

TETRAHEDRON

## 4,4'-Disubstituted 1,2,3,4-Tetrahydroisoquinolines from Alkylation of a Chiral non Racemic Lactam. An Approach to the Crinine-Type Alkaloids.

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**Abstract**: Enantiomerically pure 4,4-disubstituted tetrahydroisoquinolin-3-ones can be easily prepared by bis-alkylation of 1,2,3,4-tetrahyroisoquinolin-3-one 1 derived from (R)-(-)-phenylglycinol. The observed diastereoselectivity was explained by a rigid chelated intermediate. The obtained bis-alkylated products were used to prepare the ABC and ABD rings of the crinine alkaloid skeleton. © 1998 Elsevier Science Ltd. All rights reserved.

#### Introduction

During the last few years we have studied the diastereoselective alkylation of lactams derived from (R)-(-)-phenyglycinol in the piperidine<sup>2</sup> and piperazine<sup>3</sup> series. We recently extented this work to tetrahydroisoquinoline derivatives. Indeed, an increasing interest has emerged for the stereoselective synthesis of 4-substituted tetrahydroisoquinolines<sup>4,5,6</sup> as intermediates for the preparation of biologically active compounds. Moreover we were interested in the stereocontrolled creation of the C-4 quaternary center of the crinane skeleton by a bis alkylation of a tetrahydroisoquinoline lactam (Figure 1). This strategy appeared to be very attractive considering our previous investigations in this field. Despite a variety of approaches<sup>7</sup> for the total synthesis of crinine type alkaloids, methods relying on this approach have received no attention until now. This observation and the few number of asymmetric processes<sup>7a,7c</sup> reported in this area prompted us to investigate this strategy.

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Starting with functionalized chains supported by the newly created quaternary center, the final step would include :

i) formation of ring C by a nucleophilic attack onto the iminium salt derived from the lactam function.

ii) closure of ring D by a N-alkylation.

The aim of this work was to explore the feasibility of these individual steps.



Figure 1

#### Results and discussion

Following our previous results<sup>2,3</sup>, we designed a chiral, non racemic building block suitable for alkylation at C-4 namely 1,2,3,4-tetrahydroisoquinolin-3-one 1, derived from (R)-(-)-phenylglycinol. Optically pure 1 was obtained from O-tolylacetic acid 2 with a 35% overall yield in three steps (Scheme 1), by a radical bromination of the methyl group, an esterification of the acid function and the condensation with (R)-(-)-phenylglycinol in refluxing methanol.



(a) NBS, CCl<sub>4</sub>, hv. 64% ; (b) H<sub>2</sub>SO<sub>4</sub>, MeOH , 87% ; (c) (R)-(-)-NH<sub>2</sub>CH(Ph)CH<sub>2</sub>OH, Et<sub>3</sub>N , EtOH, 63% ; (d) LDA, Mel, THF, -78 °C, 73%, 92% d.e.

Scheme 1

During this study, we were aware that Levacher and co-workers, inspired by our methodology, prepared the same lactam 1 for the synthesis of a series of simple 4-monoalkylated tetrahydroisoquinolines<sup>4</sup>. For this model reaction, small differences in chemical yields and d.e's. were observed between our results and those of the former group.

Deprotonation-alkylation of 1 were investigated using iodomethane (Table 1, entries 1-5). Under standard conditions, a mixture of mono and dialkylated derivatives **3** and **4** was obtained in a modest to good chemical yield with a d.e. varying from 64 to 92%. The yields refer to characterized material as isolated by flash chromatography. Diastereometric *ratios* were calculated on crude product mixtures from <sup>1</sup>H NMR peak intensities.

Entry	Base (2.5 equiv)	Mel (equiv)	Products ( <i>Ratio</i> )	Compound 3 Yield % (d.e.)
1	s-BuLi	1.5	1(25) + <b>3</b> (50) + <b>4</b> (25)	37 (84)
2	<i>n</i> -BuLi	1.5	<b>1</b> (50) + <b>3</b> (50)	51 (64)
		2.5	<b>3</b> (50) + <b>4</b> (50)	n.d. (64)
3	Lihmds	2.5	<b>3</b> (60) + <b>4</b> (40)	24 (88)
4	LDA	1.5	<b>1</b> (10) + <b>3</b> (90)	73 (92)
		2.5	<b>3</b> (90) + <b>4</b> (10)	n.d. (92)
5	n-BuLi	1.5	<b>1</b> (50) + <b>3</b> (50)	n.d. (69)
	+ HMPA	2.5	3(50) + 4(50)	<u>n.d. (69)</u>

 Table 1 : Diastereoselectivity of the alkylation of 1

With strong alkyllithium bases, such as s-BuLi (2.5 equiv.), the reaction was not complete. Formation of dialkylated product 4 was observed, indicating that the second enolate was formed faster than the first one. This observation was confirmed when an excess of n-BuLi was used.

The best yields and diastereoselectivities were observed with LDA. However, contrary to Levacher's work, the addition of HMPA did improve neither the d.e. nor the chemical yield.

In the piperidine series<sup>8</sup>, we explained the diastereoselectivity of the alkylation step by the formation of a rigid chelated intermediate, resulting from the interaction between the nitrogen lone pair of the amide enolate and lithium that enhances the acidity of the proton  $\alpha$  to the carbonyl. This hypothesis was recently confirmed by Meyers<sup>9</sup> during the alkylation of bicyclic lactams. We assumed our model would apply in this case too. A 4*S* configuration was expected due to the facial differentiation (Figure 2) allowing iodomethane to approach from the less hindered side of the enolate.

Recently, the same configuration was also assigned by Levacher and co-workers who confirmed this hypothesis by means of X-ray analysis of the 4-benzyl derivative<sup>10</sup>.



Figure 2

The ease of formation of the enolate from the monoalkylated amide, prompted us to embark in a second alkylation reaction with functionalized chains which could be cyclized to construct the C or D ring of the crinane skeleton (Figure 1).

The 4-CH<sub>3</sub> lactam **3** was chosen as a substrate for model reactions. For the introduction of the ethano bridge of the D ring, a dielectrophilic reagent was required in order to connect the C-4 anionic center to the nucleophilic N-2 atom. Alkyl bromoacetates which are known as excellent electrophiles were chosen for this purpose (Scheme 2).



(a) *n*-BuLi, HMPA, then BrCH<sub>2</sub>CO<sub>2</sub>R, THF, -78 °C, N<sub>2</sub>, 52 -> 100 %, 43 -> 84 d.e. Scheme 2

When hindered bases (LDA or LiHMDS) were used, starting material was recovered unchanged, whereas s-Buli led to the formation of numerous by-products. Finally, the most efficient base found was n-BuLi. The results are summarized in Table 2.

Entry	Base	Electrophile	Temp.	Products	Yield (%)	d.e.
1	<i>n</i> -BuLi	BrCH2CO2Et	-78 ℃	5a	52	43
2	n-BuLi	BrCH2CO2t-Bu	-78 ℃	5b	70_	67
3	n-BuLi + HMPA	BrCH2CO2t-Bu	-78 ℃	5b	85	84
4	n-BuLi + HMPA	BrCH2CO2t-Bu	-78 ℃->	6	100	84
			0°C			

Table 2 : Study of the bis-alkylation reaction

Yields and d.e. were calculated from <sup>1</sup> H NMR analysis

As with lactam 1 an excess of base was necessary to give efficient deprotonation. However, in most cases, the disubstituted products **5a** and **5b** were accompanied by unreacted starting material **3** (entries 1-3).

A considerable improvement of stereochemical induction was obtained by increasing the ester bulk and by the addition of a complexing additive (entries 3-4), contrary to our previous results.

The best result was obtained when 2.5 equiv. of *n*-BuLi, 5 equivalents of HMPA and a large excess of *t*-butylbromoacetate were used (entry 4). In this experiment, the reaction mixture was allowed to warm to room temperature and stirred for 15 h., leading to C- and O-alkylated compound **6** in quantitative yield, with the same d.e. as in entry 3, indicating that the second alkylation occurred before O-alkylation.

The absolute configuration of the major diastereomer of **6** was expected to be *S*, as depicted in Scheme 3, since it likely was formed in the same way as the first substituent, i.e. *anti* to the N-Li bond. This proposal was eventually confirmed by an X-ray analysis<sup>11</sup> of major diol **7b** obtained by LiAlH4 reduction of **6** (Figure 3).

Indeed the mixture of diastereomeric amide-ester **5b** or **6** was completely reduced to the corresponding amino-alcohols whose major diastereomers **7a** and **7b** could be isolated at this stage (Scheme 3). Removal of the chiral appendage of **7a** or **7b** by hydrogenolysis afforded the enantiomerically pure amino-alcohol **8**. Cyclization of a secondary amine with a primary alcohol is theoretically possible according to various procedures. Thionyl chloride in refluxing dioxane, used in a similar case by Ninomya<sup>7h</sup> led to a complex mixture. Reaction carried out in mild conditions using PPh<sub>3</sub>, CCl<sub>4</sub> and Et<sub>3</sub>N<sup>12</sup> or PPh<sub>3</sub> and DEAD (Mitsunobu reaction<sup>13</sup>) resulted in compound **9** only, according to MS and comparaison of NMR data with those of natural crinine-types alkaloids<sup>14</sup>.

However, despite several efforts to get an analytical sample of 9, the yield of pure product was poor, due to its incomprehensible instability.



ORTEP diagram of compound (-)-7b Figure 3



(a) LAH, THF, Rfx, 52% 2 steps, 84% d.e.; (b) H<sub>2</sub>, Pd-C, MeOH, 54%; (c) PPh<sub>3</sub>, Et<sub>3</sub>N, CCl<sub>4</sub>, CH<sub>3</sub>CN, 15% Scheme 3

In the second part of this work, we turned our attention to the synthesis of the ABC ring system of crinine alkaloids. Once again, 4-methyl derivative 3 was used as the starting material.



The synthesis was to start with the alkylation at C-4 with a chain bearing end-group functionality capable of nucleophilic attack at C-3. For this purpose, we decided to explore the reactivity of the oxazolidine function, which could be obtained by RedAl<sup>®</sup> partial reduction of the lactam-primary alcohol system.

Indeed, it is well known that an oxazolidine is a potential iminium salt which can react with a large variety of nucleophilic reagents on the condition of acid-mediated ring opening<sup>15</sup>. At least, three approaches seemed possible (see Figure 4):

i) The Mannich condensation, allowing further transformations towards the substitution of natural products.

ii) The Overman cyclization of a vinylsilane, also offering the possibility of introducing functionalities on the C ring.

iii) An intramolecular Grignard reaction which, however, is not suitable for the formation of a functionalized C ring.

The first two approaches proved to be impossible to use. Indeed, we encountered problems to prepare the (Z)-(4-bromo-1-butenyl)-trimethylsilane<sup>16</sup>, a volatile compound, which appeared difficult to handle. Furthermore, alkylation with (Z)-(4-bromo-1-butenyl)-trimethylsilane or 2-( $\beta$ -bromoethyl)-2-methyl-1,3-dioxolane, resulted only in isolation of 4-hydroxy-4-methyl derivative 10 (15% yield ; 70% d.e.). Bubbling argon in THF before use

prevented the formation of the hydroxy-compound which was most likely obtained from the action of oxygen via a transient peroxyde. The alkylation reactions were, however, always unsuccesful despite halogen exchange with Nal/ CH<sub>3</sub>CN, due to the unstability of the reagents. Unfortunately, we found it to be impossible to get the above-mentioned hydroxylation reaction under control by deliberately using O<sub>2</sub>.

Partial reduction of diastereomeric tertiary alcohol 10, allowed the isolation of 11 as a single isomer after purification. NOESY experiments led to the assignement of the relative stereochemistry, as depicted in formula 11, in agreement with previous alkylation reactions (Scheme 4).



Scheme 4

The third route to be investigated was the intramolecular Grignard reaction. Alkylation of the anion derived from **3**, using 1-chloro-4-iodo-butane, gave the expected chloro derivative **12** (65% yield; 86% d.e.; unseparable diastereomers) without any problem (Scheme 5).



(a) *n*-BuLi, HMPA, I(CH<sub>2</sub>)<sub>4</sub>Cl, THF, -78 °C, 65%, 86% d. e. ; (b) RedAl°, THF, -50 °C, 61% (c) NaI, CH<sub>3</sub>CN, 90% ; (d) *t*-BuLi, THF, -78 °C, 10%.

Scheme 5

The diastereomeric mixture was reduced with RedAl<sup>®</sup>, leading, after purification, to a single oxazolidine 13 (Y = 61%). NOESY experiments showed correlations between H-1 H-3 and H $\beta$ , indicating an equatorial configuration for the oxazolidine oxygen atom. Moreover, correlations between CH3 and H-5 confirmed the equatorial position of the methyl group (Figure 5).



Whatever the experimental conditions were, it was impossible to make the corresponding Grignard reagents from 13 or its iodo analogue, obtained after halogen exchange. In most experiments, the starting material was recovered unchanged.

This failure forced us to look for an alternative route for this deceptively reaction. We therefore turned towards the intramolecular alkylithium addition to the lactams which was used by Jones<sup>17</sup> and also Meyers<sup>18</sup> in a case similar to ours. Compound **12b** was submitted to an iodide-metal exchange with t-BuLi in THF at -78 °C. The cyclized oxazolidine **14** was obtained in poor yield which proved impossible to improve despite addition of KH, as suggested by Meyers.

All attemps to accomplish oxazolidine opening (NaBH4, Pd(OH)<sub>2</sub>, Na/NH<sub>3</sub>) resulted in recovery of the starting material which was too stable to be reduced.

#### Conclusion :

During this work we were successful in the diastereoselective mono- and di-alkylations of tetrahydroisoquinoline at the C-4 position,  $\alpha$  to lactam functionality. Although difficulties emerged in applying this methodology to the synthesis of the crinine alkaloid skeleton, it is a new way to prepare chiral non racemic tetrahydroisoquinolines, otherwise not easily accessible.

#### **Experimental** section

#### General

Melting points were determined on a Kofler apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C spectra were recorded at 300.13 and 75.43 MHz respectively on a Bruker AC 300-P instrument. Chemical shifts are given in ppm with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer FTIR 1600 spectrometer as solutions in either, dichloromethane or chloroform. Optical

rotations were obtained using a Perkin-Elmer 141 polarimeter and  $[\alpha]_D$  values are expressed in units  $10^{-1}$ deg cm<sup>2</sup> g<sup>-1</sup>. Chemical ionisation mass spectra (CI.MS) were recorded on a Nermag R10-10 instrument at 30 eV using ammonia as the ionizing gas. High resolution mass spectra were recorded on a Kratos MS-80 instrument operating in chemical ionization mode at 70 eV using methane as the ionizing gas. Elementary analyses were performed by "Service de microanalyse, Institut de Chimie des Substances Naturelles du CNRS, Gif sur Yvette, France". Analytical TLC was performed on silica gel or an aluminiumoxyde F-254 plates of 0.2 mm thickness. Flash chromatography was carried out on 230-400 mesh silica gel or on 70-230 mesh aluminiumoxyd.e. Tetrahydrofuran was distilled prior to use from sodium-benzophenone ketyl. Triethylamine and ether were distilled from calcium hydride prior to use.

#### (aR)-N-[2-Hydroxy-1-phenylethyl]-1,4 dihydro-2H-isoquinolin-3-one (1)

Tolyl-acetic acid 2 (25 g, 170 mmol), *N*-bromosuccinimide (29.6 g, 170 mmol) and a catalytic amount of benzoyl peroxyde were refluxed in CCl4 (400 mL) for 1h., under a 1000 watt-lamp. The crude mixture was filtered on a pad of MgSO4 and the organic layer was concentrated *in vacuo*. The resulting yellow solid was recrystallized 4 times in CCl4 to give 25 g (64% yield) of a white crystallized solid. <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 3.85 (s, 2H), 4.58 (s, 2H), 7.28 (m, 4H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 31.7 (CH<sub>2</sub>), 38.1 (CH<sub>2</sub>), 128.3-131.5 (4 CH), 132.8 (C), 136.5 (C), 176.7 (C). IR : 1718 cm<sup>-1</sup>

Tolyl-bromide-acetic acid (1.46 g, 6.37 mmol) and concentrated sulfuric-acid (160  $\mu$ L) were dissolved in MeOH (10 mL) and stirred at room temperature for 3h.. The reaction mixture was treated with sat. aq. NH<sub>4</sub>Cl (5 mL). The aq. layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated to give 1.35 g (87% yield) of a yellow oil which was taken on without further purification.<sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 3.71 (s, 3H), 3.83 (s, 2H), 4.60 (s, 2H), 7.32 (m, 4H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 31.7 (CH<sub>3</sub>), 38.1 (CH<sub>2</sub>), 52.2 (CH<sub>2</sub>), 128.0-131.2 (4 CH), 133.3 (C), 136.3 (C), 176.4 (C). IR : 1734 cm<sup>-1</sup> Phenylglycinol (0.836 g, 6.09 mmol) and NEt<sub>3</sub> (0.850 mL, 6.09 mmol) were dissolved in EtOH (6

The benzyl-bromide-methyl ester (1.35 g, 5.54 mmol), dissolved in EtOH (1 mL), was added. After refluxing for 48h. (TLC showed completed reaction) and cooling to RT., the reaction mixture was treated with sat. aq. NH4Cl (10 mL). The aq. layer was extracted three times with ethyl acetate (50 mL) and the combined organic layers were dried over MgSO4. Removal of the solvent and purification of the residue by flash chromatography on silica gel (eluent : CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9.8/0.2) gave 0.925 g (63% yield) of the chiral 1,4-dihydroisoquinolin-3-one 3 as a yellow solid, mp 120°C (CH<sub>2</sub>Cl<sub>2</sub>-MeOH). [ $\alpha$ ]D<sup>25</sup> = -47(c = 1.05, MeOH). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 3.64 (s, 2H), 4.09 (dd, 1H, J = 8.9, 11.7), 4.11 (d, 1H, J = 15.5), 4.22 (dd, 1H, J = 5.3, 11.7), 4.45 (d, 1H, J = 15.5), 5.95 (dd, 1H, J = 3.0 and 8.9), 7.14 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 38.2 (CH<sub>2</sub>), 46.4 (CH<sub>2</sub>), 57.9 (CH), 61.4 (CH<sub>2</sub>), 125.1-128.7 (9 CH), 131.9 (C), 132.6 (C), 136;7 (C), 170.9 (C). IR : 3421, 3053, 1654 cm<sup>-1</sup>. *m/z* (CLMS) 268 [MH]<sup>+</sup>. Anal. Calcd. for C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub>: C 76.37, H 6.41, N 5.24; Found: C 76.26, H 6.64, N 5.09.

mL).

# ( $\alpha R, 4S$ )-N-[2-Hydroxy-1-phenylethyl]-4-methyl-1,4 dihydro-2H-isoquinolin-3-one (3)

A solution of 1,2,3,4-tetrahydroisoquinolin-3-one 1 (1.00 g, 3.74 mmol) in dry THF (10 mL) cooled to -78 °C was added, under nitrogen, to a solution of LDA (9.35 mmol) in dry THF (100 mL). The reaction mixture was stirred for 1h. at -78 °C, after which time, methyl iodide (350  $\mu$ L, 5.61 mmol) was added at -78 °C and the mixture was stirred for 2h. at the same temperature before being quenched with sat. aq. NH<sub>4</sub>Cl (50 mL). The aq. layer was extracted three times with ethyl acetate (50 mL) and the combinated organic layers were dried over MgSO<sub>4</sub>. Removal of the solvent and purification of the residue by flash chromatography on silica gel (eluent : ethyl acetate/cyclohexane 5.0/5.0) gave 0.77 g (73% yield) of **5** as a yellow crystallized solid. Diastereomeric excess = 92%. [ $\alpha$ ]D<sup>25</sup>=-23.5 (c = 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR data for the major diastereomer ( $\delta$ , ppm, J, Hz): (CDCl<sub>3</sub>) : 1.51 (d, 3H, J = 7.0), 3.61 (q, 1H, J = 7.0), 4.12 (d, 1H, J = 15.5), 4.18 (m, 2H), 4.30 (d, 1H, J = 15.5), 5.85 (dd, 1H, J = 5.0, 9.0), 6.92 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 1.61 (CH<sub>3</sub>), 41.9 (CH), 46.5 (CH<sub>2</sub>), 58.9 (CH), 62.1 (CH<sub>2</sub>), 125.2-128.9 (9 CH), 132.0 (C), 136.7 (C), 137.7 (C), 174.2 (C). IR : 3421, 1638 cm<sup>-1</sup>. *m/z* (CI.MS) 282 [MH]<sup>+</sup>. *Anal.* Calcd. for C<sub>18</sub>H<sub>19</sub>NO<sub>2</sub>: C 76.84, H 6.81, N 4.98; Found: C 76.51, H 7.03, N 4.92.

### $(\alpha R, 4S)$ -[N-(2-Hydroxy-1-phenylethyl)-4-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]-acetic acid ethyl ester (5a)

To a solution of 3 (0.175 g, 0.62 mmol) in dry THF (10 mL) cooled to -78 °C, was added, under nitrogen, n-BuLi (0.97 mL, 1.56 mmol). The red suspension was stirred for 30 min. at -78 °C and then, ethyl-bromo-acetate (104  $\mu$ L, 0.93 mmol) was added dropwise (turns pale yellow). The mixture was stirred for 4h, at the same temperature before being diluted with ethyl acetate (100)mL) and poured into sat. aq. NH4Cl(10 mL). The aq. layer was extracted three times with ethyl acetate (5 mL) and the combinated organic layers were dried over MgSO4 and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent :  $CH_2Cl_2$ /MeOH 95/5) to give a mixture of diastereomers (0.119 g, 52% yield, d.e. = 43%), which could be separated further. IR : 2985, 1684 cm<sup>-1</sup>.m/z (Cl.MS) 378 [MH]<sup>+</sup>. Data for the minor diastereoisomer :  $[\alpha]_D^{25}$ =-31 (c = 0.9, MeOH). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.04 (t, 3H, J = 7.1), 1.56 (s, 3H), 2.93 (d, 1H, J = 16.2), 3.16 (br s, 1H), 3.55 (d, 1H, J = 16.2), 3.94 (m, 2H), 4.08 (d, 1H, J = 16.2), 3.94 (m, 2H), 4.08 (d, 1H, J = 16.2), 3.94 (m, 2H), 4.08 (d, 1H, J = 16.2), 3.94 (m, 2H), 4.08 (d, 1H, J = 16.2), 3.94 (m, 2H), 4.08 (d, 1H, J = 16.2), 3.94 (m, 2H), 4.08 (d, 1H, J = 16.2), 3.94 (m, 2H), 4.08 (d, 16.2), 4.28 (m, 2H), 4.77 (d, 1H, J = 16.2), 6.25 (dd, 1H, J = 4.7, 9.2), 7.33 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>): 14.1 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>), 44.8 (CH<sub>2</sub>), 45.3 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 60.8 (CH<sub>1</sub>), 61.1 (CH<sub>2</sub>), 125.0-128.9 (9 CH), 129.9 (C), 136.8 (C), 171.8 (C), 174.1 (C). Data for the major diastereomer :  $[\alpha]_D^{25}$ =-56 (c = 1.2, MeOH). <sup>1</sup>H NMR (δ, ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.01 (t, 3H, J = 7.1), 1.47 (s, 3H), 2.98 (d, 1H, J = 16.7), 3.16 (br s, 1H), 3.59 (d, 1H, J = 16.7), 3.93 (m, 2H), 4.30 (d, 1H, J = 15.9), 4.31 (m, 2H), 4.58 (d, 1H, J = 15.9), 5,72 (dd, 1H, J = 5.0, 9.5), 7.32 (m, 9H).  $^{13}$ C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 14.1 (CH<sub>3</sub>), 29.3 (CH<sub>3</sub>), 43.0 (CH<sub>2</sub>), 44.6 (C), 47.4 (CH<sub>2</sub>), 60.5 (CH<sub>2</sub>), 61.0 (CH), 65.7 (CH<sub>2</sub>), 124.2-138.9 (9 CH), 136.8 (C), 138.9 (C), 171.2 (C), 174.6 (C). HRMS Calcd. for C<sub>22</sub>H<sub>25</sub>NO4 : MH<sup>+</sup>, 368.1862 found : 368.1869.

### $(\alpha R, 4S)$ -[N-(2-Hydroxy-1-phenylethyl)-4-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]-acetic acid ter-butyl ester (5b)

To a solution of 3 (0.697 g, 2.48 mmol) in dry THF (30 mL) cooled to -78 °C, was added, under nitrogen, n-BuLi (3.9 mL, 6.2 mmol) and HMPA (2.2 mL, 12.4 mmol). The red suspension was stirred for 30 min. at -78 °C and then, t-butyl-bromo-acetate (601 µL, 3.7 mmol) was added dropwise (turns pale yellow). The mixture was stirred for 4h at the same temperature before being diluted with ethyl acetate(100 mL) and poured into sat. aq. NH4Cl(100 mL). The aq. layer was extracted three times with ethyl acetate (50 mL) and the combined organic layers were dried over MgSO4 and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent : ethyl acetate) to remove HMPA. The resulting crude oil (0.997 g) consisting of more than 90% of the desired product, was taken on without further purification. Further analyses have been pursued on the pure major diastereomer isolated as an analytical sample by preparative TLC.  $[\alpha]_D^{25}$ =-55 (c = 1.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.19 (s, 9H), 1.47 (s, 3H), 2.84 (d, 1H, J = 16.0), 3.23 (br s, 1H), 3.45 (d, 1H, J = 16.0), 4.16 (m, 1H), 4.36(d, 1H, J = 15.9), 4.45 (m, 1H), 4.57 (d, 1H, J = 15.9), 5.43 (dd, 1H, J = 4.8, 9.6), 6.92 (m, 9H). <sup>13</sup>C-NMR (\delta, ppm) : ( CDCl<sub>3</sub>) : 14.1 (CH<sub>3</sub>), 28.8 (3 CH<sub>3</sub>), 38.7 (C), 48.1 (CH<sub>2</sub>), 69.4 (CH), 69.9 (CH<sub>2</sub>), 73.2 (CH<sub>2</sub>), 89.2 (C), 125.6-129.4 (9 CH), 133.7 (C), 135.7 (C), 139.0(C), 200.0 (C), 201.3 (C). IR : 3421, 1638 cm<sup>-1</sup>. m/z (CI.MS) 396 [MH]+.

## $(\alpha R, 4S)$ -[2-(4-tert-Butoxycarbonylmethyl-4-methyl-3-oxo-3,4-dihydro-1Hisoquinolin-2-yl)-2-phenyl-ethoxy]-acetic acid tert-butyl ester (6)

Compound **3** was alkylated according to the procedure described for the synthesis of **6a**, exept that the reaction mixture was stirred at -78 °C for 3h. and let at room temperature for 15h. after the addition of an excess of electrophile. <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.21 (s, 3H), 1.48 (s, 9H), 2.89 (d, 1H, J = 16.0), 3.57 (d, 1H, J = 16.0), 4.02 (d, 1H, J = 16.0), 4.21 (m, 6H), 4.62 (d, 2H, J = 16.0), 6.24 (m, 1H), 7.22 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 14.1 (CH<sub>3</sub>), 27.3 (6 CH<sub>3</sub>), 43.3 (CH<sub>2</sub>), 44.5 (C), 45.2 (CH<sub>2</sub>), 54.3 (CH), 68.5 (CH<sub>2</sub>), 69.6 (CH<sub>2</sub>), 79.9 (C), 81.4 (C), 124.1-128.0 (9 CH), 128.4 (C), 130.1 (C), 136.6 (C), 169.3 (C), 169.9 (C), 173.2 (C).

## ( $\alpha R, 4S$ )-N-[4-(2-Hydroxyethyl)-4-methyl-3,4-dihydro-1H-isoquinolin-2-yl]-2phenyl-ethanol (7a)

To a solution of lactam **5b** (0.997 g, 2.52 mmol) in dry THF (60 mL), LAH (0.904 g, 41.98 mmol) was added in small portions at 0 °C. The mixture was refluxing for 3h. and treated with H<sub>2</sub>O (904  $\mu$ L), 1N NaOH (904  $\mu$ L) and H<sub>2</sub>O (2.7 mL). The resulting aluminium salts were filtered off and washed with Et<sub>2</sub>O (3x50 mL). The organic layer was concentrated *in vacuo*. The crude yellow oil was purified by flash chromatography on aluminia gel (eluent : ethyl acetate/cyclohexane 80/20). The two diastereomers could be separated, to give 0.366 g of the major diastereomer and 0.032 g of the minor one (52% overall yield, 2 steps, d.e. = 84%). Data for the major diastereomer [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -25 (c = 0,95, CHCl<sub>3</sub>). <sup>1</sup>H NMR ( $\delta$ , ppm, J, H<sub>2</sub>) : (CDCl<sub>3</sub>) : 1.21 (s, 3H), 1.85 (m, 2H), 2.08 (d, 1H, J = 11.5), 2.89 (d, 1H, J = 11.5), 2.96 (m, 1H), 3.40 (dt, 1H, J = 4.0, 8.0), 3.61 (d, 1H, J = 14.5), 3.84 (m, 2H), 3.97 (d, 1H, J = 14.5), 4.26 (m, 1H), 6.92 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 29.2 (CH<sub>3</sub>), 38.7 (C), 47.7 (CH<sub>2</sub>),

55.1 (CH<sub>2</sub>), 58.5 (CH<sub>2</sub>), 59.2 (CH<sub>2</sub>), 62.2 (CH<sub>2</sub>), 71.3 (CH), 126.2-129.4 (9 CH), 133.8 (C), 135.4 (C), 139.4 (C). IR : 3372, 3062 cm<sup>-1</sup>. m/z (CI.MS) 312 [MH]<sup>+.</sup> HRMS Calcd. for C<sub>20</sub>H<sub>25</sub>NO<sub>2</sub> : MH<sup>+</sup>, 312.1963 found : 312.1956.

# $(\alpha R, 4S)$ -2-{2-[2-(2-Hydroxy-ethoxy)-1-phenylethyl]-4-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl}-ethanol (7b)

Compound **7b** was obtained by the reduction of **6** as for the preparation of **7a** (57% overall yield, 2 steps, d.e. = 84%). Data for the major diastereomer  $[\alpha]_D^{25} = -5$  (c = 0.95, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR (& ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.24 (s, 3H), 1.83 (m, 2H), 2.11(d, 1H, J = 11.6 Hz), 2.76 (m, 2H), 2.84 (d, 1H, J = 11.6), 3.35 (dt, 1H, J = 3.4, 12.0), 3;52 (m, 1H), 3.55 (m, 1H), 3.60 (d, 1H, J = 14.7), 3.71 (t, 1H, J = 3.5), 3.78 (m, 1H), 3.81 (m, 1H), 3.99 (dd, 1H, J = 6.7, 9.5), 4.09 (d, 1H, J = 14.7), 7.21 (m, 9H). <sup>13</sup>C-NMR (& ppm) : (CDCl<sub>3</sub>) : 28.8 (CH<sub>3</sub>), 38.7 (C), 48.1 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 57.7 (CH<sub>2</sub>), 58.6 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 69.4 (CH), 69.8 (CH<sub>2</sub>), 73.2 (CH<sub>2</sub>), 125.7-129.4 (9 CH), 133.7 (C), 135.7 (C), 138.9 (C). IR : 1640 cm<sup>-1</sup>.m/z (CLMS) 356 [MH]<sup>+</sup>· Anal. Calcd. for C<sub>22</sub>H<sub>29</sub>NO<sub>3</sub> + 0.25 MeOH : C 73.52, H 8.32, N 3.85; Found: C 73.71, H 8.21, N 3.72.

#### (45)-2-(4-Methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-ethanol (8)

Catalytic hydrogenation of the major diastereomer of the amino-diol **7a** or **7b** (0.185 g, 0.59 mmol) was carried out with 10% Pd-C in MeOH (2 mL), for 24h., under atmospheric pression of hydrogen. The catalyst was removed by filtration on a pad of celite and the filtrate was evaporated to give a crude oil which was purified by flash chromatography on silica gel (eluent : ethyl acetate/MeOH 80/20) to give the desired product as a single enantiomer (0.061 g, 54% yield).  $[\alpha]_D^{25} = +3$  (c = 0.9, CHCl<sub>3</sub>). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.32 (s, 3H), 1.86 (m, 2H), 2.84 (d, 1H, J = 11.7), 2.95 (dt, 1H, J = 6.5, 12,1), 3.10 (d, 1H, J = 11.7), 3.40 (dt, 1H, J = 3.6, 12.1), 4.05 (s, 2H), 6.92 (m, 4H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 29.1 (CH<sub>3</sub>), 37.9 (C), 48.5(CH<sub>2</sub>), 48.6 (CH<sub>2</sub>), 56.1 (CH<sub>2</sub>), 58.10 (CH<sub>2</sub>), 125.7-128.6 (4 CH), 133.8 (C), 134.1 (C), 139.9 (C). IR : 3253, 2920 cm<sup>-1</sup>. *m/z* (CI.MS) 192 [MH]<sup>+</sup>· HRMS Calcd. for C<sub>12</sub>H<sub>17</sub>NO : MH<sup>+</sup>, 192.1388 found : 192.1395.

#### (95)-9-Methyl-3,9-methano-1,2-dihydro-4H-benzo-[c]-azepine (9)

The amino-alcohol **10** (0.115 g, 0.60 mmol), Et<sub>3</sub>N (84 µL, 0.60 mmol) and CCl4 (70 µL, 0.72 mmol) were dissolved in acetonitrile (2 mL) at RT. PPh<sub>3</sub> (0.173 g, 0.66 mmol) was added at 0 °C in small portions. The reaction mixture was stirred for 60h at RT. under nitrogen before being poured into sat. aq. Na<sub>2</sub>CO<sub>3</sub> (15 mL). The aq. layer was extracted 3 times with Et<sub>2</sub>O. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. After removal of POPh<sub>3</sub> by selective recristallization in Et<sub>2</sub>O, the crude oil was purified by flash chromatography on silica gel (eluent : ethyl acetate) to give the desired product which, because of its instability, was stored as its chlorhydrate (0.019 g, 15% yield). Further analyses have been pursued on the pure amine.  $[\alpha]_D^{25} = -13$  (c = 0.95, CHCl<sub>3</sub>). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.56 (s, 3H), 1.81 (m, 1H), 1.99 (m, 1H), 2.73 (d, 1H, J = 11.2), 2.87 (m, 1H), 3.01 (d, 1H, J = 11.2), 3.32 (ddd, 1H, J = 3.5, 10.9, 16.1), 3.83 (d, 1H, J = 17.2), 4.42 (d, 1H, J = 17.2), 7.02 (m, 4H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 19.3 (CH<sub>3</sub>), 29.5 (C),

45.0(CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 63.7 (CH<sub>2</sub>), 122.5-131.9 (4 CH), 144.3(2 C). IR : 2956 cm<sup>-1</sup>. *m*/*z* (CI.MS) 173 [MH]+·

## ( $\alpha R$ ,4R)-4-Hydroxy-N-(2-hydroxy-1-phenylethyl)-4-methyl-1,4dihydro-2Hisoquinolin-3-one (10)

The lactam 3 (0.217 g, 0.77 mmol), LDA (1.5 mL, 1.93 mmol) and HMPA (670  $\mu$ L, 3.86 mmol) were reacted at - 78 °C, under argon in 10 mL of dry THF. After the addition of 4-bromo-1-(trimethyl)-silyl-1-butene (0.273 g, 1.32 mmol), the reaction mixture was stirred for 6h. at -78 °C, and then at RT. for the following night. After classical workup, the residue was purified by flash chromatography on silica gel (eluent : cyclohexane) to give 34 mg of 10 as an inseparable mixture of isomers and 40 mg of 5 (15% yield, d.e. = 70%). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>)  $\delta$  1.21 (s, 3H), 2.67 (d, OH, J = 9.5), 4.08 (d, 1H, J = 16.2), 4.16 (m, 2H), 4.24 (d, 1H, J = 16.2), 4.72 (t, 1H, J = 5.5), 7.25 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 27.6 (CH<sub>3</sub>), 46.4 (CH<sub>2</sub>), 59.8 (CH), 61.3 (CH<sub>2</sub>), 71.1 (C), 12.2-128.9 (9 CH), 135.8 (C), 139.2 (C), 175.0 (C). IR : , 3447 (large), 1648 cm<sup>-1</sup>.m/z (CI.MS) 298 [MH]<sup>+</sup>. HRMS Calcd. for C<sub>18</sub>H<sub>19</sub>NO<sub>3</sub> : MH<sup>+</sup>, 297.1365 found : 297.1366.

## (10R)-10-Hydroxy-10-methyl-3-phenyl-2,3-dihydro-5H-oxazolo-[2,3-a]-isoquinoline (11)

Compound 11 was obtained by the reduction of 10 as for the preparation of 13.  $[\alpha]_D^{25} = -184$  (c = 1.05, CHCl<sub>3</sub>). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.76 (s, 3H), 3.16 (s, OH), 3.56 (d, 1H, J = 14.7), 3.90 (dd, 2H, J = 2.9, 12.1 Hz), 4.01 (d, 1H, J = 14.7), 4.22 (s, 1H), 4.42 (t, 1H, J = 12.1), 7.37 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 21.1 (CH<sub>3</sub>), 52.2 (CH<sub>2</sub>), 68.0 (CH), 69.5 (C), 74.3 (CH<sub>2</sub>), 97.4 (CH), 126.4-128.8 (9 CH), 132.9 (C), 139.4 (C). IR : 3587, 2934, 2253 cm<sup>-1</sup>. *m*/*z* (CI.MS) 282 [MH]<sup>+</sup>. *Anal*. Calcd. for C<sub>18</sub>H<sub>19</sub>NO<sub>2</sub>, 0.25 MeOH : C 75.75, H 6.97, N 4.84; Found: C 75.81, H 6.97, N 4.98. HRMS Calcd. for C<sub>18</sub>H<sub>19</sub>NO<sub>2</sub> : MH<sup>+</sup>, 281.1416 found : 281.1412.

## ( $\alpha R$ ,4S)-4-(4-Chlorobutyl)-N-(2-hydroxy-1-phenylethyl)-4-methyl-1,4-dihydro-2H-isoquinolin-3-one (12a)

The lactam **3** (0.624 g, 2.22 mmol), *n*-BuLi (4.3 mL, 5.55 mmol) and HMPA (1,9 mL, 11.1 mmol) were reacted at - 78 °C, under nitrogen in 30 mL of dry THF, as for the preparation of **8**. After the addition of 1-iodo-4-chloro-butane (410  $\mu$ L, 3.33 mmol), the reaction mixture was stirred for 6h. at -78 °C, and then at RT. for the following night. After usual treatments, the residue was purified by flash chromatography on silica gel (eluent : ethyl acetate/cyclohexane 3.0/7.0) to give 0.532 g (65% yield) of **12a** as an inseparable mixture of isomers (d.e. = 86%). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.51 (s, 3H), 1.71 (m, 5H), 2.09 (m, 1H), 3.40 (t, 2H, J = 6.7), 4.14 (d, 1H, J = 16.0), 4.22 (m, 2H), 4.43 (d, 1H, J = 16.0), 6.01 (dd, 1H, J = 3.4, 5.4), 6.95 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 22.6 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 32.6 (CH<sub>2</sub>), 38.9 (CH<sub>2</sub>), 44.6 (CH<sub>2</sub>), 45.5 (CH<sub>2</sub>), 46.4 (C), 58.3 (CH), 61.2 (CH<sub>2</sub>), 125.1-130.3 (9 CH), 136.6 (C), 138.8 (C), 174.8 (C). IR : 3418, 3053, 1640 cm<sup>-1</sup>. *m/z* (CLMS) 370. 372 [MH]<sup>+</sup>. HRMS Calcd. for C<sub>22</sub>H<sub>26</sub>NO<sub>2</sub>Cl : MH<sup>+</sup>, 371.1652 found : 371.1649.

### (10S)-10-(4-Chlorobutyl)-10-methyl-3-phenyl-2,3-dihydro-5H-oxazolo-[2,3-a]isoquinoline (13)

To a solution of **12a** (0.116 g, 0.319 mmol), in dry THF (20 mL), a 65% solution of Red-Al<sup>®</sup>(1 mL, 3.11 mmol) was added dropwise, at -50 °C, under nitrogen. The reaction mixture was stirred at -50 °C for 3h. and treated by 1N KOH (3 mL). The aq. layer was extracted three times with ethyl acetate (15 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent : ethyl acetate/cyclohexane 2.0/8.0), to give a pale yellow oil (0.067 g, 61% yield).  $[\alpha]D^{25}$ =-71.0 (c = 1.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz): (CDCl<sub>3</sub>) : 1.46 (s, 3H,), 1.78 (m, 4H), 1.92 (m, 2H), 3.45 (d, 1H, J = 14.4), 3.49 (t, 2H, J = 6.9), 3.71 (m, 2H), 3.89 (d, 1H, J = 14.4), 4.24 (s, 1H), 4.31 (t, 1H, J = 11.9), 6.94-7.48 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (75 MHz) : 21.8 (CH<sub>3</sub>), 24.9 (CH<sub>2</sub>), 33.5(CH<sub>2</sub>), 36.8 (CH<sub>2</sub>), 42.8 (C), 44.8 (CH<sub>2</sub>), 52.5 (CH<sub>2</sub>), 68.0 (CH), 74.3 (CH<sub>2</sub>), 125.7-128.6 (9 CH), 133.9 (C), 138.2 (C), 141.9 (C). IR : 3372, 3062 cm<sup>-1</sup>.m/z (Cl.MS) 356, 358 [MH]<sup>+</sup>. HRMS Calcd. for C<sub>22</sub>H<sub>26</sub>NOCl : MH<sup>+</sup>, 355.1702 found : 355.1703.

# (7R, 13bS)-13b-Methyl-7-phenyl-1,2,3,4,6,7,9,13b-octahydro-oxazolo-[2,3-e]-phenantridine (14)

To a solution of **12b** (0.260 g, 0.56 mmol) in a dry mixture of pentane/ether (9 : 1) under nitrogen, at -78 °C, *t*-BuLi (1.7 mL, 2.24 mmol) was added dropwise. The dark red solution was stirred at the same temperature for 1/2 h.. After usual treatment, the residue was purified by flash chromatography on aluminiumoxyde (eluent : cyclohexane) to give 0.017 g (10% yield) of yellow pale oil.  $[\alpha]D^{25} = -6$  (c = 1.0, CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR ( $\delta$ , ppm, J, Hz) : (CDCl<sub>3</sub>) : 1.25 (s, 3H), 1.51 (m, 7H), 1.83 (td, 1H, J = 3.6, 13.8), 2.34 (m, 2H), 3.69 (t, 1H, J = 7.8), 3.70 (d, 1H, J = 15.2), 3.86 (d, 1H, J = 15.2), 4.10 (t, 1H, J = 7.8), 4;35 (m, 1H), 7.17 (m, 9H). <sup>13</sup>C-NMR ( $\delta$ , ppm) : (CDCl<sub>3</sub>) : 22.0 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>), 23.8 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>), 44.1 (C), 48.3 (CH<sub>2</sub>), 63.2 (CH), 74.0 (CH<sub>2</sub>), 95.1 (C), 125.3-128.6 (9 CH), 134.0 (C), 139.8 (C), 143.2 (C). IR : 1150 cm<sup>-1</sup>. *m/z* (Cl.MS) 320 [MH]<sup>+</sup>.

#### **References and Notes**

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- X-ray structure determination of 7b,  $C_{22}H_{29}NO_3$ , M= 355 g. A suitable crystal of size 11. 0.35x0.25x0.15 mm<sup>3</sup> was investigated on a Synthex P2<sub>1</sub> diffractometer (Mo K $\alpha$  radiation = 0.71069 Å, graphite monochromator). Cell dimensions were determined by a least squares fit to the setting angles of 19 reflections with  $4.25^{\circ} < 2\theta < 18.00^{\circ}$ ; orthorhombic, space group  $P2_{1}2_{1}2_{1}$ , Z = 4, a = 9.210 (3), b = 10.922 (3), c = 19.785(4) Å, V= 1990.2 (5) Å<sup>3</sup>, d<sub>x</sub>= 1.19 g.cm<sup>-3</sup>, d<sub>m</sub> = 1.20 g.cm<sup>-3</sup>,  $\mu$  = 0.08 mm<sup>-1</sup>. 3500 reflections up to 20 = 55° of which 1481 with Fo>4 $\sigma$ (Fo) were kept in refinement calculations. The structure was solved by direct methods using SHELXS86 and refined with SHELX93. Non hydrogen atoms were refined with anisotropic temperature factors; hydrogen atoms were located in difference Fourier map at observed positions. Convergence was reached at R = 0.061. The residual electron density in the final Fourier map shows no features up to 0.10 e.A<sup>-3</sup> and down to -0.11 e.A<sup>-3</sup>. Lists of the fractionnal atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U. K., as supplementary material. - Sheldrick, G.M. (1986). SHELXS86. Program for crystal structure determination. Univ. of Göttingen, Germany.

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