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Enantiospecific Synthesis of Dihydropyridines from Chiral Enamines

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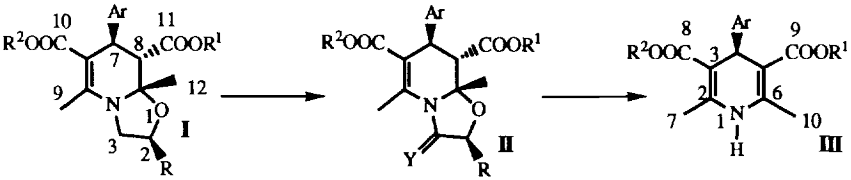
Abstract: A new asymmetric synthesis of dihydropyridines is described. This methodology is based on the use of chiral aminoalcohols to produce enamines, which were used in the synthesis of enantiopure 2-alkyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines. The known stereochemistry of these compounds was exploited to obtain 1,4-dihydropyridines with controlled configuration at C-4. Copyright © 1996 Elsevier Science Ltd

The synthesis of dihydropyridines has atracted the attention of many research groups[1] since Bossert and Vater[2] described the cardiovascular relevance of these drugs. Much research has been carried out to define the structural and conformational requirements needed for their pharmacological activity.[3] Asymmetric synthesis of both enantiomers of a large number of dihydropyridines has been achieved by three different strategies[4]: a) resolution of mixtures by chemical[5] or by enzymatic methods[6], b) use of chiral auxiliaries in the carbon framework of the reagents[7] and c) use of chiral auxiliaries in the nitrogen atom of the starting enamine. As a consequence, many qualitative and quantitative differences in the activity of each enantiomer have been reported.[8]

The latter method has been less exploited since there are only two approaches to dihydropyridines based on this strategy: chiral enamines from chiral hydrazines[9] and chiral enamines from chiral amines[10]. Related to this methodology is the synthesis of enantiopure 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines **I**, recently described by us[11]. The use of chiral enamines obtained from chiral aminoalcohols produced a diastereospecific process, yielding enantiopure derivatives from enantiopure starting enamines. The convenience of this method to introduce enantioselection in the preparation of this bicyclic system related to dihydropyridines prompted us to investigate the possibilities of conversion of this class of compounds into dihydropyridines. Direct conversion of type **I** compounds or indirect transformation through functionalized derivatives **II**, into dihydropyridines **III** has been investigated.



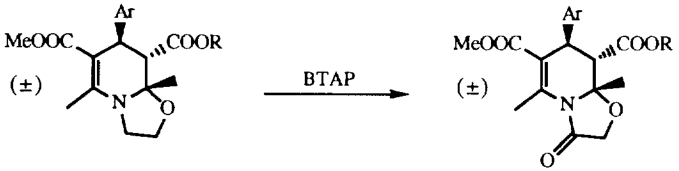
The synthetic sequence of dihydropyridines into enantiopure 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2 *a*] pyridines described in this paper is a new and specific method for the synthesis of chiral dihydropyridines in a three step process. The chirality of 1-amino-2-propanol is transmited four bonds away to the stereocenter of dihydropyridines.

METHODS AND RESULTS

Transformation of 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]]pyridines **I** into dihydropyridines could be achieved in different ways. Basic treatment of the oxazolopyridines **I** proved to be ineffective for the direct transformation into dihydropyrines **III** and the starting material was recovered unchanged. Conversion of the oxazolidine ring into a more functionalized substructure, as for example in **II**, seems to be a better way to accomplish the second step of the sequence.

The presence of functionalities at position 2 or 3 could increase the possibilities of removal of the oxazolidine ring by elimination, hydrolysis or other reactions. Accordingly, we first studied the oxidation at position C-3. This transformation would produce amides (oxazolidinones **II**), thus yielding a functionality with the required posibilities for the hydrolysis and subsequent transformation into dihydropyridines.

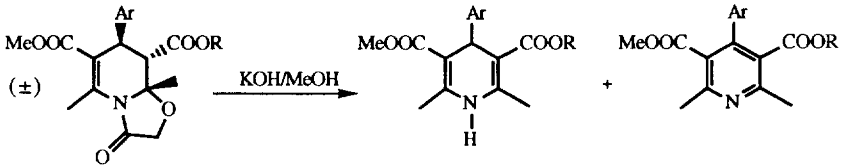
Therefore, we first tried this transformation with racemic 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines unsubstituted at 2 and 3 (**I**: R=H) as model for the transformation of pure enantiomers. This transformation was attempted by treatment with pyridinium chlorochromate[12] and Jones[13] reagent, but the best results were obtained with benzyl-triethylammonium permanganate (BTAP). This reagent has been used for the oxidation of amines into amides[14] and ethers into esters[15]. We carried out the oxidation in dichloromethane at reflux, using 5 equivalents of BTAP, with oxazolopyridines **1**-**5** to produce the oxazolidinone derivatives **6**-**10**. Oxidation at the α-position of the nitrogen atom to produce the lactam, instead of alternative oxidation in the α-position of the oxygen atom to the lactone, was established by IR (1720 cm^{-1}) and ^{13}C-NMR (168 ppm) spectroscopy. In the ^{1}H-NMR spectra of the oxidized products there is also a characteristic deshielding of the methyl group at C-8a due to the anisotropic effect produced by the presence of the carbonyl group at C-3. The spectroscopic data also showed that the already known stereochemistry at C-7, C-8 and C-8a[11,16] is maintained in the oxidation products. When acetic acid was used as solvent, a dramatic decrease in the yield of the expected oxidation products at C-3 was observed. Although the yields have not been fully optimized, the non-oxidized material was recovered unchanged and was recycled in new oxidations. As a result, the BTAP oxidation appears to be a very convenient method for the regioselective oxidation of the oxazolidine moiety to the oxazolidinone in these fused heterocyclic systems.



1: R=Me ; Ar=3-Cl-Ph
2: R=Bn ; Ar=3-Cl-Ph
3: R=Me ; Ar=3-NO_2-Ph
4: R=Bn ; Ar=3-NO_2-Ph
5: R=^{t}Bu ; Ar=3-NO_2-Ph

6: R=Me ; Ar=3-Cl-Ph
7: R=Bn ; Ar=3-Cl-Ph
8: R=Me ; Ar=3-NO_2-Ph
9: R=Bn ; Ar=3-NO_2-Ph
10: R=^{t}Bu ; Ar=3-NO_2-Ph

To discover the possibilities of transformation of these oxidized derivatives **6**-**10** into the related antihypertensive dihydropyridines, we subjected representative compounds **6** and **8** to basic treatment. Under standard conditions (KOH/MeOH) 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-3-one **6** produced a mixture of two compounds, which were identified as the dihydropyridine **11** (41%) and pyridine **12** (42%), produced by cleavage of the oxazolidinone ring. Isolation of pyridine **12**, although not an expected product of hydrolysis and cleavage of the oxazolidine moiety, can be explained in terms of the oxidation of the dihydropyridine **11** by atmospheric oxygen in the basic reaction medium.[17] Use of an inert atmosphere in the treatment of **8** and in the final experiments with enantiopure substrates avoided this unwanted oxidation to pyridine derivatives **12**. A second experiment carried out in inert atmosphere with compound **8** only produced the dihydropyridine **13**. As suspected, the presence of the carbonyl group at C-3 favors the transformation of tetrahydrooxazolo[3,2-*a*]pyridine-3-ones (**II**: R=H, Y=O) into dihydropyrines **III**, which did not occur with the starting 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines (**I**).



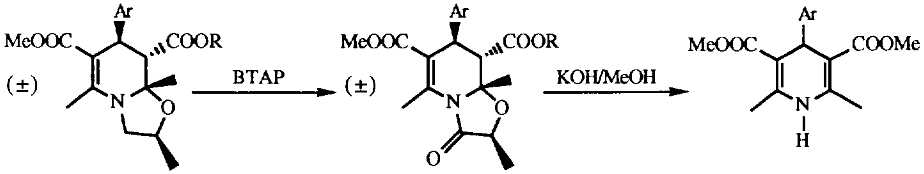
6: R=Me ; Ar=3-Cl-Ph
8: R=Me ; Ar=3-NO_2-Ph

11: R=Me ; Ar=3-Cl-Ph
13: R=Me ; Ar=3-NO_2-Ph

12: R=Me ; Ar=3-Cl-Ph

Having demonstrated the usefulness of oxazolopyridines (**II**: R=H, Y=O) for the synthesis of dihydropyridines (**III**), we used racemic 2-methyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines to check their transformation into dihydropyridines. BTAP oxidation of the 2-substituted derivatives **14** and **15** yielded the 3-oxo products **16** and **17**, which retained the relative stereochemistry of the starting materials. We also investigated the use of 3-substituted 2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines, obtained by the same methodology from enamines of 2-amino-1-butanol. However, by BTAP or Jones treatment of 3-ethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridines **18** and **19** no oxidation products at C-2 or C-3 were obtained, and the starting material was degraded when the reaction was carried out under more drastic conditions.

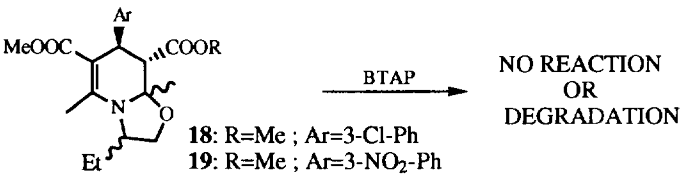
Finally, the transformation of the 2-substituted oxazolo[3,2-*a*]pyridine-3-one **16** into the already known dihydropyridine **11**, took place in convenient yield without the appearance of pyridines as oxidation products.



14: R=Me ; Ar=3-Cl-Ph
15: R=Me ; Ar=3-NO_2-Ph

16: R=Me ; Ar=3-Cl-Ph
17: R=Me ; Ar=3-NO_2-Ph

11



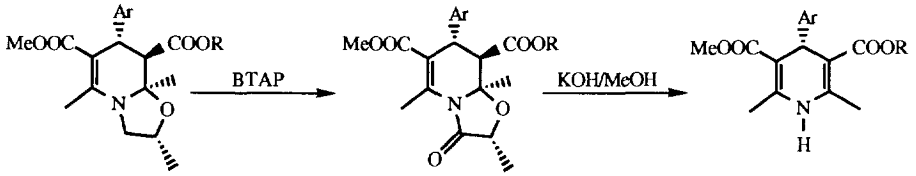
18: R=Me ; Ar=3-Cl-Ph
19: R=Me ; Ar=3-NO_2-Ph

These experiments with racemic materials demonstrated the expected posibilities of this methodology for the synthesis of enantiopure dihydropyridines from pure enantiomers of the starting 2,3,8,8a-tetrahydro-7*H*-

oxazolo[3,2-*a*]pyridines. For this, we used the previously synthesized compounds **20a**, **21** and **22a** that had been prepared from pure enantiomers of the enamines obtained from commercially available (*R*)-1-amino-2-propanol, and **20b** and **22b** from (*S*)-1-amino-2-propanol. The absolute stereochemistry of these compounds was deduced from the absolute configuration of the starting 1-amino-2-propanol and the relative stereochemistries induced at C-7, C-8 and C-8a during the formation of the tetrahydro-oxazolopyridine system. This was also confirmed by X-Ray diffraction studies of the dimethyl esters already described in our previous paper.[11]

Oxidation of compounds **20a**, **20b** and **21** produced the desired 3-oxo derivatives **23a**, **23b** and **24**, which were transformed into the pure enantiomers of 1,4-dihydropyridines **26a**, **26b** and **27**. According to the previous results, obtained with racemic materials, no stereochemical changes occur in the oxidation process and a single enantiomer is obtained in the final step. When the benzyl derivatives **22a** or **22b** were used, the first reaction produced the expected tetrahydrooxazolopyridin-3-ones **25a** or **25b**, but the basic treatment yielded an unresolvable mixture of dimethyl **11** and benzyl-methyl (**28a**) dihydropyridines. The use of the more hindered *t*-butanol as solvent for the basic treatment avoided the displacement of the benzyl ester, thus producing the pure enantiomers **28a** from **25a** and **28b** from **25b**.

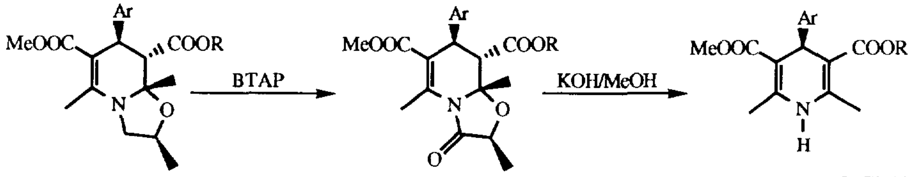
The stereochemical purity of compounds **26-28** was checked in ^{1}H-NMR with a chiral shift reagent [Eu(tfc)$_3$], which induces the appearance of duplicate sets of representative signals in racemic materials **1-10** or **14-15**; this is not detected in any of the pure enantiomers of the starting materials **20-22**, the oxidized derivatives **23-25** or the final products **26-28**.



20a: R=Et ; Ar=3-Cl-Ph
21: R=^{t}Bu ; Ar=3-Cl-Ph
22a: R=Bn ; Ar=3-Cl-Ph

23a: R=Et ; Ar=3-Cl-Ph
24: R=^{t}Bu ; Ar=3-Cl-Ph
25a: R=Bn ; Ar=3-Cl-Ph

26a: R=Et ; Ar=3-Cl-Ph
27: R=^{t}Bu ; Ar=3-Cl-Ph
28a: R=Bn ; Ar=3-Cl-Ph



20b: R=Et; Ar=3-Cl-Ph
22b: R=Bn; Ar=3-Cl-Ph

23b: R=Et; Ar=3-Cl-Ph
25b: R=Bn; Ar=3-Cl-Ph

26b: R=Et; Ar=3-Cl-Ph
28b: R=Bn; Ar=3-Cl-Ph

In conclusion, we present a new and fully stereocontrolled process for the synthesis of antihypertensive 1,4-dihydropyridines from available (*R*) and (*S*)-1-amino-2-propanol. Although three of the four stereocenters in the intermediate 2-alkyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridin-3-ones are lost in the final step, the stereocontrol obtained in the cyclization to the oxazolopyridine system ensures the configuration at C-4 of the final 1,4-dihydropyridines. In this way, the stereochemistry of the aminoalcohol is translated to the 1,4-dihydropyridine in a specific process.

EXPERIMENTAL SECTION

General.

M.p. data were determined on a Buchi 510 instrument and are uncorrected. IR spectra were obtained in KBr disks in a Beckman Acculab VIII spectrophotometer. ^{1}H NMR (200.13 MHz) and ^{13}C NMR (50.3 MHz) spectra were measured in a Bruker WP 200 SY instrument, in deuterochloroform solutions and tetramethylsilane as internal standard, unless otherwise stated. δ values are expressed in ppm and J values in Hz. Column chromatography was performed over silica gel Merck 60 (0.063-0.2 mm). For flash chromatography, an Eyela EF-10 apparatus was used, with 3-85 mL/min flow rate, over silica gel Merck 60 (0.040-0.063 mm). TLC was performed on precoated silica gel polyester plates (0.25 mm thickness) with fluorescent indicator UV254 (Polychrom SI F_{254}). Microanalyses were obtained in a Perkin-Elmer 2400 CHN elemental analyzer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Preparation of oxazolopyridines

Starting materials: **1-5**[16], **14**[11], **15**[11], **18**[11], **20a**[11] $[\alpha]_D$ +35.7 (c 1.05, $CHCl_3$), **21**[11] $[\alpha]_D$ +71.0 (c 0.98, $CHCl_3$), **22b**[11] $[\alpha]_D$ +40.5 (c 0.65, $CHCl_3$), were obtained following the methodology previously described. Compounds: **19**, **20b**, **22a**, have been obtained for the first time in the present work.

(±)-Dimethyl 7-(3-nitrophenyl)-3-ethyl-5,8a-dimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6,8-dicarboxylate (19). (37%). M. p. 165-166°C (MeOH). IR (KBr) 1740, 1690, 1535 cm^{-1}. ^{1}H NMR δ 0.99 (3H, t, J=7.3 Hz, CH_2-$\underline{CH_3}$), 1.34 (3H, s, C_{8a}-Me), 1.72 (2H, m, $\underline{CH_2}$-CH_3), 2.50 (3H, d, J =1.2 Hz, C_5-Me), 2.56 (1H, d, J =12.0 Hz, H_8), 3.30 (3H, s, C_{10}-OMe), 3.55 (3H, s, C_{11}-OMe), 3.92 (1H, dt, J_1 =5.2 Hz, J_2=7.3 Hz, H_3), 4.04 (1H, d, J =9.0 Hz, H_2), 4.15 (1H, dd, J_1=5.2 Hz, J_2=9.0 Hz, H_2), 4.18 (1H, dd, J_1=1.2 Hz, J_2=12.0 Hz, H_7), 7.40 (1H, dd, J_1 =7.7 Hz, J_2 =8.5 Hz, $H_{5'}$), 7.50 (1H, dt, J_1=1.6 Hz, J_2=7.7 Hz, $H_{6'}$), 7.90 (1H, d, J =1.6 Hz, $H_{2'}$); 8.03 (1H, dd, J_1=1.6 Hz, J_2 =8.5 Hz, $H_{4'}$). ^{13}C NMR δ 10.7 (CH_2-$\underline{C}H_3$), 17.5 (C_{12}), 18.8 (C_9), 26.7 ($\underline{C}H_2$-CH_3), 44.2 (C_7), 50.1 (OMe-13), 52.1 (OMe-14), 59.2 (C_8), 59.7 (C_3), 68.0 (C_2), 91.9 (C_6), 100.7 (C_{8a}), 121.5 ($C_{4'}$), 122.1 ($C_{2'}$), 128.9 ($C_{5'}$), 133.7 ($C_{6'}$), 147.4 ($C_{1'}$), 148.5 ($C_{3'}$), 150.4 (C_5), 167.6 (C_{10}), 171.3 (C_{11}).

(-)-(2*S*, 7*R*, 8*S*, 8a*S*)-Methyl 7-(3-chlorophenyl)-8-ethoxycarbonyl-2,5,8a-trimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate 20b. (40%). M. p. 120°C (Hexane-ether) $[\alpha]_D$ -36.9 (c 0.74, $CHCl_3$).

(-)-(2*R*, 7*S*, 8*R*, 8a*R*) Methyl 7-(3-chlorophenyl)-8-benzyloxycarbonyl-2,5,8a-trimethyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (22a). (43%). $[\alpha]_D$ -43.2 (c 0.68, $CHCl_3$)

General procedure of oxidation with benzyl(triethyl)ammonium permanganate

Oxazolopyridine (2.7 mmol) and benzyl(triethyl)ammonium permanganate (9.5 mmol) in 40 ml of dry CH_2Cl_2 were stirred at 0°C for 30 minutes. The mixture was heated at reflux for 24 hours. The precipitate was filtered and the solution was concentrate in vacuo to give a residue which was chromatographied (Hex-AcOEt 7:3) to afford the 3-oxooxazolopyridines: **6**, **7**, **8**, **9**, **10**, **16**, **17**, **23a**, **23b**, **24**, **25a**, **25b**.

(±)-Dimethyl 7-(3-chlorophenyl)-5,8a-dimethyl-3-oxo-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-*a*]pyridine-6,8-dicarboxylate 6. (38%). M. p. 121°C (MeOH). IR 1750, 1720, 1630 cm^{-1}. ^{1}H NMR δ 1.20 (3H, s, C_{8a}-Me), 2.84 (3H, d, J =2 Hz, C_5-Me), 3.25 (1H, s, H_8), 3.56 (3H, s, C_{10}-OMe), 3.77 (3H, s, C_{11}-OMe), 4.16 (1H, d, J =14.4 Hz, H_2), 4.32 (1H, d, J=14.4 Hz, H_2), 4.34 (1H, s, H_7), 7.1-7.4 (4H, m, $H_{arom.}$). ^{13}C NMR δ (Table 1). Anal. Calcd for $C_{19}H_{20}NClO_6$: C, 57.95; H, 5.12; N, 3.56. Found: C, 58.03; H, 5.13; N, 3.23.

(±)-Methyl 7-(3-chlorophenyl)-5,8a-dimethyl-8-benzyloxycarbonyl-3-oxo-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate 7. (36%). M. p. 179°C (MeOH). IR 1740, 1715, 1610 cm^{-1}. ^{1}H NMR δ 1.15 (3H, s, C_{8a}-Me), 2.81 (3H, d, J =2.0 Hz, C_5-Me), 3.29 (1H, s, H_8), 3.55 (3H, s, OMe), 3.82 (1H, d, J=14.6 Hz, H_2), 4.22 (1H, d, J=14.6, H_2), 4.35 (1H, d, J =1.6 Hz, H_7), 5.16 (1H, d, J =12.1Hz, $C\underline{H}_2$Bn), 5.26 (1H, d, J=12.1, $C\underline{H}_2$Bn); 7.1-7.3 (5H, m, $H_{\text{arom.}}$Bn), 7.1-7,5 (4H, m, 4$H_{\text{arom.}}$). ^{13}C NMR δ (Table 1).

(±) Dimethyl 7-(3-nitrophenyl)-5,8a-dimethyl-3-oxo-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-*a*]pyridine-6,8-dicarboxylate 8. (23%). M. p. 145°C (Ether). IR 1760, 1730, 1710 cm^{-1}. ^{1}H NMR δ 1.18 (3H, s, C_{8a}-Me), 2.87 (3H, d, J=2 Hz, C_5-Me), 3.27 (1H, s, H_8), 3.57 (3H, s, C_{10}-OMe), 3.80 (3H, s, C_{11}-OMe), 4.19 (1H, d, J =14.4 Hz, H_2), 4.36 (1H, d, J=14.4, Hz, H_2), 4.46 (1H, br s, H_7), 7.60 (1H, m, $H_{5'}$), 7.63 (1H, d, J =5.6 Hz, $H_{6'}$), 8.04 (1H, d, J=8.0 Hz, $H_{4'}$), 8.12 (1H, s, $H_{2'}$). ^{13}C NMR δ (Table 1). Anal. Calcd for $C_{19}H_{20}N_2O_8$: C, 56.42; H, 4.99; N. 6.93. Found: C, 56.43; H, 4.80; N 6.89.

(±) Methyl 7-(3-nitrophenyl)-5,8a-dimethyl-8-benzyloxycarbonyl-3-oxo-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate 9. (21%). M. p. 137°C (Ether). IR 1730, 1710, 1610 cm^{-1}. ^{1}H NMR δ 1.14 (3H, s, C_{8a}-Me), 2.85 (3H, d, J=2.0Hz, C_5-Me), 3.31 (1H, s, H_8), 3.58 (3H, s, OMe), 3.82 (1H, d, J=14.6 Hz, H_2), 4.22 (1H, d, J=14.6Hz, H_2), 4.47 (1H, s, H_7), 5.18 (1H, d, J=12.1Hz, $C\underline{H}_2$Bn), 5.26 (1H, d, J=12.1 Hz, $C\underline{H}_2$Bn), 7.3-7.5 (5H, m, $H_{\text{arom.}}$ Bn), 8.1 (2H, m, $H_{2'}$ and $H_{4'}$), 7.3-7.6 (2H, m, $H_{5'}$ and $H_{6'}$). ^{13}C NMR δ (Table 1). Anal. Calcd for $C_{25}H_{24}N_2O_8$: C, 62.48; H, 5.04; N 5.83. Found: C, 61.79; H, 4.84; N, 5.69.

(±)-Methyl 7-(3-nitrophenyl)-5,8a-dimethyl-8-*t*-butoxycarbonyl-3-oxo-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate 10. (20%). M. p. 195°C (MeOH). IR 1715, 1690 cm^{-1}. ^{1}H NMR δ 1.15 (3H, s, C_{8a}-Me), 1.50 (9H, s, $C(C\underline{H}_3)_3$), 2.85 (3H, d, J =2.0 Hz, C_5-Me), 3.14 (1H, s, H_8), 3.58 (3H, s, OMe), 4.19 (1H, d, J=14.6 Hz, H_2), 4.38 (1H, d, J =14.6 Hz, H_2), 4.42 (1H, s, H_7), 7.4-7.6 (2H, m, $H_{5'}$ and $H_{6'}$), 8.1 (2H, m, $H_{2'}$ and $H_{4'}$). ^{13}C NMR δ (Table 1). Anal. Calcd for $C_{22}H_{26}N_2O_8$: C, 59.17; H, 5.87; N, 6.28. Found: C, 58.29; H, 5.81; N, 6.13.

(±)-Dimethyl 7(3-chlorophenyl)-2,5,8a-trimethyl-3-oxo-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-*a*]pyridine-6,8-dicarboxylate 16. (40%). IR ($CHCl_3$) 1745, 1720, 1630 cm^{-1}. ^{1}H NMR δ 1.22 (3H, s, C_{8a}-Me), 1.45 (3H, d, J=6.9 Hz, C_2-Me), 2.82 (3H, d, J =2 Hz, C_5-Me), 3.19 (1H, s, H_8), 3.55 (3H, s, C_{10}-OMe), 3.77 (3H, s, C_{11}-OMe), 4.28 (1H, c, J=6.9 Hz, H_2), 4.31 (1H, s, H_7), 7.1-7.3 (4H, m, $H_{\text{arom.}}$). ^{13}C NMR δ (Table 1).

(±)-Dimethyl 7-(3-nitrophenyl)-2,5,8a-trimethyl-3-oxo-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-*a*]pyridine-6,8-dicarboxylate 17. (15%). M. p. 168-169°C (MeOH). IR (KBr) 1740, 1710, 1620, 1530 cm^{-1}. ^{1}H NMR δ 1.13 (3H, s, C_{8a}-Me), 1.39 (3H, d, J=6.9 Hz, C_2-Me), 2.78 (3H, d, J=2 Hz, C_5-Me), 3.13(1H, s, H_8), 3.49 (3H, s, C_{10}-OMe), 3.72 (3H, s, C_{11}-OMe), 4.22 (1H, c, J=6.9 Hz, H_2), 4.38 (1H, s, H_7), 7.4-7.6 (2H, m, $H_{5'}$, $H_{6'}$), 8.02 (1H, m, $H_{4'}$), 8.04 (1H, m, $H_{2'}$). ^{13}C NMR δ (Table 1). Anal. Calcd for $C_{20}H_{22}N_2O_8$: C, 57.41; H, 5.32; N, 6.74. Found: C, 59.31; H, 6.02; N, 7.01.

(+)-(2*R*, 7*S*, 8*R*, 8a*R*) Methyl 7-(3-chlorophenyl)-8-ethoxycarbonyl-3-oxo-2,5,8a-trimethyl-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-a]pyridine-6-carboxylate 23a. (26%). M. p. 132°(Hexane-ether). $[\alpha]_D$ +76.0 (c 2.00, $CHCl_3$). IR : 1750, 1730, 1580 cm^{-1}. ^{1}H NMR δ 1.23 (3H, s, C_{8a}-Me), 1.31 (3H, t, J=7.2 Hz, CH_2-$C\underline{H}_3$), 1.45 (3H, d, J=6.9 Hz , C_2-Me), 2.82 (3H, d, J=2.0 Hz, C_5-Me), 3.18 (1H, s , H_8), 3.55 (3H, s, OMe), 4.21 (2H, c, J=7.2 Hz, $C\underline{H}_2$-CH_3), 4.23 (1H, d, J=6.9 Hz , H_2), 4.28 (1H, s, H_7), 7.1-7.4 (4H, m, 4$H_{\text{arom.}}$). ^{13}C NMR δ (Table 1).

(-)-(2*S*, 7*R*, 8*S*, 8a*S*) Methyl 7-(3-chlorophenyl)-8-ethoxycarbonyl-3-oxo-2,5,8a-trimethyl-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-a]pyridine-6-carboxylate 23b. (48%). $[\alpha]_D$ -73.2 (c 0.71, $CHCl_3$).

(+)-(2*R*, 7*S*, 8*R*, 8a*R*)-Methyl 7-(3-chlorophenyl)-8-*t*-butyloxycarbonyl-3-oxo-2,5,8a-trimethyl-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-a]pyridine-6-carboxylate (24). (69%). M. p. 129°C (MeOH). $[\alpha]_D$ +69.3 (c 0.50, $CHCl_3$). IR (KBr) 1730, 1700, 1610 cm^{-1}. ^1H NMR δ 1.21 (3H, s, C_{8a}-Me), 1.44 (3H, d, J=7.5 Hz C_2-Me), 1.48 (9H, s, $(C\underline{H}_3)_3$), 2.81 (3H, d, J=2.0 Hz, C_5-Me), 3.06 (1H, s, H_8), 3.55 (3H, s, OMe), 4.25 (1H, s, H_7), 4.29 (1H, c, J=6.9 Hz, H_2), 7.09-7.26 (4H, m, 4Harom.) ^{13}C NMR δ (Table 1).

Table 1. ^{13}C NMR data of compounds: **6**, **7**, **8**, **9**, **10**, **16**, **17**, **23**, **24**, **25**.Solvent $CDCl_3$.
δ ppm. Internal standard TMS

C	6	7	8	9	10	16	17	23	24	25
2	67.0	67.0	67.0	67.2	67.0	74.9	74.8	74.6	74.9	74.6
3	166.2	168.7	169.0	168.1	168.2	168.3	168.0	168.2	168.5	166.2
5	144.9	145.3	145.1	145.1	145.2	145.2	145.2	145.0	145.2	145.0
6	92.5	92.3	92.5	92.4	92.5	92.1	91.0	91.2	91.6	91.1
7	42.3	42.2	42.4	42.3	42.4	42.5	42.4	42.3	42.5	42.3
8	54.3	54.6	54.1	54.6	55.6	54.5	54.2	54.7	56.0	54.7
8a	110.9	110.2	110.0	110.2	110.2	111.0	111.3	111.5	112.2	111.9
9	16.6	16.6	16.9	16.8	16.7	17.0	17.1	16.6	16.5	16.6
10	169.4	168.5	169.4	169.3	169.4	170.0	169.5	170.9	170.2	170.6
11	171.0	170.4	170.7	170.1	170.4	171.5	171.0	172.3	173.5	172.5
12	26.2	26.1	26.3	26.3	26.2	29.2	29.2	29.1	29.2	29.2
OMe	51.7	51.8	51.9	51.9	51.9	51.8	51.7	51.7	51.6	51.7
R_1	**Me**	**Bn**	**Me**	**Bn**	**^{t}Bu**	**Me**	**Me**	**Et**	**^{t}Bu**	**Bn**
	52.3	66.7 128.6(3) 128.7(2) 135.7	52.5	66.8 128.6(3) 128.7(2) 135.6	28.1 (3) 82.1	52.4	52.4	14.2 61.2	28.1 81.6	67.0 128.4(3) 128.6(2) 135.5
Me-C_2						19.6	19.4	19.5	19.6	19.4
Ar	**3-ClPh**	**3-ClPh**	**3-NO_2Ph**	**3-NO_2Ph**	**3-NO_2Ph**	**3-ClPh**	**3-NO_2Ph**	**3-ClPh**	**3-ClPh**	**3-ClPh**
1'	144.2	145.3	147.2	147.3	144.6	144.3	146.4	144.3	145.2	144.3
2'	127.3	127.3	122.5	122.5	122.4	127.3	122.3	127.2	127.2	127.2
3'	134.9	134.1	148.2	148.9	148.7	135.0	148.8	134.8	134.6	134.6
4'	125.5	125.5	122.2	122.2	122.0	125.5	122.1	125.4	125.2	125.4
5'	130.9	130.1	129.9	129.7	129.8	130.1	129.8	130.5	130.0	130.1
6'	127.7	127.5	133.4	133.4	133.4	127.8	133.3	127.8	127.8	127.6

(+)-(2*R*, 7*S*, 8*R*, 8a*R*)-Methyl 7(3-chlorophenyl)-8-benzyloxycarbonyl-3-oxo-2,5,8a-trimethyl-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-a]pyridine-6-carboxylate 25a (20%). $[\alpha]_D$ +71.1 (c 0.52, CHCl$_3$). IR 1740, 1710, 1600, 1380 cm^{-1}. ^{1}H NMR δ 1.21 (3H, s, C$_{8a}$-Me), 1.35 (3H, d, J=6.9 Hz, C$_2$-Me), 2.60 (3H, d, J=2.0Hz, C$_5$-Me), 3.23 (1H, s, H$_8$), 3.53 (3H, s, OMe), 3.90 (1H, c, J=6.9 Hz, H$_2$), 4.32 (1H, d, J=1.9 Hz, H$_7$), 5.15 (1H, d, J=11.7 Hz, $\underline{\mathrm{CH}_2}$Bn), 5.25 (1H, d, J=11.7 Hz, $\underline{\mathrm{CH}_2}$Bn), 7.09-7.10 (2H, m, H$_{5'}$, H$_{6'}$), 7.20-7.26 (1H, m, H$_{4'}$), 7.30-7.41 (6H, m, H$_{2'}$ and Bn). ^{13}C NMR δ (Table 1).

(-)-(2*S*, 7*R*, 8*S*, 8a*S*)-Methyl 7(3-chlorophenyl)-8-benzyloxycarbonyl-3-oxo-2,5,8a-trimethyl-8,8a-dihydro-2*H*, 7*H*-oxazolo[3,2-*a*]pyridine-6-carboxylate (25b). (20%). $[\alpha]_D$ -69.9 (c 1.5, CHCl$_3$)

General procedure for the preparation of dihydropyridines

500 mg (1.2 mmol) of the oxazolopyridine and 10 ml of KOH/MeOH 10%, were stirred at room temperature for 6 hours. The mixture was extracted with methylene chloride, washed with water, dried over Na$_2$SO$_4$ and concentrated in vacuo. By flash chromatography of the residue **11**, **13**, **26a**, **26b**, **27**, **28a** and **28b** were isolated.

(±)-Dimethyl 4-(3-chlorophenyl)2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 11. M. p. 194-196 (MeOH). IR 3290, 1680, 1625, 1460 cm^{-1}. ^{1}H NMR δ 2.33 (6H, s, Me$_7$ and Me$_{10}$), 3.65(6H, s, 2xOMe), 4.98 (1H, s, H$_4$), 5.90 (1H, s, N$\underline{\mathrm{H}}$), 7.1-7.3 (4H, m, H$_{\mathrm{arom.}}$).

(±)-Dimethyl 4-(3-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate 12. IR (KBr) 3430, 1725, 1725, 1560 cm^{-1}. ^{1}H NMR δ 2.62 (6H, s, Me$_7$ and Me$_{10}$), 3.61 (6H, s, 2xOMe), 7.10-7.40 (4H, m, H$_{\mathrm{arom.}}$).

(±)-Dimethyl 4-(3-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 13. IR 3300, 1690 cm^{-1} ^{1}H NMR δ 2.36 (6H, s, Me$_7$ and Me$_{10}$), 3.65 (6H, s, 2xOMe), 5.10 (1H, s, H$_4$), 5.99 (1H, s, N$\underline{\mathrm{H}}$), 7.38 (1H, t, J =7.8 Hz, H$_{5'}$), 7.64 (1H, dt, J_1=7.8 Hz, J_2=1.4 Hz, H$_{6'}$), 8.01 (1H, ddd, J_1=7.8 Hz, J_2=2.2 Hz, J_3=1,4 Hz, H$_{4'}$), 8.18 (1H, dd, J_1=2.2 Hz, J_2=1,4 Hz, H$_{2'}$). ^{13}C NMR δ 19.6 (C$_7$ and C$_{10}$), 39.6 (C$_4$), 51.3 (2xOMe), 103.1 (C$_3$ and C$_5$), 121.4 (C$_{4'}$),122.7 (C$_{2'}$), 128.6 (C$_{6'}$), 134.3 (C$_{5'}$), 145.1 (C$_2$ and C$_6$), 148.4 (C$_{3'}$), 149.6 (C$_{1'}$), 167.6 (C$_8$ and C$_9$).

(-)-(4*S*)-Methyl 4-(3-chlorophenyl)-2,6-dimethyl-3-ethoxycarbonyl-1,4-dihydropyridine-5-carboxylate 26a. (43%). M. p. 136°C (MeOH). $[\alpha]_D$ -6.0 (c 0.83, CHCl$_3$). IR 3290, 1700, 1670, 1500 cm^{-1}. ^{1}H NMR δ 1.23 (3H, t, J=7.1 Hz, CH$_2$-$\underline{\mathrm{CH}_3}$), 2.29 (6H, s, Me$_7$ and Me$_{10}$), 3.64 (3H, s, OMe), 4.10 (2H, c, J=7.1 Hz, $\underline{\mathrm{CH}_2}$-CH$_3$), 4.90 (1H, s, H$_4$), 6.45 (1H, s, N$\underline{\mathrm{H}}$), 7.09-7.28 (4H, m, 4H$_{\mathrm{arom.}}$). ^{13}C NMR δ 14.2 (CH$_2$-$\underline{\mathrm{C}}H_3$), 19.3 (C$_7$ and C$_{10}$), 39.8 (C$_4$), 50.9 (OMe), 59.8 ($\underline{\mathrm{C}}$H$_2$-CH$_3$), 103.2 and 103.5 (C$_3$ and C$_5$), 126.0 (C$_{4'}$), 126.2 (C$_{2'}$), 127.9 (C$_{6'}$), 129.1 (C$_{5'}$), 133.7 (C$_{3'}$), 144.5 and 144.7 (C$_2$, C$_6$), 149.2 (C$_{1'}$), 167.5 and 167.9 (C$_8$, C$_9$).

(+) (4*R*)-Methyl 4-(3-chlorophenyl)-2,6-dimethyl-3-ethoxycarbonyl-1,4-dihydropyridine-5-carboxylate 26b. (82%). M. p. 144°C (MeOH). $[\alpha]_D$ +5.5 (c 0.70, CHCl$_3$)

(-)-(4*S*)-Methyl 4-(3-chlorophenyl)-2,6-dimethyl-3-*t*-butoxycarbonyl-1,4-dihydropyridine-5-carboxylate 27. (80%). $[\alpha]_D$ -9.1 (c 1.50, CHCl$_3$). IR 3270, 1710, 1600, 1590 cm^{-1}. ^{1}H NMR δ 1.40 (9H, s, ($\underline{\mathrm{CH}_3}$)$_3$), 2.26 and 2.27 (3H, s, Me$_7$ and Me$_{10}$), 3.63 (3H, s, OMe), 4.91 (1H, s, H$_4$), 6.21 (1H, s, N$\underline{\mathrm{H}}$), 7.09-7.27 (m, 4H$_{\mathrm{arom.}}$). ^{13}C NMR δ 19.2 and 19.3 (C$_7$ and C$_{10}$), 28.3 (C($\underline{\mathrm{C}}$H$_3$)$_3$), 39.3 (C$_4$), 50.8 (OMe), 80.5 ($\underline{\mathrm{C}}$(CH$_3$)$_3$), 102.9 (C$_3$, C$_5$), 105.1 (C$_3$ and C$_5$), 126.1 (C$_{4'}$, C$_{2'}$), 128.0 (C$_{6'}$), 129.0 (C$_{5'}$), 133.6 (C$_{3'}$), 143.3 and 144.7 (C$_2$, C$_6$), 149.8 (C$_{1'}$), 166.8 and 168.0 (C$_8$ and C$_9$).

(+)-(4*S*) Methyl-4-(3-chlorophenyl)-2,6-dimethyl-3-benzyloxycarbonyl-1,4-dihydropyridine-5-carboxylate 28a. $[\alpha]_D$ +9.3 (c 0.48, $CHCl_3$). IR (KBr) 3390, 1710, 1660, 1500 cm^{-1}. ^1H NMR δ 2.32 and 2.34 (3H, s, Me_7 and Me_{10}), 3.62 (3H, s, OMe), 4.98 (1H, s, H_4), 5.01 (1H, d, *J*=12, CH_2-Bn), 5.15 (1H, d, *J*=12.1 Hz, CH_2Bn), 7.09-7.37 (9H, m, $H_{arom.}$). ^{13}C NMR δ: 19.6 (C_7 and C_{10}), 39.4 (C_4), 51.1 (OMe), 65.8 (CH_2-Bn), 103.2 (C_3 and C_5), 126.2 ($C_{4'}$), 126.3 ($C_{2'}$), 127.8 ($C_{6'}$), 128.4 (3xBn), 128.5 (2xBn), 129.1 ($C_{5'}$), 133.7 ($C_{3'}$), 136.3 (Bn), 144.2 and 144.9 (C_2 and C_6), 149.4 ($C_{1'}$), 167.0 and 167.7(C_8 and C_9).

(-)-(4*R*)-Methyl 4-(3-chlorophenyl)-2,6-dimethyl-3-benzyloxycarbonyl-1,4-dihydropyridine-5-carboxylate 28b. $[\alpha]_D$ -10.1 (c 0.60, $CHCl_3$).

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