α-tosylation of diol **14** was achieved with tosyl chloride and triethyl amine in CH_2Cl_2 to yield the mono-tosylated compound **15**.[24] α-Azido ester **16** was synthesized from mono-tosylated compound **15** using sodium azide in *N*,*N*-dimethylformamide at 65 °C. *N*-Boc protected amino diol **17** was obtained from the α-azido ester **16** by the two-step sequence; lithium aluminum hydride reduction followed by in situ Boc protection using $(Boc)_2O$ to give the Boc protected amino diol **17**. Selective 1,3-acetonide protection of compound **17** using 2,2-dimethoxypropane, camphor sulfonic acid in acetone gave the building block **A** (**2**) (Scheme 2).

Building block **B** was synthesized from 2-methyl anisole **6**. Vilsmeier–Haack formylation of 2-methyl anisole **6** using $POCl_3$/DMF gave the aldehyde **18**. Bromination of aldehyde **18** using *N*-bromosuccinamide in acetonitrile at room temperature for 24 h gave the bromo compound **19**.[25] Ethylene glycol protection of bromo compound **19** with cat. PTSA afforded the compound **20**. This was converted to TBS ether **22** by a three-step sequence: conversion of the bromide to phenol **21** using ^{n}BuLi, trimethyl borate, and 4-methyl morpholine *N*-oxide in tetrahydrofuran under refluxing conditions,[26] cleavage of the ethylene glycol moiety, which was followed by protection of phenol **21** as its TBS ether **22** using *tert*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2. This is concise method for the synthesis of aldehyde **22**



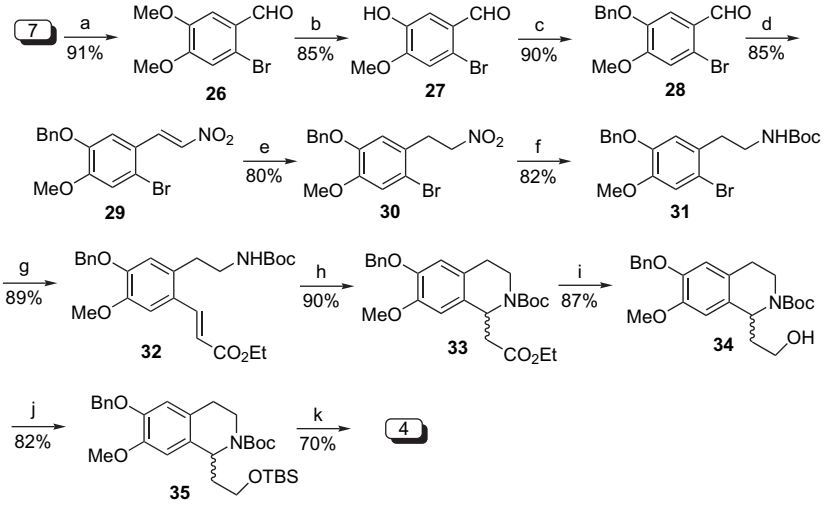
Scheme 2. (a) *m*-CPBA, CH_2Cl_2, aq KOH; (b) DIPEA, MOMCl; (c) ^{n}BuLi, TMEDA, MeI, −78 °C, THF; (d) (i) HCl, EtOH; (ii) K_2CO_3, MeI, acetone; (e) DMF–$POCl_3$; (f) ethoxycarbonylmethylenetriphenyl phosphine, benzene; (g) AD mix-α, ^{t}BuOH–H_2O (1:1); (h) TsCl, TEA, CH_2Cl_2; (i) NaN_3, DMF, 65 °C; (j) LAH, $(Boc)_2O$, THF; (k) 2,2-DMP, CSA, acetone.



Scheme 3. (a) DMF–$POCl_3$; (b) NBS, acetonitrile; (c) ethylene glycol, PTSA, benzene; (d) ^{n}BuLi, $B(OMe)_3$, NMO, THF; (e) (i) HCl, THF–H_2O; (ii) TBSCl, imidazole, CH_2Cl_2; (f) ethoxycarbonylmethylenetriphenyl phosphine, benzene; (g) AD mix-α, ^{t}BuOH–H_2O (1:1); (h) $SOCl_2$, TEA, CH_2Cl_2; (i) NaN_3, DMF, 65 °C.

from inexpensive 2-methyl anisole **6**. The two-carbon homologation of compound **22** was carried out by Wittig olefination protocol using ethoxycarbonylmethylene triphenylphosphine in benzene to give the unsaturated ester **23**. The Sharpless asymmetric dihydroxylation of unsaturated ester **23** using AD mix-α furnished the diol **24** in high enantiomeric purity (98% ee). Both the dihydroxylation reactions proceeded smoothly at room temperature in the absence of methane sulfonamide. To get the β-azido functionality, diol **24** was converted as its cyclic sulfite **25** using $SOCl_2$ and TEA followed by regioselective opening of this cyclic sulfite **25** using NaN_3 in DMF to get the β-azido ester (building block **B**) exclusively (Scheme 3).[27] This building block not only is a key intermediate for the synthesis of Ecteinascidin analogs but also for the synthesis of substituted α-hydroxy-β-phenyl alanines.[28]

Synthesis of building block **C** (**4**) started from veratraldehyde **7**. Selective bromination of veratraldehyde **7** using Br_2 in MeOH at <40 °C temperature gave the bromo compound **26**. The 5-methoxy group was selectively deprotected in the compound **26**, which was carried out using H_2SO_4 at 90 °C to give **27**.[29] Phenol **27** was protected as its benzyl ether using K_2CO_3 and benzyl bromide in acetone under reflux conditions to yield the aldehyde **28**. The next step was nitro-aldol condensation of aldehyde **28** with nitro methane and ammonium acetate in acetic acid to afford the unsaturated nitro compound **29**. Conversion of unsaturated nitro compound **29** to saturated nitro compound **30** was achieved with sodiumborohydride in EtOH at 0 °C. Lithium aluminum hydride reduction of nitro compound **30** gave the amine, which was in situ protected with $(Boc)_2O$ to yield the compound **31**. The palladium catalyzed Heck reaction of compound **31** with ethyl acrylate in polyethylene glycol (PEG-2000) gave the unsaturated ester **32**.[30] The compound **32** was subjected to aza-Michael reaction after –Boc deprotection followed by reprotection with $(Boc)_2O$ to yield tetrahydroisoquinoline **33**. Reduction of ester group to primary alcohol **34** followed by TBS protection and carboxylation yielded building block **C** (**4**) (Scheme 4).



Scheme 4. (a) Br_2, MeOH, <40 °C; (b) H_2SO_4, 90 °C; (c) K_2CO_3, BnBr, acetone; (d) nitro methane, ammonium acetate, acetic acid; (e) $NaBH_4$, EtOH; (f) LAH, $(Boc)_2O$, THF; (g) ethyl acrylate, $Pd(OAc)_2$, TEA, PEG-2000, 80 °C; (h) TFA, CH_2Cl_2, Na_2CO_3, $(Boc)_2O$; (i) $NaBH_4$, LiCl, EtOH–THF (1:1); (j) TBSCl, imidazole, CH_2Cl_2; (k) ^{n}BuLi, $ClCO_2Et$, THF.

3. Conclusion

In conclusion, we have successfully achieved the synthesis of three building blocks of ET-743 from piperonal, 2-methyl anisole, and veratraldehyde. Simple and efficient methods like Baeyer–Villiger oxidation, Vilsmeier–Haack formylation, Sharpless asymmetric dihydroxylation, and Heck reaction in PEG-2000 and aza-Michael reactions have been employed for the synthesis of these building blocks. These building blocks are also useful for the synthesis of other tetrahydroisoquinoline natural products like Saframycin, Safracin, etc. The building blocks will be utilized in the construction of hybrid natural products toward creating diverse scaffolds for screening against biological targets. The work in this direction is currently underway in our group.[31]

4. Experimental section

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 meshes. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometer. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in hertz. HPLC was recorded on SHIMADZU HPLC using chiralcel OB-H column, and hexane and isopropyl alcohol as eluents. Melting points (uncorrected) were obtained using a Buchi 535 melting point apparatus. Mass spectra were obtained on Finnegan MAT 1020B or micromass VG 70-70H spectrometer operating at 70 eV using direct inlet system.

4.1.1. 5-Methoxy methoxy benzo[*d*][1,3] dioxole (9).[21] Piperonal **5** (5.0 g, 33 mmol) and *m*-CPBA (8.4 g, 48 mmol) were refluxed in dry CH_2Cl_2 (75 mL) for 18 h. Most of the CH_2Cl_2 was removed by distillation under reduced pressure and the residue was dissolved in ethyl acetate (75 mL). The solution was washed with aq $NaHCO_3$ until effervescence ceased, then with brine, and dried over anhydrous sodium sulfate. Removal of the solvent left crude formate. The crude formate was dissolved in a little MeOH and hydrolyzed under nitrogen with a slight excess of 10% aq KOH at room temperature. After the completion of the reaction, the reaction mixture was acidified with dilute HCl and extracted with ethyl acetate twice (2×100 mL). The combined organic layers were washed with water, brine, and removal of the solvent gave phenol **8** (3.9 g, 85%), which was used further without purification. The crude phenol **8** (3.9 g, 28 mmol) and DIPEA (7.35 mL, 42 mmol) were taken in dry CH_2Cl_2 (50 mL) at 0 °C. After 10 min methoxymethyl chloride (2.27 g, 28 mmol) was added and the mixture stirred for 8 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with water and aqueous phase was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, and the solvent removed in vacuo. The crude product was purified by silica gel column chromatography to give the MOM ether **9** (4.7 g, 92%) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.65 (d, J=13.0 Hz, 1H, Ar), 6.57 (s, 1H, Ar), 6.45 (d, J=13.0 Hz, 1H, Ar), 5.90 (s, 2H, OCH_2O), 5.05 (s, 2H, OCH_2OCH_3), 3.48 (s, 3H, OCH_3); EIMS *m*/*z* 182 (M^+); IR (neat): 3080, 1300, 900 cm^{-1}.

4.1.2. 5-Methoxy methoxy-4-methyl benzo[*d*][1,3] dioxole (10).[21] A solution of MOM ether **9** (4.5 g, 24 mmol) in dry THF (75 mL) at −78 °C was treated with *n*-butyl lithium (23.1 mL, 1.6 M solution in hexane, 37 mmol) under inert atmosphere. The mixture was stirred at −78 °C for 10 min, added tetramethylethylenediamine (3.71 mL, 24 mmol) followed by MeI (1.53 mL, 24 mmol), and allowed it to warm to room temperature over a period of 2 h. Stirring was continued for another 10 h, reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (75 mL). Organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography to yield the alkylated product **10** (4.36 g, 90%) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.51 (d, J=8.6 Hz, 1H, Ar), 6.46 (d, J=8.6 Hz, 1H, Ar), 5.88 (s, 2H, OCH_2O), 5.07 (s, 2H, OCH_2OCH_3), 3.46 (s, 3H, OCH_3), 2.10 (s, 3H, $ArCH_3$); EIMS: *m*/*z* 196 (M^+); IR (neat): 3065, 1590, 890 cm^{-1}.

4.1.3. 5-Methoxy-4-methyl benzo[*d*][1,3] dioxole (11).[21,32] Concd HCl (0.5 mL) was added to a stirred solution of MOM ether **10** (4.0 g, 25 mmol) in ethanol (40 mL) and the resulting solution was refluxed for 1–3 h. After completion of the reaction (monitored by TLC) the solvent was removed in vacuo and residue was diluted with 5% $NaHCO_3$ and extracted with ethyl acetate (50 mL). Organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the phenol. To this phenol (3.0 g, 19 mmol) in acetone (30 mL) was added K_2CO_3 (5.44 g, 39 mmol) followed by MeI (2.45 mL, 39 mmol). The reaction mixture was heated to reflux (under cold water circulation) for 5 h. Reaction mixture was filtered, filtrate was concentrated in vacuo and the crude product was purified by silica gel column chromatography to afford the methyl ether **11** (3.0 g, 83% for two steps) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.53 (d, J=8.0 Hz, 1H, Ar), 6.18 (d, J=8.0 Hz, 1H, Ar), 5.85 (s, 2H, OCH_2O), 3.74 (s, 3H, OCH_3), 2.06 (s, 3H, $ArCH_3$); EIMS: *m*/*z* 166 (M^+); IR (neat): 3072, 1580, 760 cm^{-1}.

4.1.4. 6-Methoxy-7-methyl benzo[*d*][1,3] dioxole-5-carbaldehyde (12). The Vilsmeier complex was prepared by the drop wise addition of freshly distilled $POCl_3$ (1.98 mL) to dry *N*,*N*-dimethylformamide (6 mL) during 15 min with stirring and cooling in ice bath. The complex was allowed to warm to room temperature and was then added drop wise to a stirred solution of the methyl ether **11** (3.0 g, 18 mmol) in dry DMF (6 mL) at 100–110 °C. Heating and stirring were continued till completion of the reaction

(1–2 h). The mixture was poured into ice water, made just basic by the addition of aq sodium carbonate, and exhaustively extracted with ethyl acetate (3×40 mL), the combined extracts were washed successively with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to yield the aldehyde **12** (3.15 g, 90%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.18 (s, 1H, C*H*O), 7.12 (s, 1H, Ar), 6.05 (s, 2H, OCH_2O), 3.86 (s, 3H, OCH_3), 2.21 (s, 3H, ArCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.4, 160.0, 152.5, 144.0, 123.2, 113.5, 103.2, 102.0, 63.7, 8.6; EIMS: *m*/*z* 196 (M^++2), 194 (M^+), 151, 121, 67, 65; HRMS-EI calcd for $C_{10}H_{10}O_4$: 194.0579; found: 194.0576; mp 74–76 °C; IR (KBr): 2915, 1672, 1610, 1416, 1279, 927, 580 cm^{-1}.

4.1.5. Ethyl-3-(6-methoxy-7-methyl benzo[*d*][1,3] dioxol-5-yl)-(*E*)-2-propionate (13). To a stirred solution of aldehyde **12** (3.0 g, 15 mmol) in benzene (60 mL) was added ethoxycarbonylmethylene triphenylphosphine (8 g, 23 mmol) at room temperature under inert atmosphere. The reaction mixture was stirred at room temperature for 24 h. Solvent was removed under reduced pressure and residue was purified by silica gel column chromatography using hexane–ethyl acetate system to afford the unsaturated ester **13** (3.87 g, 95%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (d, *J*=16.3 Hz, 1H, ArC*H*=), 6.86 (s, 1H, Ar), 6.25 (d, *J*=16.3 Hz, 1H, =C*H*CO_2Et), 5.96 (s, 2H, OCH_2O), 4.27 (q, *J*=7.4 Hz, 2H, OC$H_2$$CH_3$), 3.72 (s, 3H, OC$H_3$), 2.18 (s, 3H, ArC$H_3$), 1.33 (t, *J*=7.4 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.2, 154.2, 148.8, 143.6, 139.3, 120.5, 116.5, 113.6, 102.6, 101.5, 62.1, 60.2, 14.3, 9.0; EIMS: *m*/*z* 264 (M^+), 234, 206, 178, 176, 147; HRMS-EI calcd for $C_{14}H_{16}O_5$: 264.0997; found: 264.1002; mp 98–100 °C; IR (KBr): 2982, 1708, 1617, 1474, 1278 cm^{-1}.

4.1.6. Ethyl-(2*R*,3*S*)-dihydroxy-3-(6-methoxy-7-methyl-benzo[*d*][1,3] dioxol-5-yl) propionate (14). To a stirred solution of AD mix-α (18.0 g) in *tert*-butyl alcohol (50 mL) and water (50 mL) at room temperature was added unsaturated ester **13** (3.5 g, 13 mmol). The reaction was stirred at room temperature for 12 h. Sodium sulfite (18.0 g) was added as a solid at 0 °C and the mixture was stirred for 30 min. Ethyl acetate (100 mL) was added; organic layer was separated, washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The pure product **14** (3.67 g, 93%) was obtained as a white solid by silica gel column chromatography with hexane–ethyl acetate (70:30) as an eluent. Enantiomeric excess was determined by HPLC using chiralcel OB-H column, and isopropanol and hexane as eluents (1:9); flow rate 1 mL/min; major isomer t_R 40.54 min, minor enantiomer t_R 42.39 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.79 (s, 1H, Ar), 5.92 (s, 2H, OCH_2O), 5.10–5.05 (m, 1H, ArC*H*OH), 4.28–4.20 (m, 3H, OC$H_2$$CH_3$, C*H*$CO_2$Et), 3.73 (s, 3H, OC$H_3$), 3.12–3.06 (br s, 1H, OH), 2.92–2.86 (br s, 1H, OH), 2.15 (s, 3H, $ArCH_3$), 1.28 (t, *J*=6.4 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.8, 150.6, 146.4, 143.2, 125.2, 113.0, 104.1, 101.1, 74.3, 69.9, 62.0, 61.1, 13.9, 9.2; EIMS: *m*/*z* 298 (M^+), 196, 180, 165, 137; HRMS-EI calcd for $C_{14}H_{18}O_7$: 298.1052; found: 298.1058; mp 114 °C; $[\alpha]_D^{25}$ −12.35 (*c* 1.00, $CHCl_3$); IR (KBr): 3500, 2926, 1733, 1412, 1208, 1091 cm^{-1}.

4.1.7. Ethyl-(3*S*)-hydroxy-3-(6-methoxy-7-methyl-benzo-[*d*][1,3] dioxol-5-yl)-2-(4-methyl phenyl sulfonyloxy)-(2*R*)-propionate (15). To a stirred solution of diol **14** (3.5 g, 11 mmol) in CH_2Cl_2 (40 mL) at 0 °C under nitrogen was added triethyl amine (2.39 mL, 17 mmol) followed by tosyl chloride (2.24 g, 17 mmol). After being stirred for 15 h at room temperature, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to afford the tosylated product **15** (4.50 g, 85%) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (d, *J*=8.2 Hz, 2H, Ar), 7.16 (d, *J*=8.2 Hz, 2H, Ar), 6.57 (s, 1H, Ar), 5.93 (s, 1H, OCH_2O), 5.88 (s, 1H, OCH_2O), 5.19–5.15 (m, 1H, ArC*H*OH), 4.94 (d, *J*=3.5 Hz, 1H, C*H*CO_2Et), 4.20 (q, *J*=7.0 Hz, 2H, OC$H_2$$CH_3$) 3.66 (s, 3H, OC$H_3$), 2.72–2.68 (m, 1H, O*H*), 2.42 (s, 3H, tosyl CH_3), 2.02 (s, 3H, ArCH_3), 1.26 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.0, 150.1, 146.5, 144.5, 142.9, 132.5, 129.2, 127.7, 122.7, 112.8, 104.1, 101.1, 80.4, 69.6, 62.0, 60.8, 21.5, 13.9, 9.1; EIMS: *m*/*z* 452 (M^+); HRMS-EI calcd for $C_{21}H_{24}O_9S$: 452.1141; found: 452.1143; mp 113 °C; $[\alpha]_D^{25}$ +47.8 (*c* 1.00, $CHCl_3$); IR (KBr): 3520, 2931, 1760, 1472, 1368, 1091, 794 cm^{-1}.

4.1.8. Ethyl-2-azido-(3*S*)-hydroxy-3-(6-methoxy-7-methyl-benzo[*d*][1,3] dioxol-5-yl)-(2*S*)-propionate (16). To a stirred solution of tosylate **15** (4.5 g, 9 mmol) in DMF (30 mL) was added NaN_3 (1.94 g, 29 mmol) as a solid in one portion. The temperature was raised to 65 °C for 12 h and then cooled to room temperature and the mixture was diluted with water, and extracted with ethyl acetate (2×60 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Solvent was removed and the crude product was purified by silica gel column chromatography (ethyl acetate–hexane 20:80) to yield the azide **16** (1.90 g, 60%) as pale yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.67 (s, 1H, Ar), 5.94 (s, 2H, OCH_2O), 5.10 (d, *J*=6.0 Hz, 1H, ArC*H*OH), 4.24 (q, *J*=7.0 Hz, 2H, OC$H_2$$CH_3$), 4.07 (d, *J*=6.0 Hz, 1H, C*H*CO_2Et), 3.75 (s, 3H, OCH_3), 2.99–2.95 (br s, 1H, O*H*), 2.17 (s, 3H, ArCH_3), 1.29 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.1, 151.4, 146.9, 143.3, 124.0, 113.3, 103.8, 101.2, 69.5, 65.9, 61.9, 61.4, 14.0, 9.3; EIMS: *m*/*z* 323 (M^+), 196, 165, 137, 67, 38; HRMS-EI calcd for $C_{14}H_{17}N_3O_6$: 323.1117; found: 323.1120; mp 109 °C; $[\alpha]_D^{25}$ −13.16 (*c* 0.60, $CHCl_3$); IR (KBr): 3500, 2931, 2108, 1736, 1472, 1090 cm^{-1}.

4.1.9. [2*S*-Hydroxy-1*R*-hydroxymethyl-2-(6-methoxy-7-methyl-benzo[1,3] dioxol-5-yl)-ethyl]-carbamic acid *tert*-butyl ester (17). To an ice-cold suspension of LAH (0.7 g, 18 mmol) in dry THF (15 mL) under nitrogen was added azido ester **16** (1.5 g, 4.6 mmol) in THF (20 mL).

The reaction mixture was stirred at room temperature for 2 h and then refluxed for 2 h until no starting material was observed. Reaction mixture was quenched with aq NaOH and water, then $(Boc)_2O$ (1.5 g, 6.9 mmol) in THF (15 mL) was added and stirring was continued for 4 h at room temperature. After completion of the reaction, the reaction mixture was filtered over the Celite and washed with ethyl acetate, filtrate was concentrated in vacuo and crude residue was purified by silica gel column chromatography to give the amino diol **17** (1.30 g, 80%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.76 (s, 1H, Ar), 5.92 (s, 2H, OCH_2O), 5.20 (d, J=7.8 Hz, 1H, ArC*H*OH), 5.08 (br s, 1H, N*H*), 4.12–4.02 (m, 1H, C*H*NH), 3.90–3.50 (m, 5H, OCH_3, CH_2OH), 3.20 (br s, 1H, O*H*), 2.17 (s, 3H, $ArCH_3$), 1.40 (s, 9H, Boc); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.3, 150.4, 146.2, 143.3, 130.0, 128.2, 126.0, 104.0, 101.1, 70.8, 62.7, 61.1, 56.3, 28.2, 9.2; ESI-MS: *m*/*z* 378 (M^++Na), 355 (M^+); HRMS-EI calcd for $C_{17}H_{25}NO_7$: 355.1631; found: 355.1628; $[\alpha]_D^{25}$ +13.6 (*c* 1.00, $CHCl_3$); IR (KBr): 3502, 2930, 1620, 1320, 895 cm^{-1}.

4.1.10. [4*S*-(6-Methoxy-7-methyl-benzo[1,3] dioxol-5-yl)-2,2-dimethyl[1,3] dioxan-5*R*-yl]ethyl]-carbamic acid *tert*-butyl ester (2). The amino diol **17** (1.0 g, 2.8 mmol) was dissolved in a mixture of acetone (10 mL) and 2,2-DMP (0.34 mL, 2.8 mmol) and a catalytic amount of CSA was added. The resulting solution was stirred at room temperature for 2 h. The reaction was quenched by the addition of triethyl amine and solvent was removed in vacuo to give the crude product, which was purified by silica gel column chromatography to give **2** (1.0 g, 90%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.83 (s, 1H, Ar), 5.91 (s, 2H, OCH_2O), 4.93 (d, J=8.8 Hz, 1H, ArC*H*O), 4.63 (br s, 1H, N*H*), 4.16–4.10 (m, 1H, C*H*NH), 3.80–3.50 (m, 5H, OCH_3, CH_2O), 2.17 (s, 3H, $ArCH_3$), 1.60 (s, 3H, $CH(CH_3)_2$), 1.46 (s, 3H, $CH(CH_3)_2$), 1.35 (s, 9H, Boc); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.6, 151.0, 146.2, 143.2, 129.5, 127.7, 123.3, 103.9, 100.6, 98.6, 68.1, 63.5, 60.8, 50.2, 28.5, 27.8, 27.6, 8.7; ESI-MS: *m*/*z* 418 (M^++Na); Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.47; H, 7.28; N, 3.62; $[\alpha]_D^{25}$ −9.16 (*c* 3.00, $CHCl_3$); IR (KBr): 2995, 1608, 1400, 960 cm^{-1}.

4.1.11. 4-Methoxy-3-methyl benzaldehyde (18).[33] This compound was prepared in the same way as aldehyde **12**, from 2-methyl anisole **6** (3.10 g, 25 mmol). The crude product was purified by column chromatography to afford **18** (3.13 g, 85%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.84 (s, 1H, C*H*O), 7.72 (d, J=9.0 Hz, 1H, Ar), 7.61 (s, 1H, Ar), 6.84 (d, J=9.0 Hz, 1H, Ar), 3.89 (s, 3H, OCH_3), 2.26 (s, 3H, $ArCH_3$); FABMS: *m*/*z* 150 (M^+); IR (KBr): 2350, 1670, 1580, 1260, 730 cm^{-1}.

4.1.12. 3-Bromo-4-methoxy-5-methyl benzaldehyde (19).[34] To a stirred solution of aldehyde **18** (3.0 g, 20 mmol) in acetonitrile (30 mL) was added *N*-bromosuccinimide (7.12 g, 40 mmol) at 0 °C under inert atmosphere. The reaction mixture was stirred for 24 h at room temperature, after completion of the reaction (monitored by TLC), diluted with ethyl acetate (60 mL), washed with water, brine, dried over anhydrous Na_2SO_4, removal of the solvent under vacuo, and purified by silica gel column chromatography to give the bromo compound **19** (3.66 g, 80%) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.95 (s, 1H, C*H*O), 7.90 (s, 1H, Ar), 7.64 (s, 1H, Ar), 3.85 (s, 3H, OCH_3), 2.40 (s, 3H, $ArCH_3$); EIMS: *m*/*z* 228 (M^+), 149, 77, 51; IR (KBr): 2352, 1660, 1570, 1210, 675 cm^{-1}.

4.1.13. 2-(3-Bromo-4-methoxy-5-methyl phenyl)-1,3-dioxolane (20). A 250 mL RB flask was charged with aldehyde **19** (3.6 g, 16 mmol), ethylene glycol (1.73 g, 27 mmol), benzene (100 mL) and catalytic amount of PTSA mono-hydrate. The flask was attached to a water separator under reflux condenser fitted with drying tube. An oil bath was placed under the flask and the reaction mixture was refluxed until close to theoretical amount of water collected in the trap, this requires about 9 h. The reaction a mixture was cooled to room temperature, solvent was removed, basified with $NaHCO_3$, extracted with ethyl acetate (2×100 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Crude residue was purified by silica gel column chromatography to give the product **20** (3.86 g, 90%) as colorless liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45 (s, 1H, Ar), 7.16 (s, 1H, Ar), 5.66 (s, 1H, OC*H*O), 4.10–3.90 (m, 4H, OCH_2CH_2O), 3.76 (s, 3H, OCH_3), 2.32 (s, 3H, $ArCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.8, 131.7, 130.2, 129.3, 126.6, 112.0, 108.8, 66.2, 55.5, 14.0; FABMS: *m*/*z* 272 (M^+); HRMS-FAB calcd for $C_{11}H_{13}BrO_3$: 272.0048; found: 272.0043; IR (KBr): 3030, 1598, 1330, 720, 682 cm^{-1}.

4.1.14. 2-(3-Hydroxy-4-methoxy-5-methyl phenyl)-1,3-dioxolane (21). A solution of bromo compound **20** (3.8 g, 13 mmol) in THF (40 mL) at −78 °C was treated with *n*-butyl lithium (1.06 g, 16 mmol). The mixture was stirred at −78 °C for 15 min, treated with trimethyl borate (4.3 g, 41 mmol) and allowed to warm to room temperature over a period of 2 h. An excess of anhydrous NMO (4.38 g, 41 mmol) was then added to the solution under a positive pressure of nitrogen and the resulting suspension was refluxed for 12 h. After dilution in ether the reaction mixture was hydrolyzed with water and the organic phase washed with water to reach pH −7. The solvent was removed under reduced pressure and crude residue was purified by silica gel column chromatography to afford the pure product **21** (2.2 g, 76%) as colorless viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.88 (s, 1H, Ar), 6.80 (s, 1H, Ar), 6.68 (s, 1H, O*H*), 5.60 (s, 1H, OC*H*O), 4.20–4.00 (m, 4H, OCH_2CH_2O), 3.80 (s, 3H, OCH_3), 2.33 (s, 3H, $ArCH_3$); FABMS: *m*/*z* 209 (M^+); IR (KBr): 3620, 3040, 1400, 960 cm^{-1}.

4.1.15. 3-(*tert*-Butyl-dimethyl-silanyloxy)-4-methoxy-5-methyl-benzaldehyde (22). Compound **21** (2.0 g, 9.5 mmol) was dissolved in 20 mL of THF containing 10 mL of 5% HCl. After 20 h at 25 °C the solvent was removed under reduced pressure to yield the aldehyde (1.3 g). To the aldehyde (1.3 g, 8.3 mmol) in dry CH_2Cl_2 (15 mL) was added imidazole (0.849 g, 12 mmol) at 0 °C

under inert atmosphere. After being stirred for 15 min TBDMSCl (1.25 g, 12 mmol) was added and stirring was continued for 6 h, then the reaction mixture was filtered with water and the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and crude residue was purified by silica gel column chromatography to afford the pure product **22** (1.9 g, 70% for two steps) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 9.80 (s, 1H, C*H*O), 7.28 (s, 1H, Ar), 7.18 (s, 1H, Ar), 3.82 (s, 3H, OCH_3), 2.35 (s, 3H, ArCH_3), 1.05 (s, 9H, SiCH(CH_3)$_3$), 0.22 (s, 6H, Si(CH_3)$_2$); Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63. Found: C, 64.19; H, 8.60; FABMS: *m/z* 280 (M^+); IR (KBr): 2947, 1695, 1578, 1499, 735 cm^{-1}.

4.1.16. Ethyl-3-[3-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-5-methyl-phenyl]-(*E*)-2-propionate (23). This unsaturated ester was prepared in the same way as unsaturated ester **13** from the aldehyde **20** (1.0 g, 3.5 mmol). Solvent was removed under reduced pressure and the crude product was purified by column chromatography to afford **23** (1.12 g, 89%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50 (d, J=16.3 Hz, 1H, ArC*H*=), 6.95 (s, 1H, Ar), 6.83 (s, 1H, Ar), 6.25 (d, J=16.3 Hz, 1H, =C*H*CO_2Et), 4.24 (q, J=7.4 Hz, 2H, OCH_2CH$_3$), 3.76 (s, 3H, OCH$_3$), 2.26 (s, 3H, ArCH$_3$), 1.34 (t, J=7.4 Hz, 3H, OCH$_2$CH_3), 1.05 (s, 9H, SiCH(CH_3)$_3$), 0.22 (s, 6H, Si(CH_3)$_2$); Anal. Calcd for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.63. Found: C, 65.07; H, 8.65; FABMS: *m/z* 350 (M^+); IR (KBr): 2978, 1712, 1610, 1480, 1260 cm^{-1}.

4.1.17. Ethyl-3-[3-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-5-methyl-phenyl]-(2*R*,3*S*)-dihydroxy-propionate (24). This was prepared in the same way as diol **14** from unsaturated ester **23** (1.0 g, 2.8 mmol) to afford **24** (1.0 g, 90%) as viscous oil. Enantiomeric excess was determined by HPLC using chiralcel OB-H column, and isopropanol and hexane as eluents (1:9); flow rate 1 mL/min; major isomer t_R 36.91 min, minor enantiomer t_R 38.53 min.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.75 (s, 1H, Ar), 6.72 (s, 1H, Ar), 4.76 (br s, 1H, ArC*H*OH), 4.29–4.20 (m, 3H, OCH_2CH$_3$, C*H*CO_2Et), 3.72 (s, 3H, OCH_3), 2.24 (s, 3H, ArCH_3), 1.29 (t, J=7.7 Hz, 3H, OCH$_2$CH_3), 1.00 (s, 9H, SiCH(CH_3)$_3$), 0.19 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.7, 149.3, 148.5, 135.3, 132.0, 121.4, 117.0, 74.7, 74.1, 61.9, 59.6, 29.6, 25.6, 16.0, 14.0, −4.6; EIMS: *m/z* 384 (M^+), 196, 180, 165, 137; Anal. Calcd for $C_{19}H_{32}O_6Si$: C, 59.34; H, 8.39. Found: C, 59.52; H, 8.26; $[\alpha]_D^{25}$ +2.83 (*c* 0.60, $CHCl_3$); IR (KBr): 3427, 2930, 1735, 1588, 1432, 1326, 1235, 1073, 840 cm^{-1}.

4.1.18. Ethyl-(3*R*)-azido-3-[3-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-5-methyl-phenyl]-(2*R*)-hydroxy-propionic acid ethyl ester (3). To an ice-cold solution of diol **24** (0.5 g, 1.3 mmol) and triethyl amine (0.53 mL, 3.9 mmol) in CH_2Cl_2 was added thionyl chloride (0.23 g, 1.9 mmol) drop wise over a period of 10 min, stirring was continued for another 5 min at 0 °C. The reaction mixture was diluted with cold ether and washed with cold water. The aqueous phase was extracted with ether and the combined organic phases washed with cold brine and concentrated in vacuo gave the cyclic sulfite **25**. The cyclic sulfite **25** was used further without any purification. The crude cyclic sulfite **25** (0.5 g, 1.1 mmol) was taken in dry DMF, added NaN_3 (0.22 g, 3.5 mmol) as a solid and the reaction mixture was heated to 65 °C for 10 h. After completion of the reaction, reaction mixture was diluted with ether and washed with water. Solvent was removed and the crude product purified by silica gel column chromatography yielded the azide **3** (0.3 g, 56% for two steps) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.74 (s, 1H, Ar), 6.66 (s, 1H, Ar), 5.60 (br s, 1H, O*H*), 4.67 (d, J=4.0 Hz, 1H, ArC*H*N_3), 4.42–4.38 (m, 1H, C*H*CO_2Et), 4.20 (q, J=7.5 Hz, 2H, OCH_2CH$_3$), 3.80 (s, 3H, OCH_3), 2.30 (s, 3H, ArCH_3), 1.28 (t, J=7.5 Hz, 3H, OCH$_2$CH_3); FABMS: *m/z* 409 (M^+); $[\alpha]_D^{25}$ +3.86 (*c* 1.00, $CHCl_3$); Anal. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.96; H, 5.76; N, 14.12; IR (KBr): 3418, 2928, 2107, 1732, 1460, 1040 cm^{-1}.

4.1.19. 2-Bromo-4,5-dimethoxy benzaldehyde (26).[29] A 250 mL RB flask was charged with MeOH (40 mL) and 3,4-dimethoxy benzaldehyde **7** (4.0 g, 24 mmol) was added with stirring. Bromine (1.35 mL, 26 mmol) was added with cooling (T<40 °C), and stirring continued at the same temperature for 1 h. Solvent was removed under vacuo, at this point the product may start to precipitate from solution. After cooling to 20 °C water was added with stirring, the resultant slurry was filtered using Buckner funnel, washed with water and cold methanol. The obtained colorless to slightly yellowish product **26** is dried in vacuo (5.30 g, 91%).

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.17 (s, 1H, C*H*O), 7.38 (s, 1H, Ar), 7.00 (s, 1H, Ar), 3.96 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.2, 154.2, 148.6, 126.2, 120.1, 115.2, 110.1, 56.3, 55.9; EIMS: *m/z* 245 (M^+); mp 143–145 °C; IR (KBr): 2350, 1670, 1580, 740 cm^{-1}.

4.1.20. 2-Bromo-5-hydroxy-4-methoxy-benzaldehyde (27).[29] A 500 mL RB flask charged with 98% sulfuric acid (25 mL) under nitrogen was heated with stirring at 90 °C. Stirring was stopped and 2-bromo-4,5-dimethoxybenzaldehyde **26** (5.0 g, 20 mmol) was added within 2 min and the reaction was allowed to proceed at 90 °C for 6 h. This mixture was then added quickly to a beaker containing ice and water to precipitate the product. The reaction mixture was cooled to 20 °C and filtered through Buckner funnel and washed with water, dried in vacuum desiccator to give the phenol **27** (4.0 g, 85%) as gray powder.

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.02 (s, 1H, C*H*O), 7.26 (s, 1H, Ar), 6.95 (s, 1H, Ar), 3.86 (s, 3H, OCH$_3$); ^{13}C NMR (50 MHz, DMSO-d_6): δ 189.9, 152.9, 145.8, 125.8, 117.1, 114.9, 114.1, 55.6; EIMS: *m/z* 231 (M^+); mp 104–106 °C; IR (KBr): 3600, 3050, 1590, 1450, 980 cm^{-1}.

4.1.21. 5-Benzyloxy-2-bromo-4-methoxy-benzaldehyde (28).[35] To a stirred solution of phenol **27** (3.0 g, 12 mmol) in acetone (30 mL) was added K_2CO_3 (3.58 g, 25 mmol), followed by benzyl bromide (1.5 mL, 12 mmol). The reaction mixture was refluxed for 4 h. After completion of the

reaction, the reaction mixture was filtered, and washed with acetone. The filtrate was concentrated in vacuo and purified by silica gel column chromatography to yield the compound **28** (3.75 g, 90%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 10.06 (s, 1H, C*H*O), 7.24–7.12 (m, 6H, Ar, Ph), 7.00 (s, 1H, Ar), 5.06 (s, 2H, CH_2Ph), 3.96 (s, 3H, OCH_3); EIMS: *m*/*z* 320 (M^+), 91; mp 139–141 °C; IR (KBr): 2357, 1678, 1586, 1501, 1262, 738 cm^{-1}.

4.1.22. 1-Benzyloxy-4-bromo-2-methoxy-5-[2-nitro-(*E*)-1-ethenyl] benzene (29). A mixture of aldehyde **28** (3.5 g, 10 mmol), nitro methane (1.18 mL, 21 mmol) and ammonium acetate (2.5 g, 32 mmol) in acetic acid (40 mL) was heated at 100 °C for 4 h under nitrogen atmosphere. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into a beaker containing ice, the yellowish solid product was separated out. The solid was filtered and washed with water several times to remove the excess acid and dried in vacuo to give the pure unsaturated nitro compound **29** (3.37 g, 85%) as yellowish solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03 (d, *J*=14.1 Hz, 1H, =CH), 7.23–7.16 (m, 5H, Ph), 7.15 (d, *J*=14.1 Hz, 1H, =C*H*), 7.06 (s, 1H, Ar) 7.00 (s, 1H, Ar), 5.07 (s, 2H, CH_2Ph), 3.97 (s, 3H, OCH_3); FABMS: *m*/*z* 364 (M^+), 363, 321, 154, 137; Anal. Calcd for $C_{16}H_{14}BrNO_4$: C, 52.77; H, 3.87; N, 3.85. Found: C, 52.74; H, 3.83; N, 3.80; mp 164 °C; IR (KBr): 2928, 1544, 1506, 1381, 1158, 1023 cm^{-1}.

4.1.23. 1-Benzyloxy-4-bromo-2-methoxy-5-(2-nitro ethyl) benzene (30). Unsaturated nitro compound **29** (3.0 g, 8 mmol) was dissolved in ethanol (50 mL) cooled to 0 °C, then $NaBH_4$ (0.939 g, 24 mmol) was added portion wise and stirred for 2 h at the same temperature. Solvent was removed under reduced pressure and the residue was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by silica gel column chromatography to give the saturated nitro compound **30** (2.38 g, 80%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.28 (m, 5H, Ph), 7.02 (s, 1H, Ar), 6.74 (s, 1H, Ar), 5.08 (s, 2H, CH_2Ph), 4.52 (t, *J*=7.3 Hz, 2H, CH_2NO_2), 3.88 (s, 3H, OCH_3), 3.30 (t, *J*=7.3 Hz, 2H, ArCH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.9, 147.7, 136.3, 128.5, 128.0, 127.4, 126.7, 116.5, 116.4, 114.8, 74.5, 71.4, 56.2, 33.4; FABMS: *m*/*z* 366 (M^+), 365, 319, 260, 184, 137; HRMS-FAB calcd for $C_{16}H_{16}BrNO_4$: 365.0263; found: 365.0259; mp 95 °C; IR (KBr): 2921, 1588, 1500, 1325, 1264, 1206 cm^{-1}.

4.1.24. 2-[2-Bromo-4-methoxy-5-benzyloxy]-1-(*tert*-butoxycarbonyl amino)-ethane (31). To an ice-cold suspension of LAH (0.209 g, 5 mmol) in dry THF (30 mL) under nitrogen was added nitro compound **30** (2.0 g, 5 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature for 1–2 h. The reaction mixture was quenched with aq NaOH and water, then $(Boc)_2O$ (1.2 g, 5 mmol) in THF (15 mL) was added and stirring was continued for 4 h at room temperature. After completion of the reaction the reaction mixture was filtered over Celite and washed with ethyl acetate, the filtrate was concentrated in vacuo and crude residue was purified by silica gel column chromatography to give the compound **31** (1.90 g, 82%) as yellowish solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48–7.25 (m, 5H, Ph), 7.00 (s, 1H, Ar), 6.75 (s, 1H, Ar), 5.08 (s, 2H, CH_2Ph), 4.55–4.40 (m, 1H, N*H*), 3.85 (s, 3H, OCH_3), 3.30 (q, *J*=7.0 Hz, 2H, NHCH_2), 2.80 (t, *J*=7.0 Hz, 2H, ArCH_2), 1.40 (s, 9H, Boc); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.2, 149.5, 148.0, 137.1, 130.6, 129.0, 128.3, 127.8, 116.9, 116.8, 115.5, 79.6, 71.7, 56.6, 40.8, 36.2, 28.8; FABMS: *m*/*z* 436 (M^+); HRMS-FAB calcd for $C_{21}H_{26}BrNO_4$: 435.1045; found: 435.1041; mp 88 °C; IR (KBr): 3375, 2923, 1706, 1504, 1255, 1025 cm^{-1}.

4.1.25. 2-[2-(Ethylpropionoate)-4-methoxy-5-benzyloxy]-1-(*tert*-butoxy-carbonyl-amino)-ethane (32). A mixture of bromo compound **31** (1.50 g, 3.4 mmol), ethyl acrylate (0.56 mL, 5 mmol), palladium acetate (0.0038 g, 0.17 mmol), and triethyl amine (0.5 mL, 5 mmol) in PEG-2000 (6.0 g) was heated at 80 °C for 18 h. After completion of the reaction (monitored by TLC) the reaction mixture was cooled, extracted with cold diethyl ether (3×50 mL), washed with water, brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and the crude residue was purified by silica gel column chromatography to afford the unsaturated ester **32** (1.39 g, 89%) as white solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (d, *J*=15.2 Hz, 1H, ArC*H*=), 7.44–7.25 (m, 5H, Ph), 7.05 (s, 1H, Ar), 6.73 (s, 1H, Ar), 6.22 (d, *J*=15.2 Hz, 1H, =C*H*CO_2Et), 5.14–5.09 (m, 3H, CH_2Ph, N*H*), 4.24 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 3.89 (s, 3H, OCH_3), 3.30–3.15 (m, 2H, NHCH_2), 2.90 (t, *J*=7.0 Hz, 2H, ArCH_2), 1.41 (s, 9H, Boc), 1.36 (t, *J*=7.0 Hz, 3H, OCH_2CH_3); ^{13}C NMR (200 MHz, $CDCl_3$): δ 167.0, 155.7, 150.2, 148.6, 141.1, 136.5, 132.3, 128.5, 128.2, 128.0, 127.4, 118.5, 117.7, 115.5, 109.7, 79.3, 60.3, 56.1, 41.8, 32.9, 28.4, 14.3; FABMS: *m*/*z* 455 (M^+), 400, 354, 154, 137; HRMS-FAB calcd for $C_{26}H_{33}NO_6$: 456.2386; found: 456.2381; mp 135 °C; IR (KBr): 3381, 2925, 1713, 1601, 1515, 1269, 1167, 1028 cm^{-1}.

4.1.26. 6-Benzyloxy-1-ethoxycarbonylmethyl-7-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (33). A 100 mL RB flask was charged with unsaturated ester **32** (1.2 g, 2.6 mmol) and 30 mL 50% TFA in CH_2Cl_2 mixture at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature. Solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (30 mL), basified with Na_2CO_3, and allowed to stir for 12 h. After completion of the reaction (monitored by TLC), $(Boc)_2O$ (0.574 g, 2.6 mmol) in CH_2Cl_2 was added and stirred for further 4 h. The reaction mixture was filtered, washed with CH_2Cl_2, filtrate was concentrated in vacuo, and crude residue was purified using silica gel column chromatography to give the tetrahydroisoquinolines **33** (1.0 g, 90%) as light yellowish solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.20 (m, 5H, Ph), 6.72–6.55 (m, 2H, Ar), 5.56–5.36 (m, 1H, ArC*H*N), 5.08 (s, 2H, CH_2Ph), 4.10 (q, *J*=7.3 Hz, 2H, OCH_2CH_3), 3.85 (s, 3H,

OCH_3), 3.40–3.09 (m, 1H, NC*H*), 2.90–2.50 (m, 5H, NC*H*, ArCH_2, CH_2CO$_2$Et), 1.45 (s, 9H, Boc), 1.35 (t, J=7.3 Hz, 3H, OCH$_2$CH_3); FABMS: *m*/*z* 455 (M^+); Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.32; H, 7.19; N, 3.19; mp 105 °C; IR (KBr): 2977, 1693, 1620, 1259 cm^{-1}.

4.1.27. 6-Benzyloxy-1-(2-hydroxy-ethyl)-7-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (34). To a stirred solution of LiCl (0.28 g, 6.5 mmol) and sodiumborohydride (0.25 g, 6.5 mmol) in ethanol (20 mL) was added ester **33** (1.0 g, 2.1 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, solvent was removed under reduced pressure. Reaction mixture was quenched with saturated ammonium chloride and extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure and the crude product was purified by silica gel chromatography (hexane–EtOAc 70:30) to yield the alcohol **34** (0.78 g, 87%) as viscous liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.42–7.25 (m, 5H, Ph), 6.65 (s, 1H, Ar), 6.54 (s, 1H, Ar), 5.23–5.17 (m, 1H, ArC*H*N), 5.07 (s, 2H, CH_2Ph), 4.11–3.96 (m, 2H, CH_2OH), 3.85 (s, 3H, OCH_3), 3.70–3.42 (m, 2H, CH_2NH), 3.14–3.04 (m, 1H, ArCH_2), 2.85–2.73 (m, 1H, ArCH_2), 2.59–2.50 (m, 1H, CH_2CH$_2$OH), 2.10–2.00 (m, 1H, CH_2CH$_2$OH), 1.45 (s, 9H, Boc); Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.67; H, 7.52; N, 3.42; FABMS: *m*/*z* 413 (M^+); IR (KBr): 3437, 2933, 1513, 1425, 1255 cm^{-1}.

4.1.28. 6-Benzyloxy-1-[2-(*tert*-butyl-dimethyl-silanyl-oxy)-ethyl]-7-methoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester (35). This compound was prepared in the same way as aldehyde **22**, from the alcohol **34** (0.7 g, 1.69 mmol). The crude material was purified by silica gel chromatography to afford **35** (0.732 g, 82%) as thick liquid.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44–7.20 (m, 5H, Ph), 6.60 (s, 1H, Ar), 6.55 (s, 1H, Ar), 5.20–4.98 (m, 3H, ArC*H*N, CH_2Ph), 4.20–3.60 (m, 6H, OCH_3, CH_2OH, CH_2NH), 3.30–2.98 (m, 1H, CH_2NH), 2.95–2.60 (m, 1H, ArCH_2), 2.58–2.45 (m, 1H, ArCH_2), 2.08–1.80 (m, 2H, CH_2CH$_2$OH), 1.45 (s, 9H, Boc), 0.92 (s, 9H, SiCH(CH_3)$_3$), 0.02 (s, 6H, Si(CH_3)$_2$); Anal. Calcd for $C_{30}H_{45}NO_5Si$: C, 68.27; H, 8.59; N, 2.65. Found: C, 68.24; H, 8.55; N, 2.61; FABMS: *m*/*z* 527 (M^+).

4.1.29. 6-Benzyloxy-1-[2-(*tert*-butyl-dimethyl-silanyl-oxy)-ethyl]-7-methoxy-3,4-dihydro-1*H*-isoquinoline-2-dicarboxylic acid-2-*tert*-butyl ester-1-ethyl ester (4). To a stirred solution of compound **35** (0.5 g, 0.94 mmol), in THF (10 mL) at −78 °C under inert atmosphere was added *n*-butyl lithium (0.093 g, 1.3 mmol). The mixture was stirred at −78 °C for 15 min and ethyl chloroformate (0.136 mL, 1.3 mmol) was added drop wise. Stirring was continued for 2 h at the same temperature and allowed to warm to room temperature. Reaction mixture was quenched with saturated NH_4Cl and extracted with diethyl ether twice (2×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography to give the product **4** (0.40 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60–7.10 (m, 5H, Ph), 6.90 (s, 1H, Ar), 6.75 (s, 1H, Ar), 5.30–5.10 (m, 2H, CH_2Ph), 4.35 (q, J=7.5 Hz, 2H, OCH_2CH$_3$), 4.28–4.10 (m, 1H, CH_2OH), 3.90–3.59 (m, 5H, OCH_3, CH_2OH, CH_2NH), 3.30–2.40 (m, 3H, CH_2NH, ArCH_2), 2.15–1.85 (m, 2H, CH_2CH$_2$OH), 1.45 (s, 9H, Boc), 1.35 (t, J=7.5 Hz, 3H, OCH$_2$CH_3) 0.90 (s, 9H, SiCH(CH_3)$_3$), 0.10 (s, 6H, Si(CH_3)$_2$); FABMS: *m*/*z* 600 (M^++1), 599 (M^+), 600 (M^+−1); Anal. Calcd for $C_{33}H_{49}NO_7Si$: C, 66.08; H, 8.23; N, 2.34. Found: C, 66.17; H, 8.12; N, 2.42; IR (KBr): 2945, 1692, 1520, 1259, 750 cm^{-1}.

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