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A Four-step Synthesis of *Erythro*-m-Chloro-3-hydroxytyrosine Ethyl Ester Enantiomerically Pure.

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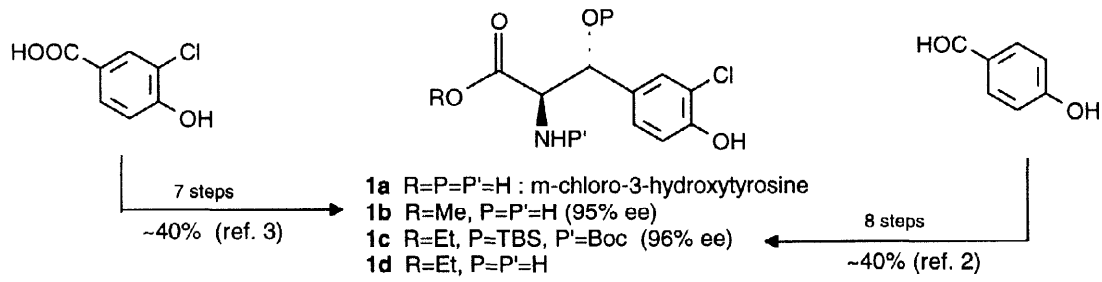
Abstract : Pure *erythro*-m-chloro-3-hydroxytyrosine having the (2*R*,3*R*)) configuration, a residue of Vancomycin and Aridicin A, has been prepared in 4 steps using an aldol addition involving a directly generated titanium enolate derived from a chiral iminoglycinate. (+)-Hydroxypinanone was used as a recoverable chiral auxiliary. The (2*S*,3*S*)-*erythro* isomer will be, of course, available from (-)-hydroxypinanone.

Erythro-(2*R*,3*R*)-m-chloro-3-hydroxytyrosine, **1a**, is present in important antibiotics such as Vancomycin, and Aridicin A.[1]

Until now two syntheses have been proposed, the key steps being either a Sharpless asymmetric dihydroxylation (**1c**)[2] or an asymmetric catalytic hydrogenation of a carbonyl followed by an electrophilic amination (**1b**).[3]



We report here a short, 4 steps, synthesis of *erythro*-(2*R*,3*R*)-m-chloro-3-hydroxytyrosine ethyl ester, **1d**, based on a diastereoselective aldol reaction using a titanium enolate directly generated from the chiral and enantiomerically pure (*RRR*)-iminoglycinate **3** and $ClTi(OEt)_3/NEt_3$ [4], Scheme 2. In this method the chiral auxiliary, (+)-(*RRR*)-hydroxypinanone **2**, is easily recovered (through extraction of the acidic aqueous phase obtained after HCl hydrolysis) and may, thus, be used again.

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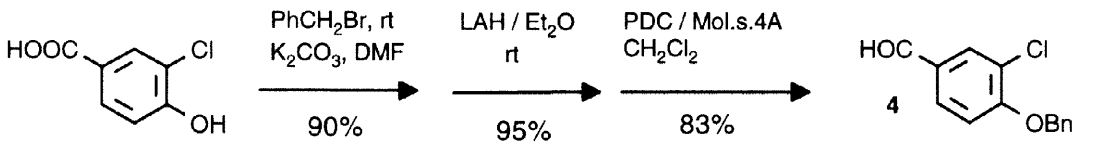
The iminoglycinate **3** was prepared in 95% yield from (+)-(*RRR*)-hydroxypinanone **2**[5] and ethyl glycinate according to a known procedure[6,7] using a catalytic amount of $BF_3.Et_2O$. And it is worth noting that p-TsOH lead to low yield (~50%).

The desired aldehyde **4** was obtained in three steps from the commercially available acid, Scheme 1.

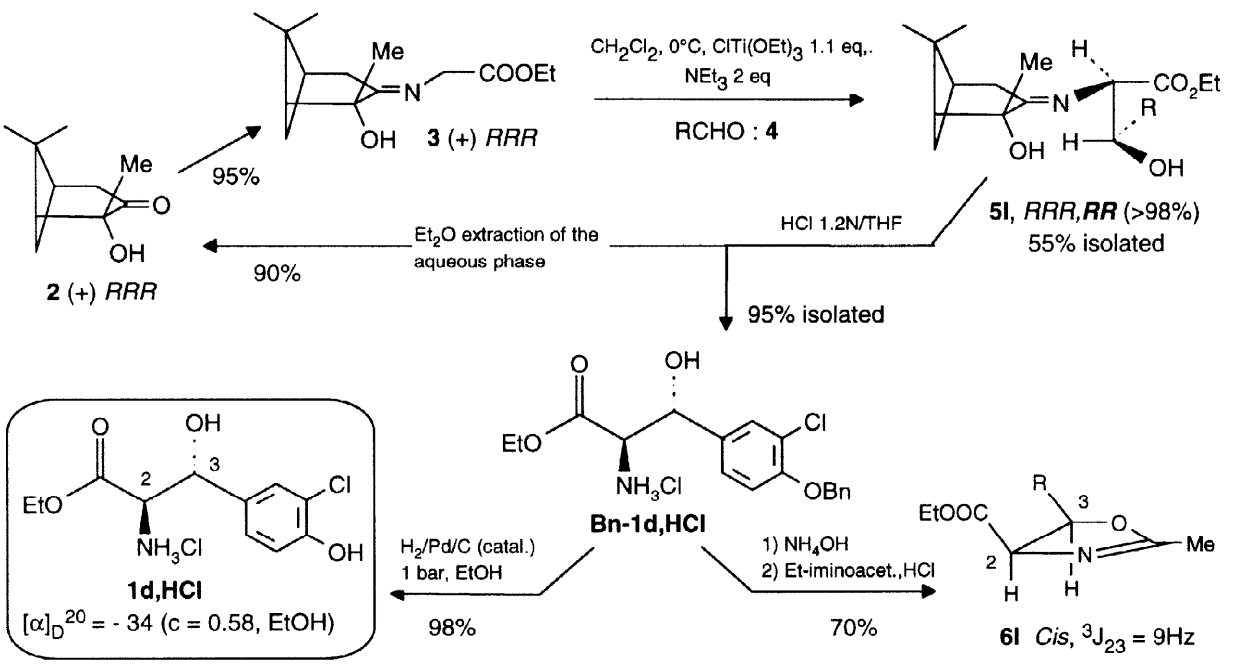
Scheme 1



It is worth noting that enantiomerically pure α-pinene must be used for the synthesis of the hydroxypinanone **2** but, because of strong auto-associations[8] due to its bi-functionality, hydroxypinanone can be enriched by crystallisation (in pentane).

The crude product of the aldol addition[9] showed only one diastereomer (from 400 MHz ^1H NMR), among the four possible, **5I**.[10] After separation of **5I** from the remaining starting materials **3** and **4** (silica gel, AcOEt/hex., 1/1) and hydrolysis (HCl 1.2 N/THF), **Bn-1d,HCl** was isolated in 95% yield.

Scheme 2



Compound **Bn-1d,HCl** was converted to the free amino alcohol **Bn-1d**[11] and then to the oxazoline **6I**[12] by treatment with ethyliminoacetate hydrochloride.[13]

The *cis* configuration was assigned to **6l** on the basis of the 8.5Hz value for the $^3J_{23}$ coupling constant. In the *cis*-oxazoline the dihedral angle H2-C2-C3-H3 is, according to molecular models, close to 0° while in the *trans* isomer this angle is close to 120° ; therefore, in accord with Karplus-Conroy curve, one expects ^3J*cis* to be larger than ^3J*trans* and in the range 9 ± 1 Hz.[14] One can thus conclude that **Bn-1d** and thus **Bn-1d,HCl** have the *erythro* structure which is in accord with our previous results.[4] On this basis it is also reasonable to assign the (2*R*,3*R*) configuration to the *erythro*-isomer **Bn-1d,HCl** obtained from (+)-(*RRR*)-hydroxypinanone **2**.[4]

After debenzylation, which must be conducted with catalytic amount of Pd/C 10% and under 1 Bar of H_2 to avoid loss of the chlorine atom on the aromatic ring, **1d,HCl**[15] was obtained in 98% yield..

The hydrochloride of m-chloro-3-hydroxytyrosine, **1d,HCl**, was thus prepared in its *erythro*-pure and enantiomerically pure (*RR*) form (on the basis of 400 MHz ^{1}H NMR), in 4 steps and with 49% overall yield.

On small scales (~150 mg of **3**) the percentages of conversion of the aldol step happened to be between 65% and 75%, this step and isolation of **5l** could thus be improved for more efficient large scale syntheses.

It must be noted also that the (2*S*,3*S*)-*erythro* isomer will also be available from the (-)-(*SSS*) enantiomer of hydroxypinanone.

Acknowledgement : We thank J.D. Sauer, Service de RMN, Université L. Pasteur de Strasbourg, for the 400 MHz NMR spectra.

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5) Discovered by Wagner in **1894** (*Ber. Chem. Gessels.*,*27*, 2272), hydroxypinanone **2** was then described and studied by Delépine M. *et al.* (*Bull. Soc. Chim. Fr.* **1937**, *4*, 1669) and Kuwata (*J. Am. Chem. Soc.* **1937**, *59*, 2509). Hydroxypinanone was used for the first time as chiral auxiliary by Yamada S.I., Shioiri T *et al.* in **1976** (ref. 6).

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7) Solladié-Cavallo A., Schwarz J., Burger V. *Tetrahedron : Asymm.* **1994**, *5*, 1621.

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9) Because commercially available $Ti(OEt)_4$ contains $Ti(OiPr)_4$, traces of the isopropyl ester corresponding to **5I** and having the same configuration is also observed due to trans-esterification (~5%).

10) In a typical experiment a solution of $ClTi(OEt)_3$ (1.8 g) in anhydrous CH_2Cl_2 (8 mL) was added, dropwise, to a solution of iminoglycinate **3** (1.9 g, 0.9 equiv.) in anhydrous CH_2Cl_2 (5 mL) at 0°C. Then aldehyde **4** (1.85 g, 0.9 equiv.) was added in one portion followed (after total dissolution) by a dropwise addition of anhydrous NEt_3 (2.25 mL, 1.8 equiv.). After 5 h stirring at 0°C, workup was performed by pouring the mixture into cold water. The aqueous phase was then extracted with Et_2O (4 x 20 mL) The combined organic phases were dried over Na_2SO_4 and the solvent evaporated under vacuum. The crude product was analyzed by ^1H NMR (200 and 400 MHz) indicating a 75% conversion. After chromatography (silica gel 230-400 mesh, AcOEt/hexane, 1/1) **5I** was isolated in 55% yield.
5I : $[\alpha]^{20}_D$ = +32 (c=1.2, $CHCl_3$). ^1H NMR (AM 400 Bruker) ($CDCl_3$/TMS) : 7.42 (3H, m), 7.38 (2H, m), 7.30 (1H, m), 7.16 (1H, dd, ^5J=2, ^3J=8.5), 6.89 (1H, d, ^3J=8.5), 5.13 (2H,s), 5.11 (1H, d, ^3J=9), 4.27 (1H, d, ^3J=9), 4.10 (2H, AB of an ABX_3) 2.45 (1H, m), 2.20 (1H, d, J=11), 1.26 (3H,s), 1.17 (3H, t, ^3J=7), 0.80 (3H, s). ^{13}C NMR (AC 200 Bruker) ($CDCl_3$/TMS) : 180.6, 170.4, 153.8, 136.5, 134.2, 129.1, 128.7, 128.0, 127.1, 126.5, 122.9, 113.4, 76.8, 73.8, 70.8, 68.3, 61.4, 50.3, 38.6, 38.3, 34.1, 28.3, 28.0, 27.3, 22.8, 14.2.

11) **Bn-1d** : (AC 200 Bruker), ^1H NMR ($CDCl_3$/TMS) : 7.40 (6H, m), 7.11 (1H, dd, ^4J=2, ^3J=8), 6.90 (1H, d, ^3J=8), 5.15 (2H, s), 4.87 (1H, d, ^3J=6), 4.12 (2H, q, ^3J=7), 3.72 (1H, d, ^3J=6), 1.15 (3H, t, ^3J=7). ^{13}C NMR ($CDCl_3$/TMS) : 173.0, 153.9, 136.4, 133.5, 128.6, 128.5, 128.0, 127.1, 125.7, 123.2, 73.3, 70.9, 61.4, 59.8, 14.2.

12) **6I** : (AC 200 Bruker), ^1H NMR ($CDCl_3$/TMS): 7.35 (5H, m), 7.30 (1H, d, ^4J=2), 7.10 (1H, dd, ^4J=2, ^3J=8), 6.90 (1H, d, ^3J=8), 5.62 (1H, d, ^3J=8.5), 5.15 (2H,s) 5.00 (1H, dq, ^3J=8.5, ^5J= ~1), 3.70 (2H, AB of an ABX_3, ^2J=12), 2.18 (3H, d, ^5J=1), 0.85 (3H, t, ^3J=7).

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15) **1d, HCl** : (AC 200 Bruker), ^1H NMR (CD_3OD/TMS): 7.35 (1H, d, ^4J=2), 7.15 (1H, dd, ^3J=8.5, ^4J=2), 6.93 (1H, d, ^3J=8.5), 5.20 (1H, d, ^3J=4), 4.27 (1H, d, ^3J=4), 4.15 (2H, AB of ABX_3), 1.17 (3H, t, ^3J=7). ^{13}C NMR (CD_3OD/TMS): 167.9, 154.5, 132.1, 129.0, 126.9, 121.7, 117.6, 71.5, 63.5, 60.1, 14.4. Anal. Calcd for $C_{11}H_{15}NO_4Cl_2$: C%, 44.61 ; H%, 5.11. Found : C%, 44.52 ; H%, 5.17.