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STEREOSPECIFIC SYNTHESES OF ERYTHRO AND THREO 5-(1',2'-DIHYDROXYETHYL)-3-ARYL-OXAZOLIDIN-2-ONES.

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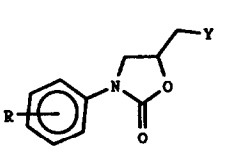
Abstract : The synthesis of 5-(1',2'-dihydroxyethyl)3-aryl-oxazolidin-2-ones **2** and **3** as pure threo and erythro diastereomers, analogs inhibitors of the enzyme monoamine oxidase MAO, is achieved in five step sequence from 1,4-dihalogeno-2-butenes (E) or (Z) through a key stereospecific tandem process based on a Payne rearrangement followed by a nucleophilic intramolecular cyclization of epoxycarbamates **7**.

For a few years, the oxazolidin-2-one moiety has been considered as the crucial structural feature of many important biologically active compounds. Some of them have been shown to be new therapeutic agents such as antispastics [1], antidepressants [2] or antibiotics. [3] For example, Toloxatone (**1a**), a competitive and reversible inhibitor of the type A monoamine oxydase (MAO A), is a leader of an old class of antidepressants which has gained a renewed interest. [2] Two other oxazolidinones, DuP 105 and 721 (**1b**, **1c**) constitute the clinical precursors of a new series of potent and original antibiotics. [3]



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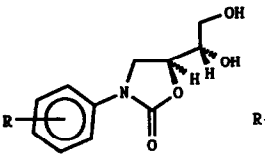
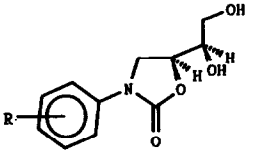


2 THREO



3 ERYTHRO

	1	**2** THREO	**3** ERYTHRO
Toloxatone	a : R = m.CH_3 Y = OH	a : R = H	d : R = p.CH_3
DuP 105	b : R = p.CH_3SO Y = $NHCOCH_3$	b : R = o.CH_3	e : R = p.(3'CH_3-$C_6H_4CH_2O$)
DuP 721	c : R = p.CH_3CO Y = $NHCOCH_3$	c : R = m.CH_3	f : R = p.(3'Cl-$C_6H_4CH_2O$)

Despite the chemical effort described, [4] the functionalization of the oxazolidinone heterocycle in a regio- and stereo-defined manner remains a synthetic challenge. [5] A very interesting intramolecular cyclization has been recently proposed by Roush's and Kishi's groups [6] based on a stereodirected process starting with a regioselective nucleophilic attack of a carbamate on an epoxide leading to functionalized oxazolidinones at C-4 carbon (**4** ⟶ **5**).

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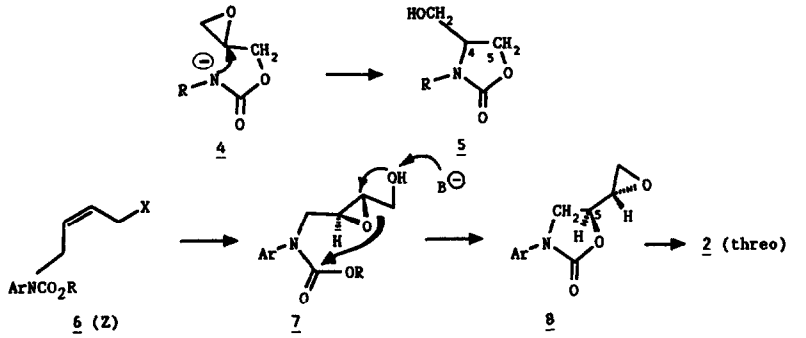
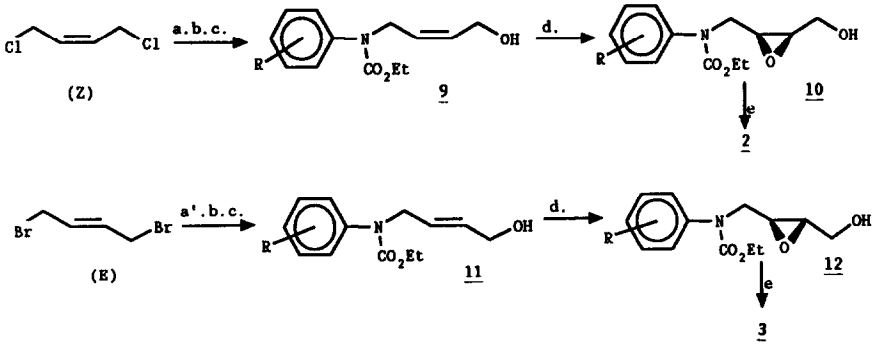
To our knowledge, there is so far no general oxazolidinone synthesis based on the opposite strategy in which the carbamate moiety is the electrophilic part in the oxirane mediated reaction. In our research program related to the preparation of new oxazolidinones inhibitors of MAO A or B, we devised a new and efficient method for the preparation of oxazolidinones **2** and **3**.[7] This methodology is based on a tandem cyclization with a sequential Payne rearrangement[8] followed by nucleophilic attack of the alkoxide anion on the carbamate moiety leading to the oxazolidinones functionalized at the C-5 position as shown, **6** ⟶ **8** for the threo series.



6 (Z) **7** **8**

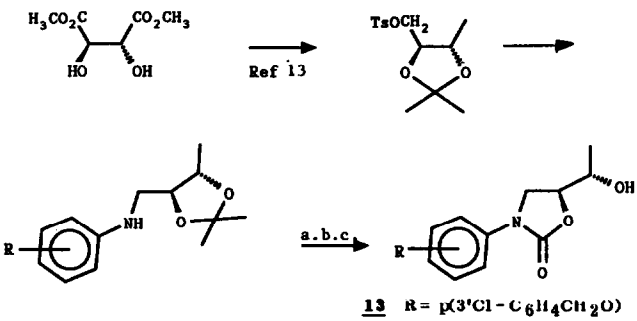
X = H, OCOR

With this strategy, pure threo and erythro 5-(1',2'-dihydroxyethyl)-3-aryl-oxazolidin-2-ones **2** and **3** could be obtained : the erythro from stereomeric (E) 1,4-hydroxy carbamate appropriately substituted : the threo series from the corresponding (Z) derivatives (**8** ⟶ **2**).
For the preparation of the desired epoxy-alcohol carbamates, we have developed a direct and convenient route from commercially available 1,4-dihalogeno-2-butenes (Z) and (E). The N-Li or N-Na salts of substitued arylcarbamates were added to two equivalents of 1,4-dichloro or dibromo-2-butenes (Z) or (E), affording the pure allylic carbamate **9** or **11** in 90 % yield. The remaining halogen was cleanly displaced by potassium acetate in DMF followed by direct treatment with potassium carbonate in methanol. The corresponding crude alcohols obtained in >70 % overall yield were used without purification. A quantitative epoxidation with MCPBA gave for each series the pure stereomeric epoxides ready to cyclize. After many attempts[9], we found experimental conditions allowing a very clean cyclisation for **10** or **12** : a solution of 0.3 eq. of NaOH (0.3 N) in t.BuOH/H_2O (1 : 5) at 80°C gave **2** and **3** in 70-80 % yield. The erythro compound (**3**) showed by ^1H-NMR a doublet of doublets (J = 3.5 Hz) for the methine proton bearing the secondary alcohol, consistently downfield compared to the multiplet observed in the threo series. There was no contamination of each series by the other one,[10] supporting a clean and efficient tandem Payne rearrangement and nucleophilic cyclization on the carbamate moiety.



Reagents : a) $ArNHCO_2Et$, NaH (1 eq.), DMF, 40°C, 5 h ; a') $ArNHCO_2Et$, BuLi (1 eq.), THF - DMF, - 78°C,0°C, 1 h ; b) AcONa (4 eq.), DMF, 80°C, 8 h ; c) K_2CO_3 (3 eq.), MeOH ; d) MCPBA(1 eq.), CH_2Cl_2, - 70°C,2 h ; e) NaOH (0.3 eq.), t.BuOH/H_2O (1 / 5), 80°C,1h

In order to establish the relative erythro/threo stereochemistry of compounds **2** and **3**, an unambigous synthesis of oxazolidinone **13** (threo)[11] with a (1'-hydroxyethyl) side chain at C-5 was achieved from the R,R (+) dimethyl tartaric ester. In an another part of our program we had in hand the preparation of the erythro series also with a 1'-hydroxyethyl side chain at C-5.[12]



13 R= p(3'Cl-$C_6H_4CH_2O$)

Reagents : a) R-C_6H_4-NH_2 (1 eq.), Et_3N (1 eq.), isopropanol, reflux 6 h ; b) HCl 6N, reflux, 2h; c) $(EtO)_2CO$ (1.2 eq.), CH_3ONa (cat.), toluene, reflux, 1 h.

The correlation between the dihydroxy series **3** and the corresponding monohydroxy oxazolidinones was established by a classical two step sequence. For example the primary hydroxyl function of **3f** was selectively tosylated in pyridine and reduced with $NaBH_4$ in DMSO at 40°C[14] to give the corresponding erythro stereomer .[15]

In conclusion, we have developed a new methodology for the stereoselective preparation of C-5 functionalized oxazolidinone-diols. These derivatives were tested in vitro for their inhibitory activity on MAO A and B from synaptosomes of rat brain. Two of them the **2f (threo)/3f (erythro)**

derivatives have shown an inhibitory activity of the B form of this enzyme with a very high selectivity.[2]

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9 - Using standard Payne conditions [8a] there was no reaction. In this crucial step higher concentration of base and reaction temperature > 80 °C gave a low chemical yield (10 %) with formation of a large number of side products.

10 - **2c** (threo) : m.p. = 112°C ; IR (film) : 3500,1730 cm^{-1} ; ^1H-NMR (DMSO-d_6, 500 MHz) : 2.32 (s,3H); 3.49 (d,2H) ; 3.52 (m,1H) ; 3.89-4.07 (dt,2H) ; 4.7-4.78 (m,2H) ; 5.22 (d,1H) ; 6.91 (d,1H) ; 7.24 (t,1H) ; 7.37 (d,2H) ; **3c** (erythro) : m.p. = 124°C. IR (film) cm^{-1} : 3450-1730 ^1H-NMR (DMSO-d_6, 500 MHz) : 2.31 (s,3H) ; 3.42 (m,2H) ; 3.73 (m,1H) ; 3.97 (dd,2H) ; 4.69 (m,1H) irradiation at 3.97 gave a doublet (J_{ab} = 3.5Hz) ; 4.77 (m,1H) ; 5.35 (d,1H) ; 6.80 (d,1H) ; 7.23 (t,1H); 7.38 (d,2H). Calc. (found) % : C : 60.75 (60.64) ; H : 6.33 (6.29) ; N : 5.9 (5.88).

11 - **13** (threo) : m.p. = 90°C ; $(\alpha)_D^{20}$ = +41° (C=1, CH_2Cl_2) R_f = 0.45 (silica gel, eluent : AcOEt/heptane : 80/20) ; IR (film) : 3100, 3300, 1700 cm^{-1} ; NMR ($CDCl_3$, 200 MHz) ; 1.37 (d,3H,J = 7Hz) ; 1.85, (OH) ; 3.8-4 (m,3H) ; 4.43-4.53 (m,1H) ; 5.02 (s,2H); 6.9-7.5 (m,8H).

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15 - Erythro stereomer : m.p. 87°C, R_f = 0.52 (silicagel, eluent AcOEt/heptane : 80/20) ; IR (film) : 3100-3300, 1700 cm^{-1} ; NMR ($CDCl_3$, 200 MHz) : 1.25 (d,3H,J = 7Hz) ; 2.1, (OH) ; 3.9-4.19 (m,3H) ; 4.4-4.5 (m,1H) ; 5.02 (s,2H) ; 6.9-7.47 (m,8H). The NMR , IR and TLC data of this material were identical with those obtained for the same derivative described in reference 12.

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