SYNTHESIS OF (2*R*,3*S*)-3-HYDROXY-2-HYDROXYMETHYLPYRROLIDINE FROM (4*S*,5*S*)-3-BENZYL-4-FORMYL-5-VINYL-2-OXAZOLIDINONE

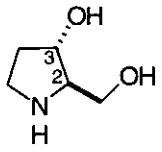
Andrew G. H. Wee,* Douglas D. McLeod, and Trent J. Rankin‡

Department of Chemistry, University of Regina, Regina, Saskatchewan, S4S 0A2, Canada

Abstract- (4*S*,5*S*)-3-Benzyl-4-formyl-5-vinyl-2-oxazolidinone (**2**), readily prepared *via* the reductive elimination of the mannose-derived iodo phenyl sulfone (**6b**), is used in the synthesis of the alkaloid (2*R*,3*S*)-3-hydroxy-2-hydroxymethylpyrrolidine (**1**).

Optically pure oxazolidinones are widely used as chiral auxiliaries in organic synthesis;[1] but their use as intermediates in synthesis has not been extensively investigated.[2] Several attributes make them attractive as synthetic intermediates: for example, (i) the 2-oxazolidinone moiety is stable toward a variety of reagents such as acidic and mildly basic as well as organometallic reagents, (ii) the 2-oxazolidinone moiety can be considered as a protected 1,2-amino alcohol unit, which can be unmasked to reveal the amino alcohol unit, and (iii) the reactions carried out on oxazolidinone derivatives are usually highly diastereoselective. In connection with our interest in the use of chiral 4,5- disubstituted 2-oxazolidinones

in synthesis of amino alcohols[3] and hydroxylated *N*- heterocycles, we have investigated the synthesis of the naturally occurring alkaloid, (2*R*,3*S*)-2-hydroxymethyl-3-hydroxypyrrolidine (**1**) starting from the oxazolidinonecarbaldehyde (**2**).



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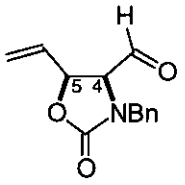
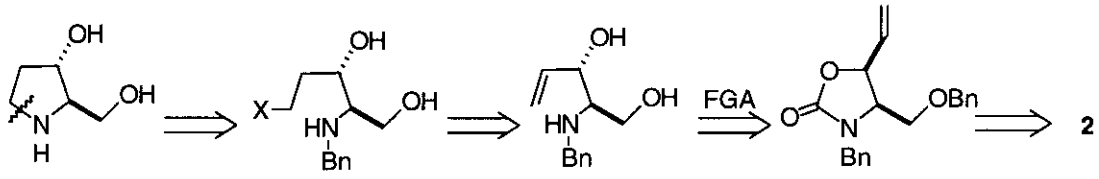


2

The pyrrolidine (**1**) was isolated from the seeds of the legume *Castanospermum australe*.[4] It has proven to be a useful intermediate for the synthesis of pyrrolizidine and indolizidine alkaloids,[5] and more recently, in the synthesis of an inhibitor of DNA repair enzyme, AlkA.[6] Five syntheses of **2** have been reported starting either from (*S*)-pyroglutamic acid,[7a,b] D[6]- or L[7c]-serine or (*Z*)-5-benzyloxy-2-penten-1-ol.[7d]



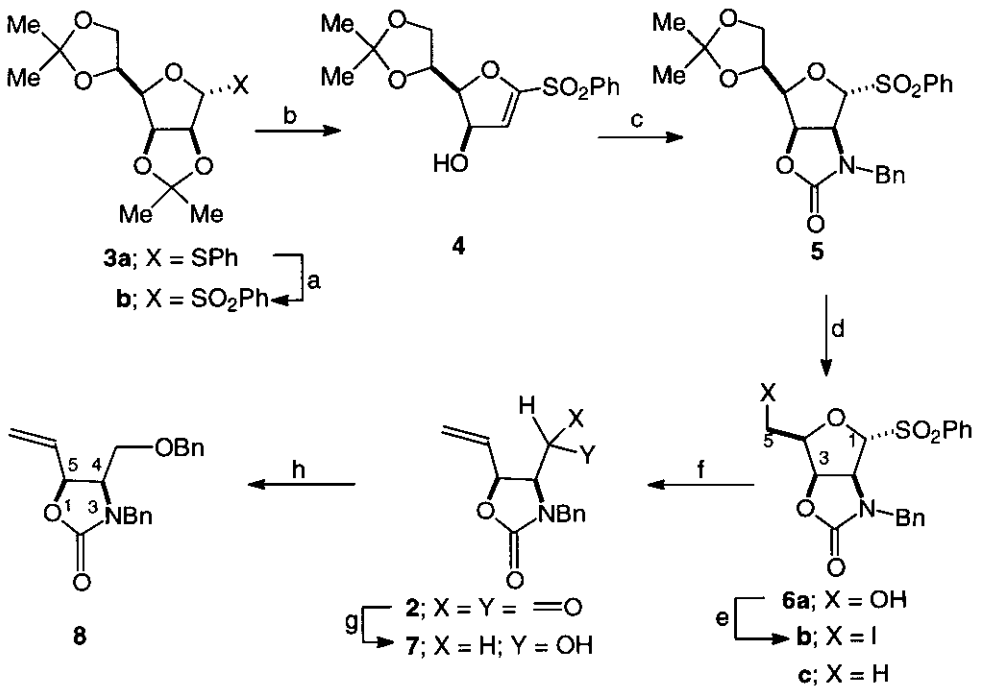
1 **10**

Chart 1

The retrosynthesis of **1** is shown in Chart 1. We envisaged that the disconnection of the C–N bond in **1** (as indicated) should result in **10** (e.g., X = OTs), which can ultimately be derived from the aldehyde (**2**). It is useful to note that the original number of carbons in **2** forms the carbon framework in **1**. Compound **2** is derived *via* the Zn/Ag-mediated reductive elimination of the readily prepared iodo phenyl sulfone (**6b**) (*vide infra*).

RESULTS AND DISCUSSION

Preparation of 2. The preparation of **2** (Scheme 1) started from the known phenylthiofuranoside (**3a**),[8] which was oxidized (*m*-CPBA) to give the phenyl sulfone (**3b**). The phenyl sulfone[9] moiety in **3b** served three purposes in the synthesis: (1) it facilitates carbanion formation at C-1 in **3b** and thence 1,2-elimination of the 2,3-*O*-isopropylidene group to give **4**, (2) it activates the 1,2-double bond in **4** to intramolecular Michael addition reaction, and (3) it would serve as a leaving group in the reductive elimination step (**6b**→**2**, *vide infra*).



Scheme 1

Reagents: a) 2.5 eq. *m*-CPBA, CH_2Cl_2; 85 %, b) BuLi, THF, HMPA (20 %), -78 °C; 80 %, c) BnNCO, KOBu-*t*, THF, rt; 75 %, d) H_5IO_6, EtOAc, rt; then $NaBH_4$, EtOH; 95 %, e) Ph_3P, pyridine, I_2, PhMe, CH_2Cl_2, 80 °C; 85 %, f) Zn/Ag, THF, 60 °C, g) $NaBH_4$, THF - EtOH, 0 °C; 91% (2 steps: f to g), h) BnBr, NaH, Bu_4N I, THF; 86 %.

Thus treatment of **3b** with BuLi in THF containing 20 % HMPA led efficiently to the heat labile furanoglycal (**4**), which was also found to slowly decompose upon prolonged storage. Intramolecular

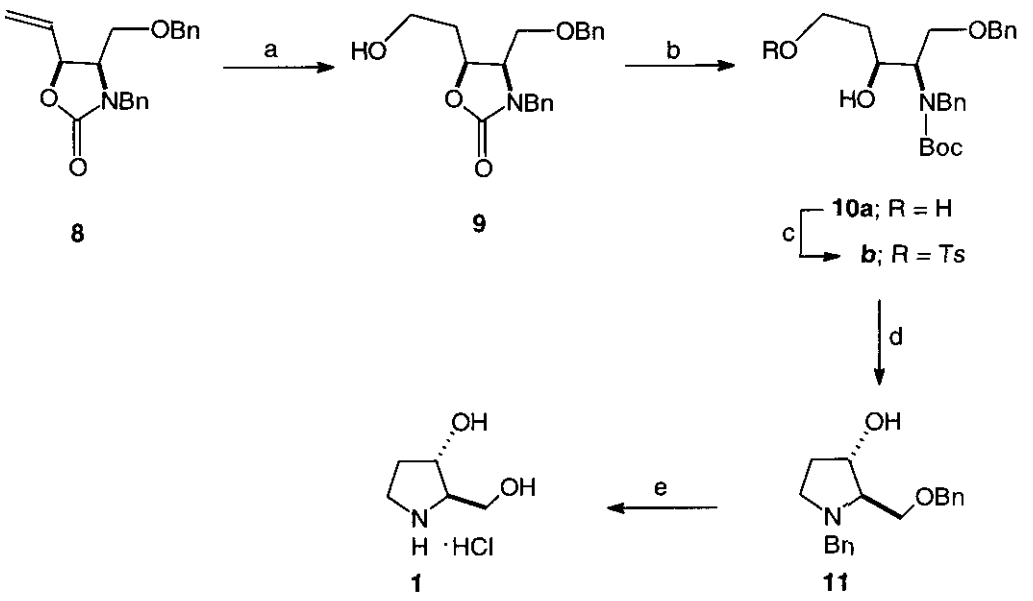
Michael addition[10] reaction of **5** with benzyl isocyanate in the presence of KOBu-*t* (20 mol %) yielded the *cis*-bicyclic oxazolidinone (**5**).[11] The 5,6-*O*-isopropylidene group in **5** was then subjected to a one-pot[12] hydrolysis/glycol cleavage to afford the corresponding aldehyde that was directly reduced with $NaBH_4$ to yield the primary alcohol (**6a**) (95 %). Subsequent iodination (PPh_3, I_2, pyridine[13]) of **6a** furnished crystalline **6b**[11] in 85 % yield.

The Zn/Ag[14]-mediated reductive elimination of **6b** in refluxing dry THF gave the corresponding aldehyde (**2**), which was reduced ($NaBH_4$, THF-EtOH) immediately to give **7**[15] in good yield. Interestingly, a small amount of the deiodinated product **6c**, which may have resulted from hydrolysis of a Reformatsky-type organozinc intermediate **6** (X = ZnI), was also obtained. This result is in contrast to the ribo analog[3] where the deiodinated compound was not formed. Subsequent benzylation of **7** gave the benzyl ether (**8**)[15] in 86 % yield.

Preparation of 1·HCl. Compound **8** was hydroborated with disiamylborane[16] which, after oxidative workup, gave the primary alcohol (**9**) (Scheme 2). It was found that no reaction occurred when one mole equivalent of disiamylborane was used even after 36 h of reaction time; however, the use of six mole equivalents of disiamylborane resulted in complete reaction after 20 h. The decreased reactivity of the terminal double bond may likely be due to steric shielding of the double bond by the adjacent *cis*-C–4-benzyloxymethyl substituent. It is interesting to note that product **9** was not formed when the bulkier 9-BBN (10 mol. equiv.) was used as the hydroborating reagent.

The primary alcohol was then subjected to base hydrolysis to furnish the very polar amino diol which was treated, *in situ*, with Boc_2O to give the *N*-Boc derivative (**10a**). Selective tosylation of the primary hydroxyl unit in **10a** gave the monotosylate (**10b**) in good yield. Some starting material was also recovered. The *N*-Boc group in **10b** was removed using TFA in CH_2Cl_2 and the reaction mixture was basified with anhydrous K_2CO_3. Ethanol (95 %) was then added and the mixture was refluxed for 3 h to

yield the cyclized *O,N*-dibenzyl-pyrrolidine (**11**) in 95 %. The ^{1}H and ^{13}C NMR and including HETCOR and 2D-COSY spectral data are in full accord with the structure.



Scheme 2

Reagents: a) $(Sia)_2BH$ (6 eq.), THF, rt; then H_2O_2, NaOH; 91 %, b) (i) 2M KOH, EtOH, reflux, ii) Boc_2O, aq. KOH, Et_2O, rt; 86 %, c) TsCl (1.2 eq.), pyridine, cat. $(i\text{-}Pr)_2NEt$, $CHCl_3$, 0 °C; 71%. d) (i) TFA, CH_2Cl_2, rt; then K_2CO_3, (ii) EtOH, reflux; 95 %, e) $Pd(OH)_2$, H_2 (1 atm), MeOH, rt; then conc. HCl; 98 %.

Hydrogenation of **11** over 20 % $Pd(OH)_2$ for 24 h gave **1**, which was isolated as its hydrochloride salt. This compound has an $[\alpha]_D^{22}$ + 40° and NMR data that were in excellent agreement with reported literature data.[7]

EXPERIMENTAL

General method. Only diagnostic absorptions in the IR spectrum are reported. Melting points were recorded using a Kofler hot-stage apparatus and are uncorrected. ^{1}H (200 MHz) and ^{13}C NMR (50 3

MHz) spectra were recorded in $CDCl_3$ unless otherwise stated. Tetramethylsilane (δ = 0.00) and the $CDCl_3$ resonance (δ = 77.0) were used as references. In the ^{13}C DEPT-135 experiment, the inverted signals of the CH_2 are indicated by (-). Elemental analyses and high resolution electron impact (70 eV) MS spectral analyses were performed at the Chemistry Department, University of Saskatchewan, Canada. Reaction progress was monitored by TLC on Merck silica gel 60 precoated (0.25 mm) on aluminum backed sheets. Air and moisture sensitive reactions were conducted under a static pressure of argon. All organic extracts were dried over anhydrous Na_2SO_4. Flash chromatography[17] was performed on Merck silica gel 60 (230-400 mesh). Unless otherwise indicated, the eluent is either a mixture of petroleum ether (bp 35-60 °C) and ethyl acetate (EtOAc) or a mixture of petroleum ether and ether. Solvents were dried by distillation from appropriate drying agents: tetrahydrofuran from sodium-benzophenone ketyl, toluene and dichloromethane from CaH_2, methanol from Mg and ethyl acetate from anhydrous K_2CO_3.

Phenylsulfonyl-2,3,5,6-di-*O*-isopropylidene-β-D-*manno*furanosyl sulfone (3b). 1-Phenylthio-β-furanoside (**3a**)[8] (9.65 g, 0.027 mol) was dissolved in CH_2Cl_2 (150 mL) and saturated aqueous $NaHCO_3$ (200 mL) was added. The biphasic mixture was cooled to 0 °C in an ice-bath and *m*-CPBA (13 g, 0.06 mol, 80 % tech.) was added portionwise. The mixture was stirred at rt for 20 h, then recooled to 0 °C and 10 % aqueous $NaHSO_3$ was added. After 1 h at rt, the aqueous phase was separated and backextracted with CH_2Cl_2 (50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 X 50 mL), dried, filtered and evaporated. The crude oil was chromatographed (2:1 petroleum ether-EtOAc) to give the desired phenyl sulfone (8.5 g, 80 %) as a thick oil which slowly crystallized. The sulfone was found to be slightly unstable and is best kept in the freezer for prolonged storage. mp: 116 – 118 °C. *IR* ν_{max}: 3062, 1380, 1162 cm^{-1}.^1H NMR, δ: 1.36 (s, 3H, Me), 1.38 (s, 3H, Me), 1.42 (s, 3H, Me), 1.46 (s, 3H, Me), 3.90 (dd, 1H, *J* = 9.1, 4.6 Hz, H-6), 4.05 (dd, 1H, *J* = 9.1, 6.2 Hz, H-6'), 4.28 (m, 1H, H-5), 4.59 (dd, 1H, *J* = 6.8, 4.0 Hz, H-4), 4.83 (br s, 1H, H-1), 4.98 (dd, 1H, *J* = 6.0, 4.0 Hz, H-3), 5.50 (dd, 1H, *J* = 6.3, 1.1 Hz, H-2), 7.55 – 7.78 (m, 3H, PhH), 7.90 (d, 2H, *J* = 7.2 Hz, Ph H).^{13}C NMR, δ: 24.5, 24.9, 25.9,

26.6, 66.3, 72.8, 80.3, 80.4, 83.9, 98.2, 109.3, 113.7, 128.9, 129.0, 134.2, 136.0. Anal. Calcd for $C_{18}H_{24}O_7S$: C, 56.24; H, 6.29. Found: C, 56.11; H, 6.18.

Phenyl 2-amino-*N*-benzyl-2*N*,3*O*-carbamoyl-2-deoxy-5,6-*O*-isopropylidene-α-D-*lyxo*furanosyl sulfone (5). Compound **3b** (8.5 g, 0.02 mol) was dissolved in a mixture of dry THF (70 mL) containing dry HMPA (4.6 mL) under Ar. The solution was cooled to -78 °C and BuLi (15.9 mL, 0.033 mol, 2.09 M in hexanes) was added dropwise *via* syringe to the mixture. The deep yellow-orange solution was stirred at -78 °C for 1 h and then the cooling bath was removed and the mixture was allowed to warm slowly to rt. The mixture was stirred at rt for 2 h and then recooled to 0 °C. Saturated aqueous NH_4Cl (15 mL) was added and then followed by EtOAc (50 mL). The organic layer was removed and the aqueous phase was re-extracted with EtOAc (2 X 50 mL). The combined organic phases were washed with saturated aqueous NaCl (70 mL), dried, filtered and evaporated. The residual yellow oil was chromatographed (1:1 petroleum ether-EtOAc) to give **4** as a pale yellow syrup (6.2 g, 86 %) which slowly crystallized on standing. The product was found to be unstable and is best kept in the freezer for prolonged storage.[1]H NMR, δ: 1.33 (s, 3H, Me), 1.38 (s, 3H, Me), 2.65 – 2.80 (br hump, 1H, OH), 3.80 (dd, 1H, J = 8.9, 4.4 Hz, H-6), 4.07 (dd, 1H, J = 8.9, 5.9 Hz, H-6'), 4.34 – 4.51 (m, 2H, H-4, H-5), 5.01 – 5.11 (m, 1H, H-3), 6.09 (d, 1H, J = 2.9 Hz, H-2), 7.50 – 7.75 (m, 3H, PhH), 7.95 (d, 2H, J = 7.2 Hz, PhH).[13]C NMR, δ: 25.1, 26.7, 66.3 (-), 72.1, 72.2, 87.6, 109.5, 110.3, 128.4, 129.2, 134.4, 137.5, 157.9.

Ene alcohol (**4**) (6.28 g, 19.3 mmol) was dissolved in dry THF (70 mL), under Ar. Benzyl isocyanate (2.62 mL, 21.2 mmol) was added and the reaction mixture was cooled to 0 °C. Potassium *t*-butoxide (0.432 g, 3.85 mmol) was added in one portion and the brown reaction mixture was stirred at 0 °C for 1 h and at rt for 20 h. Then saturated aqueous NH_4Cl (20 mL) and EtOAc (20 mL) were added. The organic phase was separated and the aqueous phase was re-extracted with EtOAc (3 X 30 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and evaporated. The crude product was chromatographed (3:1 petroleum ether-EtOAc) to give **5** (7.5 g, 85 %) as a pale yellow, viscous oil. IR

ν_{max}: 1762 cm^{-1}.^{1}H NMR, δ: 1.32 (s, 3H, Me), 1.39 (s, 3H, Me), 3.82 (dd, 1H, *J* = 8.7, 4.4 Hz, H-6), 4.03 (dd, 1H, *J* = 8.7, 6.3 Hz, H-6'), 4.33 (dt, 1H, *J* = 6.8, 4.9 Hz, H-5), 4.39 (d, 1H, *J* = 14.8 Hz, PhCH), 4.59 (s, 1H, H-1), 4.61 (d, 1H, *J* = 14.8 Hz, PhCH), 4.66 (dd, 1H, *J* = 7.3, 3.9 Hz, H-4), 4.96 (dd, 1H, *J* = 7.3, 1.4 Hz, H-2), 5.15 (dd, 1H, *J* = 7.3, 3.9 Hz, H-3), 7.30 – 7.49 (m, 5H, PhH), 7.50 – 7.83 (m, 5H, PhH).^{13}C NMR, δ: 24.8, 26.5, 47.7 (-), 60.7, 66.2 (-), 72.1, 77.2, 84.2, 95.4, 109.6, 128.4, 128.9, 128.9, 129.2, 134.6, 134.8, 135.2, 156.1. Anal. Calcd for $C_{23}H_{25}NO_7S$: C, 60.12; H, 5.48; N, 3.05. Found: C, 60.21; H, 5.54; N, 3.02.

Phenyl 2-amino-*N*-benzyl-2*N*,3*O*-carbamoyl-2-deoxy-5-hydroxy-α-D-*lyxo*furanosyl sulfone (6a). Compound **5** (2.46 g, 5.36 mmol) was dissolved in dry EtOAc (60 mL) under Ar. H_5IO_6 (1.46 g, 6.43 mmol) was added in one portion and the mixture was stirred at rt for 3 h. After reaction was complete (TLC), the reaction mixture was filtered through a Celite pad and the residue was washed with EtOAc (2 X 10 mL). The EtOAc filtrates were evaporated and the residue was taken into 95 % ethanol (25 mL) and the solution was cooled to 0 °C. $NaBH_4$ (0.61 g, 16.1 mmol) was added portionwise and the mixture was stirred at 0 °C for 15 min and at rt for 30 min. The cooled (0 °C) reaction mixture was treated with glacial AcOH (10 drops) to destroy any excess $NaBH_4$. The mixture was then evaporated and the residual oil was dissolved in EtOAc (50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 X 20 mL), brine (20 mL), dried, filtered and evaporated. The crude product was chromatographed (2:1 petroleum ether-EtOAc) to give the primary alcohol (**6a**) (2.5 g, 97 %) as a colorless oil. IR ν_{max}: 3420 – 3480, 1757 cm^{-1}.^{1}H NMR, δ: 2.20 – 2.55 (br hump, 1H, OH), 3.81 (dd, 1H, *J* = 12.3, 6.1 Hz, H-5), 3.90 (dd, 1H, *J* = 12.3, 5.1 Hz, H-5'), 4.37 (d, 1H, *J* = 14.9 Hz, PhCH), 4.62 (d, 1H, *J* = 14.9 Hz, PhCH), 4.67 (br s, 1H, H-1), 4.82 (br q, 1H, *J* = 5.1 Hz, H-4), 4.95 (dd, 1H, *J* = 7.4, 1.0 Hz, H-2), 5.13 (dd, 1H, *J* = 7.4, 4.1 Hz, H-3), 7.30 – 7.45 (m, 5H, PhH), 7.60 – 7.85 (m, 5H, PhH). The alcohol was further characterized as the *O*-acetate. ^{1}H NMR, δ: 2.09 (s, 3H, Me), 4.27 (dd, 1H, *J* = 12.3, 6.8 Hz, H-5), 4.39 (d, 1H, *J* = 15.4 Hz, PhCH), 4.62 (d, 1H, *J* = 15.4 Hz, PhCH), 4.64 (br s, 1H, H-1), 4.86 – 4.94 (m, 1H, H-4), 4.96 (dd,

1H, J = 7.6, 1.4 Hz, H-2), 5.15 (dd, 1H, J = 7.6, 4.1 Hz, H-3), 7.33 – 7.46 (m, 5H, PhH), 7.52 – 7.72 (m, 3H, PhH), 7.76 – 7.85 (d, 2H, J = 7.2 Hz, PhH). ^{13}C NMR, δ: 20.6, 47.9 (-), 60.8, 60.9 (-), 76.9, 81.7, 95.4, 128.6, 129.0, 129.2, 129.4, 134.8, 135.2, 156.1, 170.2. Anal. Calcd for $C_{21}H_{21}NO_7S$. C, 58.46; H, 4.91; N, 3.25. Found: C, 58.37; H, 4.88; N, 3.17.

Phenyl 2-amino-*N*-benzyl-2*N*,3*O*-carbamoyl-2,5-dideoxy-5-iodo-α-D-*lyxo*furanosyl sulfone (6b). Alcohol (**6a**) (5.6 g, 14 mmol) was dissolved in a mixture of dry toluene (47 mL), dry CH_2Cl_2 (35 mL) and dry pyridine (4.1 mL, 50 mmol), under Ar. In a separate flask, Ph_3P (4.7 g, 18 mmol) was dissolved in dry toluene (84 mL) and iodine (3.8 g, 15 mmol) was added. The mixture was heated at 60 °C for 30 min and then the temperature was raised to 80 °C. The solution of **6a** was added dropwise, *via* cannula, to the Ph_3P/I_2 mixture. After addition was complete, the mixture was heated at 80 °C for 4 h, during which time the reddish brown precipitate was consumed and a white precipitate was formed. The reaction mixture was cooled to rt, filtered through a Florisil pad and the solid residue washed with EtOAc (2 X 30 mL). The combined filtrates were evaporated to leave a thick oil. Chromatographic purification (3:1 petroleum ether-EtOAc) gave the desired iodide (**6b**) (5.6 g, 78 %) as a pale yellow oil. mp: 142 – 144 °C IR ν_{max}: 3050, 3025, 1755 cm^{-1}.^{1}H NMR, δ: 3.17 (dd, 1H, J = 11.8, 7.2 Hz, H-5), 3.27 (dd, 1H, J = 11.8, 6.6 Hz, H-5'), 4.36 (d, 1H, J = 14.5 Hz, PhCH), 4.58 (d, 1H, J = 14.5 Hz, PhCH), 4.65 (s, 1H, H-1), 4.91 – 5.03 (m, 2H, H-2, H-4), 5.13 (dd, 1H, J = 7.2, 3.3 Hz, H-3), 7.30 – 7.75 (m, 8H, PhH), 7.77 – 7.88 (d, 2H, J = 7.2 Hz, PhH). ^{13}C NMR, δ: -3.4 (-), 47.5 (-), 60.9, 76.9, 84.2, 95.2, 128.3, 128.7, 128.8, 128.9, 129.1, 134.5, 134.6, 134.9, 155.8. Anal. Calcd for $C_{19}H_{18}NO_5IS$: C, 45.70; H, 3.63; N, 2.81. Found: C, 45.49; H, 3.43; N, 2.60.

(4*R*,5*S*)-3-Benzyl-4-hydroxymethyl-5-vinyl-2-oxazolidinone (7). Activated Zn dust (1.75 g, 26.7 mmol) was added to a solution of AgOAc (714 mg, 4.27 mmol) in glacial AcOH (200 mL) at 110 °C (oil bath).[14] The mixture was stirred at 110 °C for 35-40 sec and then was allowed to cool slightly. Glacial AcOH was decanted off and the Zn/Ag couple was washed thoroughly with dry THF (4 X 15 mL) and then was

covered with dry THF (10 mL). The slurry of Zn/Ag couple in dry THF was heated to 65 °C and a solution of the iodo sulfone (0.60 g, 1.2 mmol) in dry THF (5 mL) was added dropwise *via* cannula to the Zn/Ag couple. The reaction mixture was heated at 65 °C for 1 h, allowed to cool to rt and the THF supernatant containing the aldehyde (**2**) was filtered through glass wool into a clean flask. The reaction flask was rinsed with THF (2 X 5 mL) and the washings filtered into the flask. The THF filtrate was cooled to 0 °C and 95 % ethanol (10 mL) was added at which time the reaction mixture turned cloudy. Sodium borohydride (0.28 g, 7.4 mmol) was added, portionwise, to the mixture and it was stirred at 0 °C for 2 h and then at rt overnight. The reaction mixture was recooled to 0 °C and glacial AcOH (0.5 mL) was carefully added. The reaction mixture was evaporated and the residual oil was taken into EtOAc (15 mL). The organic phase was washed with water (10 mL), saturated aqueous $NaHCO_3$ (3 X 10 mL), brine and then dried. The filtered solution was evaporated to give the crude crystalline primary alcohol. Chromatographic purification (40:1 CH_2Cl_2-acetone) of the crude product gave the crystalline alcohol (**7**) (250 mg, 90 %) and a small amount of reduced compound **6c** (33 mg). Compound **7**: mp: 138 – 139 °C. $[\alpha]_D^{23}$ +14.8° (c 1.01, $CHCl_3$). IR ν_{max}: 2980 – 3154, 1748 cm^{-1}. ^1H NMR ($CDCl_3$-CD_3CN), δ: 2.87 (t, 1H, *J* = 5.1 Hz, OH), 3.50 – 3.76 (m, 3H, H-4, CH_2O), 4.20 (d, 1H, *J* = 14.4 Hz, PhCH), 4.80 (d, 1H, *J* = 14.4 Hz, PhCH), 4.95 (t, 1H, *J* = 8.2 Hz, H-5), 5.32 – 5.51 (m, 2H, CH_2=), 5.99 – 6.19 (m, 1H, =CH). ^{13}C NMR ($CDCl_3$-CD_3CN), δ: 45.7 (-), 57.8 (-), 58.1, 77.1, 116.5, 119.9 (-), 127.1, 127.3, 128.1, 131.1, 135.9, 157.9. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.70; H, 6.68; N, 5.89. Compound (**6c**): IR ν_{max}: 3060, 1754, 1672, 1584 cm^{-1}. ^1H NMR, δ: 1.37 (d, 3H, *J* = 7.5 Hz, Me), 4.38 (d, 1H, *J* = 14.4 Hz, PhCH), 4.59 – 4.67 (m, 1H, H-2), 4.62 (d, 1H, *J* = 14.4 Hz, PhCH), 4.80 – 5.00 (m, 3H, H-1, H-3, H-4), 7.30 – 7.90 (m, 10H, PhH). ^{13}C NMR, δ: 13.5, 47.6, 61.2, 78.4, 80.4, 95.5, 128.4, 128.9, 129.0, 129.3, 134.5, 134.9, 135.6, 156.5. Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.11; H, 5.13; N, 3.75. Found: C, 60.99; H, 5.08; N, 3.70.

(4*R*,5*S*)-3-Benzyl-4-benzyloxymethyl-5-vinyl-2-oxazolidinone (8). The primary alcohol (**7**) (106 mg,

0.455 mmol) was dissolved in dry THF (5 mL), under Ar. The solution was added to a suspension of NaH (66 mg, 2.8 mmol, 50 % dispersion in mineral oil) and Bu_4N I (34 mg , 0.091 mmol) in dry THF (10 mL) containing benzyl bromide (70 μL, 0.59 mmol) at 0 °C. The mixture was stirred at 0 °C to rt overnight (20 h). Saturated aqueous NH_4Cl (5 mL), brine (5 mL) and then EtOAc (10 mL) were added. The aqueous phase was separated and re-extracted with EtOAc (5 mL). The combined organic phases were washed with water (10 mL), saturated NaCl (10 mL), dried, filtered and evaporated. The crude oil was chromatographed (3:1 petroleum ether-EtOAc) to give the benzyl ether (**8**) as a pale yellow oil (127 mg, 86 %). $[\alpha]_D^{21}$ -8.8° (c 1.70, $CHCl_3$). IR ν_{max}: 3087, 3030, 1747, 1604, 1586 cm^{-1}.^{1}H NMR, δ: 3.43 (dd, 1H, *J* = 14.7, 5.3 Hz, CHOBn), 3.51 (dd, 1H, *J* = 14.7, 3.5 Hz, CHOBn), 3.75 ("quintet", 1H, *J*= 4.4 Hz, H-4), 4.12 (d, 1H, *J* = 14.3 Hz, PhCHN), 4.39 (d, 1H, *J* = 14.1 Hz, PhCHO), 4.47 (d, 1H, *J* = 14.1 Hz, PhCHO), 4.81 (d, 1H, *J* = 14.3 Hz, PhCHN), 4.93 (t, 1H, *J* = 8.5 Hz, H-5), 5.30 – 5.53 (m, 2H, $=CH_2$), 5.87 – 6.06 (m, 1H, =CH), 7.15 – 7.45 (m, 10H, PhH). ^{13}C NMR, δ: 46.6 (-), 57.1, 66.6 (-), 73.2 (-), 77.1, 120.3 (-), 127.7, 127.8, 128.0, 126.4, 128.6, 131.1, 136.2, 137.2, 157.9. HRMS calcd for $C_{20}H_{21}NO_3$ (M^+) 323.1521, found 323.1525.

(4*R*,5*S*)-3-Benzyl-4-benzyloxymethyl-5-[1-(2-hydroxyethyl)]-2-oxazolidinone (9). Disiamylborane, prepared by reaction of BH_3 THF (11.2 mL, 1 M in THF) with 3-methyl-2-butene (11.2 mL, 2 M in THF) at 0 °C for 2 h, was added to a solution of **8** (590 mg, 1.83 mmol) in dry THF (5 mL), under Ar. The reaction mixture was stirred at rt for 20 h, and then recooled to 0 °C. Aqueous 10 % NaOH (11 mL) and 30 % H_2O_2 (3.2 mL) were added and the mixture was stirred at 0 °C for 2 h and at rt for 2 h. EtOAc (15 mL) were added, the aqueous phase was separated and then re-extracted with EtOAc (2 X 10 mL). The combined organic phases were washed with saturated NaCl, dried, filtered and evaporated. The crude liquid was subjected to Kugelrohr (oven temp 40 °C at 0.05 Torr) distillation to remove isoamyl alcohol. The residual oil was then chromatographed (2:1 petroleum ether-EtOAc and then EtOAc) to give the alcohol (**9**) (505 mg, 81 %) as a colorless oil. $[\alpha]_D^{22}$ -35.1° (c 1.35, $CHCl_3$). ^{1}H NMR, δ: 1.80 – 2.11 (m,

2H, CH_2), 2.55 – 2.72 (m, 1H, OH), 3.46 (dd, 1H, *J* = 10.8, 4.1 Hz, CHOBn), 3.53 (dd, 1H, *J* = 10.8, 4.1 Hz, CHOBn), 3.65 (dt, 1H, *J* = 8.2, 4.2 Hz, H-4), 3.72 – 3.84 (m, 2H, CH_2OH), 4.30 (d, 1H, *J* = 15.4 Hz, PhCHN), 4.38 (d, 1H, *J* = 11.3 Hz, PhCHO), 4.47 (d, 1H, *J* = 11.3. Hz, PhCHO), 4.62 – 4.75 (m, 1H, H-5), 4.77 (d, 1H, *J* = 15.4 Hz, PhCHN), 7.10 – 7.50 (m, 10H, PhH). ^{13}C NMR, δ: 31.6, 46.4, 56.7, 58.9, 65.7, 73.2, 74.3, 127.6, 127.7, 127.9, 128.4, 128.6, 136.1, 137.1, 158.2. HRMS calcd for $C_{20}H_{23}NO_4$ (M^+) 341.1627, found 341.1622.

(3*S*,4*R*)-5-Benzyloxy-4-[*N*-benzyl-*N*-(*t*-butyloxycarbonyl)amino]-1,3-pentanediol (10a). Compound (**9**) (505 mg, 1.48 mmol) was dissolved in a mixture of 95 % ethanol (7 mL) and 2M aqueous KOH (3 mL), under Ar. The mixture was refluxed (oil bath temperature: 100 °C) for 24 h. The reaction mixture was cooled to rt and then ethanol was evaporated . Water (5 mL) and ether (10 mL) were added to the residue and the biphasic mixture was cooled to 0 °C. Boc_2O (332 mg, 1.52 mmol) was added and the mixture was stirred at 0 °C for 2 h and at rt for 20 h. The organic phase was separated and the aqueous phase was saturated with solid NaCl. The aqueous phase was extracted thoroughly with CH_2Cl_2 (2 X 10 mL), the combined organic phases were dried, filtered and evaporated to leave a thick oil. Chromatographic purification (2:1 petroleum ether-EtOAc) afforded the desired product (490 mg, 80 %) as a viscous oil which crystallized on standing. A small amount of starting oxazolidinone (33 mg) was also recovered. $[\alpha]_D^{22}$ +21.9° (c 2.05, $CHCl_3$). IR ν_{max}: 3624 – 3166, 1669 cm^{-1}.^1H NMR, (signals are broadened due to the presence of amide rotamers) δ: 1.20 – 1.90 (m, 2H, CH_2), 1.42 (s, 9H, *t*-Bu), 2.60 – 2.95 (m, 1.2H, OH), 3.40 – 3.70 (m, 2H), 3.75 – 3.95 (m, 1H), 4.25 (br d, 1H, *J* = 16 Hz, PhCHN), 4.35 – 4.60 (m, 2H, $PhCH_2O$), 4.75 (br d, 1H, *J* = 16 Hz, PhCHN), 4.90 – 5.00 (m, 0.7H, OH), 7.15 – 7.40 (m, 10H, PhH). OH signals at δ 2.60 – 2.95 and δ 4.90 – 5.00 disappeared upon deuteration; a multiplet in the region δ 3.55 – 3.75 sharpened to a pseudo triplet (*J* = 5.9 Hz). ^{13}C NMR (discernible signals of other rotamer are given in brackets), δ: 28.3, [35.0 (-)] and 36.4 (-), [51.1 (-)] and 53.4 (-), [60.9 (-)] and 61.5 (-), 63.6, 68.3

(-) and [70.6 (-)], 73.2 (-), 74.2, 80.9, 127.3, 127.4, 127.6, 128.1, 128.4, 128.4, 137.9, 138.6, 156.6. Anal. Calcd for $C_{24}H_{33}NO_5$: C, 69.37; H, 8.00; N, 3.37. Found: C, 69.51; H, 8.00; N, 3.31.

(2*R*,3*S*)-1-Benzyl-2-benzyloxymethyl-3-hydroxypyrrolidine (11). The diol (**10a**) (490 mg, 1.19 mmol) was dissolved in dry $CHCl_3$ (5 mL) containing dry pyridine (2.5 mL) and *i*-Pr_2NEt (21 µL, 0.118 mmol), under Ar. The mixture was cooled to 0 °C and a solution of *p*-toluenesulfonyl chloride (271 mg, 1.42 mmol) in dry $CHCl_3$ (7 mL) was added dropwise, *via* a syringe pump, over a period of 3 h. The reaction mixture was stirred at 0 °C for 2 h and at rt for 36 h. Then saturated NaCl (10 mL) and 1M H_2SO_4 (15 mL) were added. The $CHCl_3$ layer was separated and washed again with 1M H_2SO_4 (10 mL). The combined acidic aqueous phases were re-extracted with CH_2Cl_2 (2 X 10 mL). The combined organic extracts were washed with water (15 mL), saturated $NaHCO_3$ (15 mL), dried, filtered and evaporated. The residual oil was chromatographed (2:1 petroleum ether-EtOAc) to give the oily monotosylate (**10b**) (383 mg, 57 %) and unreacted **10a** (95 mg) was also recovered. IR ν_{max}: 3622 – 3266, 1689, 1667, 1613 cm^{-1}. ^1H NMR, δ: 1.42 (s, 9H, *t*-Bu), 1.60 – 1.85 (m, 2H, CH_2), 2.43 (s, 3H, Me), 3.35 – 3.60 (m, 1H, OH), 3.65 – 4.12 (m, 4H), 4.25 (d, 1H, *J* = 16 Hz, PhCHN), 4.31 – 4.49 (m, 4H), 4.67 (d, 1H, *J* = 16 Hz, PhCHN), 7.11 – 7.45 (m, 12H, PhH), 7.75 (d, 2H, *J* = 7.2 Hz, ArH).

The monotosylate (**10b**) (383 mg, 0.675 mmol) was dissolved in dry CH_2Cl_2 (4 mL), cooled to 0 °C and TFA (0.4 mL) was added, under Ar. The cooling bath was removed and the mixture was stirred at rt for 3 h. The mixture was recooled to 0 °C and anhydrous K_2CO_3 (700 mg, 5 mmol) was added slowly. The mixture was evaporated and then 95 % ethanol (15 mL) and more anhydrous K_2CO_3 (1.4 g) were added. The mixture was refluxed, under Ar, for 3 h. The cooled mixture was concentrated and saturated NaCl (10 mL) and CH_2Cl_2 (10 mL) were added. The organic phase was separated and the aqueous phase was backextracted with CH_2Cl_2 (10 mL). The combined CH_2Cl_2 extracts were dried, filtered and evaporated Chromatographic purification of the residual oil (1:1 petroleum ether-EtOAc) gave the dibenzyl product (187 mg, 94 %). $[\alpha]_D^{23}$ -60.3° (c 1.45, $CHCl_3$). IR ν_{max}: 3577 – 3177, 3085, 3061, 3028, 1500 cm^{-1}. ^1H

NMR, δ: 1.60 – 1.75 (m, 1H, H-4), 1.90 – 2.10 (m, 1H, H-4'), 2.15 – 2.20 (m, 1H, OH), 2.46 (dt, 1H, *J* = 9.2, 7.5 Hz, H-5), 2.65 ("quintet", 1H, *J* = 3.7 Hz, H-2), 2.87 (dt, 1H, *J* = 9.2, 2.2 Hz, H-5'), 3.40 (dd, 1H, *J* = 9.2, 7.3 Hz, H-6), 3.44 (d, 1H, *J* = 12.8 Hz, PhCHN), 3.57 (dd, 1H, *J* = 9.2, 4.6 Hz, H-6'), 3.95 (d, 1H, *J* = 12.8 Hz, PhCHN), 4.19 ("quintet", 1H, *J* = 3.7 Hz, H-3), 4.45 (d, 1H, *J* = 20 Hz, PhCHO), 4.57 (d, 1H, *J* = 20 Hz, PhCHO), 7.18 – 7.44 (m, 10H, PhH). ^{13}C NMR, δ: 32.3 (-), 51.9 (-), 59.5 (-), 71.6, 71.9 (-), 73.4 (-), 75.6, 126.9, 127.2, 127.7, 127.9, 128.1, 128.4, 128.8, 138.0, 139.0, 149.2. Anal. Calcd for $C_{19}H_{23}NO_2 \cdot \frac{1}{4}H_2O$: C, 75.58; H, 7.85; N, 4.64. Found: C, 75.81; H, 7.77; N, 4.77.

(2*R*,3*S*)-2-Hydroxymethyl-3-hydroxypyrrolidinium hydrochloride (1·HCl). Pyrrolidine (**11**) (174 mg, 0.59 mmol) was dissolved in dry methanol (5 mL) containing 20 % $Pd(OH)_2$ (140 mg). The mixture was stirred under hydrogen gas (1 atm, balloon) for 24 h. The mixture was then filtered through a Celite pad and the residue washed with methanol (4 X 5 mL). The combined filtrates were evaporated and the residual oil was redissolved in dry methanol (2 mL) and was treated with methanolic HCl (5 drops). The mixture was left to stand at rt for 3 h and then the methanol was evaporated. The hydrochloride salt was dissolved in distilled water and then chromatographed over ion-exchange resin (Dowex 50w-8X, H^+ form) and using 2M aqueous HCl as eluent. The acidic fractions that were ninhydrin positive were combined and evaporated to dryness to leave a semi-solid product. Further drying by heating the compound at 60 °C (oil bath) under vacuum (0.05 Torr) gave **1·HCl** as a solid (quantitative yield) that was extremely hygroscopic. $[\alpha]_D^{22}$ +40° (c 1.5, H_2O); [lit.,[7b] + 43.5° (c 0.3, H_2O); lit.,[7c] + 43.1° (c 0.5, H_2O)]. ^{1}H NMR, δ (D_2O): 1.83 – 2.40 (m, 2H, H-4), 3.20 – 4.05 (m, 5H, CH_2O, CH_2N, H-2), 4.22 – 4.38 (m, 1H, H-3). ^{13}C NMR, δ (D_2O): 32.2 (-), 44.3 (-), 58.8 (-), 67.4, 71.2.

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