A NOVEL ROUTE TO CHIRAL NON RACEMIC 2-SUBSTITUTED 1,2,3,4-TETRAHYDROQUINOLINES

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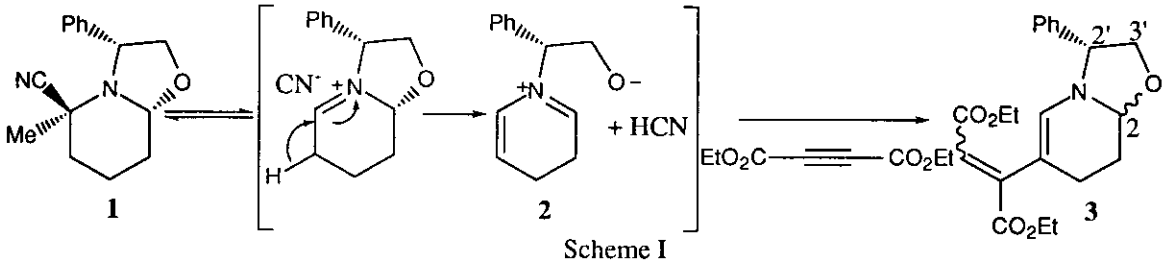
Abstract - The chiral non racemic α–cyanopiperidine (**1**) and its α–methyl derivative (**4**) react with activated alkynes. Depending on the reaction conditions, Michael adducts are obtained. Moreover, synthon (**4**) gives access to the 1,2,3,4-tetrahydroquinoline framework in one step. The substitution pattern on the aromatic ring depends on the alkyne. This constitutes a new and short synthetic method of chiral non racemic 1,2,3,4-tetrahydroquinolines.

Cyclic enamines are useful intermediates in the synthesis of numerous heterocycles.[1] The construction of piperidine, indolizidine, quinolizidine or quinolone natural products is an important target due to the potential biological activities of these compounds.

Recently, we have shown that compounds of type (**1**) react as simple enamines towards activated alkynes when heated in DMSO.[2] This reactivity prompted us to use these derivatives in Michael addition reactions. The mechanism of addition of activated alkynes to enamines has been previously examined.[3] In polar protic solvents and at low temperature the Michael addition is favoured while in polar aprotic solvents the thermal [2+2] cycloaddition is preferred.[3,4] Indeed, synthon (**1**),[5] a non racemic chiral synthetic equivalent of 1,4-dihydropyridine, when reacted with DEAD (diethyl acetylenedicarboxylate) in polar protic medium (absolute EtOH/Al_2O_3 or CH_3COOH) provided a mixture of diastereomers resulting from the Michael addition of the intermediate (**2**) and equilibrium through oxazolidine opening (Scheme I). The major derivative (**3**) could be isolated after purification in 23% yield (based on recovered starting material). Its structure was deduced on the basis of spectroscopic data. In particular, two singlets at 4.54 and 7.95 ppm in the ^{1}H-NMR spectrum and the corresponding carbon resonances at 89.3 and 133.4 ppm in the ^{13}C-NMR spectrum were diagnostic of the dienamine function. Although the *E* configuration seemed more favorable the double bond geometry could not be determined. It was not possible to ascertain the configuration of the oxazolidine-piperidine junction by NMR-spectroscopy since the H-2/H-3 *J* values are almost identical in both C-2 isomers. An attempt using NOE difference NMR-spectrometry[6] was not conclusive. It must be noticed that no racemization has been obseved at the benzylic chiral center all along the use of phenylglycinol as chiral auxiliary in the laboratory.[7] For this reason a 2' *R* absolute configuration

has been assigned for compound (3) and all new derivatives described in this paper. It was thus interesting to take advantage of this reactivity for a double Michael addition.



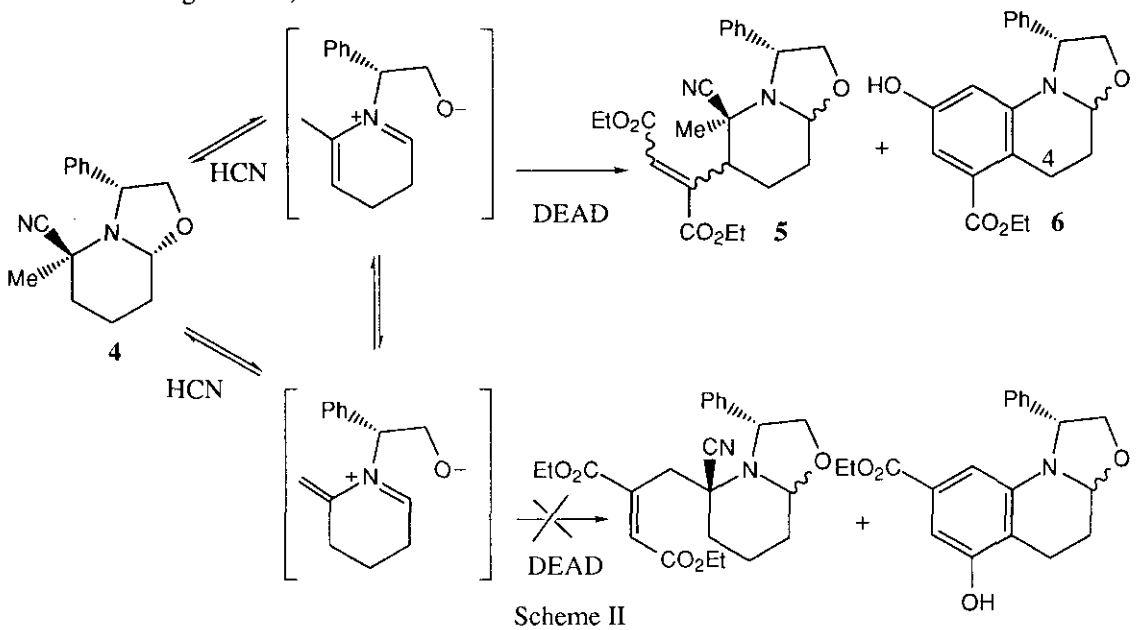
Scheme I

Indeed, it has previously[2] been demonstrated that an alkyl substituent α to the cyano group in compounds of type (**4**) favored the enamine formation through the more stable substituted iminium. As shown in Scheme II, cyano-methyl-phenyloxazolopiperidine (**4**)[8] can exist in equilibrium with two isomeric "exo" and "endo"-enamines due to the methyl substituent. The reactivity of such isomeric enamines towards Michael acceptors has been earlier reported for 2-methylindole[9] and *N*-methylpiperideine.[10] Contribution of both the "exo"- and "endo"-enamines was then observed. Using the same strategy a cyclic enamine such as dehydroquinolizidine was chosen to react with propiolaldehyde to afford the tricyclic alkaloid judolinine.[11]

We were interested in this particularity for the construction of a functionalized aromatic ring since the preparation of chiral non racemic 1,2,3,4-tetrahydroquinolines in two steps starting from a preformed heterocyclic ring could provide a new synthetic tool. 1,2,3,4-Tetrahydroquinolines possess interesting pharmacological profiles and are reported for instance as cardiotonic agents,[12] antihypertensives[13] and vasopressin antagonists.[14] Recently, 2-substituted 1,2,3,4-tetrahydroquinolines were used as key intermediates in the synthesis of pyrroloquinolines which were found to be potent histamine and platelet activating factor antagonists.[15] Some natural products isolated from the *Galipea* genus[16] possess a chiral center at C-2. Several methods[17] have been described for the synthesis of 1,2,3,4-tetrahydroquinolines but only a few have paid attention to stereocontrol. Three main strategies based on a preformed aromatic ring have been reported for their preparation : the reduction of the heterocyclic ring of quinolines,[18] the formation of the C-4-C-10 bond starting from conveniently substituted anilines[19] and the reaction of olefins with *N*-methoxymethylanilines[20] or with *N*-aryl Schiff bases.[21] Recently, the [4+2] cycloaddition of 2,3-bis(phenylsulfonyl)-1,3-butadiene to *N*-methyl-2,3-piperideine followed by elimination of the phenylsulfones was the first reported method using a piperideine to afford 1,2,3,4-tetrahydroquinolines.[22]

In analogy with **1**, compound (**4**) was treated with DEAD in dry EtOH/Al_2O_3 at 50 °C and EtOH/Al_2O_3 at 80°C as well as in CH_3COOH at 40 °C leading to the isolation of two classes of compounds. The nature of the isolated products was markedly dependent on the reaction conditions. In dry EtOH at 50°C during 48 h the main diasteromeric compound (**5**) (Scheme II) could be isolated in 15% yield suggesting the participation of the more reactive "endo-enamine" as for **1**. ^{1}H- and ^{13}C-NMR spectra showed a methyl group (1.12 ppm and 25.1 ppm) in addition to a nitrile functionality revealed by the ^{13}C-NMR spectrum (117.4 ppm) thus excluding the participation of the "exo-enamine" in the first step (Scheme II). The stereochemistry of **5** as depicted in scheme II is proposed on the basis of axial addition of the cyano group on the intermediate iminium under stereoelectronic control.

More interestingly a secondary product was isolated in 12% yield (19% based on recovered starting material) and was shown to be identical to the main compound obtained in 35% yield (71% based on recovered starting material) when **4** was reacted with DEAD in acetic acid.



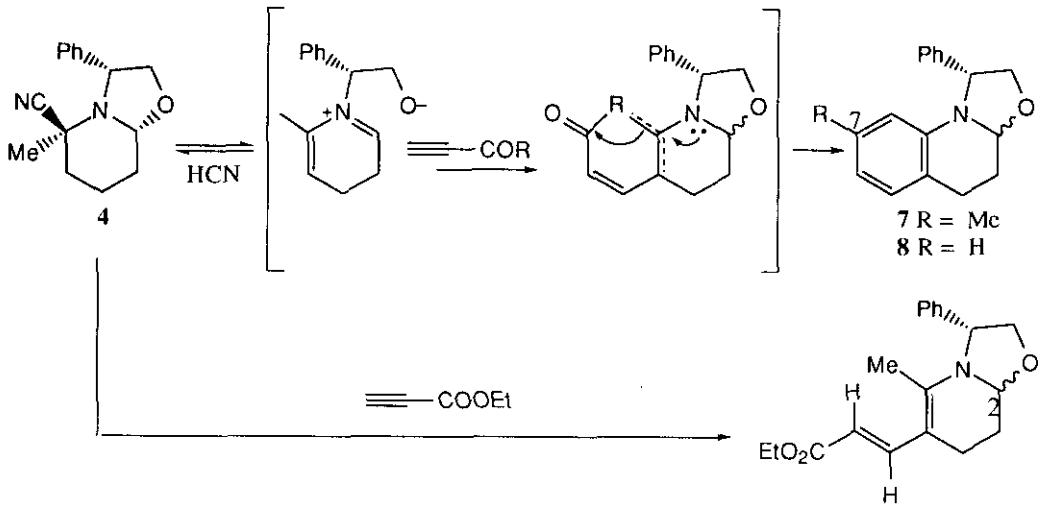
Scheme II

The aromatic structure of this compound was deduced from the ^{1}H- and ^{13}C-NMR spectra of the predominant oxazolidine diastereomer (**6**): two doublets at 5.92 and 6.63 ppm with small J values (2 Hz) were characteristic of *meta* aromatic protons of a 5,7-disubstituted tetrahydroquinoline system. In addition to the corresponding carbon resonances at 102.3 and 105.1 ppm, three downfield quaternary carbon resonances (140.0, 145.0 and 154.4) were observed for the newly formed substituted aromatic ring. NOE difference NMR-spectrometry was not conclusive to determine the configuration at C-2.[6] Thus, while irradiation of the H-2' triplet at 4.65 ppm gave no effect at 5.20 ppm (H-2), enhancement of one of the aromatic protons at 5.92 ppm was observed. This result allowed the assignment of the resonances of the aromatic protons of **6**. The resonances of the corresponding carbons were assigned by correlation spectroscopy. These values are in good agreement with the expected data for a 5-carboethoxy-7-hydroxy-1,2,3,4-tetrahydroquinoline.

Application of this new synthetic method to the reaction of **4** with 3-butyn-2-one should give access to the formation of a methyl substituted 1,2,3,4-tetrahydroquinoline (Scheme III). Indeed, reaction of **4** with 3-butyn-2-one in dry EtOH/Al_2O_3 at 50° C led to tetrahydroquinoline (**7**) (15% yield) as the sole isolated compound. Its structure was determined by ^{1}H- and ^{13}C-NMR spectra. In particular a methyl group was easily distinguished at 2.12 ppm in addition to three aromatic protons : one singlet at 6.12 ppm and two doublets at 6.47 and 6.92 ppm (J = 7.5 Hz) which were significant of the substitution pattern represented in formula (**7**). The low yield probably resulted from the preferred *trans* configuration of the ketonic intermediate as already reported.[11]

In order to develop a general synthetic method for the preparation of chiral non racemic 1,2,3,4-tetrahydroquinolines, we reacted compound (**4**) with two other alkynes : propiolaldehyde and ethyl

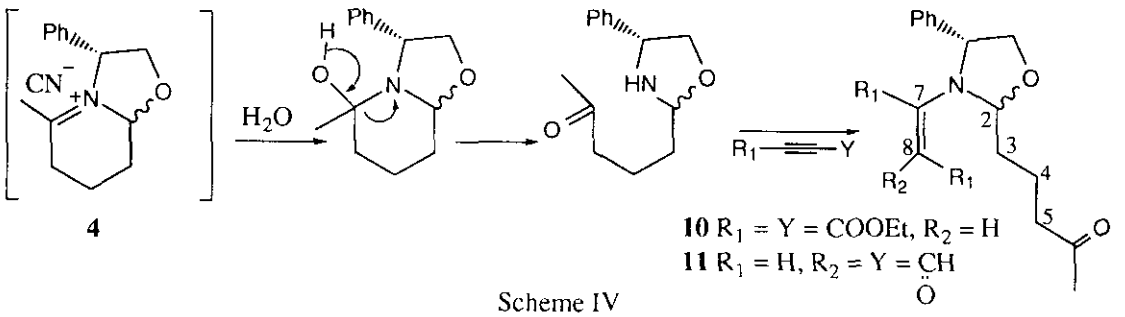
propiolate. In the first case, addition of propiolaldehyde dimethyl acetal in the presence of dry formic acid[23] furnished the desired tetrahydroquinoline (**8**) in moderate yield (Scheme III). The characteristic aromatic pattern of the new 1,2,3,4-tetrahydroquinoline was revealed by its ^{1}H- and ^{13}C-NMR spectra (two doublets at 6.27 and 7.04 ppm, J = 8 Hz and two triplets at 6.63 and 6.94 ppm, J = 8 Hz).



Scheme III **9**

Reaction with ethyl propiolate led to the isolation of two diastereomers (**9**) at C-2 as a result of a Michael addition without further cyclisation (Scheme III). Again this is probably due to the preferred *E*-configuration of the Michael adducts leading to the more stable compounds (**9**).

The use of EtOH containing a small percentage of water permitted the isolation of ketone (**10**) in 25% yield (37% based on recovered starting material) in addition to tetrahydroquinoline (**6**) (14%). The formation of compound (**10**) should result from the solvation by H_2O of the iminium intermediate as shown in Scheme IV. The same reaction was observed when the addition of propiolaldehyde was conducted in formic acid/water 98:2, leading to ketone (**11**).



Scheme IV

In conclusion we herein report a new synthetic method for the conversion of methyl-substituted latent enamines into the 1,2,3,4-tetrahydroquinoline framework. The two step-procedure starting from synthon (**1**) involves (i) methylation to compound (**4**) in quantitative yield[8] and (ii) condensation with an activated alkyne. The moderate yields are not optimized and counterbalanced by the easiness of the reaction. Although achieved only on four alkynes there is no obvious limitation of the method for providing

1,2,3,4-tetrahydroquinolines with or without 5-and /or 7-substitution on the aromatic ring. Addition of nucleophiles to the oxazolidine function followed by the hydrogenolysis of the chiral auxiliary[7] should give access to a series of chiral non racemic 2-substituted 1,2,3,4-tetrahydroquinolines.

Moreover the dienamine framework (**3**) obtained by Michael addition should constitute a good substrate for cycloaddition reactions leading to chiral heterocycles while the isolation of compound (**7**) opens interesting perspectives by taking advantage of the iminium-enamine reactivity of synthon (**4**).

EXPERIMENTAL

Diester (**3**) :

3 g (13.2 mmol) of synthon (**1**) was dissolved in 10 mL of ethanol and added to a suspension of 2 g of Al_2O_3 (Merck, type I, activated at 130°C for 1 h) in 10 mL of EtOH. The reaction mixture was stirred under argon for 15 mn. DEAD (2.50 g, 14.5 mmol) was slowly added and the mixture heated at 80°C under stirring and argon atmosphere for 24 h. After cooling and filtration the reaction mixture was poured into water and extracted several times with CH_2Cl_2. Evaporation to dryness and flash chromatography on silica gel of the crude residue using cyclohexane-ether as eluent (1:1) afforded 1.5 g of starting material **1** and 900 mg of a major compound which was subjected to further purification. Flash chromatography using ether-cyclohexane 7:5 yielded 545 mg of amorphous **3** and 220 mg of an unseparable mixture of **3** and its diastereomer. (yield 23% / starting material) $[\alpha]_D$ = -27° (c=1, $CHCl_3$), IR (ν cm^{-1}) : 1733, 1695, 1577, 1255; ^{1}H-NMR (300 MHz, $CHCl_3$, δ, ppm) : 1.07 (t, *J*=7 Hz, 3H, Me), 1.18 (t, *J*=7 Hz, 3H, Me), 1.95-2.12 (m, 1H, H-3), 2.15-2.25 (m, 1H, H-3), 2.78-2.98 (m, 2H, H-4), 3.91 (dd, *J*=9, 6.5 Hz, 1H, H-3'), 4.03 (q, *J*=7 Hz, 2H, OCH_2) 4.23-4.40 (m, 3H, H-3' and OCH_2), 4.54 (s, 1H, EtOOC-C<u>H</u>=C), 4.77 (t, *J*=6.5 Hz, 1H, H-2'), 5.14 (dd, *J*=9, 2 Hz, 1H, H-2), 7.1-7.4 (m, 5H, Ar Hs), 7.95 (s, 1H, C=C<u>H</u>-N) ; ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm), 13.3 (Me), 13.7 (Me), 29.1 (C-4), 34.8 (C-3), 59.4 (OCH_2), 62.0 (OCH_2), 62.5 (C-2'), 72.9 (C-3'), 89.3 (EtOOC-<u>C</u>H=C), 91.2 (C-2), 126.2 (Ar C-H), 128.0 (Ar C-H), 128.7 (Ar C-H), 130.7 (C) 133.4 (C=<u>C</u>H-N), 137.9 (C), 140.7 (C), 164.6 (ester), 166.6 (ester) ; MS (CI, NH_3) : *m/z* 372 $(M+1)^+$; HRMS (*m/z*) 371.1719 (calcd for $C_{21}H_{25}O_5N$: 371.1732).

Diester (**5**) *and 5-carboethoxy-7-hydroxy-1,2,3,4-tetrahydroquinoline* (**6**) :

Method A : 2 g (8.26 mmol) of compound (**4**) was dissolved in 20 mL of dry EtOH. 1.2 g of Al_2O_3 (Merck, type I, activated at 130°C for 1h) was added and the mixture stirred under argon atmosphere for 15 min. 1.7 g (10 mmol) of DEAD was added dropwise and the reaction mixture was maintained at 50°C for 48 h. Evaporation to dryness under vacuum and purification of the residue by flash chromatography on silica gel using cyclohexane/ether (6/4) as eluent afforded 700 mg of unreacted starting material, 510 mg of the Michael adduct (**5**) (15% and 22% based on recovered starting material) and 350 mg of tetrahydroquinoline (**4**) (12% or 19% based on recovered starting material) in addition to the inseparable mixtures of **5** and **6** with their C-2 isomers.

Method B : 605 mg (2.5 mmol) of compound (**4**) was dissolved in 8 mL of glacial acetic acid and the solution was heated at 40 °C under stirring and argon atmosphere. 552 mg (3.25 mmol) of DEAD was then

added dropwise and heating was continued for 24 h at the same temperature. Evaporation to dryness under vacuum and purification by flash chromatography on silica gel using cyclohexane/ether (6/4) as eluent afforded 300 mg of unreacted starting material and 300 mg of pure tetrahydroquinoline (**6**) (35% and 71% based on unreacted starting material) in addition to the corresponding diastereomeric mixture.

Diester (**5**) : $[\alpha]_D$ = - 106° (c=1, $CHCl_3$) ; IR (ν cm^{-1}) : 2350, 1725, 1638, 1257; ^{1}H-NMR (δ, ppm) : 1.12 (s, 3H, Me), 1.26 (t, *J*=7 Hz, 3H, Me), 1.28 (t, *J*=7 Hz, 3H, Me), 1.72 (dddd, *J*=12, 12, 11, 5 Hz, 1H, H-3), 1.9-2.2 (m, 2H, H-4), 2.22 (ddd, *J*=12, 3, 2 Hz, 1H, H-3), 2.59 (dd, *J*=12, 4 Hz, 1H, H-5), 3.75 (dd, *J*=8.5, 4 Hz, 1H, H-3'), 4.07 (dd, *J*=8.5, 5 Hz, 1H- H-3') 4.17 (q, *J*=7 Hz, 2H, OCH_2), 4.25-4.35 (m, 4H, H-2, H-2' and OCH_2), 6.18 (s, 1H, H-11), 7.2-7.4 (m, 5H, Ar Hs); ^{13}C-NMR (75.5 MHz, $CDCl_3$, δ ppm) : 13.6 (Me), 13.9 (Me), 25.1 (Me), 27.2 (C-4), 29.0 (C-3). 50.9 (C-5), 60.9 (OCH_2), 61.0 (C-6), 61.7 (OCH_2), 61.8 (C-2'), 75.0 (C-3'), 91.2 (C-2), 117.4 (C≡ N) 124.3 (EtOOC-C=C), 126.7 (Ar C-H), 127.5 (Ar C-H), 128.6 (Ar C-H), 143.8 (Ar C), 146.5 (EtOOC-C=C), 164.3 (ester) , 167.3 (ester) ; MS (CI, NH_3) : *m/z* 413 $(M+1)^+$, HRMS (CH_4-CI), *m/z* : 413.2076 (M+H, calcd for $C_{23}H_{28}N_2O_5$ +H : 413.2090).

5-carboethoxy-7-hydroxy-1,2,3,4-tetrahydroquinoline (**6**): $[\alpha]_D$ = - 92° (c=1, $CHCl_3$) ; IR (ν cm^{-1}) : 3420, 1715, 1609, 1220 ; ^{1}H-NMR (δ, ppm) : 1.30 (t, *J*=7 Hz, 3H, Me), 1.58 (dddd, 13, 13, 10, 5 Hz, 1H, H-3), 2.36 (dddd, *J*=13, 5, 5, 4 Hz, 1H, H-3), 2.70 (ddd, *J*=17, 13, 5 Hz, 1H, H-4), 3.34 (ddd, *J*=17, 5, 5 Hz, 1H, H-4), 3.68 (t, *J*=8 Hz, 1H, H-3'), 4.32 (q, *J*=7 Hz, 2H, O-CH_2), 4.54 (t, *J*=8 Hz, 1H, H-3'), 4.65 (t, *J*=8 Hz, 1H, H-2'), 5.20 (dd, *J*=10, 4 Hz, 1H, H-2), 5.92 (d, *J*=2 Hz, 1H, H-6 or H-8), 6.63 (d, *J*=2 Hz, 1H, H-8 or H-6), 7.25-7.35 (m, 5H, Ar Hs) ; ^{13}C-NMR (δ ppm) : 14.1 (Me), 21.8 (C-4), 26.3 (C-3), 60.8 (OCH_2), 63.4 (C-2'), 74.0 (C-3'), 89.5 (C-2), 102.3 (C-6 or C-8), 105.1 (C-8 or C-6), 116.0 (C-10), 125.7, 126.7, 128.7 (Ar C-H), 130.5 (C-5), 140.0 (Ar C), 145.0 (C-9), 154.4 (C-7), 168.0 (ester) ; MS (CI, NH_3) : *m/z* 340 $(M+1)^+$; HRMS (*m/z*) : 340.1549 (M+H, calcd for $C_{20}H_{21}NO_4$ +H : 340.1546).

7-Methyl-2-phenyl-oxazolo-1,2,3,4-tetrahydroquinoline (**7**):

1 g (4.13 mmol) of **4** was reacted with 340 mg (5 mmol) of 3-butyn-2-one in the presence of 500 mg of activated Al_2O_3 in 5 mL of dry ethanol. The reaction mixture was maintained at 50° C for 72 h under argon atmosphere. Extraction as usual and purification by flash chromatography on silica gel using cyclohexane:acetone (9/1) as eluent afforded 450 mg of unreacted starting material and 165 mg (15% and 27% based on recovered starting material) of pure amorphous tetrahydroquinoline (**7**) isolated from the corresponding diastereomeric mixture : $[\alpha]_D$ = - 49° (c=1, $CHCl_3$); IR (ν cm^{-1}) : 1614, 1506, 733, 701; ^{1}H-NMR (δ, ppm) : 1.6-1.8 (m, 1H, H-3), 2.12 (s, 3H, Me), 2.2-2.4 (m, 2H, H-4, H-3), 2.7-2.9 (m, 1H, H-4), 3.70 (t, *J*=8.5 Hz, 1H, H-3'), 4.54 (dd, *J*=8.5, 7.5 Hz, 1H, H-3'), 4.70 (t, *J*=7.5 Hz, 1H, H-2'), 5.21 (dd, *J*=9, 4 Hz, 1H, H-2), 6.12 (s, 1H, H-8), 6.47 (d, *J*=7.5 Hz, 1H, H-6 or H-5), 6.92 (d, *J*=7.5 Hz, 1H, H-5 or H-6), 7.3-7.5 (m, 5H, Ar Hs) ; ^{13}C-NMR (δ ppm) : 24.4 (C-4), 26.5 (C-3), 30.2 (Me), 63.5 (C-2'), 74.0 (C-3'), 90.0 (C-2), 112.4 (C-8), 117.7 (C-6), 119.8 (C-10), 126.4, 127.3, 128.8 (Ar C-H) 127.6 (C-5), 136.8 (C-7), 141.0 (Ar C), 143.4 (C-9); MS (CI, NH_3) : *m/z* 266 $(M+1)^+$; HRMS (CH_4-CI), *m/z* : 266.1542 (M+H, calcd for $C_{18}H_{19}NO$+H : 266.1545).

2-Phenyl-oxazolo-1,2,3,4-tetrahydroquinoline (**8**):

250 mg (1 mmol) of **4** was dissolved in 3 mL of anhydrous CH_2Cl_2. Propiolaldehyde [freshly prepared from propiolaldehyde diethyl acetal (10 mmol, 1.45 mL) and anhydrous formic acid (12 mL)[21a,b]] in 10 mL of anhydrous CH_2Cl_2 was slowly added. After addition of a catalytic amount of hydroquinone, the reaction mixture was heated for 24 h at 40°C with stirring under argon atmosphere. It was then poured into water, neutralized with a saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2 to yield 318 mg of a crude residue which was purified by flash chromatography with cyclohexane/ether (95/5). 50 mg (20%) of amorphous tetrahydroquinoline (**8**) was first eluted as an amorphous compound. 40 mg (16%) of unreacted compound (**4**) was recovered.

$[\alpha]_D$ = -17° (c = 1, $CHCl_3$); ^{1}H-NMR (δ, ppm) : 1.6-1.8 (m, 1H, H-3), 2.3-2.4 (m, 1H, H-3), 2.8-2.9 (m, 2H, H-4), 3.71 (t, *J* = 9 Hz, 1H, H-3'), 4.56 (dd, *J* = 9, 8 Hz, 1H, H-3'), 4.39 (t, *J* = 8 Hz, 1H, H-2'), 5.25 (dd, *J* = 9, 4 Hz, 1H, H-2), 6.27 (d, *J* = 8 Hz, 1H, H-7), 6.63 (td, *J*= 8, 1 Hz, 1H, H-9), 6.94 (td, *J* = 8, 1 Hz, 1H, H-8), 7.04 (d, *J* = 8 Hz, 1H, H-10), 7.3-7.5 (m, 5H, Ar Hs) ; ^{13}C-NMR (δ ppm) : 24.9 (C-4), 26.3 (C-3), 63.6 (C-2'), 74.1 (C-3'), 90.0 (C-2), 111.6 (C-8), 116.9 (C-6), 125.8, 127.2, 127.4, 127.7, 128.8 (Ar C-H), 140.4 (Ar C), 143.4 (C-9); MS (CI, NH_3) : *m/z* 252 $(M+1)^+$, HRMS (CI, CH_4), *m/z* : 252.1372 (M+H, calcd for $C_{17}H_{17}NO$ +H : 252.1388).

Esters (**9**):

500 mg (2 mmol) of **4** was reacted with 0.3 mL (2.2 mmol) of ethyl propiolate in the presence of 300 mg of activated Al_2O_3 in 10 mL of dry ethanol. The reaction mixture was heated at 50°C under argon atmosphere for 24 h. Extraction followed by purification by flash chromatography afforded two diastereomers at C-2, (**9a**) (157 mg) and (**9b**) (78 mg) in 50% and 20% yields, respectively.

(**9b**) : $[\alpha]_D$ = + 390° (c= 1, $CHCl_3$); IR (ν cm^{-1}) : 1725, 1640, 1259; ^{1}H-NMR (δ, ppm) : 1.26 (t, *J* = 7 Hz, 3H, Me), 1.5-1.7 (m, 1H, H-3), 1.88 (s, 3H, Me), 2.1-2.5 (m, 3H, H-3, H-4), 3.72 (dd, *J* = 9, 7 Hz, 1H, H-3'), 4.15 (q, *J* = 7 Hz, 2H, OCH_2), 4.46 (dd, *J* = 9, 7 Hz, 1H, H-3'), 4.92 (t, *J* = 7 Hz, 1H, H-2'), 5.08 (dd, *J* = 13, 4 Hz, 1H, H-2), 5.41 (d, *J* = 15 Hz, 1H, H-8), 7.2-7.4 (m, 5H, Ar Hs), 7.71 (d, *J* = 15 Hz, 1H, H-7); ^{13}C-NMR (δ ppm) : 14.4 (Me), 15.6 (Me), 20.1 (C-4), 26.4 (C-3), 59.2 (OCH_2), 61.9 (C-3'), 73.9 (C-2'), 88.9 (C-6), 102.8 (C-5), 104.6 (C-8) 125.6, 127.7, 129.0 (Ar C-H), 141.4 (Ar C), 143.3 (C-7), 150.7(C-6), 169.0 (ester); MS (CI, NH_3) : *m/z* 314 $(M+1)^+$, HRMS (CH_4-CI), *m/z* : 314.1760 (M+H, calcd for $C_{19}H_{23}NO_3$+H : 314.1756).

(**9a**) : $[\alpha]_D$ = - 142° (c= 1, $CHCl_3$); IR (ν cm^{-1}) : 1725, 1640, 1259; ^{1}H-NMR (δ, ppm) : 1.25 (t, *J* = 7 Hz, 3H, Me), 1.8-2.0 (m, 1H, H-3), 1.85 (s, 3H, Me), 2.2-2.6 (m, 3H, H-3, H-4), 3.93 (d, *J* = 8 Hz, 1H, H-3'), 4.11 (q, *J* = 7 Hz, 2H, OCH_2), 4.20 (dd, *J* = 8, 7 Hz, 1H, H-3'), 4.79 (dd, *J* = 7 Hz, 1H, H-2), 4.85 (d, *J* = 7 Hz, 1H, H-2'), 5.38 (d, *J* = 15 Hz, 1H, H-8), 7.2-7.4 (m, 5H, Ar Hs), 7.20 (d, *J* = 15 Hz, 1H, H-7); ^{13}C-NMR (δ ppm) : 14.4 (Me), 15.4 (Me), 21.1 (C-4), 26.2 (C-3), 58.4 (OCH_2), 61.1 (C-3'), 74.1 (C-2'), 87.9 (C-6), 102.3 (C-5), 103.7 (C-8) 125.8, 127.6, 129.2 (Ar C-H), 134.4, 141.4 (Ar C), 143.3 (C-7), 154.5(C-6), 168.5, 169.9 (esters); MS (CI, NH_3) : *m/z* 314 $(M+1)^+$, HRMS (CH_4-CI), *m/z* : 314.1754 (M+H, calcd for $C_{19}H_{23}NO_3$+H : 314.1756).

Ketone (**10**) :

2 g (8.2 mmol) of **4** was dissolved in 20 mL of EtOH. The procedure was identical as in method A (1.2 g of activated Al_2O_3, 1.7 g of DEAD) except for the temperature : 80 °C and reaction time : 24 h. Flash chromatography as usual gave 640 mg of unreacted starting material in addition to 830 mg (25% and 37% based on recovered starting material) of ketone (**10**) as an oil and 380 mg (14%, 20% based on recovered starting material) of a diastereomeric mixture of 1,2,3,4-tetrahydroquinoline (**6**).

$[\alpha]_D$ = - 56.5° (c=1, $CHCl_3$) ; IR (ν cm^{-1}) : 1734, 1717, 1577, 1223 ; ^{1}H-NMR (δ, ppm) : 1.01 (t, *J*=7 Hz, 3H, Me), 1.09 (t, *J*=7 Hz, 3H, Me), 1.6-2.5 (m, 6H), 2.10 (s, 3H, Me), 3.80 (dd, *J*=9, 6.5 Hz, 1H, H-3'), 3.99 (q, *J*=7 Hz, 2H, OCH_2), 4.14 (q, *J*=7 Hz, 2H, OCH_2), 4.29 (dd, *J*=9, 6.5 Hz, 1H, H-3'), 4.50 (s, 1H, H-8), 4.70 (t, *J*=6.5 Hz, 1H, H-2'), 5.05 (d, *J*=9 Hz, 1H, H-2), 7.15-7.40 (m, 5H, Ar-Hs) ; ^{13}C-NMR (δ ppm) : 13.9 (Me), 14.2 (Me), 19.3 (C-4), 29.8 (Me), 32.5 (C-3), 42.6 (C-5), 59.3 (OCH_2), 61.9 (OCH_2), 62.4 (C-3'), 72.8 (C-2'), 88.9 (C-2), 92.0 (C-8), 126.1, 127.9 , 129.1 (Ar C-H), 138.2 (Ar C), 149.8 (C-7), 164.6 (ester), 166.6 (ester), 208.0 (C=O); MS (CI, NH_3) : *m/z* 404 $(M+1)^+$, HRMS (CH_4-CI), *m/z* : 404.2073 (M+H, calcd for $C_{22}H_{29}NO_6$+H : 404.2049).

Ketone (**11**) :

Identical procedure was used as for the obtention of tetrahydroquinoline (**8**) except the use of formic acid/water (98/2). The ketone (**11**) was obtained with 30% yield after flash chromatography and elution with CH_2Cl_2/MeOH (95/5). $[\alpha]_D$ = - 21° (c=1, $CHCl_3$) ; IR (ν cm^{-1}) : 1710, 1647, 1611; ^{1}H-NMR (δ, ppm) : 0.8-1.0 (m, 1H), 1.8-2.7 (m, 5H), 2.20 (s, 3H, Me), 4.00 (dd, *J*= 8, 6 Hz, 1H, H-3'), 4.30 (t, *J*= 8 Hz, 1H, H-3'), 4.65 (dd, *J*= 8, 6 Hz, 1H, H-2'), 5.05 (m, 2H, H-2, H-8), 7.0-7.5 (m, 5H, Ar Hs), 7.14 (d, 1H, *J* = 15 Hz, H-7), 9.05 (d, 1H, *J* = 6 Hz, aldehyde) ; ^{13}C-NMR (δ ppm) : 18.7 (C-4), 32.7 (C-3), 42.5 (C-5), 29.5 (Me), 63.0 (C-3'), 73.2 (C-2'), 92.5 (C-2), 105.2 (C-8), 126.3, 128.3, 129.0, (Ar CH), 137.8 (Ar C), 151.4 (C-7), 174.7 (C=O, aldehyde), 207.9 (C=O, ketone); MS (CI, NH_3) : *m/z* 288 $(M+1)^+$, HRMS (CH_4-CI), *m/z* : 288.1598 (M+H, calcd for $C_{17}H_{21}NO_3$.+H : 288.1599).

REFERENCES

1. G.V. Boyd, "The chemistry of enamines : Heterocyclic synthesis from enamines", Part 2, ed. by Z. Rappoport, Wiley Interscience **1994**, p. 1365-1440.
2. M.-C. Lallemand, N. Kunesch, and H.-P. Husson, *Tetrahedron Lett.*, **1995**, *36*, 2053.8
3. W. Verboom, G.W. Visser, W.P. Trompenaars, D.N. Reinhoudt, S. Harkema, and G.J. van Hummel, *Tetrahedron*, **1981**, *37*, 3525.
4. R.M. Letcher, M.C.K. Choi, R.M. Acheson, and R.J. Prince, *J. Chem. Soc., Perkin Trans I*, **1983**, 501.
5. M. Bonin, D. Grierson, J. Royer, and H.-P. Husson, *Org. Syntheses*, **1992**, *70*, 54.
6. S. Arséniyadis, P.Q. Huang, N. Morellet, J.-C. Belœil, and H.-P. Husson, *Heterocycles*, **1990**, *31*, 1789.
7. J. Royer and H.-P. Husson, "Advanced in the Use of Synthons in Organic Chemistry : Chemistry of Potential and Reversed Iminium Systems" Vol. 2, ed. by A. Dondoni, JAI Press **1995**.
8. L. Guerrier, J. Royer, D. Grierson, and H.-P. Husson, *J. Am. Chem. Soc.*, **1983**, *105*, 7754.
9. R.M. Letcher, M.C.K. Choi, R.M. Acheson, and R.J. Prince, *J. Chem. Soc., Perkin Trans. I*, **1983**, 501.

10. D. Schumann, H.-J. Müller, and A.-L. Naumann, *Liebigs Ann. Chem.*, **1982**, 2057.
11. J. Bohlmann and O. Schmidt, *Chem. Ber.*, **1964**, *97*, 1354.
12. F. Santangelo, C. Casagrande, G. Miragoli, and V. Vecchietti, *Eur. J. Med. Chem.*, **1994**, *29*, 877.
13. J.M. Evans, G. Stemp, C.D. Nicholson, and D. Angersbach, U.S. Pat. 4,808,619 (1989) (*Chem. Abstr.*, **1989**, *111*, 134012z).
14. H. Ogawa, H. Miyamoto, K. Kondo, H. Yamashita, K. Nakaya, M. Tanaka, and K. Kitano, PCT Int. Appl. WO 9401,113 (1994) (*Chem. Abstr.*, **1994**, *120*, 290828m); H. Ogawa, H. Miyamoto, K. Kondo, H. Yamashita, K. Nakaya, H. Komatsu, M. Tanaka, S. Takara, M. Tominaga, and Y. Yabuchi, Jpn Kokai Tokkyo Koho JP 04,321,669 (1992) (*Chem. Abstr.*, **1993**, *119*, 249979c).
15. D. Paris, M. Cottin, P. Demonchaux, G. Augert, P. Dupassieux, P. Lenoir, M.J. Peck, and D. Jasserand, *J. Med. Chem.*, **1995**, *38*, 669.
16. J. Schläger and W. Leeb, *Monatsh. Chem.*, **1950**, *81*, 714.
17. Houben-Weyl - Methoden der organischen Chemie, E 16 d (II). D. Klamann, Georg Thieme Verlag Stuttgart, New York 1992.
18. G.W. Gribble and P.W. Heald, *Synthesis*, **1975**, 650; B.S. Rauckman, M.Y. Tidwell, J.V. Johnson, and B. Roth, *J. Med. Chem.*, **1989**, *32*, 1927.
19. V.N. Gogte, S.K. Kamat, and B.D. Tilak, *Indian J. Chem.*, **1972**, *10*, 325; M. Mori, S. Kudo, and Y. Ban, *J. Chem. Soc., Perkin Trans. 1*, **1979**, 771; B.C. Söderberg, E.S. Helton, L.R. Austin, and H.H. Odens, *J. Org. Chem.*, **1993**, *58*, 5589; A.R. Katritzky, B. Rachwal, and S. Rachwal, *J. Org. Chem.*, **1995**, *60*, 2588; A.R. Katritzky, B. Rachwal, and S. Rachwal, *J. Org. Chem.*, **1995**, *60*, 3993; A.R. Katritzky, B. Rachwal, and S. Rachwal, *J. Org. Chem.*, **1995**, *60*, 7631.
20. T. Shono, Y. Matsumura, K. Inoue, H. Ohmizu, and S. Kashimura, *J. Am. Chem. Soc.*, **1982**, *104*, 5753.
21. T. Kametani, H. Takeda, Y. Suzuki, and T. Honda, *Heterocycles*, **1984**, *22*, 275; K. Narasaka and T. Shibata, *Heterocycles*, **1993**, *35*, 1039 and references cited therein.
22. A. Padwa, M. Meske, and A. Rodriguez, *Heterocycles*, **1995**, *40*, 191.
23. F. Barbot, L. Poncini, B. Randriandelina, and P. Miginiac, *J. Chem. Res. (S)*, **1981**, 4010; A. Gorgues, A. Simon, A. Le Coq, A. Hercouet, and F. Corre, *Tetrahedron*, **1986**, *42*, 351; A. Gorgues, D. Stephan, A. Belyasmine, A. Khanous, and A. Le Coq, *Tetrahedron*, **1990**, *46*, 2817.

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