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A DIASTEREOSELECTIVE SYNTHESIS OF GIROLLINE

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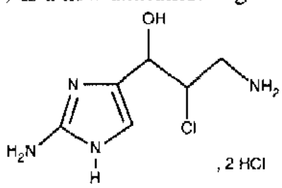
Summary: *Girolline (RP 49532, 1), a new antitumour agent, was prepared in the racemic series using an oxidation-reduction sequence starting from (±)-erythro-β-chloro-γ-hydroxy- 1-triphenylmethyl- -1H-4-imidazolepropanamine 3. The heterocyclic amino function was introduced via the coupling reaction of 9 with an aryldiazonium salt, followed by the reduction-deprotection of the 2-arylazo derivative **10**.*

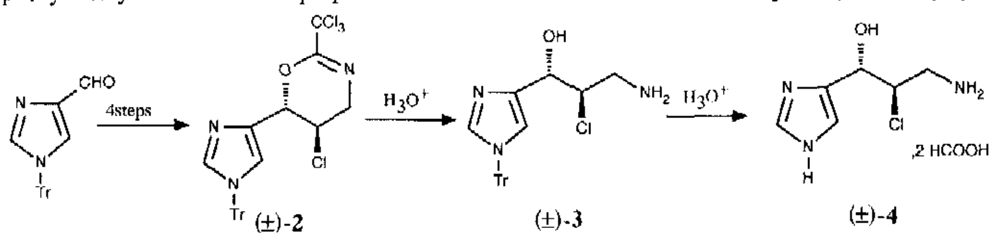
Girolline (RP 49532 ,**1**) is a new antitumour agent extracted from a New Caledonian marine sponge[1].



1 *(threo)*

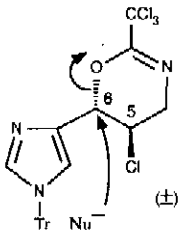
Until now, its configuration has not been determined. Therefore, a practical method was required in order to allow the preparation of each diastereoisomer and to provide sufficient material for further pharmacological studies.

We have previously described[2] a diastereoselective preparation of (±)-*erythro*-β-chloro-γ-hydroxy- -1-triphenylmethyl-1H-4-imidazolepropanamine **3** which afforded (±) *erythro*-β-chloro-γ-hydroxy-



-1H-4-imidazolepropanamine **4** after N-triphenylmethyl (Tr) deprotection. The *erythro* compound **4** was used to assign the *threo* configuration to the natural product[3].

Our first attempts to prepare the epimer of (±)-aminochlorohydrin **3** starting from compounds **2**, **5** or **6** were fruitless. For example, the ring opening of **2** did occur using potassium acetate in acetic acid at reflux,



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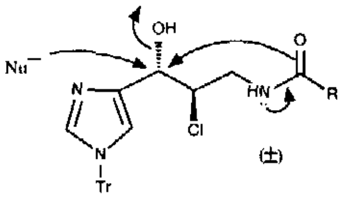
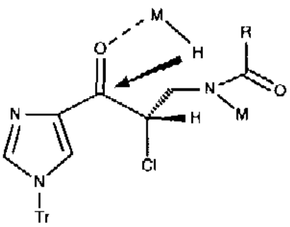


5 : R=OtBu
6 : R=CCl_3

but with only partial inversion at carbon-6. Furthermore, activation of the hydroxy function of **5** or **6** could not be easily achieved, due to its low reactivity.

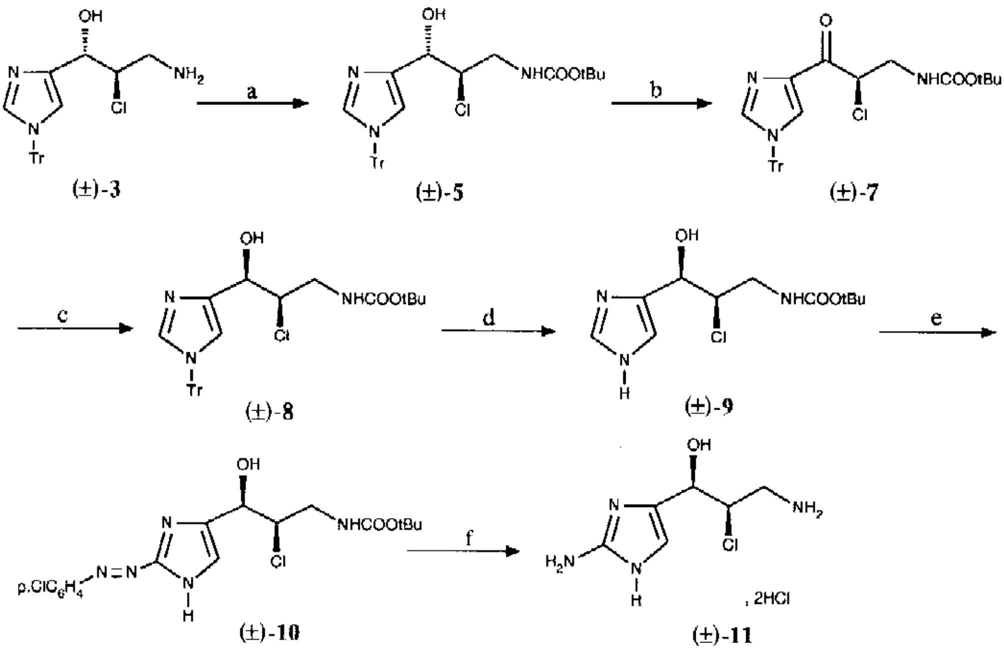
A remaining option was an oxydation-reduction sequence. This required the preparation of an α-chloro ketone followed by a diastereoselective reduction. According to the dipolar model represented below[4], such a ketone should be reduced selectively using a non-electrophilic and sterically hindered hydride such as L-Selectride.



Due to the low stability of RP 49532 in a basic medium, the tert-butoxycarbonyl group was selected for the protection of the primary amine.

Treatment of compound **3** with di-tert-butyl dicarbonate gave **5**[5] in 90% yield. Oxidation was achieved using manganese dioxide (88% yield), and the stable α-chloroketone **7** was diastereoselectively reduced, using L-Selectride in THF at -70°C, to afford the predicted (±)-*threo*-aminochlorohydrin **8** (80% *yield; 100% d.e.-established by HPLC)*.

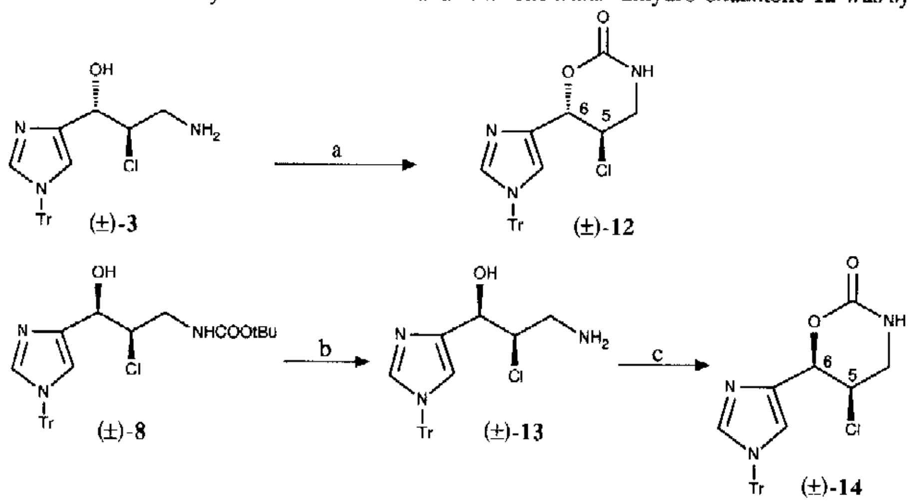
The classical route to 2-aminoimidazoles proceeds *via* the coupling of an aryldiazonium salt with an unprotected imidazole[6]. Thus, the N-triphenylmethyl group of compound **8** was specifically cleaved in refluxing n-propanol to give **9** in 84% yield[7]. Coupling of the latter with p-chlorophenyldiazonium chloride in aqueous basic medium afforded the 2-arylazo-imidazole **10** as the major product (58% yield). The protecting group of the chain amino function was maintained throughout the above sequence in order to prevent triazene formation. Hydrogenation over platinum oxide with concomitant *in situ* deprotection in hydrochloric methanol afforded, after chromatographic purification, (±)-*threo*-2-amino-β-chloro-γ-hydroxy--1H-4-imidazolepropanamine **11** (45% yield). This compound exhibited the same physical and analytical data as the natural product. HPLC analysis on a chiral stationary phase[8] confirmed that **11** is a 1:1 mixture of



Reagents: (a) $(BOC)_2O$, CH_2Cl_2, 20°C, 1 h. (b) MnO_2 (20 equiv.), CH_2Cl_2, reflux, 5 h. (c) $(i\text{-}Bu)_3BLiH$, THF, -70°C, then NH_4Cl/H_2O. (d) n-PrOH, AcOH (cat.), reflux, 24 h. (e) MeOH, H_2O, Na_2CO_3, 2°C then $p\text{-}ClC_6H_4N_2^+Cl^-$, H_2O, 2°C, 20 min. (f) H_2 (1atm.), PtO_2(10%), MeOH, HCl (2 equiv.), 20°C, 24 h. then HCl(excess).

RP 49532 and its enantiomer. Moreover, **11** displayed the same profile of biological activity as RP 49532, but with a two-fold decrease in potency.

The *erythro* and *threo* configurations of compounds **5** and **9** , respectively, were confirmed by ^{1}H-NMR studies of their cyclic derivatives **12** and **14**. The *trans* dihydro-oxazinone **12** was synthesized



Reagents: (a) Im_2CO (2 equiv.), $CHCl_3$, 20°C, 3 h. (b) Et_2O, HCl (2 equiv.), 20°C, 7 h. (c) Im_2CO (1 equiv.), $CHCl_3$, 20°C, 7 h.

from **3** by reaction with 1,1'-carbonyldiimidazole (85% yield). The *cis* dihydro-oxazinone **14** was prepared from **8** by a selective deprotection of the t-butoxycarbonyl group (47% yield) followed by a cyclisation of the intermediate **13** with 1,1'-carbonyldiimidazole (56% yield). The vicinal coupling constants for dihydro-oxazinones **12** ($J_{5H,6H}$=4Hz) and **14** ($J_{5H,6H}$=1Hz) are unambiguously in favour of a *trans* and a *cis* orientation of the H-5 and H-6 atoms, respectively.

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References and notes:

1 - A. Ahond, M. Bedoya-Zurita, M. Colin, C. Fizames, P. Laboute, F. Lavelle, D. Laurent, C. Poupat, J. Pusset, M. Pusset, O. Thoison and P. Potier, *C. R. Séances Acad. Sci. Paris*, (série 2), **307**, 145 (1988).
2 - A. Commerçon and G. Ponsinet, *Tetrahedron Lett.*, **31**, 3871 (1990).
3 - M. Bedoya Zurita, A. Ahond, C. Poupat and P. Potier, *Tetrahedron*, **45**, 6713 (1989).
4 - M. Nogradi, "*Stereoselective Synthesis*", VCH Publ., 131-148 (1987) and references therein.
5 - All new compounds exhibited IR, ^{1}H and ^{13}C-NMR spectra, mass spectral or combustion data in agreement with the structures indicated. We mention below the ^{1}H-NMR data and, in some cases, the melting points for material crystallizing directly upon removal of solvent from a chromatography fraction.
5: mp:168°C, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.42(d,1H,J=2Hz), 7.35(m,9H), 7.15(m,6H), 6.84(br d,1H), 4.67(br d,1H,J=7.5Hz), 4.32(td,1H,J=7.5Hz,5Hz), 3.85(ddd,1H,J=15Hz,5Hz), 3.50(ddd,1H,J=15Hz,5Hz); 1.45(s,9H).
7: foam, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.70(br d,1H), 7.52(d,1H,J=1.5Hz), 7.40(m,9H), 7.15(m,6H), 5.50(t,1H,J=6Hz), 3.80(ddd,2H,J=7Hz,6Hz), 1.43(s,9H).
8: mp:132°C, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.44(br d,1H,J=1.5Hz), 7.35(m,9H), 7.15(m,6H), 6.92(br s,1H), 4.98(br d,1H,J=3Hz), 4.35(td,1H,J=6.5Hz,3Hz), 3.70(ddd,1H,J=15Hz,6.5Hz), 3.40(ddd,1H,J=15Hz,6.5Hz), 1.45(s,9H).
9: foam, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.64(s,1H,), 7.13(s,1H), 5.00(d,1H,J=3.5Hz), 4.36(td,1H,J=6Hz,7Hz), 3.73(ddd,1H,J=15Hz,7.5Hz), 3.40(ddd,1H,J=15Hz,6Hz), 1.48(s,9H).
10: mp:194°C, ^{1}H NMR(200MHz, DMSO)δ 7.87(dd,2H,J=8.5Hz), 7.66(dd,2H), 7.32(s,1H), 4.92(m,1H), 4.42(m,1H), 3.40(m,2H), 1.43(s,9H).
11: foam, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.45(br s,1H), 7.30(m,9H), 7.10(m,6H), 6.92(br s,1H), 5.40(br d,1H,J=4Hz), 4.70(br dd,1H,J=14Hz,4Hz), 3.40 and 3.80(ABX,2H,J=14Hz,4Hz,4Hz).
13: foam, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.42(d,1H,J=1.5Hz), 7.33(m,9H), 7.15(m,6H), 6.90(br d,1H), 5.08(d,1H,J=3Hz), 4.40(td,1H,J=5Hz,4Hz), 3.33(dd,1H,J=14Hz,4Hz), 3.16(dd,1H,J=14Hz,5Hz).
14: foam, ^{1}H-NMR(250MHz, $CDCl_3$)δ 7.55(br d,1H,J=1.5Hz), 7.30(m,9H), 7.10(m,6H), 7.00(br d,1H,J=1.5Hz), 5.80(br s,1H), 4.83(m,1H), 3.6 and 3.95(ABX,2H,J=14Hz,4Hz,1.5Hz).
6 - W. Nagai, K.L. Kirk and L.A. Cohen, *J. Org. Chem.*, **38**, 1971 (1973).
7 - K.L. Kirk, *J. Heterocyclic Chem.*, **22**, 57 (1985).
8 - HPLC analyses were performed on a Crownpak CR column provided by Daicel, Japan : J. Cousin, Rhône-Poulenc Rorer, unpublished results.

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