Pergamon

Tetrahedron 56 (2000) 2379–2390

TETRAHEDRON

Transformation of Vitamin B_6 to (+)-Deoxypyridinoline, a useful Biochemical Marker for Diagnosis of Bone Diseases

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Received 8 December 1999; revised 8 February 2000; accepted 9 February 2000

Abstract—A versatile chiral synthesis of the cross-link (+)-deoxypyridinoline (Dpd, **2**) was achieved starting from vitamin B_6 (**7**). The key steps in the synthesis of (+)-**2** are transformation of B_6 (**7**) to the chloride (**3d**) and construction of three α-amino acid chains by utilizing (*R*)-(−)-Schollkopf's reagent (**4**), Wittig reagent (*R*)-(−)-**5**, and iodide (*S*)-(−)-**6**. (+)-Dpd (**2**) is a degradation product of bone collagen and has been found to be a useful marker for diagnosis of osteoporosis and other metabolic bone diseases.

Introduction

Bone is a complex and highly specialized form of connective tissue which serves several functions, including support of the body, protection of internal organs and as a reservoir for minerals.[1] In order for bones to respond and adapt to the mechanical stress and maintain serum mineral metabolism, they undergo constant remodeling. The bone remodeling, which is also called bone turnover, begins with resorption of old bone by osteoclasts, followed by formation of new bone by osteoblasts. Any alterations or imbalance in the remodeling process results in the metabolic bone diseases. Collagen, a family of structurally related proteins, which are synthesized by osteoblasts, constitutes approximately 95% of bone.[1] Inter- and intramolecular cross-links such as pyridinoline (Pyd, **1**)[2] and deoxypyridinoline (Dpd, **2**)[3] (Fig. 1) are formed from the adjacent lysine and hydroxylysines present in collagen fibrils by a lysyl oxidase mediated enzymatic process.[4] During the process of bone resorption these cross-links (**1**, **2**) are released into the serum and excreted in urine.[5] It has been found that the pyridinium cross-link Dpd (**2**) is a clinically useful marker for diagnosis of osteoporosis,[6] a bone disease which affects the aged population, particularly postmenopausal women. Additionally, Dpd (**2**) also has been found to have clinical utility in diagnosis of cancer,[7] Paget's disease[8] and other metabolic bone diseases.[9] Currently, Dpd (**2**) is isolated in a very low yield at a high cost from bones (e.g. sheep, ox, turkey) by 6–9 M HCl hydrolysis at 110°C, a process that could affect the integrity of the stereocenters in Dpd.[10] Therefore, Dpd (**2**) became an attractive synthetic target due to its novel structural features and practical applications in diagnosis of osteoporosis and other bone diseases. Waelchli et al.[11] reported the first synthesis Dpd (**2**) in an unspecified diastereomeric purity, which involved the construction of a substituted pyridine ring from amino acid components

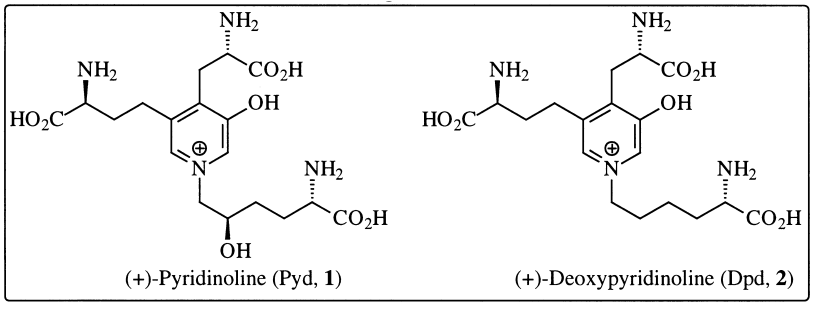

Figure 1.

Keywords: bone collagen; cross-links; deoxypyridinoline; poly-amino acids; osteoporosis.

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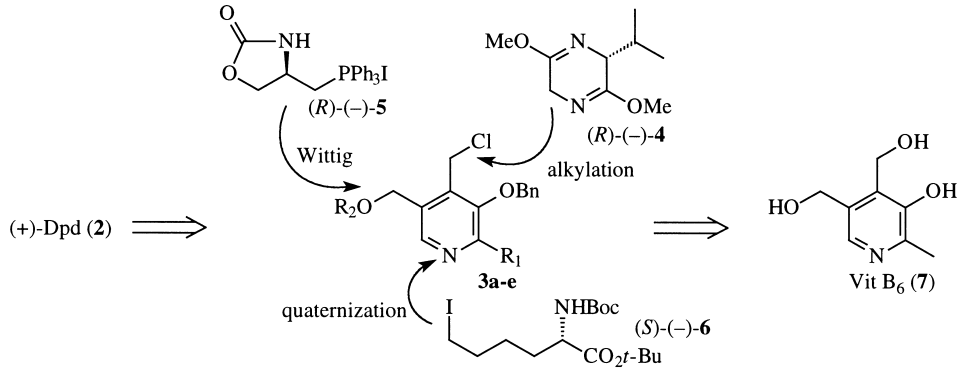


Figure 2. 3a: R_1=Me, R_2=PMB; **3b**: R_1=Me, R_2=H; **3c**: R_1=Me, R_2=Ac; **3d**: R_1=H, R_2=H; **3e**: R_1=$(CH_2)_2CO_2(CH_2)_2OSi(Me_3)$, R_2=H.

utilizing aldol chemistry. The subsequent synthetic studies have adopted this aldol strategy to achieve the chiral synthesis of (+)-Dpd (**2**)[12] in fewer steps.[13,14] In this paper, we describe a conceptually different approach for the synthesis of (+)-Dpd (**2**) starting from vitamin B_6 (**7**).[15]

Results and Discussion

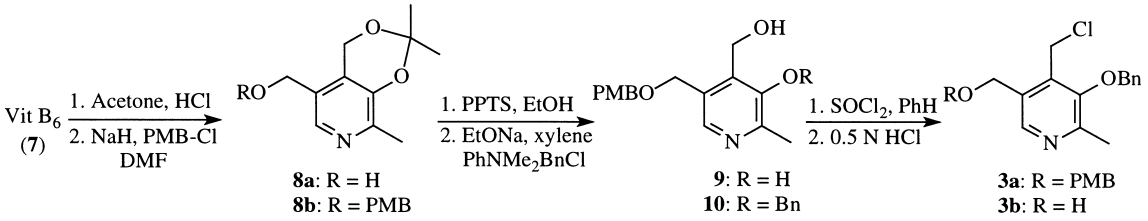
In this strategy, we envisioned the synthesis of (+)-Dpd (**2**) (Fig. 2) from a 3-hydroxypyridine derivative (**3d**) via construction of three α-amino acid chains sequentially. This synthetic strategy will have the diversity and flexibility needed for preparation of Dpd-analogs from any of the three α-amino acid chains and also from the 2-position of the pyridine ring, which otherwise is difficult to achieve by utilizing the aldol approach. Thus, the 4-amino acid chain in (+)-Dpd (**2**) was introduced by utilizing (*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (Schollkopf's reagent, **4**)[16] via alkylation methodology and subsequent hydrolysis. The 5-amino acid chain could be extended by Wittig reaction utilizing (*R*)-(−)-4-{[iodo(triphenyl) phosphoranyl]methyl}-1,3-oxazolidin-2-one (**5**),[17] and finally, the lysine chain at the 1- position of pyridine ring was installed via quaternization with (*S*)-(−)-*tert*-butyl-[(2-*tert*-butoxycarbonyl)amino]-6-iodohexanoate (**6**). The key synthon, **3d**, could be easily prepared from an inexpensive vit B_6 (pyridoxine hydrochloride, **7**).

Introduction of amino acid chain at the 4-position of (+)-Dpd (2)

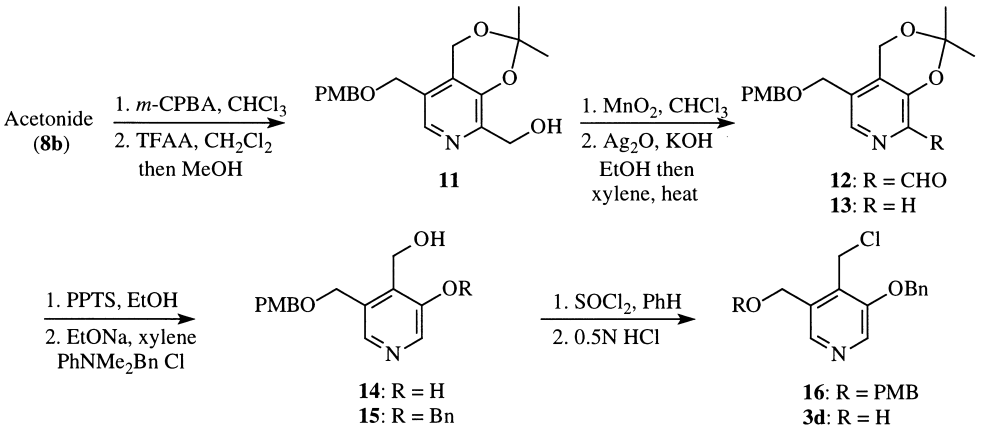
We contemplated introduction of the first amino acid, the alanine-unit, at 4-position of (+)-Dpd (**2**) utilizing (*R*)-(−)-**4**, and thus chloride (**3d**) was needed for alkylation. In order to determine the need for a protective group at the 5-hydroxymethyl group on the pyridine ring in **3d**, and also to optimize the alkylation reaction with (*R*)-(−)-**4**, we first prepared chlorides (**3a**–**b**) for alkylation. Thus, the phenolic and 4-hydroxymethyl groups in vitamin B_6 (**7**) were protected as (Scheme 1) acetonide (**8a**)[18] and the 5-hydroxymethyl group was transformed to the corresponding *p*-methoxybenzyl (PMB) ether (**8b**) in 95% yield. The acetonide protective group in **8b** was then hydrolyzed using pyridinium *p*-toluenesulfonate (PPTS) and the phenolic group was selectively protected as its benzyl ether using benzyldimethylphenylammonium chloride[19] to give the hydroxy compound (**10**). The hydroxy functionality in **10** was then converted to the corresponding chloride (**3a**) using $SOCl_2$ and the PMB group was subsequently hydrolyzed using 0.5 N HCl to give **3b** in 82% yield.

The chloride (**3d**), which lacks the methyl group at the 2-position, was prepared (Scheme 2) from acetonide (**8b**). Thus, **8b** was oxidized with *m*-chloroperoxybenzoic acid to the corresponding *N*-oxide, which without purification was converted to 2-hydroxymethyl compound (**11**) in 86% yield. The hydroxy compound (**11**) was oxidized with MnO_2 to give the aldehyde (**12**) in 89% yield, which upon further oxidation with silver oxide followed by decarboxylation gave the desmethyl compound (**13**) in 81% yield. The acetonide protective group in **13** was hydrolyzed using PPTS to give **14**, in which the phenolic group was then selectively protected as its benzyl ether (**15**). The hydroxy functionality in **15** was converted to the corresponding chloride (**16**) and further hydrolyzed with HCl to afford the desired **3d** in 61% yield.

The alkylation of (*S*)-(+)-Schollkopf's reagent (**4**) (Table 1) was initially carried out (Scheme 3) with 0.5 equiv. of chloride (**3a**) using *n*-BuLi at −78°C (entry 1) and the



Scheme 1.



Scheme 2.

reaction progress was monitored by TLC. After the disappearance of starting material (**3b**) (2 h), the mixture was quenched with sat. NH_4Cl solution at −78°C. The crude product was purified by silica gel column chromatography to afford (*R*,*S*/*S*,*S*)-**17a** in 84% yield and 79:21 diastereomeric ratio. However, the alkylation of (*R*)-(−)-**4** with chloride (**3b**) (entry 2) under similar conditions gave (*S*,*R*)-(−)-**17b** in 76% yield and >98% de. Surprisingly, the alkylation of chloride (**3d**), which lacks the methyl group at 2-position, (entry 4) under identical conditions gave (*S*,*R*/*R*,*R*)-**17d**[20] as a mixture of diastereomers in 69:31 ratio and 69% yield along with recovered (*R*)-(−)-**4** (68%). These results clearly suggest that the methyl group at 2-position of **3b** has a dramatic effect on chiral recognition in the alkylation step. Lower selectivities were observed for asymmetric induction steps involving the pyridine substrates.[21] This was attributed to the coordination of the nucleophile with pyridyl nitrogen, thus disrupting the transition state. In the present study, we believe that the excellent selectivity observed for **3b** was due to the steric hindrance of a substituent at the 2-position, which prevents such participation. However, the actual substrate **3d**, which lacks the methyl group, gave moderate selectivity in the alkylation step (69:31 ratio). This was further evident from the alkylation (entry 5) of **3e**, which has propionate group at 2-position, and gave (*S*,*R*)-(−)-**17e** in >98% de. (*S*,*R*)-(−)-**17e** is useful for the preparation of corresponding Dpd-analog needed for preparation of immunoreagents from 2-position.[22]

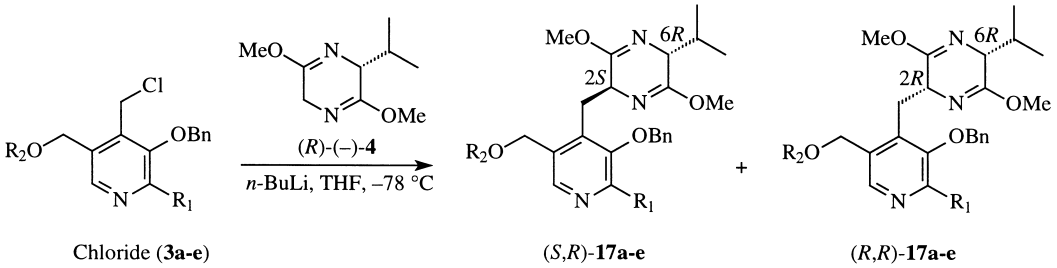
Introduction of amino acid chain at the 5-position of (+)-Dpd (2)

Having introduced the masked amino acid functionality at the 4-position, which is in the form of dihydropyrazine, we then proceeded (Scheme 4) to introduce an amino acid chain at the 5-position of (+)-Dpd (**2**). Although our attempts to separate the isomeric mixture (*S*,*R*/*R*,*R*)-**17d** by a variety of

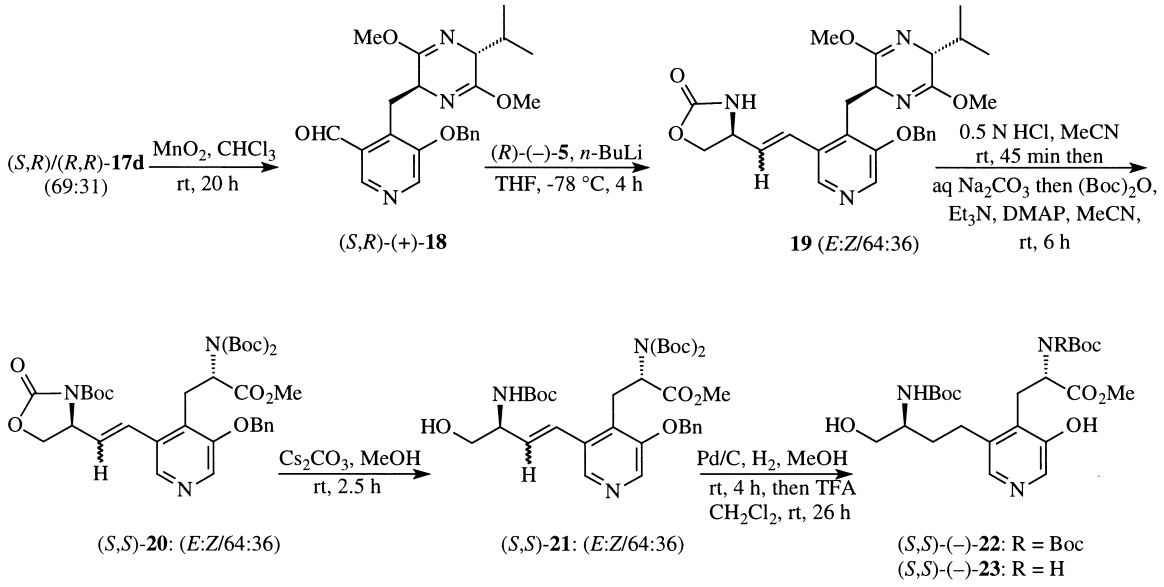
Table 1. Alkylation of Schollkopf's reagent (**4**) with chlorides (**3a**–**e**)

Entry	Chloride (**3**)			Reaction conditions	Alkylated product (**17**)			
		R_1	R_2	Solvent/Temp (°C)/Time (h)		Ratio (*S*,*R*)/(*R*,*R*)[a]	Yield[b] (%)	$[\alpha]^{23}_D$
1.	**3a**	Me	PMB	THF/−78/2	**17a**	79:21[c]	84	
2	**3b**	Me	H	THF/−78/2	**17b**	>98:2	65	−43.1
3.	**3c**	Me	Ac	THF/−78/2	**17c**	88:12[c]	44	
4.	**3d**	H	H	THF/−78/5	**17d**	69:31	69	
5.	**3e**	$(CH_2)_2CO_2(CH_2)_2TMS$	H	THF/−78/4	**17e**	>98:2	69	−35.1

[a] The diastereomeric ratio of **17a**–**e** was determined by ^1H NMR of the crude and purified products.
[b] Isolated yield.
[c] (*S*)-(+)-**4** was used and therefore the stereochemistry of the diastereomers of **17a** and **17c** is (*R*,*S*/*S*,*S*).

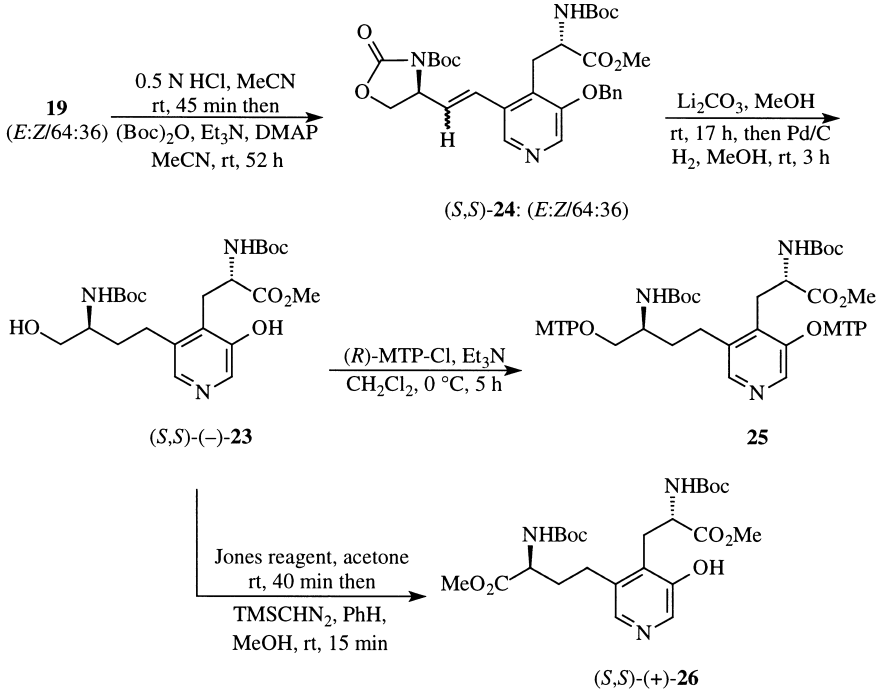


Scheme 3.

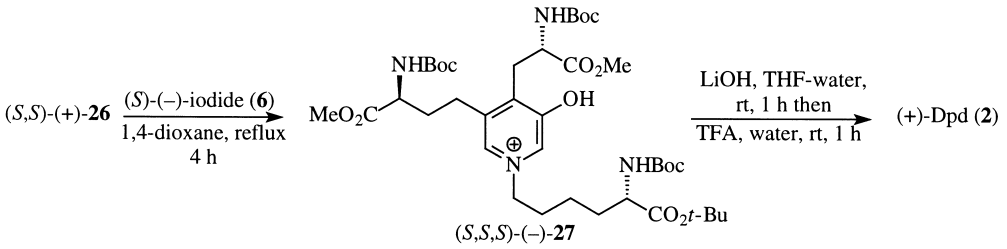


Scheme 4.

techniques, including preparative HPLC, were unsuccessful, to our delight, the corresponding diastereomeric mixture of aldehydes **18** were easily separable. Thus, crude (*S*,*R*/*R*,*R*)-**18**, which was obtained by oxidation of (*S*,*R*/*R*,*R*)-**17d** with MnO_2, was separated by silica gel column chromatography to afford the desired major isomer, (*S*,*R*)-(+)-**18** in 52% yield and >98% de. Wittig reaction of major aldehyde (*S*,*R*)-(+)-**18** with the ylide generated from (*R*)-(−)-**5** using *n*-BuLi in THF at −78°C, gave the olefin **19** in good yield (71%) as a mixture of *E*:*Z*-isomers (64:36). Hydrolysis of dihydropyrazine ring in **19** was carried out using 0.5N HCl in MeCN, and the protection of the resulting free amine, which was obtained by neutralizing with aq. Na_2CO_3, using $(Boc)_2O$ in MeCN afforded the tri-Boc compound (*S*,*S*)-**20** (*E*:*Z*/64:36) in 50% overall yield. The compound (*S*,*S*)-**20** was then subjected to hydrolysis with cesium carbonate in MeOH,[23] and the resulting product (*S*,*S*)-**21** (*E*:*Z*/64:36) was hydrogenated over 10% Pd/C in methanol to afford (*S*,*S*)-(−)-**22** in good overall yield. Concerned with the sensitivity of bis-(*tert*-butoxycarbonyl)-amino group in (*S*,*S*)-(−)-**22** for subsequent oxidation and quaternization steps, it was therefore selectively hydrolyzed with trifluoroacetic acid[12b] in CH_2Cl_2 to give (*S*,*S*)-(−)-**23** in 69% yield.



Scheme 5.



Scheme 6.

Alternatively, we found that **19** (*E*:*Z*/64:36) could be transformed to **24** (*E*:*Z*/64:36) (Scheme 5) in which the amino-ester group at 4-position was protected as mono-Boc-ester. Thus, reaction of the HCl salt of the amine, which was obtained by hydrolysis of **19** using 0.5 N HCl, with $(Boc)_2O$ afforded (*S*,*S*)-**24** (*E*:*Z*/64:36) in 46% yield. None of the tri-Boc compound (*S*,*S*)-**20**, which was isolated previously from the reaction of free amine of (*S*,*S*)-**20**, was observed. The selective formation of (*S*,*S*)-**24** can be attributed to the presence of the HCl salts of Et_3N/DMAP, and avoids a step at latter stages to remove one of the Boc groups using TFA. (*S*,*S*)-**24** (*E*:*Z*/64:36) was then subjected to hydrolysis under milder conditions, lithium carbonate in MeOH, and the resulting product was hydrogenated over 10% Pd/C in methanol to afford (*S*,*S*)-(−)-**23** in good overall yield (53%). The enatiomeric purity of (*S*,*S*)-(−)-**23** was determined to be >95% ee by converting it to the corresponding bis-MTP ester (**25**) using (*R*)-MTP-Cl and triethylamine in CH_2Cl_2. Finally, oxidation of (*S*,*S*)-(−)-**23** with Jones reagent[24] in acetone at room temperature followed by esterification of the crude product using trimethylsilyl diazomethane in MeOH–benzene[25] afforded (*S*,*S*)-(+)-**26** in 54% yield.

Completion of the synthesis of (+)-Dpd (2)

The 3-hydroxypyridine derivative (*S*,*S*)-(+)-**26** requires only elaboration of lysine chain at 1-position for completion of (+)-Dpd (**2**) synthesis. Thus, quaternization of (*S*,*S*)-(+)-**26** with (*S*)-(−)-**6**[12] was carried out (Scheme 6) in refluxing 1,4-dioxane for 4 h, and the product was purified by preparative reverse phase HPLC to afford the pyridinium compound (*S*,*S*,*S*)-(−)-**27** in 27% yield. Finally, alkaline hydrolysis of the methyl esters in (*S*,*S*,*S*)-(−)-**27** using LiOH and the removal of Boc and *t*-butyl protective groups was carried out by treating the crude product with TFA–water (9.5:0.5 ratio). Purification of the resulting crude product by preparative reversed phase HPLC and lyophilization afforded (+)-Dpd (**2**) in 84% yield as its TFA salt.

In summary, a versatile synthesis of (+)-deoxypyridinoline (**2**), a biochemical marker for diagnosis of osteoporosis was developed starting from vitamin B_6 (**7**).

Experimental

General methods and materials

^1H and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz) and the chemical shifts (δ) were reported in ppm relative to TMS and coupling constants (*J*) were reported in Hz. Electrospray ionization mass spectrometry (ESI-MS) was carried on a Perkin–Elmer (Norwalk, CT) Sciex API 100 Benchtop system employing Turbo Ionspray ion source and HRMS were obtained on a Nermang 3010 MS-50, JEOL SX102-A mass spectrometers. Thin layer chromatography was performed on pre-coated Whatman MK6F silica gel 60 Å plates (layer thickness: 250 μm) and visualized with UV light and/or using a $KMnO_4$ solution ($KMnO_4$ (1.0 g), NaOH (8.0 g) in water (200 mL)) or phosphomolybdic acid reagent (20 wt% solution in ethanol). Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). THF was freshly distilled from a purple solution of sodium and benzophenone. CH_2Cl_2 was freshly distilled from CaH_2 under nitrogen. Analytical reversed phase (RP) HPLC was performed using a Waters μBondapak RCM C18 10μ (8×100 mm) column. Preparative reversed phase (RP) HPLC was performed using a Waters μBondapak RCM C18 10μ (40×100 mm) column. Optical rotations were measured on Autopol III polarimeter from Rudolph Research, Flanders, NJ. Melting points were recorded in open capillary tubes on an Electrothermal Melting Point Apparatus and were uncorrected (see Ref. 12a for more details).

(2,2,8-Trimethyl-4H-[1,3]dioxino[4,5-c]pyridin-5-yl)methanol (**8a**)[18] and the Wittig reagent, (*R*)-(−)-**5**[17] from (*R*)-(−)-serine were prepared according to the known procedures. The chloride (**3c**) was prepared from **3b** (Ac_2O, pyridine, rt, 24 h, in 48%), and 2-(trimethylsilyl) ethyl-3-[3-(benzyloxy)-4-(chloromethyl)-5-(hydroxymethyl)-2-pyridinyl]propanoate (**3e**) from aldehyde (**13**) in 5 steps (1. $Ph_3P{=}CHCO_2(CH_2)_2TMS$ [prepared from $BrCH_2COBr$, $TMS(CH_2)_2OH$, Py, CH_2Cl_2, 0°C, 1 h (96%) then PPh_3, PhH, reflux, 18 h, then KOH, CH_2Cl_2–H_2O (70%)], CH_2Cl_2, rt, 1.5 h, then 5% Pd/C MeOH, H_2, 15 Psi, 35 min (84%); 2. PPTS, ethanol, reflux, 28 h (41%); 3. NaOEt, benzyldimethylphenylammonium chloride, xylene, reflux, 5 h (88%); 4. $SOCl_2$, PhH, reflux, 1 min (95%); 5. DDQ, CH_2Cl_2–H_2O, rt, 45 min (63%)).

5-{[(4-Methoxybenzyl)oxy]methyl}-2,2,8-trimethyl-4H-[1,3]dioxino[4,5-c]pyridine (8b). NaH (60% dispersion in mineral oil, 24.1 g, 602.8 mmol, 6.3 equiv.) was washed with hexane (2×50 mL) and dry DMF (600 mL) was added. The suspension was heated to 70°C and a solution of **8a** (20.0 g, 95.69 mmol) in anhydrous DMF (300 mL) was added via a double ended needle. After the addition was complete, the heating bath was removed and the mixture was allowed to reach 45°C. The mixture was cooled

with an ice bath, and *p*-methoxybenzyl chloride (PMB-Cl, 15.6 mL, 114.83 mmol, 1.2 equiv.) was added over 5 min. After the addition was over, the cooling bath was removed and the mixture was stirred for 15 h at room temperature. The reaction was cooled with an ice bath, quenched carefully with water (500 mL), diluted with an additional amount of water (5.5 L) and ether (1.5 L). The aqueous layer was separated and extracted with ether (1.5 L). The combined ether extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude compound was purified by silica gel column chromatography (50% EtOAc in hexanes) to afford 29.9 g of **8b** in 95% yield as pale yellow thick oil. Analytical RP HPLC: MeCN:0.1% aq acetic acid/50:50, 1.0 mL/min, 225 nm, R_t: 12.62 min, 99%; ^{1}H NMR ($CDCl_3$): δ 7.94 (s, 1H), 7.23 (d, 2H, J=8.7 Hz), 6.88 (d, 2H, J=8.7 Hz), 4.85 (s, 2H), 4.42 (s, 2H), 4.39 (s, 2H), 3.79 (s, 3H), 2.41 (s, 3H), 1.54 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 159.3, 148.1, 145.9, 139.7, 129.5, 128.2, 126.3, 125.9, 113.8, 99.6, 71.7, 66.9, 58.6, 55.2, 24.7, 18.5; ESI-MS (*m*/*z*): 330 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{17}H_{24}NO_4$ 330.1705 $(M+H)^+$; observed, 330.1707.

General procedure for hydrolysis of acetonide: e.g. 4-(hydroxymethyl)-5-{[(4-methoxybenzyl)oxy]methyl}-2-methyl-3-pyridinol (9)

PPTS (2.22 g, 8.81 mmol, 2 equiv.) was added to a solution of **8b** (1.45 g, 4.41 mmol) in absolute ethanol (35 mL) under nitrogen and refluxed for 20 h. The mixture was cooled to room temperature, quenched with $NaHCO_3$ (30 g) and the solvent was removed on a rotary evaporator. The residue was diluted with water (75 mL) and $CHCl_3$ (75 mL). The aqueous layer was separated and extracted with $CHCl_3$ (75 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was triturated with ether (50 mL) and the precipitate was filtered, washed with ether (50 mL) and dried to give 0.78 g of **9** in 61% yield. ^{1}H NMR (CD_3OD): δ 7.78 (s, 1H), 7.25 (d, 2H, J=8.7 Hz), 6.88 (d, 2H, J=8.7 Hz), 4.89 (s, 2H), 4.47 (s, 2H), 4.45 (s, 2H), 3.78 (s, 3H), 2.39 (s, 3H); ESI-MS: 290 $(M+H)^+$.

General procedure for preparation of benzyl ether: e.g. (3-(benzyloxy)-5-{[(4-methoxybenzyl)oxy]methyl}-2-methyl-4-pyridinyl)methanol (10)

NaOEt (21% solution in ethanol, 1.0 mL, 3.1 mmol, 1.1 equiv.) was added dropwise to a solution of benzyldimethylphenylammonium chloride (0.9 g, 4.23 mmol, 1.5 equiv.) in absolute ethanol (15 mL) at −78°C and stirred for 20 min. The mixture became heterogenous. It was then added via cannula to a solution of **9** (0.815 g, 2.82 mmol) in absolute ethanol (15 mL) at −78°C. After stirring the reaction at −78°C for 15 min, the cooling bath was removed and the reaction was allowed to reach room temperature. Ethanol was removed in vacuo, and dry toluene (20 mL) was added and then azeotroped to remove traces of ethanol. Dry xylene (25 mL) was added to the residue and the mixture was heated to reflux for 4 h. Xylene was removed on a rotary evaporator in vacuo and the residue was partitioned between $CHCl_3$ (100 mL) and sat. NH_4Cl solution (100 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude compound was purified by silica gel column chromatography (40% EtOAc in hexanes) to afford 0.81 g of **10** in 74% yield. Analytical RP HPLC: MeCN:0.1% aq. acetic acid/50:50, 1.0 mL/min at 225 nm, R_t: 12.81 min, >99%; ^{1}H NMR ($CDCl_3$): δ 8.21 (s, 1H), 7.49–7.33 (m, 5H), 7.29 (d, 2H, J=8.8 Hz), 6.90 (d, 2H, J=8.8 Hz), 4.97 (s, 2H), 4.69 (d, 2H, J=6.9 Hz), 4.61 (s, 2H), 4.56 (s, 2H), 3.81 (s, 3H), 3.42 (t, 1H, J=6.9 Hz), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.5, 154.3, 151.8, 145.2, 141.8, 136.5, 130.7, 129.8, 128.7, 128. 6, 128.3, 128.1, 114.0, 76.7, 72.5, 68.3, 56.2, 55.2, 19.7; ESI-MS (*m*/*z*): 380 $(M+H)^+$.

3-(Benzyloxy)-4-(chloromethyl)-5-{[(4-methoxybenzyl)-oxy]methyl}-2-methylpyridine (3a). A solution of $SOCl_2$ (0.27 mL, 3.73 mmol, 1.77 equiv.) in benzene (10 mL) was added to a solution of **10** (0.80 g, 2.11 mmol) in benzene (20 mL) at 0°C dropwise over 20 min using syringe pump. After addition was complete, the mixture was heated to reflux for 1 min in a pre-heated oil bath and cooled immediately in an ice-bath. Solvent was removed on a rotary evaporator to afford 0.90 g of chloride (**3a**) as HCl salt in 98% yield. Analytical RP HPLC: MeCN:0.1% aq. acetic acid/65:35, 1.0 mL/min, 225 nm, R_t: 13.25 min, >99%; ^{1}H NMR ($CDCl_3$): δ 8.51 (s, 1H), 7.45–7.36 (m, 5H), 7.26 (d, 2H, J=8.7 Hz), 6.91 (d, 2H, J=8.7 Hz), 5.10 (s, 2H), 4.69 (s, 2H), 4.64 (s, 2H), 4.60 (s, 2H), 3.83 (s, 3H), 2.82 (s, 3H); ESI-MS (*m*/*z*): 398 and 400 $(M+H)^+$.

The HCl salt of **3a** (0.40 g, 0.92 mmol) was dissolved in CH_2Cl_2 (50 mL) and washed with saturated aq. $NaHCO_3$ (30 mL). The organic layer was dried (Na_2SO_4), concentrated on a rotary evaporator and purified by silica gel column chromatography (40% EtOAc in hexanes) to afford 0.32 g of **3a** in 87% yield. Analytical RP HPLC: MeCN:0.1% aq. acetic acid/65:35, 1.0 mL/min, 225 nm, R_t: 13.61 min, >99%; ^{1}H NMR ($CDCl_3$): δ 8.29 (s, 1H), 7.51–7.36 (m, 5H), 7.28 (d, 2H, J=8.7 Hz), 6.90 (d, 2H, J=8.7 Hz), 4.98 (s, 2H), 4.73 (s, 2H), 4.65 (s, 2H), 4.51 (s, 2H), 3.81 (s, 3H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.3, 153, 7, 145.6, 138.2, 136.3, 130.7, 129.5, 128.7, 128.4, 127.9, 113.8, 75.9, 72.3, 66.7, 55.2, 35.5, 19.8; ESI-MS (*m*/*z*): 398 and 400 $(M+H)^+$.

5-(Benzyloxy)-4-(chloromethyl)-6-methyl-3-pyridinyl]-methanol (3b). The hydrochloride salt of **3a** (0.80 g, 1.847 mmol) in 0.5N HCl solution (30 mL) was heated to reflux for 15 min (the heterogenous reaction mixture became clear in 5 min). The reaction was cooled to room temperature and concentrated to dryness under reduced pressure. The residue was suspended in $CHCl_3$ (100 mL) and washed with saturated $NaHCO_3$ (75 mL). Organic layer was dried (Na_2SO_4), concentrated and purified on silica gel column chromatography (75% EtOAc in hexanes) to afford 0.418 g of **3b** in 82% yield. Analytical RP HPLC: MeCN:0.1% aq. acetic acid/50:50, 1.0 mL/min at 225 nm, R_t: 9.05 min, >99%; ^{1}H NMR ($CDCl_3$): δ 8.39 (s, 1H), 7.52–7.36 (m, 5H), 4.99 (s, 2H), 4.85 (d, 2H, J=5.8 Hz), 4.77 (s, 2H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 153.3, 151.4, 144.5, 137.8, 136.2, 133.7, 128.7, 128.5, 127.9, 76.0, 59.8, 35.3, 19.5; ESI-MS (*m*/*z*): 278 and 280 $(M+H)^+$.

(5-{[(4-Methoxybenzyl)oxy]methyl}-2,2-dimethyl-4H-[1,3]dioxino[4,5-c]pyridin-8-yl)methanol (11). *m*-CPBA

(50–60%, 34.5 g, 99.96 mmol, 1.1 equiv.) was added to a solution of the PMB-ether (**8b**, 29.9 g, 90.88 mmol) in $CHCl_3$ (750 mL) in five portions over a 5 min period at room temperature. After stirring the mixture for 2 h, it was quenched with saturated aq. Na_2SO_3 (500 mL). The organic layer was separated and washed with saturated aq. $NaHCO_3$ (500 mL). Organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator to give 31.0 g of the corresponding *N*-oxide in almost quantitative yield.

Trifluoroacetic anhydride (6.0 mL, 42.5 mmol, 0.51 equiv.) was added to a solution of the *N*-oxide (28.5 g, 82.6 mmol) in CH_2Cl_2 at 0°C and stirred for 5 min. An additional amount of TFAA (15.3 mL, 108.6 mmol, 1.3 equiv.) was added, the cooling bath was removed and the mixture stirred for 5 h at room temperature. The mixture containing the trifluoroacetate of **11** was cooled with an ice-bath and dry MeOH (150 mL) was added. The mixture was concentrated on a rotary evaporator and the resulting oily residue was dissolved in $CHCl_3$ (700 mL). The $CHCl_3$ layer was washed with saturated aq. $NaHCO_3$ solution (700 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude compound was purified on silica gel column (60% EtOAc in hexanes) to afford 26.8 g of **11** in 86% yield. R_f: 0.52 (60% EtOAc in hexanes); Analytical RP HPLC: MeCN:0.1% aq. acetic acid/50:50, 1.0 mL/min at 225 nm, R_t: 16.47 min, 99%; ^{1}H NMR ($CDCl_3$): δ 8.02 (s, 1H), 7.24 (d, 2H, J=8.6 Hz), 6.89 (d, 2H, J=8.6 Hz), 4.87 (s, 2H), 4.69 (s, 2H), 4.44 (s, 2H), 4.42 (s, 2H), 4.26 (br s, 1H, OH), 3.80 (s, 3H), 1.54 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 159.3, 147.5, 144.6, 138.9, 129.5, 129.3, 127.6, 126.4, 113.8, 100.0, 71.9, 66.8, 59.5, 58.6, 55.2, 24.6; ESI-MS (*m*/*z*): 346 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{19}H_{24}NO_5$, 346.1658 $(M+H)^+$; observed, 346.1645.

5-{[(4-Methoxybenzyl)oxy]methyl}-2,2-dimethyl-4H-[1,3]dioxino[4,5-c]pyridine-8-carbaldehyde (12). MnO_2 (85%, 45.5 g, 444.6 mmol, 13.0 equiv.) was added to a solution of **11** (11.8 g, 34.2 mmol) in $CHCl_3$ (550 mL) at room temperature. The mixture was stirred for 21 h and filtered through Celite powder. The filtrate was concentrated on a rotary evaporator to give 10.41 g of aldehyde (**12**) in 89% yield. R_f: 0.59 (50% EtOAc in hexanes); Analytical RP HPLC: MeCN:0.1% aq. acetic acid/50:50, 1.0 mL/min at 225 nm, R_t: 11.20 min, 99%; ^{1}H NMR ($CDCl_3$): δ 10.32 (s, 1H), 8.27 (s, 1H), 7.26 (d, 2H, J=8.8 Hz), 6.89 (d, 2H, J=8.8 Hz), 4.91 (s, 2H), 4.49 (s, 2H), 4.47 (s, 2H), 3.82 (s, 3H), 1.62 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 189.3, 159.5, 151.1, 141.3, 139.5, 133.6, 129.6, 129.1, 128.9, 113.9, 100.9, 72.5, 66.6, 58.6, 55.2, 24.7; ESI-MS (*m*/*z*): 343 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{19}H_{21}NO_5$, 344.1498 $(M+H)^+$; observed, 344.1485.

5-{[(4-Methoxybenzyl)oxy]methyl}-2,2-dimethyl-4H-[1,3]-dioxino[4,5-c]pyridine (13). Ag_2O (14.7 g, 63.55 mmol, 2 equiv.) and aq. KOH (5.4 g, 95.33 mmol, 3.0 equiv. dissolved in H_2O (275 mL)) were added sequentially to a solution of aldehyde (**12**, 10.9 g, 31.77 mmol) in EtOH (275 mL) at room temperature. The resulting heterogeneous mixture was stirred for 1 h, and filtered through Celite powder. The filtrate was concentrated on a rotary evaporator, the residue was diluted with water (400 mL) and EtOAc (800 mL), and the pH was adjusted to 4.5 with 6N HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc (200 mL). The combined organic extracts were washed with brine (150 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator to give 9.5 g of the corresponding carboxylic acid in 83% yield.

The crude acid (13.6 g, 37.88 mmol) was suspended in xylenes (350 mL) and heated to reflux. The mixture became clear in 5 min, and reflux was continued for an additional 20 min. The mixture was cooled to about 50°C and concentrated on a rotary evaporator. The resulting oily residue was dissolved in $CHCl_3$ (300 mL) and washed with aq. $NaHCO_3$ solution (200 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography (40% EtOAc in hexanes) to afford 9.7 g of **13** in 81% yield. R_f: 0.65 (50% EtOAc in hexanes); Analytical RP HPLC: MeCN:0.05% aq. trifluoroacetic acid/40:60, 1.0 mL/min at 225 nm, R_t: 8.64 min, 99%; ^{1}H NMR ($CDCl_3$): δ 8.15 (s, 1H), 8.07 (s, 1H), 7.25 (d, 2H, J=8.8 Hz), 6.89 (d, 2H, J=8.8 Hz), 4.86 (s, 2H), 4.45 (s, 2H), 4.42 (s, 2H), 3.81 (s, 3H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.4, 148.2, 141.1, 139.7, 129.5, 129.4, 128.5, 127.0, 113.9, 99.8, 72.1, 66.9, 58.6, 55.2, 24.6; ESI-MS (*m*/*z*): 316 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{18}H_{22}NO_4$, 316.1549 $(M+H)^+$; observed, 316.1549.

4-(Hydroxymethyl)-5-{[(4-methoxybenzyl)oxy]methyl}-3-pyridinol (14). Hydrolysis of **13** (9.6 g, 30.476 mmol) using PPTS (12.7 g, 50.49 mmol, 1.65 equiv.) in absolute ethanol (170 mL) by following the procedure described for **9** gave 5.2 g of **14** in 62% yield as a pale yellow solid. mp: 95–97°C; R_f: 0.27 (90% EtOAc in hexanes); Analytical RP HPLC: MeCN:0.1% aq. acetic acid/50:50, 1.0 mL/min at 225 nm, R_t: 7.58 min, 97%; ^{1}H NMR ($CDCl_3$): δ 8.09 (s, 1H), 7.95 (s, 1H), 7.26 (d, 2H, J=8.5 Hz), 6.89 (d, 2H, J=8.5 Hz), 4.85 (s, 2H), 4.49 (s, 2H), 4.47 (s, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.4, 153.2, 140.7, 138.5, 133.6, 131.1, 129.6, 129.1, 113.9, 72.2, 67.4, 58.1, 55.2; ESI-MS (*m*/*z*): 276 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{15}H_{18}NO_4$, 276.1236 $(M+H)^+$; observed, 276.1237.

(3-(Benzyloxy)-5-{[(4-methoxybenzyl)oxy]methyl}-4-pyridinyl)methanol (15). Reaction was carried out on **14** (5.1 g, 18.54 mmol) and followed the procedure described for **10** to afford 2.0 g of **15** in 30% yield as pale yellow solid. Mp: 75–6°C; R_f: 0.49 (80% EtOAc in hexanes); Analytical RP HPLC: MeCN:0.1% aq. acetic acid/50:50, 1.0 mL/min at 225 nm, R_t: 12.29 min, 97%; ^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.20 (s, 1H), 7.44–7.30 (m, 5H), 7.27 (d, 2H, J=8.8 Hz), 6.89 (d, 2H, J=8.8 Hz), 5.19 (s, 2H), 4.77 (s, 2H), 4.61 (s, 2H), 4.53 (s, 2H), 3.80 (s, 3H), 3.25 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 159.5, 152.8, 143.8, 137.1, 135.9, 135.7, 132.2, 129.7, 128.9, 128.7, 128.3, 127.3, 113.9, 72.4, 71.2, 67.8, 55.8, 55.2; ESI-MS (*m*/*z*): 366 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{22}H_{24}NO_4$, 366.1705 $(M+H)^+$; observed 366.1721.

3-(Benzyloxy)-4-(chloromethyl)-5-{[(4-methoxybenzyl)-oxy]methyl}pyridine (16). Reaction of **15** (1.95 g, 5.34 mmol) with $SOCl_2$ (0.69 mL, 9.45 mmol, 1.77 equiv.) in dry benzene (70 mL) was carried out by following the procedure described for **3a** to afford 2.26 g of **16** as a HCl salt in 97% yield. Mp: 124–6°C; Analytical RP HPLC:

MeCN:0.1% aq. acetic acid/65:35, 1.0 mL/min at 225 nm, R_t: 11.50 min, >99%; ^{1}H NMR ($CDCl_3$): δ 8.51 (s, 1H), 8.47, (s, 1H), 7.44–7.41 (m, 5 H), 7.27 (d, 2H, J=8.6 Hz), 6.91 (d, 2H, J=8.6 Hz), 5.35 (s, 2H), 4.72 (s, 2H), 4.69 (s, 2H), 4.62 (s, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159.5, 154.4, 141.6, 138.1, 133.6, 133.4, 129.7, 129.2, 129.1, 128.3, 127.5, 124.9, 114.1, 73.3, 72.6, 64.9, 55.3, 33.2; ESI-MS (*m*/*z*): 384, 386 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{22}H_{23}ClNO_3$, 384.1366 $(M+H)^+$; observed, 384.1371.

[5-(Benzyloxy)-4-(chloromethyl)-3-pyridinyl]methanol (3d). The HCl salt of **16** (2.24 g, 5.34 mmol) was suspended in 0.5N HCl (60 mL) and followed the procedure described for **3b** to afford 0.873 g of **3d** in 61% yield. R_f: 0.45 (EtOAc); Analytical RP HPLC: MeCN:0.1% aq. acetic acid/50:50, 1.0 mL/min at 225 nm, R_t: 8.34 min, 95%; ^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.29 (s, 1H), 7.48–7.36 (m, 5H), 5.25 (s, 2H), 4.85 (s, 2H), 4.82 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 152.4, 142.7, 135.8, 135.0, 134.8, 132.9, 128.7, 128.3, 127.3, 71.1, 60.1, 34.8; ESI-MS (*m*/*z*): 264 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{14}H_{15}ClNO_2$, 264.0791 $(M+H)^+$; observed, 264.0787.

General procedure for alkylation of Schollkopf's reagent (4) with chlorides (3a–e): e.g. (5-(benzyloxy)-4-{[(2*S*,5*R*)/(2*R*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl]methyl}-3-pyridinyl) methanol (17d)

n-BuLi (2.5 M solution in hexanes, 2.08 mL, 5.19 mmol, 3.0 equiv.) was added dropwise to a solution of (*R*)-(−)-**4** (0.956 g, 5.19 mmol, 3.0 equiv.) in THF (16 mL) at −78°C under nitrogen. The resulting pale yellow solution was stirred for 25 min. A solution of **3d** (0.455 g, 1.73 mmol) in THF (16 mL) was added dropwise via a double ended needle over a 5 min period. The mixture was then stirred for 5 h and quenched with saturated aq. NH_4Cl solution (10 mL) at −78°C. The mixture was allowed to warm to room temperature and diluted with EtOAc (75 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with EtOAc (50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude compound was purified by silica gel column chromatography (15% EtOAc in hexanes to 3% MeOH in EtOAc) to afford 0.492 g of (*S*,*R*/*R*,*R*)-**17d** in 69% yield (colorless solid) as a mixture diastereomers [ratio: (*S*,*R*:*R*,*R*)/69:31]. R_f: 0.18 (EtOAc); Analytical RP HPLC: MeCN:0.1% aq. acetic acid/50:50, 1.0 mL/min at 225 nm, R_t: 20.03 min, 31% [(*R*,*R*)-**17d**] and 21.78 min, 69% [(*S*,*R*)-**17d**]; ^{1}H NMR ($CDCl_3$): δ 8.37 (s, 31/100 H), 8.32 (s, 69/100 H), 7.45–7.36 (m, 5H), 5.28–5.16 (m, 2H), 4.78–4.69 (m, 1H), 4.23–4.15 (m, 1H), 3.97 (dd, 69/100 H, J=4.4, 3.6 Hz), 3.90–3.81 (m, 1 H+31/100 H), 3.66 (s, 69/100, 3 H), 3.61 (s, 3H), 3.60 (s, 31/100, 3H), 2.81–2.69 (m, 1H), 2.32–2.21 (m, 31/100 H), 2.16–2.06 (m, 69/100 H), 1.08 (d, 31/100, 3H, J=6.86 Hz), 0.97 (d, 69/100, 3H, J=6.86 Hz), 0.75 (d, 31/100, 3H, J=6.86 Hz), 0.71 (d, 69/100, 3H, J=6.86 Hz); ESI-MS (*m*/*z*): 412 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{23}H_{30}N_3O_4$ 412.2236 $(M+H)^+$; observed, 412.2224. 0.501 g of (*R*)-(−)-**4** was recovered in 68% yield with no loss of optical purity.

(2*R*,5*S*)/(2*S*,5*S*)-2-[(3-(Benzyloxy)-5-{[(4-methoxybenzyl)-oxy]methyl}-2-methyl-4-pyridinyl)methyl]-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (17a). Reaction of **3a** (0.740 g, 1.864 mmol) using *n*-BuLi (2.33 mL, 3.728 mmol, 2.0 equiv.) and (*S*)-(+)-**4** (0.685 g, 3.728 mmol, 2.0 equiv.) was carried out by following the procedure described for (*S*,*R*/*R*,*R*)-**17d** to afford 0.885 g of (*R*,*S*/*S*,*S*)-**17a** in 84% yield and 79:21 ratio. R_f: 0.42 (60% EtOAc in hexanes); Analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid/50:50, 2.0 mL/min at 225 nm, R_t: 6.49 min, 96%; ^{1}H NMR ($CDCl_3$): δ 8.25 and 8.24 (two s, 1H), 7.53–7.49 (m, 2H), 7.44–7.26 (m, 5H), 6.90–6.86 (m, 2H), 4.91–4.80 (m, 2H), 4.70–4.10 (m, 5H), 3.81 and 3.80 (two s, 3H), 3.80–3.78 (m, 1H), 3.65 and 3.61 (two s, 3H), 3.49 and 3.46 (two s, 3H), 3.41–3.45 (m, 1H), 2.86–2.66 (m, 1H), 2.56 (s, 3H), 2.20–2.10 (m, 1H), 1.04 (d, J=6.9 Hz) and 0.98 (d, J=6.9 Hz, 3H), 0.71 (d, J=6.9 Hz) and 0.60 (d, J=6.9 Hz, 3H); ESI-MS (*m*/*z*): 546 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{32}H_{40}N_3O_5$ 546.2968 $(M+H)^+$; observed, 546.2978.

(−)-(5-(Benzyloxy)-4-{[(2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl]methyl}-6-methyl-3-pyridinyl)-methanol (17b). Reaction of **3b** (0.72 g, 2.6 mmol) using *n*-BuLi (4.88 mL, 7.8 mmol, 3.0 equiv.) and (*R*)-(−)-**4** (1.435 g, 7.8 mmol, 3.0 equiv.) was carried out by following the procedure described for (*S*,*R*/*R*,*R*)-**17d** to afford 0.710 g of (*S*,*R*)-(−)-**17b** in 65% yield and >98% de. R_f: 0.27 (3% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$): δ 8.28 (s, 1H), 7.55–7.36 (m, 5H), 5.25–5.09 (m, 1H), 4.94–4.86 (m, 2H), 4.74–4.44 (m, 2H), 4.20–4.10 (m, 1H), 3.95–3.92 (m, 1H), 3.77–3.71 (m, 1H), 3.62 (s, 3H), 3.60 (s, 3H), 2.77–2.69 (m, 1H), 2.57 (s, 3H), 2.20–2.10 (m, 1H), 0.95 (d, 3H, J=6.6 Hz), 0.70 (d, 3H, J=6.9 Hz); ESI-MS (*m*/*z*): 426 $(M+H)^+$, 448 $(M+Na)^+$.

(5-(Benzyloxy)-4-{[(2*S*,5*R*/(2*R*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl]methyl}-6-methyl-3-pyridinyl)methyl acetate (17c). Reaction of **3c** (0.028 g, 0.088 mmol) using *n*-BuLi (0.11 mL, 0.176 mmol, 2.0 equiv.) and (*S*)-(+)-**4** (0.032 g, 0.176 mmol, 2.0 equiv.) was carried out by following the procedure described for (*S*,*R*/*R*,*R*)-**17d** to afford 0.018 g of (*R*,*S*/*S*,*S*)-**17c** in 44% yield and 88:12 ratio. R_f: 0.47 (60% EtOAc in hexanes); Analytical RP HPLC: MeCN:0.1% aq. formic acid/50:50, 2.0 mL/min at 225 nm, R_t: 5.37 min, 96%; ^{1}H NMR ($CDCl_3$): δ 8.23 (s, 1H), 7.55–7.36 (m, 5H), 5.30–5.14 (m, 2H), 4.93–4.83 (m, 2H), 4.30–4.20 (m, 1H), 3.90–3.80 (m, 1H), 3.65 and 3.62 (two s, 3H), 3.54 and 3.53 (two s, 3H), 3.50–3.40 (m, 1H), 2.80–2.68 (m, 1H), 2.57 (s, 3H), 2.20–2.10 (m, 1H), 2.08 and 2.07 (two s, 3H), 1.03 and 0.95 (two d, 3H, J=6.6 and 6.9 Hz), 0.70 and 0.63 (two d, 3H, J=6.6, 6.9 Hz); ESI-MS (*m*/*z*): 467 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{26}H_{34}N_3O_5$ 468.2498 $(M+H)^+$; observed, 468.2494.

(−)-2-(Trimethylsilyl)ethyl-3-(3-(benzyloxy)-5-(hydroxymethyl)-4-{[(2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl]methyl}-2-pyridinyl)propanoate (17e). The reaction of **3e** (2.42 g, 5.56 mmol) using (*R*)-(−)-**4** (3.07 g, 16.69 mmol, 3.0 equiv.) and following the procedure described for (*S*,*R*)/*R*,*R*)-**17d** afforded 0.492 g of (*S*,*R*)-(−)-**17e** in 69% yield as a syrup and >98% de. $[\alpha]_D^{23}$=−35.1 (*c* 0.695, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.29 (s, 1H), 7.53–7.38 (m, 5H), 4.71 (d, 1H, J=11.8 Hz), 4.49–4.45 (m, 1H), 4.20–4.14 (m, 2H), 3.93 (t, 1H, J=3.6 Hz),

3.79–3.48 (m, 2H), 3.60 (s, 6H), 3.19 (t, 2H, J=7.4 Hz), 2.95–2.71 (m, 3H), 2,17–2.14 (m, 1H), 1.02–0.95 (m, 5H), 0.69 (d, 3H, J=6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 173.4, 166.7, 162.8, 153.9, 151.9, 145.4, 140.6, 136.6, 134.9, 128.4, 128.1, 127.8, 75.2, 62.4, 61.9, 60.3, 55.1, 53.3, 52.8, 32.3, 32.0, 31.0, 26.9, 19.1, 17.4, 17.2, −1.5; ESI-MS (m/z): 584 $(M+H)^+$; HRMS (FAB, m/z): calcd for $C_{31}H_{46}N_3O_6Si$, 584.3156 $(M+H)^+$; observed 584.3182.

(+)-5-(Benzyloxy)-4-{[(2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl]methyl}nicotinaldehyde (18). MnO_2 (85%, 1.6 g, 15.81 mmol, 13.0 equiv.) was added to a solution of alcohol (*S*,*R*/*R*,*R*)-**17d**, (0.50 g, 1.21 mmol) in $CHCl_3$ (50 mL) at room temperature and stirred for 20 h. The mixture was filtered through Celite powder and the filtrate was concentrated on a rotary evaporator. Purification of the crude product by silica gel column chromatography (40% EtOAc in hexane) afforded 0.26 g of (*S*,*R*)-(+)-aldehyde (**18**) in 52% yield (major isomer) and >98% de. R_f: 0.66 (70% EtOAc in hexanes); Analytical RP HPLC:MeCN:.05% aq. trifluoroacetic acid/45:55, 1.0 mL/min at 225 nm, R_t: 5.88 min, 99%; $[\alpha]_D^{23}$=+2.9 (*c*, 0.975, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 10.37 (s, 1H), 8.73 (s, 1H), 8.48 (s, 1H), 7.51–7.37 (m, 5H), 5.35–5.26 (m, 2H), 4.22–4.16 (m, 1H), 3.88 (t, 1H, J=3.5 Hz), 3.83 (dd, 1H, J=12.6, 4.2 Hz), 3.70 (s, 3H), 3.49 (s, 3H), 3.25 (dd, 1H, J=12.6, 10.0 Hz), 2.24–2.15 (m, 1H), 0.99 (d, 3H, J=6.8 Hz), 0.65 (d, 3H, J=6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 164.5, 162.8, 153.0, 143.5, 138.7, 137.7, 135.9, 130.6, 128.6, 128.1, 126.8, 70.8, 60.9, 54.7, 52.6, 52.5, 31.8, 28.5, 19.0, 16.7; ESI-MS (m/z): 410 $(M+H)^+$; HRMS (FAB, m/z): calcd for $C_{23}H_{28}N_3O_4$, 410.2080 $(M+H)^+$; observed, 410.2083.

(4*S*)-4-[(*E*:*Z*)-2-(5-(Benzyloxy)-4-{[(2*S*,5*R*)-5-isopropyl-3,6-dimethoxy-2,5-dihydro-2-pyrazinyl]methyl}-3-pyridinyl)ethenyl]-1,3-oxazolidin-2-one (19). *n*-BuLi (1.6 M solution in hexanes, 1.18 mL, 1.87 mmol, 3.0 equiv.) was added dropwise to (*R*)-(−)-**5** (0.45 g, 0.935 mmol, 1.5 equiv.) suspended in THF (9.0 mL) at −78°C under nitrogen. The resulting pale yellow solution was stirred for 15 min. A solution of (*S*,*R*)-(+)-aldehyde (**18**, 0.255 g, 0.623 mmol) in THF (9.0 mL) was added dropwise via a double ended needle to the above ylide solution over 5 min. The mixture was then stirred for 4 h and quenched with saturated aq. NH_4Cl solution (10 mL) at −78°C. The mixture was allowed to warm to room temperature and diluted with H_2O (20 mL) and EtOAc (50 mL). Organic layer was separated and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator. Purification of the crude product by silica gel column chromatography (5% MeOH in EtOAc) afforded 0.22 g of olefin (**19**) in 71% yield as a mixture of *E*:*Z* isomers (ratio: 64:36). R_f: 0.29 (3% MeOH in EtOAc); ^{1}H NMR ($CDCl_3$): δ 8.33 (s, 64/100 H), 8.26 (s, 36/100 H), 8.23 (s, 64/100 H), 7.86 (s, 36/100 H), 7.48–7.34 (m, 5H), 6.92 (d, 64/100 H, J=15.9 Hz), 6.86 (d, 36/100 H, J=11.5 Hz), 6.10 (dd, 64/100 H, J=15.8, 7.4 Hz), 5.87 (dd, 36/100 H, J=11.5, 8.9 Hz), 5.66 (br s, 36/100 H), 5.53 (br s, 64/100 H), 5.23–5.14 (m, 2H), 4.66–4.53 (m, 2 H), 4.45–4.37 (m, 36/100 H), 4.32–4.24 (m, 64/100 H), 4.21–4.14 (m, 1H), 3.89–3.83 (m, 1H), 3.67 (s, 64/100, 3H), 3.62 (s, 36/100, 3H), 3.52 (s, 36/100, 3H), 3.48 (s, 64/100, 3H), 3.43 (dd, 64/100 H, J=13.2, 5.2 Hz), 3.16–3.11 (m, 36/100 H), 2.95–79 (m, 1H), 2.28–2.17 (m, 1H), 1.02 (d, 3 H, J=6.9 Hz), 0.66–0.63 (m, 3H); ESI-MS (m/z): 493 $(M+H)^+$; HRMS (FAB, m/z): calcd for $C_{27}H_{33}N_4O_5$, 493.2445 $(M+H)^+$; observed, 493.2453.

***tert*-Butyl-(4*S*)-4-[(*E*:*Z*)-2-(5-(benzyloxy)-4-{(2*S*)-2-[bis(*tert*-butoxycarbonyl)amino]-3-methoxy-3-oxopropyl}-3-pyridinyl)ethenyl]-2-oxo-1,3-oxazolidine-3-carboxylate (20).** 0.5N HCl (9.0 mL) was added to a solution of olefin (**19** 1.0 g, 2.03 mmol) in CH_3CN (45 mL) at room temperature and stirred for 45 min. The mixture was concentrated and the residue was diluted with EtOAc (75 mL) and saturated aq. $NaHCO_3$ solution (75 mL). Organic layer was separated and the aqueous layer was extracted with EtOAc (3×75 mL). The combined organic layers were dried (Na_2SO_4), and concentrated on rotary evaporator to give 0.885 g of the crude residue which was dissolved in CH_3CN (10 mL) under nitrogen. To this mixture, Et_3N (0.93 mL, 6.68 mmol, 3.0 equiv.), $(Boc)_2O$ (3.06 mL, 13.37 mmol, 6.0 equiv.) and DMAP (0.055 g, 0.445 mmol, 0.2 equiv.) were added at room temperature. After stirring the mixture for 6 h, it was concentrated on a rotary evaporator and the crude product was purified by silica gel column chromatography (75% EtOAc in hexanes) to afford 0.7 g of **20** in 50% yield for two steps (*E*:*Z*/64:36 ratio). R_f: 0.73 (EtOAc); Analytical RP HPLC: MeCN:0.1% aq. acetic acid/55:45, 1.0 mL/min, 225 nm, R_t: 23.9 min, 99%; ^{1}H NMR ($CDCl_3$): δ 8.23 (s, 64/100 H), 8.21 (s, 36/100 H), 8.15 (s, 64/100 H), 8.06 (s, 36/100 H), 7.47–7.32 (m, 5H), 6.84 (d, 64/100 H, J=15.8 Hz), 6.63 (s, 36/100 H, J=11.7 Hz), 6.09 (dd, 64/100 H, J=15.8, 7.9 Hz), 5.85 (dd, 36/100 H, J=11.6, 9.3 Hz), 5.44–5.40 (m, 36/100 H), 5.29 (dd, 64/100 H, J=8.4, 5.9 Hz), 5.22–5.19 (m, 2H), 5.00–4.92 (m, 36/100 H), 4.91–4.82 (m, 64/100 H), 4.51–4.40 (m, 1 H), 4.17–4.08 (m, 1H), 3.73 (s, 3H), 3.62–3.49 (m, 2H), 1.51 (s, 64/100, 9H), 1.46 (s, 36/100, 9H), 1.33 (s, 18H); ESI-MS (m/z): 698 $(M+H)^+$; HRMS (FAB, m/z): calcd for $C_{36}H_{48}N_3O_{11}$, 698.3283 $(M+H)^+$; observed, 698.3275.

Methyl-(2*S*)-3-(3-(benzyloxy)-5-{(*E*:*Z*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-1-butenyl}-4-pyridinyl)-2-[bis(*tert*}-butoxycarbonyl)amino]propanoate (21). Cesium carbonate (0.083 g, 0.25 mmol, 0.25 equiv.) was added to a solution of **20** (0.70 g, 1.00 mmol.) in MeOH (35 mL) at room temperature. After stirring the mixture for 2.5 h, it was concentrated on a rotary evaporator. The residue was dissolved in $CHCl_3$ (200 mL), washed with water (100 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography (EtOAc) to give 0.53 g of **21** in 78% yield. R_f: 0.21 (80% EtOAc in hexanes); Analytical RP HPLC: MeCN:0.05% aq. trifluoroacetic acid/50:50, 1.0 mL/min, 225 nm, R_t: 13.93 min, 24% (*Z*-isomer) and 14.75 min, 76% (*E*-isomer); ^{1}H NMR ($CDCl_3$): δ 8.27 (s, 64/100 H), 8.16 (br s, 63/100 H and 1 H), 7.46–7.28 (m, 5 H), 6.67 (d, 64/100 H, J=15.9 Hz), 6.51 (d, 36/100 H, J=11.5 Hz), 6.05 (dd, 64/100 H, J=15.9, 5.1 Hz), 5.81–5.68 (m, 36/100 H), 5.40–5.10 (m, 4H), 4.42–4.24 (m, 1H), 3.79–3.62 (m, 5H), 3.59–3.29 (m, 2H), 1.45 (s, 64/100, 9H), 1.41 (s, 36/100, 9H), 1.34 (s, 36/100, 18H), 1.32 (64/100, 18H); ESI-MS

(*m*/*z*): 672 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{35}H_{50}N_3O_{10}$, 672.3491 $(M+H)^+$; observed, 672.3487.

(−)-Methyl-(2*S*)-2-[bis(*tert*-butoxycarbonyl)amino]-3-(3-{(3*S*)-3-[(*tert*-butoxycarbonyl)amino]-4-hydroxybutyl}-5-hydroxy-4-pyridinyl)propanoate (22). 2N HCl solution (0.225 mL, 0.453 mmol, 1.05 equiv.) was added dropwise to a stirred solution of **21** (0.29 g, 0.43 mmol) in MeOH (20 mL) over 5 min. After the addition was complete, the mixture was concentrated on rotary evaporator to dryness. The residue was dissolved in MeOH (20 mL) and hydrogenated in presence of 10%Pd/C (50% wet with water, 0.060 g, 10% wt/wt) at 20 psi for 4 h. The reaction was filtered through Celite and filtrate was concentrated. The residue was dissolved in $CHCl_3$ (100 mL) and washed with saturated aq. $NaHCO_3$ solution (50 mL). Organic layer was dried (Na_2SO_4), concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography (10% MeOH in EtOAc) to afford 0.21 g of (−)-**22** in 83% yield as a white solid. Mp: 103–4°C; R_f: 0.15 (5% MeOH in EtOAc); Analytical RP HPLC: MeCN:0.05% aq. trifluoroacetic acid/40:60, 1.0 mL/min, 225 nm, R_t: 10.17 min, 93%; $[\alpha]_D^{23}=-63.8$ (*c* 0.48, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.03 (s, 1H), 7.95 (s, 1H), 5.26 (dd, 1H, *J*=9.4, 4.8 Hz), 4.97 (br d, 1H), 3.77 (s, 3H), 3.74–3.60 (m, 3H), 3.49 (dd, 1H, *J*=14.0, 4.8 Hz), 3.36 (dd, 1H, *J*=14.0, 9.4 Hz), 2.69 (t, 2H, *J*=7.9 Hz), 1.90–1.69 (m, 2H),1.44 (s, 9H), 1.36 (s, 18H); ESI-MS: *m*/*z* 584 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{28}H_{46}N_3O_{10}$, 584.3183 $(M+H)^+$; observed, 584.3193.

(−)-Methyl-(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(3-{(3*S*)-3-[(*tert*-butoxycarbonyl)amino]-4-hydroxybutyl}-5-hydroxy-4-pyridinyl)propanoate (23). TFA (0.08 mL, 1.038 mmol, 3.5 equiv.) was added to a solution of (−)-**22** (0.173 g, 0.296 mmol) in CH_2Cl_2 (12 mL) at room temperature. After stirring the mixture for 26 h, it was concentrated on a rotary evaporator and the residue was dissolved in MeOH (20 mL). The mixture was then stirred for 6 h at room temperature. It was then concentrated on a rotary evaporator and crude product was purified on preparative RP HPLC (MeCN:0.1% aq. trifluoroacetic acid/35:65, 45.0 mL/min at 225 nm). The product was lyophilized to afford 0.122 g of (−)-**23** as its TFA salt in 69% yield as white powder. Analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid/35:65, 2.0 mL/min at 225 nm, R_t: 4.0 min, 99%; $[\alpha]_D^{23}=-25.2$ (*c* 0.42, MeOH); ^1H NMR ($CDCl_3$): δ 8.66 (s, 1H), 7.96 (s, 1H), 5.66 (br d, 1H, *J*=7.3 Hz), 5.35 (br d, 1H, *J*=7.69 Hz), 4.55–4.38 (m, 1H), 3.70 (br s, 6H), 3.38–3.24 (m, 2H), 2.89–2.82 (m, 2H), 1.88–1.79 (m, 2H), 1.44 (s, 9H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 170.9, 156.6, 156.2, 155.5, 142.2, 141.6, 131.3, 125.9, 80.7, 79.8, 64.1, 52.8, 52.7, 51.9, 32.2, 29.6, 28.3, 28.2, 26.9; ESI-MS (*m*/*z*): 484 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{23}H_{37}N_3O_8$, 484.2659 $(M+H)^+$; observed, 484.2681.

***tert*-Butyl-(4*S*)-4-[(*E*:*Z*)-2-(5-(benzyloxy)-4-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methoxy-3-oxopropyl}-3-pyridinyl)ethenyl]-2-oxo-1,3-oxazolidine-3-carboxylate (24).** 0.5 N HCl solution (7 mL) was added to a solution of **19** (0.76 g, 1.54 mmol) in CH_3CN (34 mL) at room temperature and stirred for 45 min. The mixture was concentrated on a rotary evaporator and dried under vacuum to give a residue (0.90 g) which was dissolved in dry CH_3CN (20 mL). To this mixture Et_3N (1.60 mL, 11.54 mmol, 6.0 equiv.), $(Boc)_2O$ (2.65 mL, 11.54 mmol, 6.0 equiv.) and DMAP (0.07 g, 0.576 mmol, 0.3 equiv.) were added sequentially at room temperature. The mixture was stirred for 52 h, concentrated and purified by silica gel column chromatography (EtOAc) to afford 0.42 g of (*S*,*S*)-**24** in 46% yield for two steps. Analytical RP HPLC: MeCN:0.1% aq. acetic acid/50:50, 2.0 mL/min, 225 nm, R_t: 4.77 min, 99%; ^1H NMR ($CDCl_3$): δ 8.25 (br s, 1H), 7.51–7.36 (m, 5H), 7.01–6.92 (m, 1H), 6.06 (dd, 1H, *J*=15.4 and 8.5 Hz), 5.48 (br d, 1H, *J*=9.3 Hz), 5.30–5.19 (m, 2H), 4.98–4.90 (m, 1H), 4.58–5.52 (m, 2H), 4.22 (dd, 1H, *J*=9.3 and 4.7 Hz), 3.69 (br s, 3H), 3.31 (dd, 1H, *J*=12.9 and 4.9 Hz), 2,98 (dd, 1 H, *J*=13.2 and 10.7 Hz), 1.55 (s, 9H), 1.28 (s, 9H); ESI-MS (*m*/*z*): 598 $(M+H)^+$.

(−)-Methyl-(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(3-{(3*S*)-3-[(*tert*-butoxycarbonyl)amino]-4-hydroxybutyl}-5-hydroxy-4-pyridinyl)propanoate (23). Lithium carbonate (0.010 g, 0.14 mmol, 0.20 equiv.) was added to a solution of (*S*,*S*)-**24** (0.42 g, 0.703 mmol) in MeOH (10 mL) at room temperature. After stirring the mixture for 17 h, it was concentrated on a rotary evaporator and dissolved in $CHCl_3$ (200 mL). The solution was washed with water (100 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography (EtOAc) to afford 0.295 g (74%) which was (0.28 g, 0.49 mmol) was dissolved in MeOH (20 mL) and 2N HCl solution (0.25 mL, 0.514 mmol, 1.05 equiv.) was added with stirring. After the addition was complete (5 min), the mixture was concentrated on rotary evaporator to dryness. The residue was dissolved in MeOH (20 mL) and hydrogenated over 10% Pd/C (50% wet with water, 0.056 g) at 20 psi for 3 h. The mixture was filtered through celite powder and the filtrate was concentrated. The residue was purified by preparative RP HPLC (MeCN:0.1% aq. trifluoroacetic acid/28:72, 45 mL/min at 225 nm) and lyophilized to afford 0.155 g of (*S*,*S*)-(−)-**23** in 53% yield. Analytical RP HPLC: MeCN:0.05% aq. TFA/30:70, 2.0 mL/min, 225 nm, R_t: 4.84 min, 99% and was identical to the compound prepared above.

Bis-Mosher ester (25). Et_3N (0.032 mL, 0.226 mmol, 5.0 equiv.) and (*R*)-(−)-α-methoxy-(α-trifluoromethyl phenylacetyl chloride (0.025 mL, 0.135 mmol, 3.0 equiv.) were added sequentially to a 0°C solution of (*S*,*S*)-(−)-**24** (0.027 g, 0.045 mmol) in CH_2Cl_2 (4 mL) under nitrogen. After stirring the mixture for 5 h, it was quenched with water (10 mL) and stirred for 10 min. The mixture was diluted with CH_2Cl_2 (20 mL) and separated the organic layer. It was dried (Na_2SO_4) and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography (40% EtOAc in hexane) to afford 0.034 g of bis-MTP ester (**25**) in 68% yield and >95% ee. Analytical RP HPLC: MeCN:0.05% aq. trifluoroacetic acid/65:35, 2.0 mL/min, 225 nm, R_t: 5.78 min, 96%; ^1H NMR ($CDCl_3$): δ 8.27 (s, 1H), 7.65–7.39 (m, 10H), 4.98 (br d, 1H, *J*=8.2 Hz), 4.46–4.23 (m, 3H), 4.05–3.93 (m, 1H), 3.71 (s, 3H), 3.65 (br s, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 2.88–2.70 (m, 3H), 2.64–2.55 (m, 1H), 1.83–1.71 (m, 2H), 1.45 (s,

9H), 1.33 (s, 9H); ^{19}F NMR ($CDCl_3$+α,α,α-trifluorotoluene): δ −8.01, −8.77; ESI-MS (*m*/*z*): 916 $(M+H)^+$, 1832 $(2\times M+H)^+$.

(+)-Methyl-(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-(4-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methoxy-3-oxopropyl}-5-hydroxy-3-pyridinyl)butanoate (26). Jones' reagent (0.30 mL, 0.422 mmol, 4.0 equiv.) was added to a solution of (−)-**23** (0.063 g, 0.11 mmol) in acetone (10 mL) at room temperature. After stirring the mixture for 40 min, the reaction was quenched with 5% aq. Na_2CO_3 solution (2 mL). The mixture was diluted with MeOH (20 mL) and filtered through the Celite powder. The filtrate was concentrated on a rotary evaporator and the residue diluted with EtOAc (50 mL) and H_2O (10 mL). The pH was adjusted to 4.8 using phosphate buffer (pH 4.0). The organic layer was separated and the aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated on a rotary evaporator. The residue was dissolved in MeOH–benzene (10 mL, 1:5 ratio) and a solution of $TMSCH_2N_2$ (2.0 M solution in hexanes, 0.25 mL, 0.5 mmol, 4.5 equiv.) was added at room temperature. The resulting pale yellow mixture was stirred for 15 min and concentrated on a rotary evaporator. The residue was purified by silica gel column chromatography (5% MeOH in EtOAc) to afford 0.030 g of (*S*,*S*)-(+)-**26** in 54% yield. R_f: 0.34 (5% MeOH in EtOAc); Analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid/35:65, 2.0 mL/min, 225 nm, R_t: 6.65 min, 99%; $[\alpha]_D^{23}$=+17.3 (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H), 7.93 (s, 1H), 5.68 (br d, 1H, *J*=7.0 Hz), 5.53 (br d, 1H, *J*=6.6 Hz), 4.45–4.36 (m, 2H), 3.77 (s, 3H), 3.69 (s, 3H), 3.14 (d, 1H, *J*=6.6 Hz), 2.75 (t, 2H, *J*=7.7 Hz), 2.18–1.8 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 172.7, 172.2, 155.4, 153.8, 140.2, 137.2, 133.7, 132.5, 128.3, 80.1, 77.4, 53.4, 52.4, 52.3, 33.9, 28.8, 28.3, 28.2, 26.0; ESI-MS (*m*/*z*): 512 $(M+H)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{24}H_{38}N_3O_9$, 512.2608 $(M+H)^+$; observed, 512.2620.

(−)-Pyridinium compound (27). A mixture of (*S*,*S*)-(+)-**26** (0.062 g, 0.12 mmol) and (*S*)-(−)-**6** (0.075 g, 0.182 mmol, 1.5 equiv.) in 1,4-dioxane (1.5 mL) was refluxed for 4 h under nitrogen. The solvent was removed on a rotary evaporator to dryness and the crude product was purified by preparative RP HPLC (MeCN:0.1% aq. trifluoroacetic acid/50:50, 45.0 mL/min at 225 nm). The product was lyophilized to afford 0.031 g of (−)-**27** in 27% yield. Analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid/50:50, 2.0 mL/min, 225 nm, R_t: 8.95 min, 98%; $[\alpha]_D^{23}$=−16.4 (*c* 0.495, MeOH); ^{1}H NMR (CD_3OD): δ 8.38 (s, 1H), 8.12 (s, 1H), 4.68–4.60, (m, 1H), 4.51–4.30 (m, 2H), 4.19–4.10 (m, 1H), 3.97–3.91 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.46–3.38 (m, 1H), 3.22–3.18 (m, 1H), 3.02–2.84 (m, 2H), 2.20–1.45 (m, 8H), 1.46 (s, 9H), 1.45 (s, 9H), 1.43 (s, 9H), 1.34 (s, 9H); ESI-MS (*m*/*z*): 797 $(M)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{39}H_{65}N_4O_{13}$, 797.4543 $(M)^+$; observed, 797.4542.

(+)-Deoxypyridinoline (Dpd, 2). A solution of LiOH (monohydrate, 0.0055 g, 0.13 mmol, 4.0 equiv.) in water (1.0 mL) was added to a solution of (−)-**27** (0.030 g, 0.033 mmol) in THF (3.0 mL) at room temperature. After stirring the mixture for 1 h it was concentrated on a rotary evaporator to dryness. A mixture of TFA (4.75 mL) and water (0.25 mL) was added to the above residue at room temperature and stirred for 1 h. The solvent was removed to dryness and the crude product was purified by preparative RP HPLC: (MeCN:0.1% aq. trifluoroacetic acid/2:98, 25.0 mL/min at 225 nm). Lyophilization of the product afforded 0.0237 g of (+)-Dpd-TFA (**2**) salt in 84% yield. Analytical RP HPLC: MeCN:0.1% aq. trifluoroacetic acid/2:98, 1.0 mL/min, 225 nm, R_t: 4.06 min, 99%; $[\alpha]_D^{23}$=+36.2 (*c* 0.54, MeOH), Lit[12]: $[\alpha]_D^{23}$=+31.6 (*c* 0.25, MeOH); ^{1}H NMR (D_2O): δ 8.13 (s, 1H), 8.05 (s, 1H), 4.39–4.28 (m, 2H), 4.06–3.97 (m, 1H), 3.77–3.28 (m, 1H), 3.26–3.17 (m, 1H), 3.28–3.15 (m, 2H), 2.90–2.64 (m, 2H), 2.09–1.71 (m, 6H), 1.38–1.16 (m, 2H); ^{13}C NMR (D_2O+5 μL MeOH): δ 173.2, 172.9, 172.4, 156.0, 141.6, 141.5, 136.4, 129.4, 61.7, 53.7, 53.6, 52.5, 30.7, 30.4, 29.9, 28.1, 26.1, 21.6; ESI-MS (*m*/*z*): 413 $(M)^+$; HRMS (FAB, *m*/*z*): calcd for $C_{18}H_{29}N_4O_7$, 413.2036 $(M)^+$; observed, 413.2050.

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