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Asymmetric Synthesis of Proline Derivatives from (2*R*) and (2*S*)-2-*tert*-Butyl-3-Benzoyl-4-Methyleneoxazolidin-5-one.

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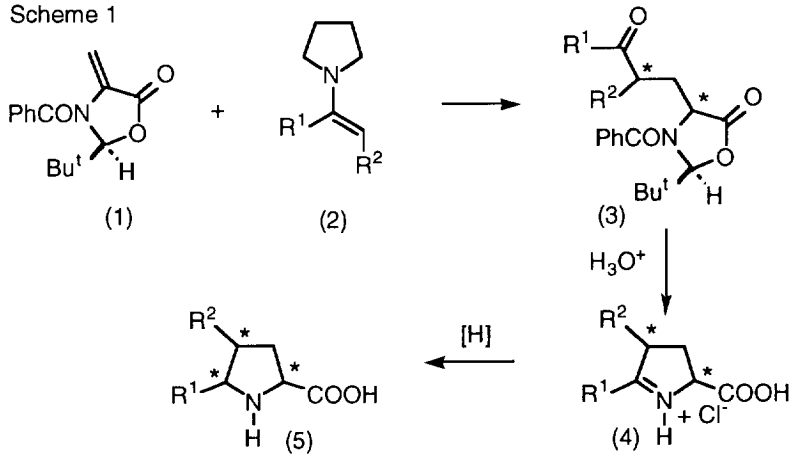
Abstract: The conjugate addition of enamines (2a,b) to the chiral oxazolidinones (1) or *ent*-(1) favours *cis* 2,4-substituted oxazolidinone adducts while *trans* 2,4-substituted oxazolidinone adducts are favoured from the addition reactions of enamine (2c). The diastereomeric adducts from the addition of (2a) to (1) are readily separated and can be converted to (5*R*, 2*S*) and (5*S*, 2*R*) 5-iso-propyl proline efficiently and in good overall yield. The extenstion of this protocol to the synthesis of perhydroindole carboxylic acid suffered from poor overall stereochemical control.

New methods for the asymmetric synthesis of non-proteinogenic amino acids are of prime importance.[1,2] Conformationally restricted peptides incorporating amino acid analogues have been used to increase the bioavailability and biostability and to probe the tertiary structure-activity relationships of proteins and peptides.[3] Substituted proline derivatives are of particular interest for providing conformational constaint in proteins[4] and are also of interest as antiogensin converting enzyme inhibitors[5] and ligands for asymmetric synthesis.[6] In this paper we report a new method for the asymmetric synthesis of proline derivatives using the chiral oxazolidinones (1) and *ent*-(1).[7-10] The general synthetic protocol that we have developed is outlined in Scheme 1, and involved the conjugate addition of an enamine (2) to the oxazolidinone (1) to give the ketone

Scheme 1



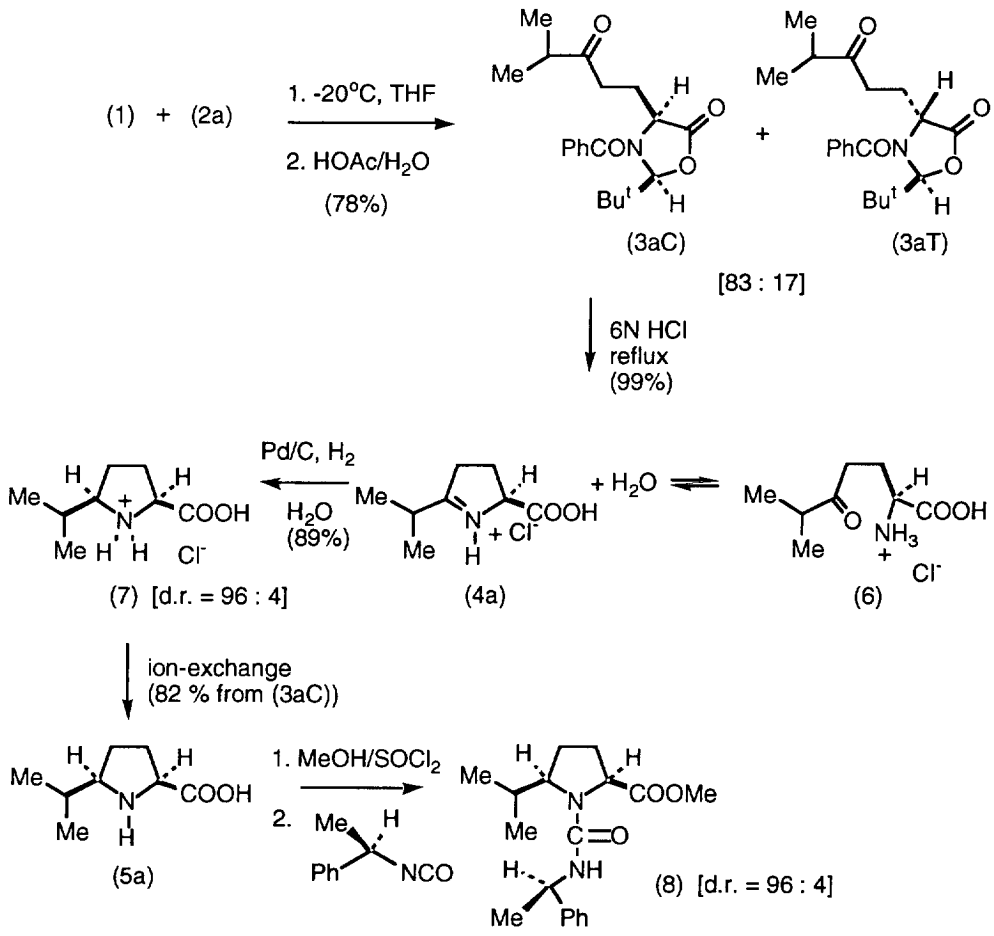
a; $R^1 = Pr^i$, $R^2 = H$
b; R^1, $R^2 = (CH_2)_3$
c; R^1, $R^2 = (CH_2)_4$

(3). Acid hydrolysis of the oxazolidinone ring of (3) and then reduction of the iminium function of the resulting hydrochloride salt (4) afforded the substituted proline (5).

Results and Discussion

The oxazolidinone (1) reacted with the enamine (2a) at room temperature over 16 h or at -20°C over 14 days to give, after mild acid hydrolysis, a mixtutre in which the *cis* 2,4-substituted-oxazolidinone (3aC) was favoured over its *trans* counterpart (3aT) (Scheme 2). The lower reaction temperature gave the highest diastereoselectivity (83 : 17). Higher reaction temperatures resulted in very poor diastereoselectivities. The diastereomeric adducts could be separated by column chromatography and the stereochemistry of (3aT) was determined by a single crystal X-ray structure determination (Fig. 1). A similar ratio (*cis* : *trans* = 84 : 16) of *cis* and *trans* adducts was observed from the conjugate addition of the anion of 2-nitropropane to the oxazolidinone (1).[11] Treatment of diastereomerically pure oxazolidinone (3aC) with 6N hydrochloric acid at reflux for 2h gave a product that had ^{1}H NMR specral data in d6-DMSO similar to that reported for the

Scheme 2



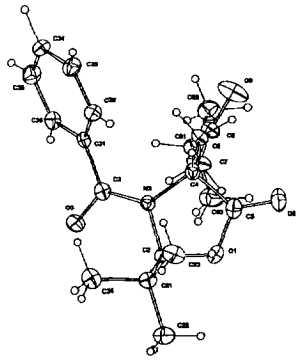
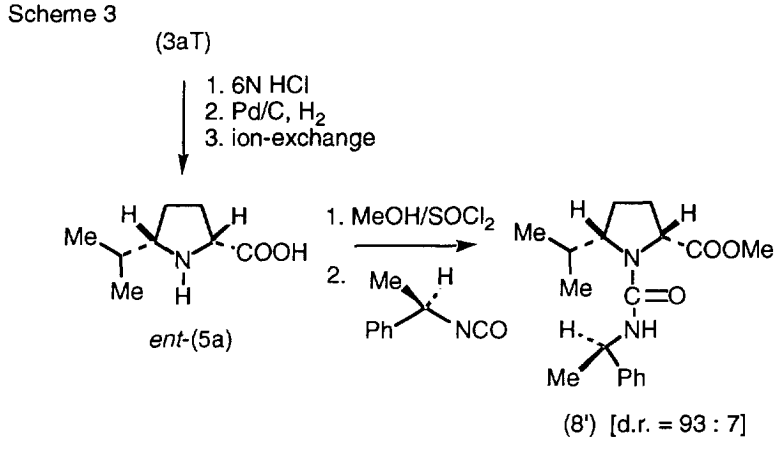


Figure 1: Molecular projection of the single crystal X-ray structure of (3aT), 20% thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have arbitary radii of 0.1Å.

iminium salt (4a).[12] ^{13}C NMR analysis of this product in D_2O showed resonances consistant with an equilibrium mixture (ca 10 : 90) of (4a) and the ketone (6) in which the ketone (6) was the major component (^{13}C NMR (D_2O) δ 205.3, (CO), 172.0 (COOH)). Hydrogenation of an aqueous solution of the mixture of (6) and (4a) over palladium on carbon gave a 96 : 4 mixture of *cis*-5-isopropylproline hydrochloride (7) and its *trans* isomer. Recrystallization of this mixture gave pure (7) that had spectral data in close agreement for that reported previously for (7).[12a,b] The reduction of related iminium salts to give *cis*-5-substituted prolines is well documented.[13] Passing an aqueous solution of (7) through a column of Dowex 50 ion-exchange resin gave the free amino acid (5a) in 82% overall yield from (3aT).. The specific rotation of our (5a) $([\alpha]_D^{23}$ -63.3, c .51, MeOH) was in close harmony with that reported for (5a) (lit.[12] $[\alpha]_D$ -65.3, c 0.9, MeOH) that had previously been prepared by resolution of the racemate.[12a]

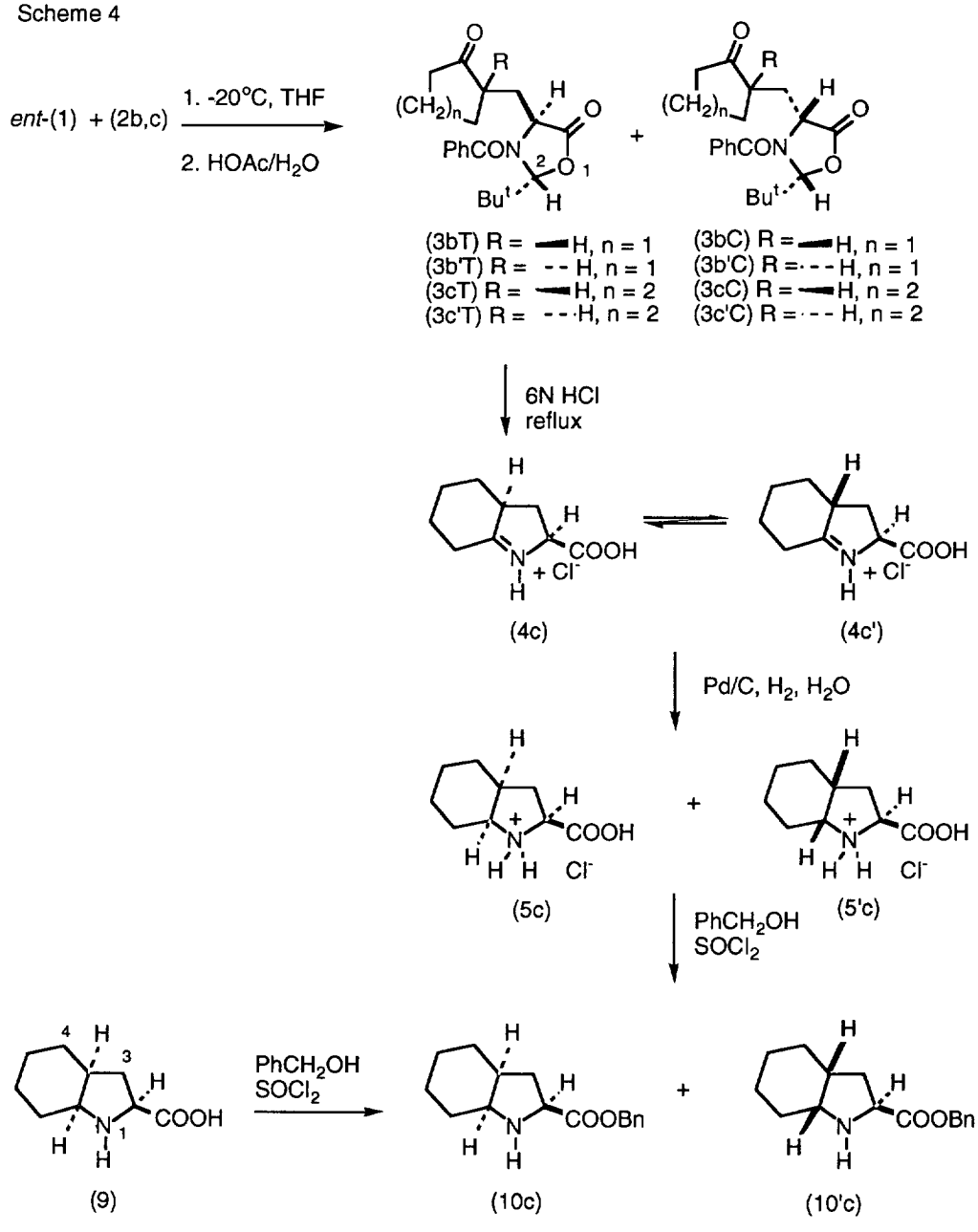
Scheme 3



To further substantiate the (2*S*) stereochemistry of (5a), the ketone (3aT) was converted, via an analogous set of reactions to those described above, to *ent*-(5a) $([\alpha]_D^{23}$ +56.3, c 0.35, MeOH) as shown in Scheme 3. The absolute (2*S*, 5*R*) stereochemistry of (5a) and (2*R*, 5*S*) stereochemistry of *ent*-(5a) was confirmed by circular dichroism measurements that showed that (2*S*, 5*R*)-(5a), like (*S*)-proline and the other naturally occuring proteinogenic amino acids, had a positive CD curve between 200 and 230 nm in water,[14] while (2*R*, 5*S*)-*ent*-(5a) had a negative CD curve over the same wavelength range. The enantiomeric purities of (5a) and *ent*-(5a)

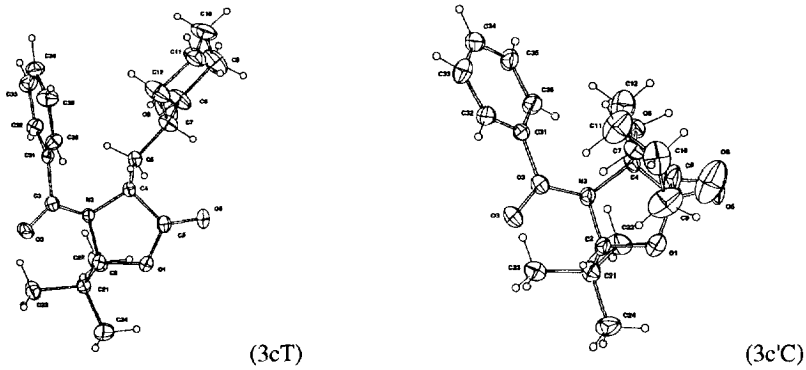
were determined to be 92 and 86% respectively from ^{1}H NMR analysis of their diastereomeric carbamates ((8) and (8') respectively) prepared from the reaction of the methyl esters of (5a) and *ent*-(5a) with (*R*)-(+)-1-phenylethylisocyanate respectively (Schemes 2 and 3).

Scheme 4



The reaction of enamine (2b) with *ent*-(1) in THF initially at -20°C for 7 days gave after a mild acid hydrolysis a mixture of four diastereomeric adducts in 82% yield after column chromatography. The stereochemical assignments at C-4 to these adducts were based on the literature precedent that H-2 in *cis*-2-*tert*-butyl-4-substituted-oxazolidin-5-ones is observed upfield of H-2 in *trans*-2-*tert*-butyl-4-substituted-oxazolidin-5-ones.[15] This difference in chemical shifts for H-2 was also observed in the ^{1}H NMR spectra of (3aC) and (3aT). From ^{1}H NMR analysis the two *cis* isomers (3bC) and (3b'C) were favoured over the two *trans* isomers (3bT) and (3b'T) in a ratio of 78 : 22. However, when the enamine addition reaction was performed at higher temperatures the *cis* to *trans* isomer ratio approached 50 : 50 and at room temperature the *trans* isomer was slightly favoured. The ratio of (3bT) to (3b'T) and of (3bC) to (3b'C) varied slightly (10-20%) with each reaction and the ratios changed after purification on silica gel due to epimerization at C-1'. The absolute stereochemistry at C-1' of the individual adducts could not be ascertained.

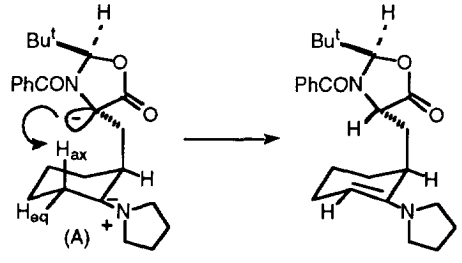
In contrast, the reaction of (1) and enamine (2c) gave predominatley *trans* adducts (3cT) and (3c'T) at reaction temperatures ranging from -20°C to room temperature. The best diasteoselectivity was observed when the reaction was initiated at -78°C and then maintained at -20°C for 20 days. The ratio of *trans* [(3cT) + (3c'T)] to *cis* [(3cC) + (3c'C)] products was 87 : 13 and the yield of the four diastereoisomers after column chromatography was 70%. The stereochemistry of one *trans* adduct (3cT) and one *cis* adduct (3c'C) was determined by X-ray structural determinations (Fig.2). The preference for *trans* 2,4-substituted



(3cT) (3c'C)

Figure 2: Molecular projection of the single crystal X-ray structures of (3cT) and (3c'C), 20% thermal ellipsoids are shown for the non-hydrogen atoms; hydrogen atoms have arbitary radii of 0.1Å.

oxazolidinone adducts in this latter reaction may be due to a facile intramolecular proton transfer of the axial hydrogen (H_{ax}) in the zwitterion intermediate (A) to the H-4 position on the oxazolidinone ring. From an inspection of molecular models such an intramolecular proton transfer seems less likely in the other two enamine reactions.



Hydrolysis of either *trans* adducts (3cT) or (3c'T) gave the same mixture of iminium salts. Molecular modelling (BIOSYM and the Insight II force field or PCMODEL and the MMX force field) of the two possible iminium salts (4c) and (4c') suggested that the former salt should be thermodynamically favoured over the latter. Catalytic reduction of the mixture of (4c) and (4c') gave a 77 : 33 mixture of the amino acid hydrochloride salts (5c) and (5c'). This mixture was converted to a mixture of the benzyl esters (10c) and (10c') that could not be readily separated. The major diastereomeric product was identical to (10c) that was prepared from an authentic sample of (9),[16,17,18] while the minor product had ^{1}H NMR spectral data that was identical to that reported for (10c').[17] Thus reduction of (4c) and (4c') occured mainly from the expected convex face of these iminium ions, however the diastereoselectivity of this hydrogenation was much less than that observed in the mono-cyclic iminium ion (4a).

In conclusion, the conjugate addition of enamines (2a,b) to the chiral oxazolidinones (1) or *ent*-(1) favours *cis* 2,4-substituted oxazolidinone adducts while *trans* 2,4-substituted oxazolidinone adducts are favoured from the addition reactions of enamine (2c). The diastereomeric adducts from the addition of (2a) to (1) are readily separated and can be converted to (5*R*, 2*S*) and (5*S*, 2*R*) 5-iso-propyl proline efficiently and in good overall yield. The extenstion of this protocol to the synthesis of perhydroindole carboxylic acid suffered from poor overall stereochemical control.

Experimental

The enamine (2a)[19] and oxazolidinones (1)[9] and *ent*-(1)[9] were prepared according to the literature.The other enamines were purchased from Aldrich company. THF was distilled from Na/benzophenone ketyl; CH_2Cl_2 was dried by storage over 4A molecular sieves. Other solvents and reagents were used as purchased unless otherwise indicated. All NMR spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian unity 400 or 300 NMR spectrometer in CDCl3 solution unless otherwise indicated. Infrared spectra were determined with a Perkin Elmer 783 IR spectrophotometer by using nujol mulls. Melting points were measured on a capillary melting point apparatus and are uncorrected. Circular dichorism spectra were measured with a Jasco-500 spectropolarimeter, using a 0.2 cm cell. Optical rotations at the sodium D line were measured on a JASCO DIP-370 digital polarimeter.

X-ray Structure Determinations.

The room temperature (~295K) single crystal X-ray structure determinations are derivative of unique diffractometer data sets (2r/r scan mode; monochromatic Mo $K\alpha$ radiation, $\lambda = 0.7109_3$ Å) yielding N independent reflections, N_0 of these with $I > 3\sigma(I)$ being considered 'observed' and used in the full matrix least squares refinement without absorption correction after solution by direct methods. Anisotropic thermal parameters were refined for C, N, O; $(x, y, z, U_{iso})_H$ were also refined. Conventional residuals R, R_w on $/F/$ are quoted at convergence, statistical weights derivative of $\sigma^2(I) = \sigma^2(I_{diff}) + 0.0004\ \sigma^4(I_{diff})$ being used; chiralities were adopted from the chemistry. Neutral atom complex scattering factors were employed, computation using the XTAL 3.0 program system implemented by S. R. Hall.[20] Full tabulations of atom coordinates and thermal parameters, molecular geometries and structure factor amplitudes have been deposited with the Cambridge Crystallographic Data Centre. Details of the specimens and refinement are as follows:

(3aT) - $C_{20}H_{27}NO_4$, M = 345.4. Orthorhombic, space group $P2_12_12_1$ (D_2^4, No. 19), a = 19.154(7), b = 16.527(6), c = 6.054(5) Å, V = 1916 Å^3. D_c(Z = 4) = 1.20 g. cm.$^{-3}$; F(000) = 744. μ_{Mo} = 0.8 cm.$^{-1}$; specimen: 0.12 x 0.15 x 0.62 mm. $2r_{max}$ = 55°; N = 2528, N_o =1120; R = 0.043, R_w = 0.040.
(3cT) - $C_{21}H_{27}NO_4$, M = 357.5. Orthorhombic, space group $P2_12_12_1$, a = 20.117(4), b = 15.714(5), c = 6.064(3) Å, V = 1917 Å^3. D_c(Z = 4) = 1.24 g. cm.$^{-3}$; F(000) = 768. μ_{Mo} = 0.9 cm.$^{-1}$; specimen: 0.79 x 0.48 x 0.08 mm. $2r_{max}$ = 50°; N = 1962, N_o =1246; R = 0.087, R_w = 0.089.
(3c'C) - $C_{21}H_{27}NO_4$, M = 357.5. Monoclinic, space group $P2_1$ (C_2^2, No. 4), a = 9.267(3), b = 21.95(2), c = 10.321(3) Å, V = 1982 Å^3. D_c(Z = 4) = 1.20 g. cm.$^{-3}$; F(000) = 768. μ_{Mo} = 0.8 cm.$^{-1}$; specimen: 0.38 x 0.57 x 0.43 mm. $2r_{max}$ = 50°; N = 3582, N_o =2839, R = 0.049, R_w = 0.055.

(2*S*,4*S*)-3-Benzoyl-2-*tert*-butyl-4-[(3'-oxo-4'-methyl)-1'-pentyl]oxazolidin-5-one (3aC) and (2*S*, 4*R*) (3aT): To a stirred solution of the oxazolidinone **(1)** (0.057g, 0.22 mmol) in dry dichloromethane (5 mL) was added dropwise 2-*N*-pyrrolidino-3-methyl-1-butene (2a) (0.061g, 0.4 mmol) at -78°C. The reaction mixture was kept at -78°C for 24h and then in the refrigerator (-20°C) for 14 days until no more of the starting material could be detected by TLC. Aqueous 10% acetic acid (5mL) was added and the mixture was stirred rapidly at room temperature for 2 h. The solution was washed with 5% $NaHCO_3$, water, and then dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography. Elution with 20% ethyl acetate/hexane gave a mixture of (3aC) and (3aT) (0.058 g, 78%). The two isomers **(3aC)** and **(3aT)** were separated by careful column chromatography on silica gel using 20% ethyl acetate/hexane as eluent.

(3aT): Mp 138°C, $[\alpha]_D^{23}$ -79.2 (c 0.50, $CHCl_3$). ^{1}H NMR δ 7.47-7.63 (m, 5H, Ph), 6.23 (s, 1H, H2), 4.51 (dd, J=2.8, 6.4 Hz, 1H, H4), 2.48 (septet, J=6.9 Hz, 1H, C<u>H</u>Me$_2$), 2.31 (t, J=7.6 Hz, 2H, H2'α, 2'β), 1.94 (m, 1H, H1'α), 1.53 (br, 1H, H1'β), 1.04 (s, 9H, C<u>Me</u>$_3$), 1.02 (d, J=7.2Hz, 3H, CH<u>Me</u>Me), 1.00 (d, J =6.8Hz, 3H, CHMe<u>Me</u>). ^{13}C NMR ($CDCl_3$) δ 211.4 (CO), 172.8 (CO), 170.8 (CO), 135.2 (C), 132.2 (CH), 129.0 (CH), 127.2 (CH), 94.6 (CH), 57.3 (CH), 40.6 (CH), 39.6 (<u>C</u>Me$_3$), 33.2 (CH_2), 25.4 (CH_2), 24.5 (C<u>Me</u>$_3$), 18.0 (CH_3), 17.9 (CH_3). IR 1755, 1680, 1610, 1550, 1330, 1310, 1000, 920, 870, 715, 690, 650 cm^{-1}. Mass spectrum (FAB, +ve) *m/z* 346 (20%, M+H$^+$), 260 (35%), 196 (98%), 136 (60%), 105 (100%). Anal Cald for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88.; N, 4.05. Found: C, 69.53; H, 8.00; N, 3.94%.

(3aC): Oil, $[\alpha]_D^{23}$+25.2 (c 0.88, $CHCl_3$), ^{1}H NMR δ 7.39-7.50 (m, 5H, Ph), 6.07 (1H, H4) 3.95 (t, J=7.2 , Hz, 1H, H2), 2.75 (m, 1H, H2'α), 2.73 (m, 1H, H1'α), 2.50 (septet, J=6.8 Hz, 1H, C<u>H</u>Me$_2$), 2.26 (m, 1H, CH-2'β), 2.16 (m, 2H, H1'β), 1.03 (d, J=6.8 Hz, 3H, CH<u>Me</u>Me), 1.03 (s, 9H, C<u>Me</u>$_3$), 1.01 (d, J= 6.8 Hz, 3H, CHMe<u>Me</u>). ^{13}C NMR δ 212.4 (CO), 173.8 (CO), 172.0 (CO), 135.4 (C), 130.1 (CH), 128.7 (CH), 126.5 (CH), 95.6 (CH), 57.1 (CH), 40.7 (CH), 36.8 (<u>C</u>Me$_3$), 36.3 (CH_2), 28.4 (CH_2), 25.1 (C<u>Me</u>$_3$), 18.1(CH_3), 18.0 (CH_3). Mass spectrum (FAB, +ve) *m/z* 346 (12%, M+H$^+$), 331 (15%), 260 (20%), 219 (11%), 196 (32%), 137 (26%), 106 (100%) .

(1'*S*, 2*S*, 4*R*) , (1'*R*, 2*S*, 4*R*) , (1'*R*, 2*S*, 4*S*) and (1'*S*, 2*S*, 4*S*) 3-Benzoyl-2-*tert*-butyl-4-(2'-oxo-1'-cyclopentyl)methyloxazolidin-5-one (3bT), (3b'T), (3bC), and (3c'C): To a stirred solution of the oxazolidinone (1) (1.9g, 7.3 mmol) in dry THF (10ml), was added dropwise 1-*N*-pyrrolidino-cyclopentene (2b) (0.401g, 3mmol) at -78°C. The reaction mixture was kept in the refrigerator (-20°C) for 7 days. Aqueous 10% acetic acid (30ml) was added and the mixture was stirred rapidly at room temperature for 2 h.

The solution was extracted with dichloromethane (2x10 ml) and washed with 5% $NaHCO_3$, water, and then dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography using 30% ethyl acetate/hexane as eluent to give a mixture of four diastereoisomers (0.28g, yield 82%). These four diastereoisomers could not be separate by column chromatography. One pure *trans* isomer (T1) was obtained after six crystalizations from ethyl acetate/hexane, while one pure *cis* isomer (C1) was obtained pure after five crystalizations of the mother liquors from methanol and then from ethyl acetate/hexane. The other *trans* (T2) and *cis* (C2) diastereomeric products could not be obtained diastereomerically pure.

(T1): Mp 215°C, $[\alpha]_D^{23}$ -88.0 (c 0.25, $CHCl_3$). ^1H NMR δ 7.55-7.6 (m, 5H, Ph), 6.23 (s, 1H, H2), 4.46 (dd, J=2.8, 10 Hz, 1H, H4), 2.18 (m, 2H), 1.92 (m, 3H), 1.70 (m, 2H), 1.49 (m, 1H), 1.22 (m, 1H), 1.00 (s, 9H, $C\underline{Me}_3$). ^{13}C NMR δ 218.0(CO), 172.8 (CO), 170.0 (CO), 135.3 (ArC), 132.3 (CH), 129.1 (CH), 127.5 (CH), 94.9 (CH), 56.7 (CH), 44.2 (CH), 40.0 ($\underline{C}Me_3$), 36.9 (CH_2), 31.9 (CH_2), 29.1 (CH_2), 24.6 (C-$\underline{Me}_3$) 20.4 (CH_2). IR 1755, 1700, 1615, 1330, 1300, 1113, 1010, 830, 800, 715, 695, 650 cm^{-1}. Mass spectrum (ES, +ve) *m/z* 344 ($M+H^+$, 100%), 288 (35%), 252 (60%), 205 (28%), 132 (65%). Anal Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H , 7.34; N , 4.08. Found: C, 70.13; H, 7.44; N, 4.06%.

(T2): ^1H NMR (in part) δ 6.20 (s, 1H, H2), 4.85 (dd, J=7.6, 3.6 Hz), 1.04 (s, 9H, $C\underline{Me}_3$).

(C1): Mp = 155°C, $[\alpha]_D^{23}$ -18.0 (c 0.50, $CHCl_3$). ^1H NMR δ 7.35-7.65 (m, 5H, Ph), 6.07 (s, 1H, H2), 4.00 (dd, J=3.2, 12 Hz, 1H, H4), 2.60 (m, 1H), 2.52 (m, 1H), 2.30 (m, 1H), 2.00 (m, 1H), 1.90 (m, 2H), 1.71 (m, 1H), 1.60 (m, 1H), 1.05 (s, 9H, $C\underline{Me}_3$), 0.60 (m, 1H). IR 1755, 1700, 1615, 1330, 1300, 1113, 1010, 830, 800, 715, 695, 650 cm-1. Mass spectrum (ES, +ve) *m/z* 344 (M+H+, 100%), 288 (35%), 252 (60%), 205 (28%), 132 (65%).

(C2): ^1H NMR (in part) δ 6.09 (s, 1H, H2), 4.35 (dd, J=4.4, 12.4 Hz, 1H, H4), 1.02 (s, 9H, $C\underline{Me}_3$).

(1'*S*, 2*S*, 4*R*) , (1'*R*, 2*S*, 4*R*) , (1'*R*, 2*S*, 4*S*) and (1'*S*, 2*S*, 4*S*)-3-Benzoyl-2-*tert*-butyl-4-(2'-oxo-1'-cyclohexyl)methyloxazolidin-5-one (3cT) , (3c'T), (3cC) and (3c'C): To a stirred solution of the oxazolidinone (**1**) (1.9g, 7.3 mmol) in dry THF (30ml), was added dropwise 1-*N*-pyrrolidino-cyclohexene (**2c**) (3.70g, 21mmol) at -84°C (liquid nitrogen/ethyl acetate slush bath). The reaction mixture was kept at -78°C for 48 h and then in the refrigerator (-20°C) for 20 days. Aqueous 10% acetic acid (30ml) was added and the mixture was stirred rapidly at room temperature for 2 h. The solution was extracted with dichloromethane (2x40 ml) and washed with 5% $NaHCO_3$, water, then dried ($MgSO_4$). The solvent removed in vacuo. The product was purified by column chromatography using 20% ethyl acetate/hexane as eluent to give a mixture of four diasterioisomers (1.89g, yield 70%). Careful separation of this mixture by careful column chromatoghraphy gave pure **(3cT)** and **(3c'T)** and a mixture of two minor diastereoisomers **(3cC)** and **(3c'C)**. Pure **(3cC)** was obtained by crystallization of this mixtures from ethyl acetate/hexane.

(3cT): Mp 128-130° C, $[\alpha]_D^{23}$ +16.9° (c 1.51, $CHCl_3$). ^1H NMR (400 MHz) δ 7.45-7.74 (m, 5H, Ph), 6.21 (s, 1H, H2), 4.68 (dd, J=4.4, 10 Hz, 1H, H4), 2.81 (m, 1H), 2.26 (m, 2H), 1.98 (m, 1H), 1.81 (m, 1H), 1.71 (m, 1H), 1.65 (m, 1H), 1.52 (m, 1H), 1.50 (m, 1H), 1.10 (m, 1H), 1.05 (m, 1H), 1.01 (s, 9H, $C\underline{Me}_3$).^{13}C NMR δ 212.0 (CO), 172.9 (CO), 170.9 (CO), 135.5 (C), 132.1 (CH), 128.7 (CH), 127.8 (CH), 94.6 (CH), 55.9 (CH),

45.5 (CH), 41.7 (CH_2), 40.0(C-Me_3), 34.9 (CH_2), 33.2 (CH_2), 27.8 (CH_2), 24.8, 24.7(CMe_3). IR 1760, 1680, 1610, 1220, 1185, 1150, 1040, 1000, 720, 690, 650 cm^{-1}. Mass spectrum (CI, +ve) *m/z* 358 (15%, $M+H^+$), 272 (50%), 236 (30%), 208 (50%). Anal Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.70; H, 7.69; N, 3.58%.

(3c'T): Mp 155°C, $[\alpha]_D^{23}$ +62.6° (c 1.53, $CHCl_3$), ^1H NMR (300 MHz) δ 7.43-7.63 (m, 5H, Ph), 6.20 (s, 1H, H2), 4.38 (dd, J=3, 9.3 Hz, 1H, H4), 2.53 (m, 1H), 2.11-2.40 (m, 3H), 2.00 (m, 2H), 1.25- 1.78 (m, 4H), 1.02 (s, 9 H, CMe_3), 0.88 (m, 1H).^{13}C NMR δ 210.3 (CO), 173.0 (CO), 170.6 (CO), 135.7 (C), 132.0 (CH), 129.0 (CH), 127.5 (CH), 94.8 (CH), 55.9 (CH), 45.5 (CH), 41.7 (CH_2), 39.9 (CMe_3), 33.0 (CH_2), 31.5 (CH_2), 27.5 (CH_2), 24.8 (CH_2), 24.7 (CMe_3).

(3cC): Mp 169° C, $[\alpha]_D^{23}$ -5.6° (c .81, $CHCl_3$). ^1H NMR (400 MHz) δ 7.35-7.70 (m, 5H, Ph), 6.07 (s, 1H, H2), 4.00 (dd, J=3.6, 12 Hz, 1H, H4), 2.60 (m, 1H), 2.50 (m, 1H), 2.40 (m, 1H), 2.25 (m, 1H), 2.00 (m, 1H), 1.60 (m, 2H), 1.50 (m, 2H), 1.06 (s, 9H, CMe_3), 0.60 (m, 1H).^{13}C NMR δ 212.0 (CO), 174.2 (CO), 172.1 (CO), 135.7 (CH), 130.2 (CH), 128 (CH) 126.6 (CH), 95.5 (CH), 55.0 (CH), 46.0 (CH), 42.0 (CH_2), 36.8 (CH_2), 33.1 (CH_2), 32.1 (CMe_3), 27.7 (CH_2), 25.1 (CMe_3), 24.9 (CH_2).

(3c'C): ^1H NMR (in part) δ 6.08 (s, 1H , H2), 4.25 (dd, J=4, 12.4Hz, 1H, H4), 1.03 (s, 9H, CMe_3).

(5*S*)-Δ'-2-Isopropylpyrrolidine-5-carboxylic Acid hydrochloride (4a): A suspension of ketone **(3aC)** (1.00g, 2.89 mmol) in 6N HCl (10 mL) was heated at reflux (100-110°C) for 24 h. The solution was allowed to cool to ambident and then extracted with CH_2Cl_2 (2x30ml). The aqueous layer was evaporated to dryness under vacuo and the oily yellowish crude product (0.55g, 99%), was used in the following reduction step. ^1H NMR (400 MHz, D_2O) δ 5.06 (t, 1H, αCH), 3.21 (m, 2H), 3.09 (septet, J=6.8 Hz, 1H, $CHMe_2$), 2.62 (m, 1H), 2.33 (m, 1H), 1.23 (d, J=7.2 Hz, 6H, $CHMe_2$). ^1H NMR (400 MHz, d6-DMSO) δ 5.11 (t, 1H, αCH), 3.20 (m, 3H, CH_2, $CHMe_2$), 2.50 (m, 1H), 2.20 (m, 1H), 1.24 (d, J=6.8 Hz, 3H, Me), 1.22 (d, J=6.8 Hz, 3H, Me) ^{13}C NMR (300 MHz , D_2O, MeOH as internal reference, δ 49.0) δ 205.3 (CO), 172.0 (CO), 66.8 (αC), 34.9 ($CH(Me)_2$), 34.9 (βCH_2), 23.9 (γCH_2), 18.3 (MeMeCH), 18.2 (MeMeCH). Mass spectrum (FAB, +ve) *m/z* 156 ($C_8H_{14}NO_2^+$, 100%), 110 (45%), 105 (20%).

(2*S*, 5*R*)-*cis*-5-Isopropylproline hydrochloride (7): To a solution of the imine **(4a)** (0.50g, 2.61mmol) in water (10 mL) was added 10% Pd/C (0.050 g) and the mixture was stirred under 1 atmosphere of hydrogen gas for 48h at RT. The mixture was then filtered and concentrated under vacuo to give the white solid hydrochloride salt **(7)** (0.45g, 89%).^1H NMR (300 MHz , $CDCl_3$) δ 4.25 (dd, J=6, 9.3Hz, 1H, αCH), 3.17 (m, 1H, δCH), 2.23 (m, 1H, β1CH), 2.09 (m, 2H, β2CH, γ1CH), 1.78 (m, 1H, $CHMe_2$), 1.58 (m, 1H, γ2CH), 0.88 (d, J=6.6 Hz, 3H, CHMeMe), 0.80 (d, J=6.9 Hz, 3H, CHMeMe).^{13}C NMR (D_2O) δ 180.4 (CO), 76.7 (αCH) 68.1 (δCH), 39.1 ($CH(Me)_2$, 35.8 (γCH_2), 35.7, (β CH_2), 27.9 (Me), 27.3 (Me). Mass spectrum FAB (+ve) *m/z* 158 ($C_8H_{16}NO_2^+$, 100%), 112 (45%), 105 (20%).

(2*S*, 5*R*)-(-)-*cis*-5-Isopropylproline (5a): The amino acid hydrochloride **(7)** (400 mg, 2.65 mmol) was dissolved in water (15 mL) and poured on to a column of Dowex 50-X8 (H^+). The colmun was eluted with water until the eluent had a pH of 6.-7. The pure amino acid was obtained by eluting with 0.1 M aqueous ammonia. The basic eluent was evaporated under reduced pressure to dryness to give white crystals (305mg,

93%) which were crystallized from methanol and ether. Mp. 195°C (dec) (lit. [12] 211-214°C), $[\alpha]_D^{23}$ -63.3 (c 0.51, MeOH)[lit.[12] $[\alpha]_D$ -65.3° (c 0.90, MeOH]. ^{1}H NMR (300 MHz, D_2O) δ 4.05 (dd, J=4, 9.6 Hz, 1H, αCH), 3.25 (m, 1H, δCH), 2.25 (m, 1H, β1CH), 2.10 (m, 2H, β2CH, γ1CH), 1.90 (m, 1H, $CHMe_2$), 1.58 (m, 1H, γCH_2), 1.02 (d, J=6.6Hz, 3H, MeMeCH), 0.93 (d, J=6.9 Hz, 3H, MeMeCH). ^{13}C NMR δ 174.5 (CO), 67.6 (αCH), 60.8 (δCH), 30.4 ($CHMe_2$), 28.4 (βCH_2), 27.1 (γCH_2), 19.0 (MeMeCH), 18.3 (MeMeCH). Mass spectrum (FAB, +ve) *m/z* 158 ($M+H^+$, 100%), 112 (40%). IR 3420, 1580, 1270, 920 cm^{-1}.

(2*R*, 5*S*)-(+)-*cis*-5-Isopropylproline *ent*-(5a): Mp. 195-198°C (dec) (lit.[12] 216-214°C), $[\alpha]_D^{23}$ +56.3 (c 0.35, MeOH) [lit.[12] $[\alpha]_D$ +64.7° (c 0.80], MeOH]. ^{1}H NMR spectrum was identical to that of (5a) above. Mass spectrum (FAB, +ve) *m/z* 158 ($M+H^+$, 100%), 112 (40%).

(2*S*, 5*R*)-(-)-*cis*- 5-Isopropylproline methyl ester: A solution of the free amino acid **(5a)** (56 mg, .35 mmol) in methanol (10 mL) was treated dropwise with thionyl chloride (30 mg, 2.5 mmol) at 0°C and allowed to stand at room tempreature overnight. After evaporation of methanol, the resultant methyl ester hydrochloride was dissolved in water. The aqueous mixture was carefully made basic with $NaHCO_3$ and then extracted with dichloromethane. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give 40 mg of a yellowish oil (yield 66%). ^{1}H NMR (300MHz, $CDCl_3$) δ 3.76 (dd, J =6, 9 Hz, 1H, αCH), 3.73 (s, 3H, OMe), 2.72 (m, 1H, γ1CH), 2.07 (m, 1H), 1.88 (m, 2H, $CHMe_2$), 1.60 (m, 1H), 1.32 (m, 1H), 1.02 (d, J=6.6 Hz, 3H, MeMeCH), 0.92 (d, J=6.9 Hz, 3H, MeMeCH).

Enantiomeric purity of (2*S*, 5*R*)-(-)-*cis*-5-Isopyopylproline methyl ester: (*R*)-(+)-α-methylbenzylisocyanate (0.03mL, 21mmol) was added to a solution of (2*S*, 5*R*)-*cis*-5-isopropylproline methyl ester (15mg, 0.15 mmol) in $CDCl_3$ in an NMR tube. After shaking the mixture for 30 min. the homogeneous solution was used directly for NMR analysis of the optical purity of (3aC) and (3aT). The urea (8), after purification by PTLC, had ^{1}H NMR (300 MHz) δ 7.20-7.36 (m, 5H, Ph) 5.14 (d, J=6.9 Hz, 1H, NH), 4.99 (dq, J=6.6, 7.2 Hz 1H, CH_3CHN), 4.37 (t, J=7.2Hz, αCH), 3.74 (m, 1H, δCH), 3.70 (s, 3H, OMe), 2.06 (m, 3H, $CHMe_2$, βCH_2), 1.82 (m, 2H, γCH_2), 1.47 (d, J=6.9Hz, MeNHCH), 0.95 (d, J=6.9Hz, 3H, CHMeMe), 0.83 (d, J=6.9Hz, 3H, CHMeMe). ^{13}C NMR (300 MHz) δ 170.0 (CO), 158.0 (CO), 144 (ArC), 128.5 (CH), 126.9(CH), 1215.8 (CH), 64.0 (αCH), 60 (γCH), 52.2 (OMe), 50.0 (CHPh), 30.7 ($CH(Me)_2$), 27.9 (γCH_2), 26.3 (βCH_2), 23.0 (MeCHN), 19.9 (MeMeCH), 17.3 (MeMeCH). Mass spectrum (ES +ve) *m/z* 319 (M^++1, 100%), 172 (12%).

(2*S*, 3a*S*)-3,3a,4,5,6,7-Hexahydro-(2H)-indole-2-carboxylic acid hydrochloride (4c): A suspension of (3cT) (0.71g, 2 mmol) and 6 N hydrochloric acid (10 mL) was heated under reflux during 4-5h. After evaportion to dryness the yellow residue (0.40g, yield 98%) was used in the following hydrogenation reaction without purification. ^{1}H NMR δ 4.98 (m, 1H, H2), 3.23 (m, 1H), 2.94 (m, 1H), 2.84 (m, 1H), 2.65 (m, 1H), 2.56 (m, 1H), 1.45-2.30 (m, 7H). Mass spectrum (CI, +ve) *m/z* 168 ($C_9H_{14}NO_2^+$, 20%), 124 ($C_9H_{14}NO_2^+$-CO_2, 15%).

(2*S*, 3a*R*)-3,3a,4,5,6,7-Hexahydro-(2H)-indole-2-carboxylic acid hydrochloride (4c'): Prepared by the same procedure described for **(4c)** but starting from (3c'T) except that the reaction mixture was heated to reflux overnight.

Preparation of (2*S*, 3a*S*, 7a*S*) and (2*S*, 3a*R*, 7a*S*)-Perhydroindole-2-carboxylic acid hydrochloride (9) and (9'): A mixture of imine (4c) (0.40g, 2 mmol) and 10% Pd/C (0.09 g) in water was hydrogenated for 16 h under a ballon of hydrogen gas at room tempreature. The catalyst was removed by filtration and the filtrate was evaporated to dryness in vacuo to give a mixture of the hydrochloride salts (9) and (9') (375 mg, 90%) in a ratio of 70:30. **(major):** ^{1}H NMR (D_2O, DHO internal reference at δ 4.75) δ 4.40 (t, 1H, H2), 3.73 (m, 1H, H7a), 2.34 (m, 2H), 2.11 (m, 1H), 1.80 (m, 1H), 1.70-1.20 (m, 7H). **(minor):** ^{1}H NMR (inpart) δ 4.49 (t, 1H). Mass spectrum (CI, +ve) *m/z* 170 ($C_9H_{16}NO_2^+$, 100%), 124 (70%).

(2*S*, 3a*S*, 7a*S*) and (2*S*, 3a*R*, 7a*R*)-Perhydroindole-2-carboxylic acid benzyl ester(10c) and (10c'): Thionyl chloride (59 mg, 5 mmol) was addead dropwise to a solution of (5c) and (5c') (205 mg, 1 mmol) and benzyl alcohol (5 ml) at -5°C. After stirring overnight at room temperature water was added and the reaction mixture was extracted with diethyl ether. The aqueous layer was made basic with satd. $NaHCO_3$ and extracted with dichloromethane. The organic phase was dried ($MgSO_4$), filtered and concentrated to give 215 mg (72%) of a mixture of benzyl esters (10c) and (10c'). The 300 MHz ^{1}H NMR was in agreement with the ^{1}H NMR of an authentic sample of (10c) that was prepared from (9)[16] as described above. **(10c):** ^{1}H NMR δ 7.35 (s, 5H, Ph), 5.18 (s, 2H, C<u>H</u>$_2$Ph), 3.81 (dd, 1H, H2), 3.07 (q, J = 4.8 Hz, 1H), 2.19 (m, 1H), 2.3-1.8 (m, 3H), 1.76-1.61 (m, 3H), 1.52-1.32 (m, 3H), 1.29-1.20 (m, 2H). **(10c'):** ^{1}H NMR (in part) δ 7.38 (s, 5H, Ph), 5.16 (m, 2H, <u>CH</u>$_2$Ph), 3.95 (t, J=8.4 Hz, 1H, H2), 3.30 (q, J= 4.4 Hz, 1H).

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