Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 8, pp. 1947-1955, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00254-5

Synthesis of New Chiral Auxiliaries Derived from (*S*)-Tryptophan

Giuliana Cardillo, Luca Gentilucci, Claudia Tomasini* and Laura Tomasoni

Dipartimento di Chimica "G. Ciamician" and C.S.F.M., Università di Bologna, Via Selmi, 2 - 40126 Bologna - ITALY

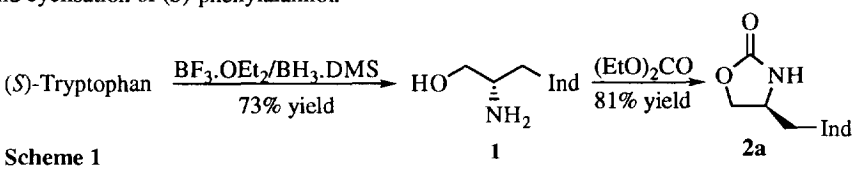
Abstract. The synthesis of chiral aminoalcohols **4** derived from (*S*)-tryptophan is described, by reaction of the protected amino acid **3** with various Grignard reagents. The aminoalcohols were transformed into the corresponding oxazolidin-2-ones **2** and acylated with 2-butenoyl chloride and 2-hexenoyl chloride, affording the imides **5a-e**. The conformational analysis of both the oxazolidin-2-ones **2** and the Michael acceptors **5** was performed by means of ^{1}H NMR, NOEDIF experiments and semiempirical AM1 calculations.

Recently the potential utility of homochiral vicinal amino alcohols in asymmetric synthesis has been extensively demonstrated. β-Amino alcohols are useful in various enantioselective syntheses for the preparation of chiral building blocks and valuable auxiliaries.[1] Furthermore 1,3,2-chiral oxazaborolidines can be easily obtained by reaction of β-amino alcohols or α-amino acids with boron derivatives, such as BH_3.THF or boronic acids and have recently gained prominence as catalyst for a variety of enantioselective reactions, such as enantioselective Diels-Alder reaction and reduction of carbonyl compounds.[2] As the three-dimensional arrangement of the catalyst is peculiar for the reaction stereoselectivity, several 1,2,3-oxazaborolidines containing the indolyl moiety have been designed.[3]

Moreover amino alcohols are precursors of oxazolidin-2-ones, which have extensive use in the diastereomeric induction for the carbon-carbon or carbon-heteroatom bond formation in reactions such as aldol condensation,[4] alkylation and 1,4-asymmetric induction.[5] As the steric hindrance of the substituents at C_4 and C_5 is crucial for the diastereoselectivity of the reaction, good results have been obtained with bulky groups at C_5.

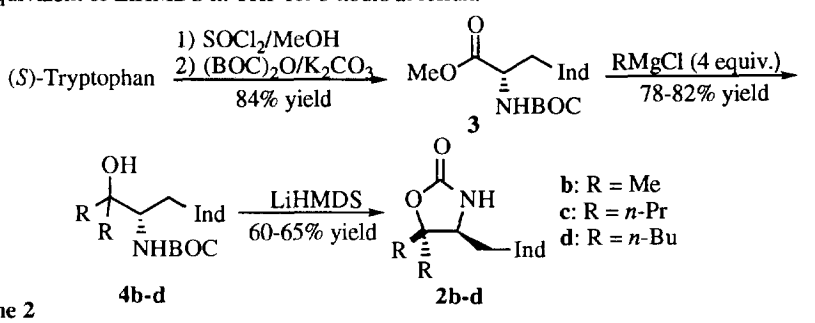
In the last few years we have become interested in the use and preparation of chiral auxiliaries, and their use in the asymmetric conjugate addition to α,β-unsaturated carbonyl compounds for the synthesis of optically active β-substituted carbonyl compounds.[6] The origin of diastereoselection has in a rapidly increasing number of cases being attributed to a through-space intramolecular interaction between π electron system, that leads to compact structures that present only one sterically available face to their reaction partners. This phenomenon has been called π-stacking effect [7] and has been envisaged in the presence of naphthyl or indolyl moieties in the proximity of the reaction centres. Those electron-rich substituents hinder one face of the system, producing high diastereoselection.

Here we describe the synthesis of new oxazolidin-2-ones **2** containing the indolylmethyl moiety at C_4 and various alkyl substituents at C_5, as useful chiral auxiliary for diastereoselective conjugate additions.[8] In the preparation of oxazolidin-2-ones **2**, our hypothesis is that the different substituents at C_5 affect the validity of the chiral auxiliary, being responsible for different conformations of the indolyl moiety. We initially prepared the oxazolidin-2-one **2a**, with no substituents at C_5 (Scheme 1), by reduction of (*S*)-tryptophan with diborane to (*S*)-tryptophanol, followed by reaction with diethyl carbonate, according to the Evans procedure for the synthesis and cyclisation of (*S*)-phenylalanilol.[9]



Scheme 1 **1** **2a**

To synthesise the 4-indolylmethyl-5,5-dialkyl-oxazolidin-2-ones **2b-d**, the *N*-protected amino ester **3** was treated with various Grignard reagents in THF (Scheme 2). The reaction was efficient with diverse alkyl reagents but any attempt of utilising *i*-PrMgBr did not afford the corresponding amino alcohol. So the (*S*)-1,1-dialkyl-2-*N*-BOC-3-indolyl-propanols **4b-d** were obtained by reaction of **3** with 4 equivalents of MeMgCl, *n*-PrMgCl and *n*-BuMgCl respectively in dry THF at room temperature for 4 hours with 78-82% yield. The amino alcohols **4b-d** were then transformed with good yield into the corresponding oxazolidin-2-ones **2b-d**, by reaction with 1 equivalent of LiHMDS in THF for 3 hours at reflux.



Scheme 2 **4b-d** **3** **2b-d**

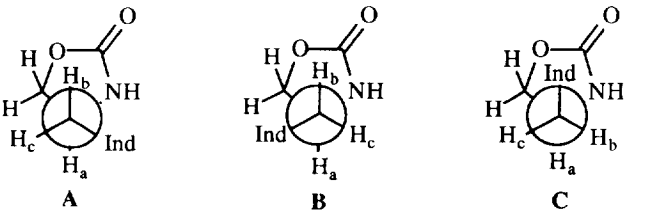
The preferential conformation assumed by the indolylmethyl moiety at C_4 of the oxazolidin-2-ones **2a-d** was analysed by means of ^1H NMR (Table 1) and semiempirical AM1 calculations [10] (Figures 1 and 2).

Table 1. ^1H NMR Most Representative Data for Oxazolidin-2-ones **2a-2d.**

Compound	δ_{Ha}	δ_{Hb}	δ_{Hc}	J_{Ha-Hb} (Hz)	J_{Ha-Hc} (Hz)	J_{Hb-Hc}(Hz)
2a	4.19 (m)	3.02 (m)		-	-	-
2b	3.81 (dd)	2.84 (dd)	2.99 (dd)	10.9	3.4	14.1
2c	3.85 (dd)	2.86 (dd)	3.01 (dd)	10.9	2.0	12.6
2d	3.85 (dd)	2.86 (dd)	3.01 (dd)	11.4	2.9	14.1

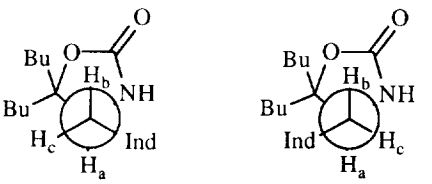
From the ^{1}H NMR analysis, no preferential conformation can be ascertained for the indolylmethyl moiety of the oxazolidin-2-one **2a**. In agreement, the energies of the three possible staggered conformations **A**, **B** and **C** have very similar energies (Figure 1). The energies have been calculated by means of semiempirical AM1 calculations.[10]

Figure 1

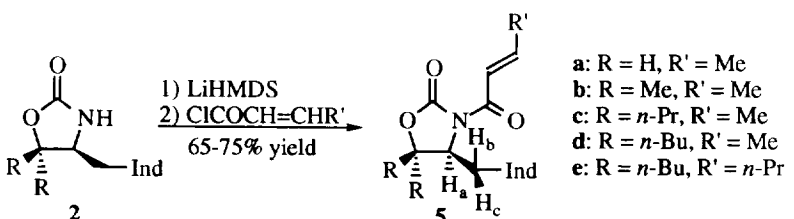


On the other hand for oxazolidin-2-ones **2b-d**, hydrogens H_a, H_b and H_c form an ABX system with three coupling constants, $J_{Ha,Hb}$, $J_{Ha,Hc}$, and $J_{Ha,Hb}$, typical of a staggered conformation. The semiempirical AM1 calculations [10] performed on the two staggered conformations **D** and **E** of **2d**, in agreement with the coupling constants of the ABX system (Figure 2), show that the conformation **D** is 6.3 Kcal/mol more stable than the conformation **E**, thus showing the effect of two substituents at C_5.

Figure 2



The oxazolidin-2-ones **2a-d** were then transformed into the Michael acceptors **5a-e** by treatment of the heterocycles with LiHMDS followed by addition of but-2-enoyl chloride or hex-2-enoyl chloride in THF at 0 °C for 1 hour.



Scheme 3

The analysis of the ^{1}H NMR signals of H_a, H_b and H_c of imides **5** shows that the signals of hydrogens H_a, H_b and H_c varies as a function of R and of the deuterated solvent (Table 2).

Table 2. ^{1}H NMR Most Representative Data for Imides **5a-5e**.

Entry	Compound	Solvent	δHa	δHb	δHc	^{J}Ha-Hb (Hz)	^{J}Ha-Hc (Hz)	^{J}Hb-Hc (Hz)
1	**5a**	$CDCl_3$	4.83 (m)	2.94 (dd)	3.49 (dd)	9.9	3.3	14.1
2	**5b**	$CDCl_3$	4.66 (dd)	3.14 (dd)	3.29 (dd)	9.9	2.7	14.8
3	**5b**	C_6D_6	4.57 (dd)	2.83 (dd)	3.25 (dd)	10.0	2.6	14.8
4	**5c**	$CDCl_3$	4.76 (dd)	3.22 (m)		7.1	5.3	-
5	**5d**	$CDCl_3$	4.78 (t)	3.23 (d)		6.2	6.2	-
6	**5d**	C_6D_6	4.90 (dd)	3.04 (dd)	3.22 (dd)	9.2	2.8	15.0
7	**5e**	$CDCl_3$	4.76 (t)	3.22 (d)		6.3	6.3	-

Indeed prochiral hydrogens H_b and H_c show peculiar behaviour on going from **5a** to **5e**, when the ^{1}H NMR spectrum is recorded in $CDCl_3$. While in **5a** and **5b** they appear as two doublets of doublets with different coupling constants with H_a, in the more hindered **5d** and **5e** H_b and H_c appear as a single doublet. In order to evaluate this behaviour, we have recorded the ^{1}H NMR spectra of **5b** and **5d** also in C_6D_6. While the ABX system of **5b** has the same arrangement in $CDCl_3$ (entry 2) and C_6D_6 (entry 3), **5d** shows a different pattern in the two solvents (entries 5 and 6), so that the presence of a doublet which accounts for both H_b and H_c in $CDCl_3$ can be attributed to the casual superimposition of the H_b and H_c chemical shift. The energies of the three staggered conformations **F**, **G** and **H** and of the eclipsed conformation **I** of **2d** were calculated with semiempirical AM1 calculations [10] (Figure 3) and disclosed that the staggered conformation **F** is the most stable. The other two possible eclipsed conformations are not minima.

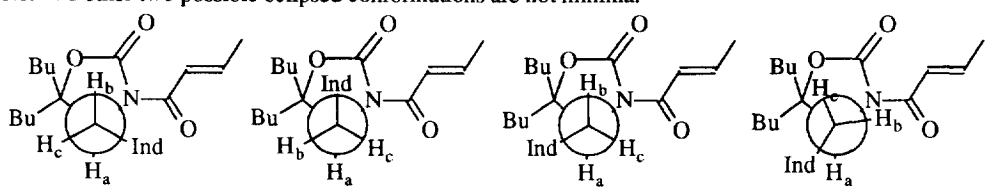


Figure 3

NOE difference experiments were performed on imides **5a**, **5b** and **5d** (Figure 4), to confirm the above conformational analysis and to examine the orientation of the indolyl group with respect to the oxazolidin-2-one ring.

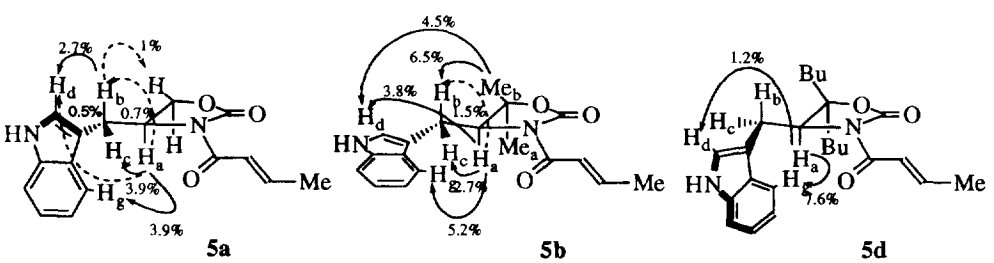


Figure 4

The NOE difference experiments performed on **5a** confirm the staggered conformation of the C_4-$C_{4'}$ bond and let us presume that the indolyl group lies preferentially almost perpendicular to the oxazolidin-2-one group, remote from the α,β-unsaturated system. Thus a very low diastereomeric ratio in the 1,4-addition reaction can be foreseen. The results of NOE difference experiments performed on imide **5b** show a slightly different situation. The staggered conformation of the C_4-$C_{4'}$ bond is similar to **5a**, but in this case the indolyl group is almost parallel to the oxazolidin-2-one system. Finally the results of the NOE difference experiments performed on **5d** suggest that the C_4-$C_{4'}$ bond lies in a preferential staggered conformation with the indolyl group vicinal to the α,β-unsaturated system. Furthermore an orientation of the indolyl group with the 6-membered ring under the oxazolidin-2-one plane is depicted, owing to the high NOE effect between H_a and H_g.

In conclusion we propose the conformations shown in Figure 4 for **5a**, **5b** and **5d**, which show that different substituents at C_5 strongly affect the conformation of the indolylmethyl moiety, which is more pushed towards the acyl residue at N_3 by more hindered substituents at C_5. These results lead us to predict an increase in the diastereoselectivity from **5a** to **5e**, when an addition reaction will be performed on the α,β-unsaturated system.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively. Chemical shifts are reported in ppm relative to the solvent peak of $CHCl_3$, defined to be d 7.27. Infrared spectra were recorded with an FT-IR spectrometer. NOE values were obtained by 1-0 steady state difference experiments. Melting points were determined in open capillaries and are uncorrected. Flash chromatography was performed with Merck silica gel 60 (230-400 mesh). THF was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from P_2O_5. MeMgCl was purchased as 2M solution in THF, while *n*-PrMgCl and *n*-BuMgCl were purchased as 2M solutions in diethyl ether.

(*S*)-2-Amino-3-(1H-indol-3-yl)-propan-1-ol (1)

$BF_3.OEt_2$ (66.7 mmol, 6.15 mL) was added dropwise at rt to a stirring solution of *L*-tryptophan (50 mmol, 10.2 g) in anhydrous THF (45 mL). The mixture was refluxed for 2 h, then a solution of BH_3.DMS (2M solution in diethyl ether, 57.5 mmol, 28.8 mL) was added for a period of 20 min and the solution was refluxed for an additional 6 h. A 1:1 mixture of H_2O/THF (6.2 mL) and 5M NaOH (37.5 mL) were added and the mixture was refluxed for 12 h. The THF was removed under reduced pressure, then the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, concentrated and the residue was crystallized from ethyl acetate (73 % yield, 36.5 mmol, 6.94 g). IR (nujol) 3300, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (bs, 3H, NH_2 + OH) 2.67 (dd, 1H, J=8.5 Hz, J=14.3 Hz, C*H*HOH), 2.88 (dd, 1H, J=4.8 Hz, J=14.3 Hz, CH*H*OH), 3.23 (m, 1H, C*H*NH_2), 3.40 (dd, 1H, J=7.3 Hz, J=10.7 Hz, C*H*H-Ind), 3.68 (dd, 1H, J=3.8 Hz, J=10.7 Hz, CH*H*-Ind), 6.94 (s, 1H, Ind), 7.11 (t, 1H, J=7.5 Hz, Ind), 7.19 (t, 1H, J=7.5 Hz, Ind), 7.34 (d, 1H, J=7.5 Hz, Ind), 7.59 (d, 1H, J=7.5 Hz), 8.60 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 29.9, 52.9, 66.3, 111.2, 112.2, 118.8, 119.2, 121.9, 122.7, 127.5, 136.4; $[\alpha]_D^{20}$ -21.0 (c 1.58, MeOH), lit.[11] $[\alpha]_D$ -19.0 (c 1.0, MeOH); mp 83-84 °C, lit.[11] 84-85 °C. Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.4; H, 7.4; N, 14.7. Found: C, 69.3; H, 7.5; N, 14.7.

(*S*)-4-(1H-Indol-3-ylmethyl)-oxazolidin-2-one (2a)

A stirring solution of aminoalcohol (**1**) (26.65 mmol, 5.07 g) and K_2CO_3 (2.65 mmol, 0.37 g) in diethyl carbonate (55.3 mmol, 6.7 mL) was heated at 135 °C for 3 h in a round bottomed flask equipped with a Vigreux condenser. A mixture of ethanol and diethyl carbonate was distilled and the reaction was monitored by

TLC. When the reaction was complete, the mixture was cooled in an ice bath and the product **(2a)** was crystallized and filtered off (81% yield, 21.6 mmol, 4.67 g). IR (film) 3400, 3290, 1750, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (m, 2H, C*H*$_2$-Ind), 4.19 (m, 2H, CHN + C*H*HCHOCO), 4.49 (m, 1H, CH*H*OCO), 5.34 (s, 1H, NH), 7.08 (s, 1H, Ind), 7.15 (t, 1H, J=7.5 Hz, Ind), 7.24 (t, 1H, J=7.5 Hz, Ind), 7.40 (d, 1H, J=7.5 Hz, Ind), 7.56 (d, 1H, J=7.5 Hz, Ind), 8.24 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 31.3, 52.8, 69.9, 110.0, 111.5, 118.2, 119.7, 122.4, 122.8, 127.0, 136.3, 159.5; $[\alpha]_D^{20}$ +6.4 (c 1.0, MeOH); mp 145-146 °C. Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.6; H, 5.6; N, 13.0. Found: C, 66.8; H, 5.7; N, 13.1.

***N*-*t*-butyloxycarbonyl-*L*-tryptophan methyl ester (3)**

$SOCl_2$ (40 mmol, 2.9 mL) was added dropwise to anhydrous MeOH (60 mL) at -15 °C and the mixture was stirred for 1 hour at -15 °C. Then solid tryptophan (20 mmol, 4.1 g) was added in one portion and the mixture was stirred overnight and warmed up. The reaction was monitored by TLC. When the reaction was complete, the solvent was removed under reduced pressure and the tryptophan methyl ester was obtained pure in quantitative yield and directly protected without any further purification.

A solution of di-*tert*-butyl dicarbonate (20 mmol, 4.36 g) in acetone (50 mL) was added dropwise at 0 °C to a stirring solution of tryptophan methyl ester (20 mmol, 4.36 g) and K_2CO_3 (20 mmol, 2.7 g) in H_2O (50 mL). After 2 hours, acetone was removed under reduced pressure and replaced with ethyl acetate. The mixture was separated and the organic layer was dried over Na_2SO_4 and concentrated. Product **(3)** was obtained pure after crystallization from ethyl acetate in 84% overall yield (16.8 mmol, 5.34 g). IR (nujol) 3384, 3310, 1736, 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H, $OC(CH_3)_3$), 3.30 (d, 2H, J=5.2 Hz, C*H*$_2$-Ind), 3.69 (s, 3H, OCH_3), 4.67 (dt, 1H, J=5.2 Hz, J=8.0 Hz, CHN), 5.10 (d, 1H, J=8.0 Hz, NH), 7.00 (s, 1H, Ind), 7.12 (t, 1H, J=7.0 Hz, Ind), 7.21 (t, 1H, J=7.0 Hz, Ind), 7.36 (d, 1H, J=7.0 Hz, Ind), 7.56 (d, 1H, J=7.5 Hz, Ind), 8.20 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 27.4, 28.3, 52.2, 54.2, 79.8, 110.2, 111.2, 118.7, 119.6, 122.2, 122.7, 136.1, 172.7; $[\alpha]_D^{20}$ -5.8 (c 2, MeOH), lit.[12] $[\alpha]_D$ -4.2 (c 0.3, MeOH); mp 142-144 °C, lit.[12] 145-146 °C. Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.1; H, 7.0; N, 8.8. Found: C, 64.0; H, 7.1; N, 8.7.

(*S*)-1,1-Dialkyl-2-*N*-*t*-butyloxycarbonylamino-3-(1H-indol-3-yl)-propan-1-ol (4)

RMgCl (14 mmol) (R = Me, *n*-Pr, *n*-Bu) was added dropwise at 0 °C under inert atmosphere to a stirring solution of **(3)** (3.5 mmol, 1.1 g) in anhydrous THF (20 mL). The mixture was stirred for 4 hours at rt, till all the starting material was consumed, then water was added and the mixture was concentrated under reduced pressure. The residue was dissolved in water (100 mL) and 6M HCl was added till the solution reached pH 6, then the mixture was extracted twice with ethyl acetate. The organic layer was separated, dried over Na_2SO_4 and concentrated. The product **(4)** was obtained pure after silica gel chromatography (cyclohexane:ethyl acetate 1:1 as eluant).

4b: 80% yield, solid. IR (film): 3480, 3430, 3400, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 9H, $OC(CH_3)_3$), 1.34 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.05 (bs, 1H, OH), 2.83 (m, 1H, C*H*H-CHN), 3.20 (dd, 1H, J=2.5 Hz, J=14.9 Hz, CH*H*-CHN), 3.83 (m, 1H, CHN), 4.66 (bs, 1H, NH), 7.07 (s, 1H, Ind), 7.12 (t, 1H, J=7.5 Hz, Ind), 7.19 (t, 1H, J=7.5 Hz, Ind), 7.35 (d, 1H, J=7.5 Hz, Ind), 7.59 (d, 1H, J=7.5 Hz, Ind), 8.02 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 26.6, 27.5, 28.2, 28.3, 59.8, 79.3, 111.1, 113.2, 118.7, 119.4, 122.1, 127.9, 136.5, 156.7; $[\alpha]_D^{20}$ -35.8 (c 0.6, $CHCl_3$); mp 139-140 °C. Anal. Calcd. for $C_{18}H_{26}N_2O_3$: C, 67.9; H, 8.2; N, 8.8. Found: C, 68.0; H, 8.1; N, 8.9.

4c: 82% yield, solid. IR (film): 3440, 3335, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (m, 6H, $CH_2CH_2CH_3$), 1.37 (m, 13H, CH_2CH_2-CH_3 + $OC(CH_3)_3$), 1.61 (m, 4H, $CH_2CH_2CH_3$), 2.51 (bs, 1H, OH), 2.92 (m, 1H, C*H*HCHN), 3.14 (dd, 1H, J=2.7 Hz, J=14.8 Hz, CH*H*CHN), 3.94 (m, 1H, CHN), 4.76 (bs, 1H, NH),

7.10-7.21 (m, 3H, Ind), 7.34 (d, 1H, J=7.7 Hz, Ind), 7.60 (d, 1H, J=7.7 Hz, Ind), 8.13 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.0, 23.4, 25.6, 25.8, 28.1, 28.3, 35.9, 36.1, 57.0, 79.2, 111.1, 113.2, 118.7, 119.3, 121.9, 128.0, 136.5, 156.6; $[\alpha]_D^{20}$ -33.4 (c 1.3, $CHCl_3$); mp 130-132 °C. Anal. Calcd. for $C_{22}H_{34}N_2O_3$: C, 70.5; H, 9.2; N, 7.5. Found: C, 70.3; H, 9.3; N, 7.4.

4d: 78% yield, solid. IR (film) 3410, 3295, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.36 (m, 17H, $CH_2CH_2CH_2CH_3$ + $OC(CH_3)_3$), 1.60 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.91 (m, 1H, CHHCHN), 3.14 (dd, 1H, J=3.0 Hz, J=15.1 Hz, CHHCHN), 3.93 (m, 1H, CHN), 4.74 (d, 1H, J=9.9 Hz, NH), 7.14 (m, 3H, Ind), 7.33 (d, 1H, J=7.5 Hz, Ind), 7.60 (d, 1H, J=7.7 Hz, Ind), 8.13 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.0, 23.4, 25.6, 25.8, 28.2, 28.3, 35.9, 36.1, 57.0, 79.1, 111.1, 113.2, 118.7, 119.3, 121.9, 128.0, 136.5, 156.6; $[\alpha]_D^{20}$ -48.3 (c 4.2, $CHCl_3$); mp 130-131 °C. Anal. Calcd. for $C_{24}H_{38}N_2O_3$: C, 71.6; H, 9.5; N, 7.0. Found: C, 71.8; H, 9.3; N, 6.9.

(*S*)-4-(1H-Indol-3-ylmethyl)-5,5-dialkyl-oxazolidin-2-one (2)

LiHMDS (1M solution in THF, 5 mmol, 5 mL) was added dropwise at 0 °C under inert atmosphere to a stirring solution of alcool (**4**) (5 mmol) in anhydrous THF (25 mL). The mixture was refluxed for 3 h, then water was added and the THF was removed under reduced pressure. Additional water was added to the residue and the mixture was washed twice with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Compound (**2**) was obtained pure as a waxy solid after silica gel chromatography (cyclohexane : ethyl acetate 6/4 as eluant).

2b: 60% yield. IR (film) 3400, 3300, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (s, 6H, CH_3), 2.84 (dd, 1H, J=10.9 Hz, J=14.1 Hz, CHHCHN), 2.99 (dd, 1H, J=3.4 Hz, J=14.1 Hz, CHHCHN), 3.81 (dd, 1H, J=3.4 Hz, J=10.9 Hz, CHN), 5.15 (bs, 1H, NH), 7.05 (s, 1H, Ind), 7.15 (d, 1H, J=7.4 Hz, Ind), 7.23 (t, J=7.4 Hz, Ind), 7.40 (d, 1H, J=7.4 Hz, Ind), 7.55 (d, 1H, J=7.4 Hz, Ind), 8.42 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.5, 26.5, 27.5, 61.7, 83.3, 110.1, 111.6, 117.9, 119.2, 121.9, 122.7, 126.6, 136.3, 158.5; $[\alpha]_D^{20}$ -74.0 (c 1.5, $CHCl_3$). Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.8; H, 6.6; N, 11.5. Found: C, 68.9; H, 6.5; N, 11.5.

2c: 65% yield. IR (film): 3299, 1740, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, 3H, J=7.4 Hz, $CH_2CH_2CH_3$), 1.03 (t, 3H, J=7.4 Hz, $CH_2CH_2CH_3$), 1.44 (m, 4H, $CH_2CH_2CH_3$), 1.75 (m, 4H, $CH_2CH_2CH_3$), 2.86 (dd, 1H, J=10.9 Hz, J=12.6 Hz, CHHCHN), 3.01 (dd, 1H, J=2.0 Hz, J=12.6 Hz, CHHCHN), 3.85 (dd, 1H, J=2.0 Hz, J=10.9 Hz, CHN), 5.16 (bs, 1H, NH), 7.04 (s, 1H, Ind), 7.15 (t, 1H, J=7.7 Hz, Ind), 7.23 (t, 1H, J=7.7 Hz, Ind), 7.39 (d, 1H, J=7.7 Hz, Ind), 7.52 (d, 1H, J=7.7 Hz, Ind), 8.52 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.4, 14.5, 16.6, 16.9, 27.0, 34.8, 39.6, 60.3, 87.0, 110.9, 111.6, 118.1, 119.7, 122.4, 122.6, 126.7, 136.5, 158.3; $[\alpha]_D^{20}$ -12.4 (c 0.6, $CHCl_3$). Anal. Calcd. for $C_{18}H_{24}N_2O_2$: C, 72.0; H, 8.1; N, 9.3. Found: C, 72.2; H, 8.1; N, 9.2.

2d: 62% yield. IR (film) 3300, 1735, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=7.1 Hz, $CH_2CH_2CH_2CH_3$), 0.99 (t, 3H, J=6.9 Hz, $CH_2CH_2CH_2CH_3$), 1.38 (m, 8H, $CH_2CH_2CH_2CH_3$), 1.77 (m, 4H, $CH_2CH_2CH_2CH_3$), 2.86 (dd, 1H, J=11.4 Hz, J=14.1 Hz, CHHCHN), 3.01 (dd, 1H, J=2.9 Hz, J=14.1 Hz, CHHCHN), 3.85 (dd, 1H, J=2.9 Hz, J=11.4 Hz, CHN), 5.28 (bs, 1H, NH), 7.03 (s, 1H, Ind), 7.15 (t, 1H, J=7.4 Hz, Ind), 7.23 (t, 1H, J=7.4 Hz, Ind), 7.40 (d, 1H, J=7.4 Hz, Ind), 7.52 (t, 1H, J=7.4 Hz, Ind), 8.71 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.9, 23.2, 25.3, 25.6, 27.0, 32.3, 37.0, 60.4, 87.2, 110.8, 111.7, 118.0, 119.6, 122.2, 122.7, 126.7, 136.5, 158.4; $[\alpha]_D^{20}$ -35.3 (c 2.3, $CHCl_3$). Anal. Calcd. for $C_{20}H_{28}N_2O_2$: C, 73.1; H, 8.6; N, 8.5. Found: C, 73.3; H, 8.8; N, 8.4.

(*S*)-4-(1H-indol-3-ylmethyl)-5,5-dialkyl-3-(1-oxo-but-2-enyl)-oxazolidin-2-one (5)

LiHMDS (1M solution in THF, 4.8 mmol, 4.8 mL) in anhydrous THF (10 mL) and, after 30 min, crotonyl chloride (techn., 90%, 4.8 mmol, 0.51 mL) in anhydrous THF (5 mL) were added dropwise at 0 °C under inert atmosphere to a stirring solution of oxazolidin-2-one **(2)** (4 mmol) in anhydrous THF (20 mL) . After 1 h, water was added and THF was removed under reduced pressure. To the residue were added water and ethyl acetate, the organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The product was obtained pure after silica gel chromatography (cyclohexane : ethyl acetate 9/1 as eluant).

5a: 70% yield, solid. IR (nujol) 3360, 1796, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (d, 3H, J=5.4 Hz, CH=CHC*H*$_3$), 2.94 (dd, 1H, J=9.9 Hz, J=14.1 Hz, C*H*HCHN), 3.49, (dd, 1H, J=3.3 Hz, J=14.1 Hz, CH*H*CHN), 4.21 (m, 2H, CH_2O), 4.83 (m, CHN), 7.02 (s, 1H, Ind), 7.13-7.40 (m, 5H, Ind + C*H*=C*H*), 7.78 (d, 1H, J=7.8 Hz, Ind), 8.43 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 18.5, 54.4, 66.8, 111.2, 118.7, 119.7, 121.9, 122.3, 122.8, 146.8, 165.0; $[\alpha]_D^{20}$ -14.0 (c 1.7, $CHCl_3$); mp 122-123 °C. Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.6; H, 5.7; N, 9.9. Found: C, 67.5; H, 5.6; N, 9.9.

5b: 75% yield, solid. IR (nujol) 3460, 1771, 1680, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H, CH_3CO), 1.43 (s, 3H, CH_3CO), 1.96 (d, 3H, J=6.5 Hz, CH=CHC*H*$_3$), 3.14 (dd, 1H, J=9.9 Hz, J=14.8 Hz, C*H*HCHN), 3.29, (dd, 1H, J=2.7 Hz, J=14.8 Hz, CH*H*CHN), 4.66 (dd, 1H, J=2.7 Hz, J=9.9 Hz, CHN), 6.99 (s, 1H, Ind), 7.13-7.38 (m, 5H, Ind + C*H*=C*H*), 7.91 (d, 1H, J=7.1 Hz, Ind), 8.47 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1, 18.4, 21.8, 25.2, 28.5, 62.4, 82.2, 110.7, 111.1, 119.1, 119.5, 122.1, 122.2, 122.7, 127.1, 136.0, 146.4, 152.8, 165.4; $[\alpha]_D^{20}$ -87.0 (c 1.2, $CHCl_3$); mp 78-80 °C. Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.5; N, 9.0. Found: C, 69.3; H, 6.4; N, 9.0.

5c: 70% yield, solid. IR (nujol) 3300, 1775, 1680, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, 6H, J=7.1 Hz, $CH_2CH_2CH_3$), 1.16 (m, 4H, $CH_2CH_2CH_3$), 1.56 (m, 4H, $CH_2CH_2CH_3$), 1.96 (d, 3H, J=6.6 Hz, CH=CHC*H*$_3$), 3.22 (m, 2H, C*H*$_2$CHN), 4.76 (dd, 1H, J=5.3 Hz, J=7.1 Hz, CHN), 7.03 (s, 1H, Ind), 7.12-7.38 (m, 5H, Ind + CH=CH), 7.87 (d, 1H, J=7.6 Hz, Ind), 8.04 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 16.1, 16.6, 18.3, 24.7, 33.9, 39.0, 60.8, 86.3, 110.4, 111.1, 118.9, 119.3, 121.8, 122.0, 122.5, 127.1, 135.9, 146.2, 153.0, 165.1; $[\alpha]_D^{20}$ -60.0 (c 0.9, $CHCl_3$); mp 35-36 °C. Anal. Calcd. for $C_{22}H_{28}N_2O_3$: C, 71.1; H, 7.7; N, 7.6. Found: C, 71.0; H, 7.9; N, 7.6.

5d: 73% yield; waxy solid. IR (film) 3300, 1770, 1680, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, 3H, J=7.0 Hz, $CH_2CH_2CH_2CH_3$), 0.82 (t, 3H, J=7.1 Hz, $CH_2CH_2CH_2CH_3$), 1.20 (m, 8H, $CH_2CH_2CH_2CH_3$), 1.62 (m, 4H, $CH_2CH_2CH_2CH_3$), 1.95 (d, 3H, J=6.6 Hz, CH=CHC*H*$_3$), 3.23 (d, 2H, J=6.2 Hz, C*H*$_2$CHN), 4.78 (t, 1H, J=6.2 Hz, CHN), 7.00 (s, 1H, Ind), 7.17 (m, 3H, Ind + CH=CH), 7.29 (t, 1H, J=7.1 Hz, Ind), 7.33 (d, 1H, J=7.1 Hz, Ind), 7.85 (d, 1H, J=7.1 Hz, Ind), 8.31 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.7, 18.4, 22.6, 22.9, 24.8, 24.9, 25.4, 26.8, 31.6, 36.6, 61.0, 86.5, 110.9, 111.1, 119.1, 119.5, 122.0, 122.2, 122.4, 127.2, 136.0, 146.2, 153.1, 165.3; $[\alpha]_D^{20}$ -47.2 (c 2.3, $CHCl_3$). Anal. Calcd. for $C_{24}H_{32}N_2O_3$: C, 72.7; H, 8.1; N, 7.1. Found: C, 72.5; H, 8.1; N, 6.9.

5e: 65% yield, oil. IR (film): 3400, 1760, 1680, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (t, 3H, J=7.0 Hz, $CH_2CH_2CH_2CH_3$), 0.80 (t, 3H, J=6.9 Hz, $CH_2CH_2CH_2CH_3$), 0.96 (t, 3H, J=7.4 Hz, $=CHCH_2CH_2CH_3$), 1.05-1.58 (m, 14 H, $CH_2CH_2CH_2CH_3$ + $CH_2CH_2CH_2CH_3$ + $=CHCH_2CH_2CH_3$), 2.26 (dt, 2H, J=7.4 Hz, $=CHCH_2CH_2CH_3$), 3.22 (d, 2H, J=6.3 Hz, CH_2Ind), 4.76 (t, 1H, J=6.3 Hz, CHN), 7.02 (s, 1H, Ind), 7.13-7.36 (m, 5H, Ind + CH=CH), 7.86 (d, 1H, J=7.0 Hz, Ind), 8.15 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.6, 13.7, 21.2, 22.5, 22.8, 24.8, 25.3, 31.5, 34.5, 36.5, 61.0, 86.5, 110.7, 111.1, 119.0, 119.4, 120.7,

121.9, 122.5, 127.1, 135.9, 151.0, 153.1, 165.4; $[\alpha]_D^{20}$ -50.7 (c 0.6, $CHCl_3$). Anal. Calcd. for $C_{26}H_{36}N_2O_3$: C, 73.5; H, 8.6; N, 6.6. Found: C, 73.3; H, 8.5; N, 6.5.

Acknowledgement:
We thank Consiglio Nazionale delle Ricerche (Progetto Finalizzato 'Chimica Fine II') and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Fondi 40%).

References and Notes

* email address: tomasini@ciam01.cineca.it

1. For recent reviews, see: (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
2. (a) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763; (b) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetr. Lett.* **1991**, *32*, 5287; (c) Corey, E. J.; Choi, S. *Tetr. Lett.* **1991**, *32*, 2857.
3. See for example: (a) Seerden, J.-P. G.; Scheeren, H. W. *Tetr. Lett.* **1993**, *34*, 2669; (b) Corey, E. J.; Link, O. *Tetr. Lett.* **1992**, *33*, 4141; (c) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetr. Lett.* **1992**, *33*, 6907.
4. (a) Heathcock. In *Asymmetric Synthesis*; Morrison J. D., Ed.; Academic Press; Orlando, FL, 1984; Vol. 3, p. 111-112; (b) Masamune S., Choy W., Petersen J. S., Sita L. R. *Angew. Chem., Int. Ed. Engl. 1985*, 24, *1-30.*
5. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis, Tetrahedron Organic Chemistry Series, Vol. 9*; Baldwin, J. B.; Magnum, P. D. Eds.; Pergamon Press, Oxford, 1992.
6. (a) Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Treré A. *J. Org. Chem.*, **1993**, *58*, 5615; (b) Cardillo, G.; De Simone, A.; Gentilucci, L.; Tomasini C. *J. Chem. Soc., Chem. Comm.* **1994**, 735; (c) Cardillo, G.; De Simone, A.; Gentilucci, L.; Sabatino, P.; Tomasini C. *Tetr. Lett.* **1994**, *35*, 5051.
7. Maddaluno, J. F.; Gresh, N.; Giessner-Prettre, C. *J. Org. Chem.*, **1994**, *59*, 793.
8. For two recent reports on the preparation of 4,5,5-trisubstituted oxazolidin-2-ones from α-amino acids see: (a) Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *J. Org. Chem.*, **1994**, *59*, 4680; (b) Davies, S. G.; Sanganee, H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 671.
9. Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77.
10. For the semiempirical AM1 calculations we have employed the HYPERCHEM modelling package, designed and distributed by Hypercube Inc., 419 Phillip Street, Waterloo, Ont., N2L 3X2, Canada.
11. Hvidt, T.; Szarek, W. A.; Maclean, D. B. *Can. J. Chem.* **1988**, *66*, 779.
12. Sato, K.; Kozikowsky, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073.

(*Received in UK* 23 *May* 1995; *accepted* 11 *July* 1995)