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DIASTEREOSELECTIVE CHLOROCYCLOFUNCTIONALIZATION OF N-ALLYLIC TRICHLOROACETAMIDES : SYNTHESIS OF AN ANALOGUE AND POTENTIAL PRECURSOR OF RP49532

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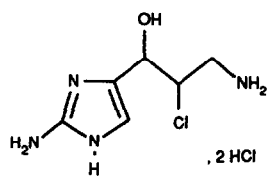
Summary: *Treatment of (E)-N-cinnamyl trichloroacetamide with hypochlorous acid yielded trans-dihydro-oxazine 8 which was easily hydrolyzed to (±)-erythro-β-chloro-γ-hydroxy-γ-phenyl-propanamine 2. Applied to the imidazole series, this chlorocyclization gave 15, a potential intermediate in the synthesis of RP49532.*

RP49532 (1), known as "girolline", is a natural product extracted from the New Caledonian marine sponge *Pseudaxinissa cantharella.* This compound exhibited high *in vitro* and *in vivo* antitumoral activities on P388 leukaemic cells[1].



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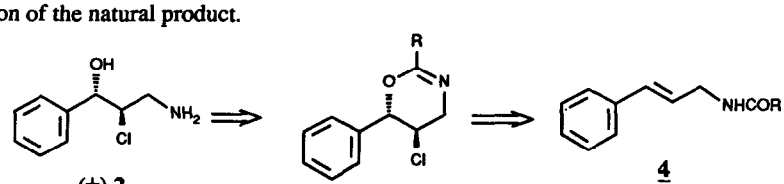
Due to the difficulty of obtaining large amounts of natural product from sponges and in order to provide sufficient material for pharmacological and clinical evaluations, a practical approach to the synthesis of RP49532 was required. Furthermore we considered useful to possess a general methodology for the preparation of various β-chloro-γ-hydroxy-γ-substituted-propanamines, applicable either to the synthesis of the natural product in the imidazole series or in other heterocyclic series and enabling structure-activity relationship studies.

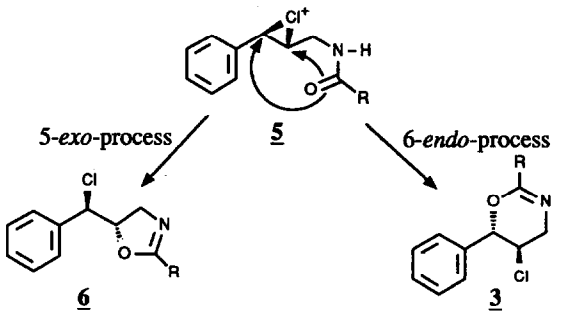
Because the configuration of RP49532 was unknown, it was necessary to synthesize each of the diastereomers unambiguously. A diastereoselective and general method to prepare *erythro* compounds such as 2 was applied. From our results Bedoya-Zurita *et al.*[2] could confirm the *threo* configuration of the natural product.



(±)-2 (±)-3 **4**

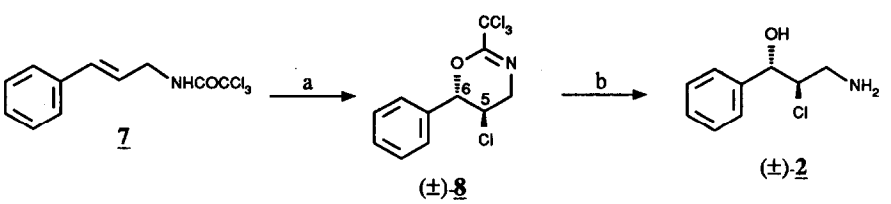
A retrosynthetic analysis allowed us to consider of potential interest the 5,6-dihydro-1,3-oxazines **3** which should yield the required aminochlorohydrins **2** after acidic hydrolysis. Compounds **3** seemed accessible from N-acylated allylic amines by intramolecular cyclization.

According to the results of Cardillo *et al.*, who described an intramolecular iodocyclization of O-allylic trichloroacetimidates[3-5], we expected that an analogous chlorocyclization process would occur with (E)-N-cinnamyl amide **4**, leading to the formation of intermediate **5**. This chloronium species could lead either to dihydro-oxazole **6** or to dihydro-oxazine **3**, following either a 5-*exo* or a 6-*endo* process, respectively.



The 6-*endo* closure, in contrast to the 5-*exo*, is generally disfavoured[6] due to geometrical factors, but seems possible in this case due to the presence of the phenyl group able to stabilize an incipient carbonium ion[7].

When the reaction was tested on N-allylic trichloroacetamide **7**, using hypochlorous acid generated *in situ* as a chloronium precursor, the product obtained was the six-membered ring **8**[8] (58% yield), as confirmed by the characteristic C=N IR absorption[3a] at ν=1690 cm^{-1}. As for the configuration of the product, the mechanistically predictable *trans* structure was confirmed by the ^{1}H-NMR spectrum of **8** in which the vicinal coupling constant ($J_{5H,6H}$= 7Hz) is in agreement with a *trans* axial orientation of the H-5 and H-6 atoms[3a,4a].

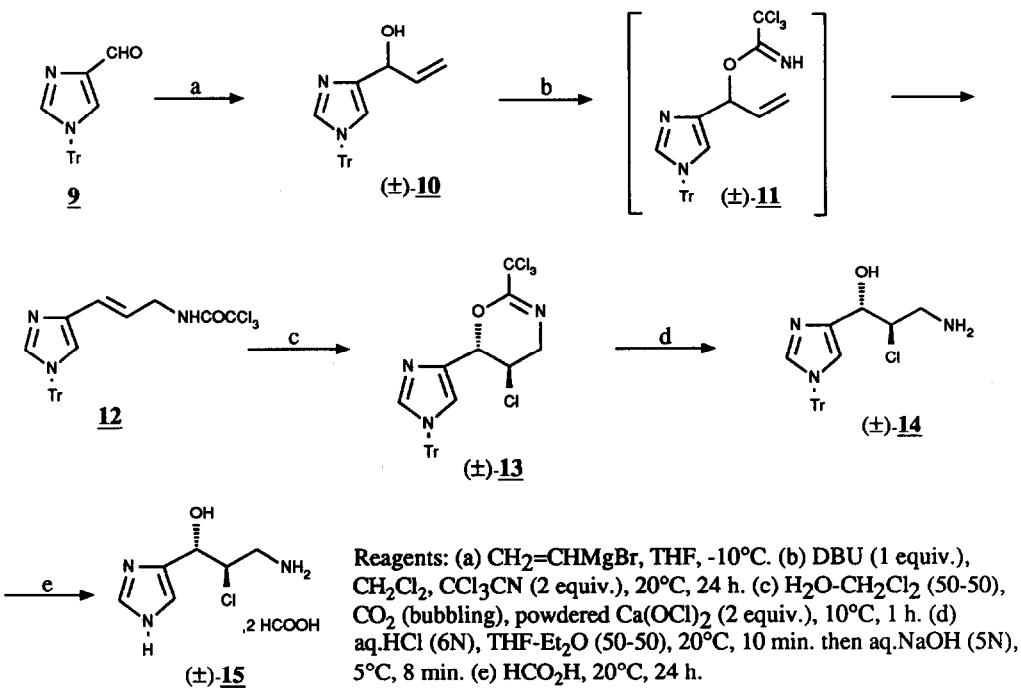


Reagents: (a) H_2O-Et_2O (50-50), CO_2 (bubbling) then powdered $Ca(OCl)_2$ (1.5 equiv.) 20°C, 1h. (b) aq.HCl (5N), MeOH, 20°C, 1 h., then aq.NaOH (5N), 0-5°C.

Hydrolysis of dihydro-oxazine **8** was performed using 5N hydrochloric acid. Thus the (±)-*erythro*-aminochlorohydrin **2** was diastereoselectively prepared (95% yield).

This methodology was then applied to the imidazole series. We expected that allylic alcohol **10**, obtained by condensation of vinyl magnesium bromide with N-triphenylmethyl (Tr) protected aldehyde **9**[9] (87% yield), would react with trichloroacetonitrile in presence of a strong base such as DBU to give the intermediate trichloroacetimidate **11**[10]. Surprisingly, **11** was not detected and led directly to the target (E)-N-allylic trichloroacetamide **12**, recovered in relatively low yield (22%)[11].

As in the benzene series, **12** reacted with hypochlorous acid to give the expected *trans*-dihydro-oxazine **13** in satisfactory yield (55%). Hydrolysis using 6N hydrochloric acid, followed by neutralization at 0°C, afforded (±)-*erythro*-aminochlorohydrin **14** (92% yield), still containing the N-trityl group[12].



9 (±)-**10** (±)-**11** **12** (±)-**13** (±)-**14** (±)-**15**

Reagents: (a) CH_2=CHMgBr, THF, -10°C. (b) DBU (1 equiv.), CH_2Cl_2, CCl_3CN (2 equiv.), 20°C, 24 h. (c) H_2O-CH_2Cl_2 (50-50), CO_2 (bubbling), powdered $Ca(OCl)_2$ (2 equiv.), 10°C, 1 h. (d) aq.HCl (6N), THF-Et_2O (50-50), 20°C, 10 min. then aq.NaOH (5N), 5°C, 8 min. (e) HCO_2H, 20°C, 24 h.

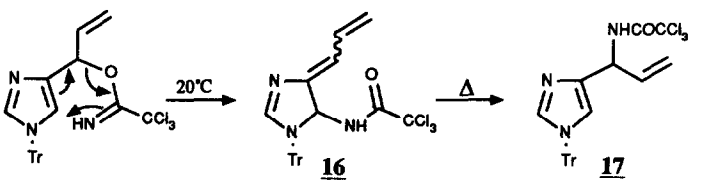
On treatment with concentrated hydrochloric acid or with formic acid, N-deprotection was achieved in 98% yield. Thus (±)-*erythro*-β-chloro-γ-hydroxy-1H-4-imidazolepropanamine **15**, an analogue and potential precursor of RP49532, was prepared in a diastereoselective manner.

Acknowledgement: we are indebted to M. Vuilhorgne and coll. for analytical assistance.

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 - M. Bedoya-Zurita, A. Ahond, C. Poupat and P. Potier, *Tetrahedron*, **45**, 6713 (1989) and footnotes therein.
3 - (a) A. Bongini, G. Cardillo, M. Orena, S. Sandri and C. Tomasini, *J. Org. Chem.*, **51**, 4905 (1986); (b) G. Cardillo, M. Orena, S. Sandri and C. Tomasini, *Tetrahedron*, **42**, 917 (1986).
4 - For the halocyclization of N-allylic p.nitrobenzamides see: (a) S.P. MacManus and R.A. Hames, *Tetrahedron Lett.*, **46**, 4549 (1973); (b) S.P. MacManus, D.W. Ware and R.A. Hames, *J. Org. Chem.*, **43**, 4288 (1978); (c) S.P. MacManus and D.W. Ware, *Tetrahedron Lett.*, **48**, 4271 (1974).
5 - Some aryl allylic urethanes reacted regioselectively with bromonium or iodonium dicollidine perchlorate to give six-membered ring products. See: K. A. Parker and R. O'Fee, *J. Am. Chem. Soc.*, **105**, 654 (1983).
6 - J. E. Baldwin, *J. Chem. Soc. Chem. Comm.*, 734 (1976).
7 - For a relevant report on O-allylic trichloroacetimidates see ref. 3a.
8 - 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.
2: oil, ^{1}H-NMR(400MHz, $CDCl_3$)δ 7.30 and 7.40(m,5H), 4.90(d,1H,J=7Hz), 4.05(bdd,1H), 3.15(br s,2H).
8: mp:75°C, ^{1}H-NMR(400MHz, $CDCl_3$)δ 7.30 and 7.50(m,5H), 5.40(d,1H,J=7Hz), 4.20(ddd,1H,J=7Hz,7Hz,5Hz), 3.80 and 4.00(AB quartet, 2H).
10: mp:170°C, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.45(br d,1H,J=1.5Hz), 7.35(m,9H), 7.15(m,6H), 6.74(br d,1H), 6.10(ddd,1H,J=17.5Hz,10Hz,6Hz), 5.40(br d,1H,J=17.5Hz), 5.20(m,2H).
12: mp:195°C, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.43(d,1H,J=1.5Hz), 7.35(m,9H), 7.16(m,6H), 7.06(br t,1H), 6.80(d,1H,J=1.5Hz), 6.50(br d,1H,J=15Hz), 6.33(t,1H,J=15Hz,6.5Hz), 4.10(t,2H,J=6.5Hz).
13: mp:168°C, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.45(d,1H,J=1.5Hz), 7.35(m,9H), 7.10(m,6H), 7.00(br d,1H,J=1.5Hz), 5.53(m,1H), 4.73(q,1H,J=3.5Hz), 3.90(dd,1H,J=17.5Hz,3.5Hz), 3.82(ddd,1H,J=17.5Hz,3.5Hz,8.5Hz).
14: foam, ^{1}H-NMR(200MHz, $CDCl_3$)δ 7.42(d,1H,J=2Hz), 7.33(m,9H), 7.15(m,6H), 6.88(br d,1H), 4.90(d,1H,J=7Hz), 4.30(td,1H,J=7Hz,6Hz), 3.15(m,2H).
15: foam, ^{1}H-NMR(200MHz, D_2O)δ 8.70(m,2H),8.55(br s,1H), 7.50(br s,1H), 5.22(m,1H), 4.55(m,1H), 3.62(dd,1H,J=13.5Hz,2Hz), 3.30(dd,1H,J=13.5Hz,9Hz).
9 - (a) J.L. Kelley, C.A. Miller and E.W. McLean, *J. Med. Chem.*, **20**, 721 (1977); (b) J.M. Kokosa, R.A. Szafasz and E. Tagupa, *J. Org. Chem.*, **48**, 3605 (1983).
10 - (a) L.E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976); (b) L.A. Clizbe and L.E. Overman, *Org. Synth.*, **58**, 4 (1978).
11 - In fact an unexpected [3,3]-sigmatropic rearrangement occurred competitively, involving the 4,5-double bond of the imidazole ring and leading to **16** as the major product. Compound **16** was transformed easily to **17** when heated.



12 - The *erythro* stereochemistry assigned to **14** was confirmed by ^{1}H-NMR studies on cyclic derivatives: A. Commerçon and C. Gueremy, in preparation.

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