ON THE 2,4-RELATIVE STEREOCHEMISTRY OF N-SUBSTITUTED OXAZOLIDINES DERIVED FROM PHENYLGLYCINOL

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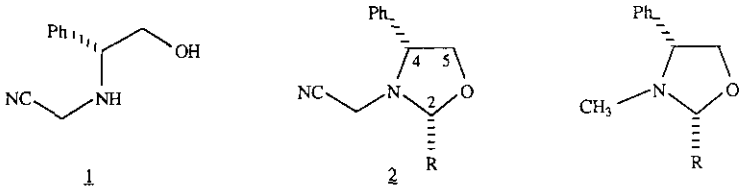
Abstract - ^{1}H and ^{13}C nmr spectroscopy using n.O.e difference, NOESY and ROESY techniques and ^{3}J CH coupling constants allowed confirmation of the (2R, 4R) absolute configuration of the (R)-(-)phenylglycinol derived oxazolidines 2M to 5M and demonstrated that the *trans* 2,4-relative stereochemistry was erroneously implied on the basis of misinterpreted nmr spectra (H-4, H-5 assignements).

INTRODUCTION

The application of "chiral pool" derived synthetic intermediates to organic synthesis has provided highly practical and efficient means of preparing chiral molecules.[1,2] As part of a programme designed to synthesize biologically active nitrogen containing natural products we have developed versatile synthetic routes to piperidine, pyrrolidine, indolizidine and pyrrolizidine alkaloids achieving chemo- and enantioselective transformations through the use of (R)-(-)phenylglycinol derived synthons.

The synthetic approaches described are suitable for convenient introduction of substituents at α,α'-N positions, while simple variation of the nature of substituents can generate a range of nitrogen-heterocycles. These efforts have culminated in some total[3] or formal total syntheses[4] of enantiomerically homogeneous natural compounds. Among the synthons investigated for an easy access to chiral amino acids, amino alcohols and amines the (-)-N-cyanomethyl-4-phenyl-1,3-oxazolidine[5] and its 2-substituted derivatives (Figure 1) showed moderate diastereoselectivity. In spite of modest d.e. these chirons are of potential synthetic utility because they provide a stereocontrolled synthesis of biologically active natural compounds[5,6] using well established methodologies. In an attempt to gain further insight into these stereoselective processes we have investigated the 2,4-relative stereochemistry by 1 and 2D nmr techniques.

Five 2,4-substituted oxazolidines 2 to 6 were synthesized. The configurations at C-2 and C-4 of all compounds studied were unambiguously assigned by ^{1}H and ^{13}C nmr spectroscopy using n.O.e. difference,[7] NOESY,[8] ROESY[9] techniques and $^{3}J_{CH}$ coupling constants (Gated Decoupling).[10]



1 2

2 R = $(CH_2)_2CH_3$ 6a R = C_2H_5

3 R = $CH{=}C(CH_3)_2$ 6b R = C_3H_7

4 R = $CH_2{-}OCH_3$

5 R = $(CH_2)_2{-}OCH_3$

Figure 1

RESULTS AND DISCUSSION

The mechanistic and stereochemical aspects of oxazolidine ring formation have been extensively investigated ; full discussion is beyond the scope of this paper. The results we present are intended only to provide an orientation for synthetic chemists. References are made where appropriate to discussion of specific points of interest.

Oxazolidines 2 to 5 derived from the optically active N-cyanomethylphenylglycinol 1 and the corresponding aldehydes were composed mainly of one diastereoisomer (>96%). The initial product of the oxazolidine ring formation is a mixture of two diastereoisomers. Isomers detected after the reaction work-up are denoted as M (major) and those that virtually disappear during the reaction course as m (minor). In every case the isomers M have been isolated as pure compounds. Isomer m corresponds to the kinetic product of the reaction and undergoes conversion to M within hours via the intermediate iminium ion.

We turned our attention to the configurational assignment of the isolated isomers M and especially to the configuration at C-2, which has been a controversial point in the literature.[11] Before the n.O.e. spectroscopic studies could be performed, the assignements for the ring protons had to be established using ^1H-^1H COSY and ^1H-^{13}C correlation techniques.

The configuration of the oxazolidine C-2 carbon in each compound investigated was assigned by ^1H (^1H) n.O.e. difference spectroscopy. *This technique appears to be a reliable method to settle the question of* configuration at C-2.[12]

The spatial relationship of H-2 and H-4 is clearly demonstrated by means of 1D difference n.O.e. experiments. Presaturation of the H-2, H-4 or N-Me resonances resulted in the expected enhancements for a 2/4-*cis* relative stereochemistry. The 2,4-*trans*/2,4-*cis* isomerization was monitored by 400 MHz ^1H-nmr in $CDCl_3$ at room temperature (Figure 2). A notable difference was observed between the chemical shifts of H-2 protons of the isomeric species 2M, 2m, the one situated syn to the nitrogen lone pair being the more deshielded. This applies

to all isomeric couples synthesized. It is assumed that the N-substituents will adopt a position *trans* to the 2,4-*cis* groups.[11]

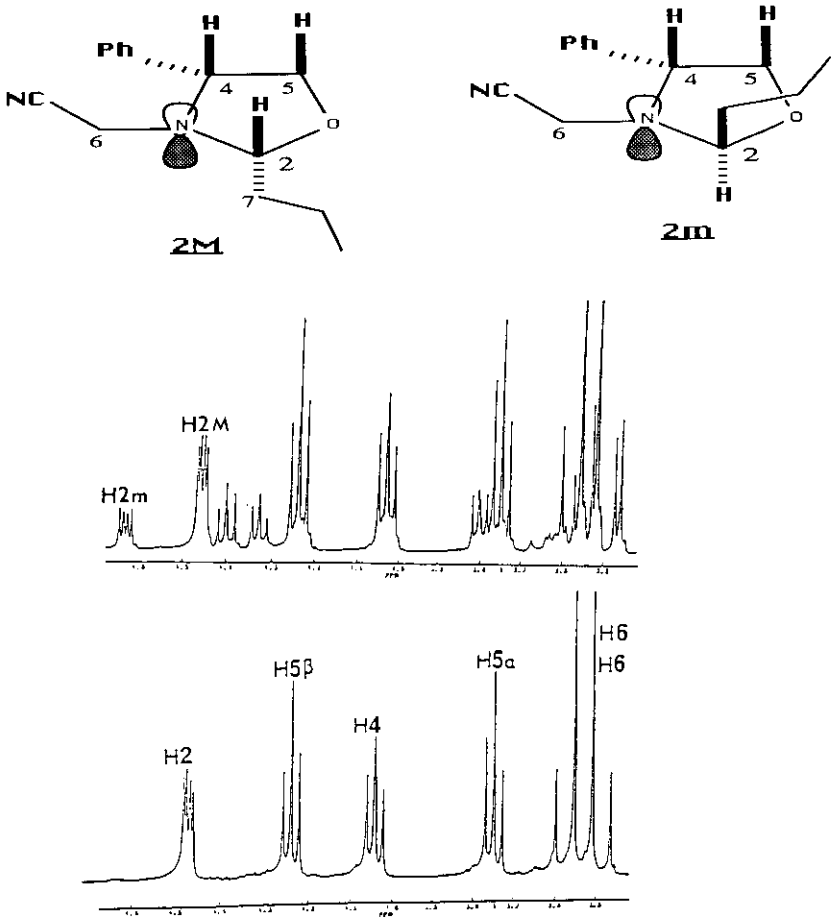


Figure 2 : Reaction of 1 with butyraldehyde in an nmr tube ($CDCl_3$/TMS). Above : 3 h in the tube ; Below : at the equilibrium (>9 h).

The reaction followed by nmr showed the virtual disappearance of the starting material signals within minutes and the appearance of signals due to 2M and those due to 2m, the latter of which was subsequently reduced in intensity as the signals due to 2M, increased. At the equilibrium (>9 h) the nmr spectrum showed a minor and major set of signals (4:96) identified as the oxazolidine diastereoisomers 2m and 2M respectively.

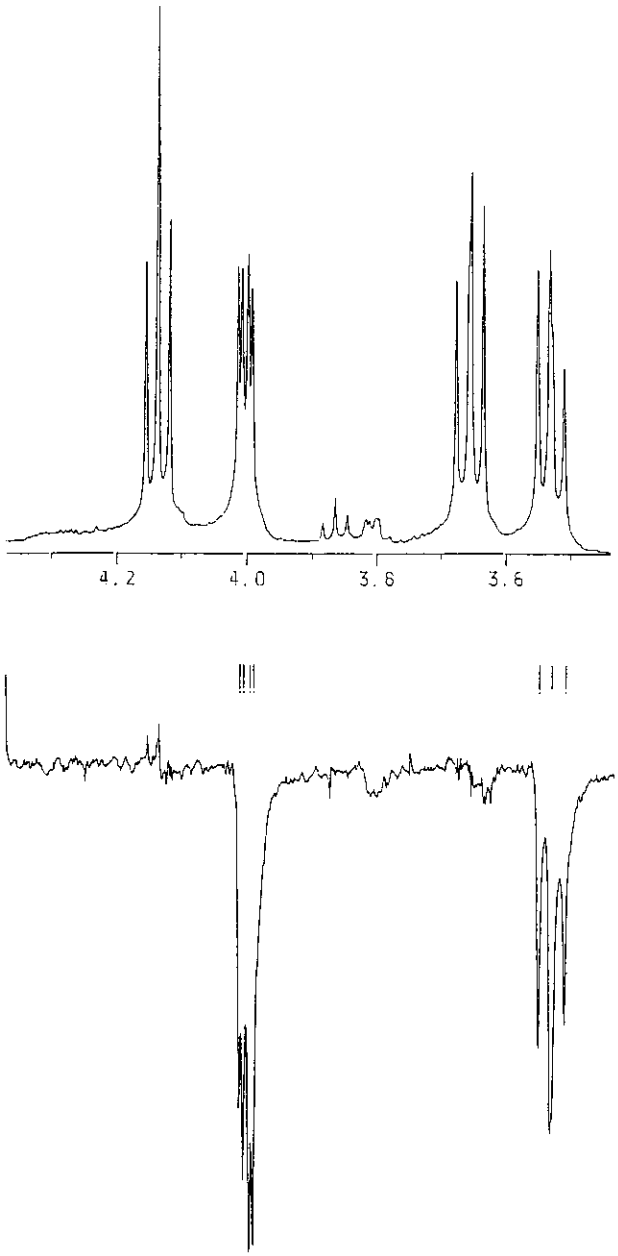


Figure 3 : 1D Difference n.O.e. on 6b (unpurified reaction crude).

Above : 400 MHz normal spectrum ; Below : irradiation of N-Me (2.15 ppm) group ; n.O.e. on H-2 (3.99 ppm) and H-4 (3.52 ppm).

An equilibrium will allow inversion of the N-C-O(C-2) center and thus conversion of 2m to 2M, the latter oxazolidine being more stable.

Even though the era of controversy concerning the 2,4-relative stereochemistry seems to be over, recent reports from a research group[13,14] prompted us to pursue our studies. These investigators have attributed the *cis* stereochemistry to the valine-derived 2,4-substituted oxazolidines while they repeatedly [14] suggested a *trans*-2,4 relationship for those derived from R-(-)-2-N-methylamino-2-phenylethanol.

Starting from our well characterized *cis*-2,4-(2R, 4R)-2-propyl-N-cyanomethyl-4-phenyl-1,3-oxazolidine we synthesized an analogue 6b of the supposedly *trans*-2,4-(2S, 4R)-2-ethyl-N-methyl-4-phenyl-1,3-oxazolidine 6a.

As expected, treatment of 2M with Li-NH_3-THF at -78°C for 15 minutes and subsequent quenching with solid NH_4Cl[4] resulted in the rapid formation of the decyanated target 6b, the structure of which has been confirmed by the same nmr techniques as above. It should be pointed out that the compound (a single diastereoisomer) obtained in this way presented identical (keeping in mind that it is a one carbon homologue) ^1H, ^{13}C nmr data with 6a and had the same specific rotation value.

A more thorough investigation using XH-correlation spectroscopy showed that while the assignments for most protons were well established, to our surprise the literature data was inconsistent in the H-4, H-5 assignments.[14] Furthermore on the basis of the observed n.O.e.'s. (Figure 3) and long range carbon-proton couplings ($^3J_{CH}$) one can conclude that the H-4, H-2 and N-Me protons are oriented *cis* to each other (for interatomic distances see Table I). The angular dependence of $^3J_{CH}$ has been used to help establish the conformations of carbohydrates,[15] nucleosides[16] etc. As for Karplus ^1H-^1H system[17] a minimum for $^3J_{CH}$ occurs with a dihedral angle of 90°, a maximum at 0° and a larger maximum at 180°. The vicinal coupling constants between the carbon atom of the N-methyl group and hydrogen atoms at the 2- and 4-positions of the 1,3-oxazolidine ring were observed as ca. 5Hz in 2M and 3M. Dihedral angles, as calculated from MacroModel[18] are : 50.5°(6M), 53.6°(6m) for C-N-C-H_4 and 49.7°(6M), 86.4°(6m) for C-C-C-H_2 thus suggesting that only the *cis*-2,4 stereochemistry can match the experimental results

1D Difference n.O.e. experiments and $^3J_{CH}$ coupling constants demonstrated conclusively that the protons at the C-2 and the C-4 positions were in a *cis* spatial relationship. Given the importance that bears the 2,4-relative stereochemistry we tried to remove all ambiguity by means of NOESY and also of ROESY techniques, as the latter is more appropriate for small molecules. Indeed the NOESY experiment (Figure 4) didn't prove wholly convincing thus making the ROESY experiment indispensable. Observation of transient n.O.e.'s in the rotation frame (Figure 5) confirmed unequivocally the 2,4-*cis* stereochemistry.

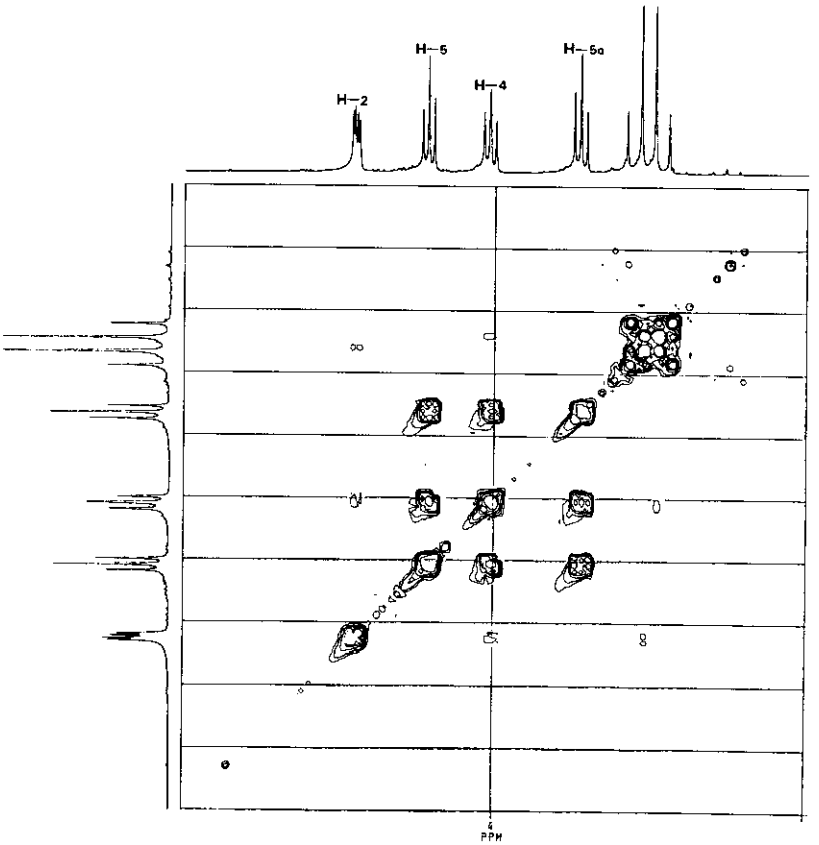


Figure 4 : 400 MHz NOESY spectrum of 2M.

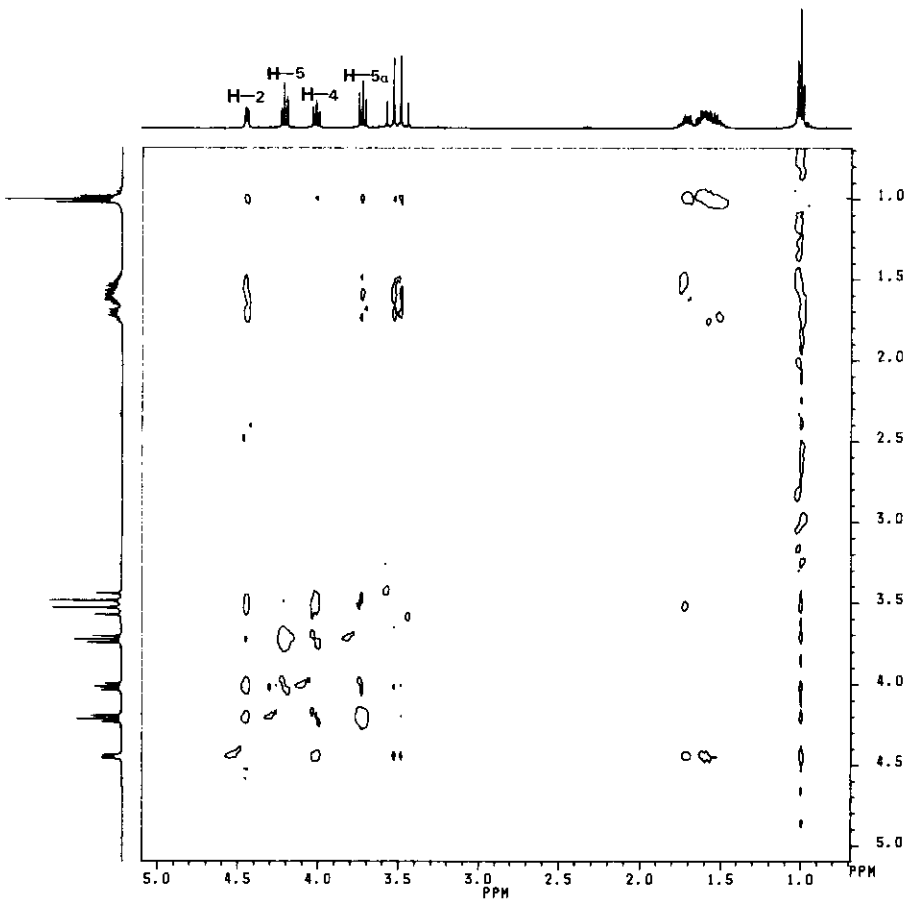


Figure 5 : 400 MHz ROESY spectrum of 2M.

	H-2	H-4	H-5α	H-5b	N-Me
N-Me	2.44	2.44	4.53	4.55	
H-5b	3.27	2.39			4.65
H-5α	3.76	3.08			4.42
H-4	2.49		3.10	2.45	2.79
H-2		3.73	3.32	3.73	3.06

Table 1. Internuclear distances , in Å , measured with a molecular modeling system (MacroModel) for the lowest energy conformers of 6M and 6m . Data for the 2,4-cis isomer are above and left of the diagonal and data for the 2,4-trans isomer are below and right .

EXPERIMENTAL

Ir spectra were recorded neat on a Perkin Elmer model 297 instrument. Optical rotations were determined in $CHCl_3$, MeOH or hexane (as indicated) using a Perkin Elmer 243 Polarimeter. Mass spectral data, recorded on AEI MS-50 are reported in the form : m/z (intensity relative to base peak = 100). ^1H Nmr were recorded on a Bruker AM400-wide bore-(^1H-400, ^{13}C-100MHz) in $CDCl_3$. Chemical shifts are expressed in ppm downfield from TMS (the ^1H nmr data are presented in the order : δ value of signal, peak multiplicity : s, singlet ; d, doublet ; t, triplet ; q, quartet ; m, multiplet), coupling constants in Hz and integrated number of protons. For compound 2M T_1 values in seconds are added in the end. It should be pointed out that ^1H nmr spectra were identical within a temperature range of -40°C to +40°C. T_1 values were estimated by using an inversion recovery sequence D1-180-VD-90-FID. Determination of n.O.e. effects by the NOEDIFF method were performed with the aid of Aspect 3000 microprograms which allowed direct accumulations of difference FID's. Samples were prepared as 10% (w/w) solutions in $CDCl_3$, degassed by several freeze-pump-thaw cycles and sealed in nmr tubes. ^{13}C Spectra were obtained either at 50 or 100 MHz on a Bruker AC200 or AM400 respectively. For all compounds investigated ^{13}C resonances were assigned by the SEFT technique.[19] The NOESY spectrum of Figure 4 was recorded with the usual 90°-t_1-90° pulse sequence, with t_m randomly varied around 1s. The data matrix was 512x1024 pts, zero filled to 1024x1024 before FT. The COSY ^1H-^1H spectra were recorded with the 90°-t_1-45° sequence (matrix size 512x1024 pts, zero filled to 1024x1024 before FT). Heteronuclear shift correlation spectra were obtained using the pulse sequence : delay-$\pi/2(^1H)$-$t_{1/2}$-$\pi(^{13}C)$-$t_{1/2}$-Δ^1-$\pi/2(^1H)$,$\pi/2(^{13}C)$-$\Delta 2$-acquisition with broadband decoupling.[20] A 1-s recycle delay was used with delay times $\Delta 1 = 1/(2J) = 3.8$ms and $\Delta 2 = 1/(4J) = 1.9$ms. In the F_2 and F_1 domains, 2048 and 1024 points were used, respectively. ROESY spectra were recorded with a spin-locking time of 1s (matrix size 512x2048, spectral width 8KHz.[21]

(-)-(2R,4R)-2-Propyl-N-cyanomethyl-4-phenyl-1,3-oxazolidine 2M : (-)-N-cyanomethylphenylglycinol (336 mg, 1.9 mmol) and butyraldehyde (0.34 ml, 3.8 mmol) were dissolved in 10 ml of dry CH_2Cl_2 and heated to reflux for 1 h in the presence of 1.5 g of 4Å molecular sieves. The reaction mixture was then cooled to room temperature and filtered through celite. Removal of the solvent by rotary evaporation and subsequent SiO_2 flash chromatography (EtOAc-hexane 1:4) yielded 380 mg (90%) of 2 as an oil (96/4 mixture). Ir (film) : 3070-2840, 2220, 1720, 1680, 1600, 1450, 1375, 1280, 1180, 1145, 1040 cm^{-1} ; ^1H nmr : δ 1.01(t, J = 7.5, 3H, 1.6s), 1.48-1.77(m, 4H), 3.48(d, J = 17.2H, 0.8s), 3.49(d, J = 17.8, 1H, 0.8s), 3.57(d, J = 17.8, 1H, 0.8s), 3.75(t, J = 8.0, 1H, 1.4s), 4.03(t, J = 8.0, 1H, 1.99s), 4.25(t, J = 8.0, 1H, 1.35s), 4.46(dd, J = 6.0, 2.5, 1H, 2.1s), 7.36(m, 5H, 3.1s) ; ^{13}C nmr : δ 14.1, 17.2, 35.4($2CH_2$), 36.2, 65.8, 73.0, 93.7, 114.3, 127.7, 128.1, 128.4, 128.8, 137.5 ; EIms : 230(M^+, 1), 186(100) 158(34), 103(24) ; $[\alpha]^{20}_D$= -165° (c = 0.6, $CHCl_3$) ; Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01 ; H, 7.88 ; N, 12.17 ; Found : C, 73.20 ; H, 7.80 ; N, 12.09.

(2S,4R)-2-Propyl-N-cyanomethyl-4-phenyl-1,3-oxazolidine 2m : ^1H Nmr : δ 1.00(t, J = 7.5, 3H), 1.40-1.70(m, 4H), 3.43(d, J = 17.5, 1H), 3.55(d, J = 17.5, 1H), 3.79(t, J = 7.5, 1H), 4.32(t, J = 7, 1H), 4.40(t, J = 7.5, 1H), 4.63(dd, J = 7.5, 4, 1H), 7.30(m, 5H) ; ^{13}C nmr : δ 13.6, 18.1, 33.2, 35.3, 64.7, 71.5, 93.0, 116.8, 127.1, 127.8, 127.9, 138.0.

(-)-(2R,4R)-2(1'-Isobutenyl)-N-cyanomethyl-4-phenyl-1,3-oxazolidine 3M : A mixture of 2.5 g (14.2 mmol) of N-cyanomethylphenylglycinol, 2.7 ml (28.4 mmol) of freshly distilled 3-methylcrotonaldehyde an approximately 2 g of 4Å molecular sieves was refluxed in dry dichloromethane (50 ml) for 6 h. The reaction mixture worked-up as for 2 yielded 2.4 g (70%) of 4 accompanied by 20% of unreacted starting materiel. IR (film) : 3060-2840, 2230, 1675, 1445, 1375, 1250, 1200, 1180, 1160, 1080, 1060 ; ^1H nmr : δ 1.83(s, 3H), 1.86(s, 3H), 3.39(d, J = 18, 1H), 3.52(d, J = 18, 1H), 3.81(t, J = 8.0, 1H), 4.02(t, J = 8.0, 1H), 4.26(t, J = 8.0, 1H), 5.01(d, J = 8.4, 1H), 5.21(m, 1H), 7.33(m, 5H) ; ^{13}C nmr : δ 18.0, 25.7, 34.7, 64.5, 72.7, 89.5, 113.9, 121.6, 127.5, 127.8, 128.1, 128.6, 137.1, 142.1 ; CIms : 243 (MH^+, 100), 216(99) ; Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56. Found : C, 74.22 ; H, 7.59 ; N, 11.41.

(-)-(2R,4R)-2-Methoxymethyl-N-cyanomethyl-4-phenyl-1,3-oxazolidine 4M : A solution of 4.2 g (24 mmol) of N-cyanomethylphenylglycinol, 14.4 g (120 mmol) of methoxyacetaldehyde dimethylacetal and 6.8g (72 mmol) of lithium tetrafluoroborate in CH_3CN-H_2O (98-2 ; 50 ml) was introduced into a preheated oil bath in order to increase the reaction temperature rapidly and the mixture was refluxed for 2.5h. If the temperature of the mixture is increased over a longer time period polymers are formed. The reaction mixture was then made alkaline (solid Na_2CO_3) and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated. After purification as for 2, 3.97 g (71%) of 4 (> 96/4 mixture) were obtained as an oil. Ir (film) : 3080-2870, 2230, 1600, 1420, 1200, 1130, 1060 cm^{-1} ; ^1H nmr : δ 3.42(s, 3H), 3.47(d, J = 17.7

1H), 3.53(dd, J = 9.9, 4.2, 1H), 3.61(dd, J = 9.9, 4.2, 1H), 3.75(dd, J = 8, 8.8, 1H), 3.85(d, J = 17.7, 1H), 4.08(dd, J = 8, 6.9, 1H), 4.24(dd, J = 8, 6.9, 1H), 4.62(dd, J = 5.4, 4.2, 1H), 7.30(m, 5H) ; ^{13}C nmr : δ 37.2, 59.5, 66.1, 73.4, 75.1, 91.6, 114.6, 127.7, 128.5, 128.9, 136.7 ; EIms 232 (M^+, 0.7), 231(1), 187(100), 159(32), 132(22), 104(20), 103(31), 91(5), 77(9) ; $[\alpha]^{20}_D$ = -177° (c = 1, $CHCl_3$) ; Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22 ; H, 6.94 ; N, 12.06. Found : C, 67.19 ; H, 6.88 ; N, 11.98.

(-)-(2R,4R)-2--Methoxyethyl)-N-cyanomethyl-4-phenyl-1,3-oxazolidine 5M : To a solution of 239 mg (1.36 mmol) of N-cyanomethylphenylglycinol, 24 mg (0.13 mmol) of p-toluenesulfonic acid in 3 ml C_6H_6 were added 0.5 ml (4.1 mmol) of acrolein dimethyl acetal (freshly distilled). The reaction mixture was refluxed for 1 h, cooled to room temperature, poured into water and neutralized with a few drops of aqueous sodium bicarbonate. Extraction with dichloromethane yielded 274 mg (83%) of 5 as an oil after purification as for 2. Ir (film) : 3000-2850, 2250, 1765, 1720, 1640, 1490, 1460, 1330, 1225, 1180, 1160, 1095 ; ^1H nmr : δ 1.98-2.16(m, 2H), 3.42(s, 3H), 3.53(d, J = 17.0, 1H), 3.65(dd, J = 11.8, 5.0, 2H), 3.71(d, J = 17.0, 1H), 3.78(t, J = 8.0, 1H), 4.09(t, J = 8.0, 1H), 4.26(t, J = 8.0, 1H), 4.61(dd, J) 6.0, 2.4, 1H), 7.30(m, 5H) ; ^{13}C nmr : δ 33.9, 36.3 ($2CH_2$), 58.7, 65.8, 68.4, 73.0, 92.1, 114.4, 127.7, 128.5, 128.9, 137.3 ; Eims : 246(M^+, 4), 186(100), 159(98), 132(68), 103(99), 104(99) ; Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27, H, 7.37 ; N, 11.37. Found : C, 68.39 ; H, 7.41 ; N, 11.29.

(-)-(2R,4R)-2-Propyl-N-methyl-4-phenyl-1,3-oxazolidine 6M : 650 mg of 2M in 5 ml of THF was added to a flask containing ca. 100 ml of liq NH_3 at -70°C. The reaction mixture was stirred at this temperature for 15 min and quenched with an excess of solid NH_4Cl. Hexane was added periodically while ammonia was allowed to evaporate. When the reaction mixture reached room temperature water was added followed by hexane extraction. The combined organic phases where washed with water, dried over Na_2SO_4 and concentrated. Compound 6M (579 mg, 96%) was obtained as a pure oil after SiO_2 flash chromatography (EtOAc-hexane 1:2). Ir (film) : 3070, 3050, 2800-2950, 1600, 1490, 1210, 1130 cm^{-1} ; ^1H nmr : δ 0.97(t, J = 7, 3H), 1.40-1.75(m, 4H), 2.15(s, 3H), 3.52(dd, J = 8.9, 7.4, 1H), 3.65(dd, J = 8.9, 7.4, 1H), 3.99(dd, J = 6.1, 2.4, 1H), 4.13(t, J = 7.3, 1H), 7.20-7.40(m, 5H) ; ^{13}C nmr : δ 14.0, 17.0, 35.7, 36.1, 70.0, 74.0, 97.6, 127.4, 128.6, 139.1 ; Eims : 205(M^+, 4), 204(7), 162(100), 134(63), 105(19), 104(11), 103(18), 91(17), 77(10) ; [a]$^{20}_D$ - 103° (c = 0.725 hexane) ; Anal. Calcd for : $C_{13}H_{19}NO$: C, 76.05 ; H, 9.33 ; N, 6.82. Found : C, 76.01 ; H, 9.39 ; N, 6.79.

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