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A Three-step Synthesis of an Enantiomerically Pure Halostachine Analogue Starting from η^6 (o-Tolualdehyde)-Chromium-tricarbonyl.

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Abstract: *An optically pure (+)-S-Halostachine analogue* **5a** *was synthesized in 57% total yield and in three steps from optically pure(-)-aR-[o-tolualdehyde]-chromium-tricarbonyl complex* **2a**. *Various optically pure Halostachine analogues having an ortho-substituted aromatic ring and of both configurations (R and S) are thus available by this route. An X-ray structure of the intermediate complexed oxazoline* **3bI** *allowed to confirm the model we proposed for the approach of a nucleophile on these arene complexes.*

Introduction.

During studies on the use of chiral arene-chromium-tricarbonyl complexes in enantioselective synthesis[1] we have investigated the reaction of tosylmethylisocyanide 1 (TosMic) with chiral and racemic arene-chromium-tricarbonyl complexes **2a**,**2b**[2] and found that under Schöllkopf's conditions[3] (K_2CO_3/MeOH) but at 0°C only one diastereomer of the four possible was obtained indicating complete diastereoselectivity.

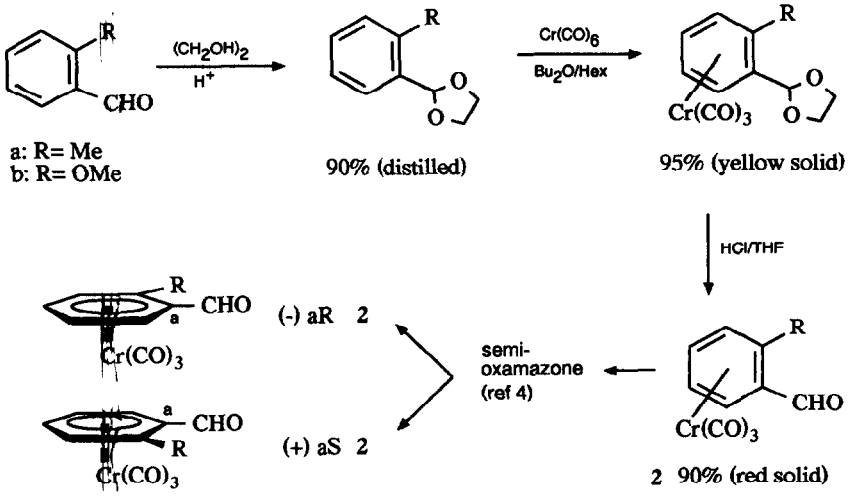
We want to report here an application of this methodology to the synthesis of an optically pure Halostachine analogue starting from optically pure complex **2a**.

Results.

Synthesis

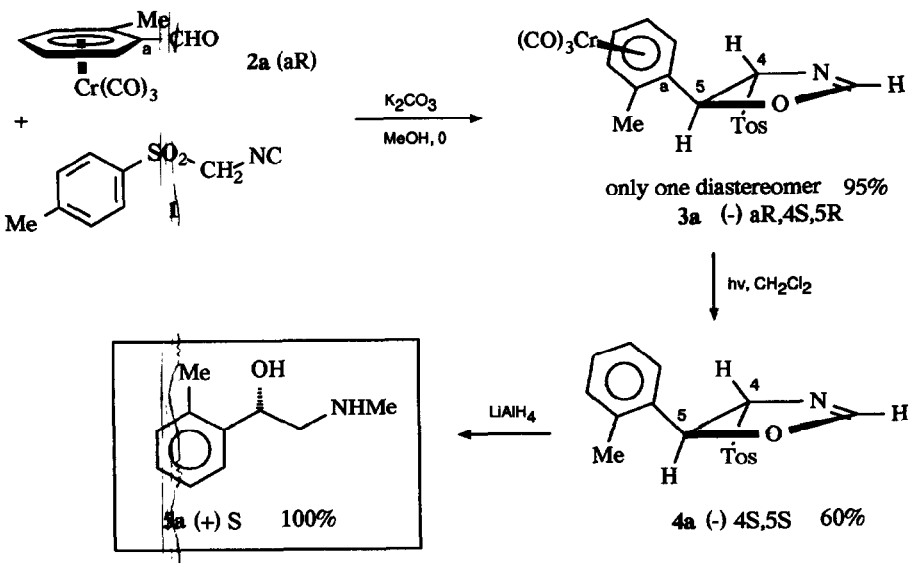
The synthesis and the resolution of complex **2a** were achieved by the usual method[1,4] as shown on scheme 1. The optical purity of both enantiomers of complex **2a** has been checked by 200MHz ^1H NMR in the presence of $Eu(hfc)_3$ [5].

Scheme 1



The pure (-)-*aR* complex **2a** was condensed with the tosylmethylisocyanide **1** in the presence of K_2CO_3 in MeOH to give, in 95% yield, only one diastereomer (out of the four possible) of oxazoline (-)-**3a** ($[\alpha]_D$ = -299 (c, 2.9; $CHCl_3$)), scheme 2.

Scheme 2



After decomplexation (hν/CH_2Cl_2, 60%)[6], the optically pure oxazoline (-)-**4a** ($[\alpha]_D$ = -170 (c, 3.1; $CHCl_3$)) was then quantitatively reduced with 3 molar equivalents of $LiAlH_4$ in THF to give the (+)-*S*-**5a** Halostachine analogue ($[\alpha]_D$ = +42 (c, 3.8 ; $CHCl_3$)).

Since natural (-)-Halostachine has the *R* configuration[7] and on the basis that introduction of an ortho-methyl on the aromatic ring will have a negligible effect and will not invert the sign of the rotation, we assume that (-)-**5a** will also have the *R* configuration. ***Therefore the S configuration was assigned to the*** (+)-**5a** ***obtained.***

^1H NMR

The 200 MHz ^1H NMR spectrum of crude complex **3a** showed only one singlet for the two methyl groups (δ = 2.48 ppm), a normal $(AB)_2$ system for the aromatic protons of the tosyl group ($\Delta\nu_{AB}$ = 84 Hz) and a normal AX system for protons H4 and H5 (δ = 5.03 and 5.91 ppm, $\Delta\nu_{AX}$ = 176 Hz) with a coupling constant of 5.5 Hz.

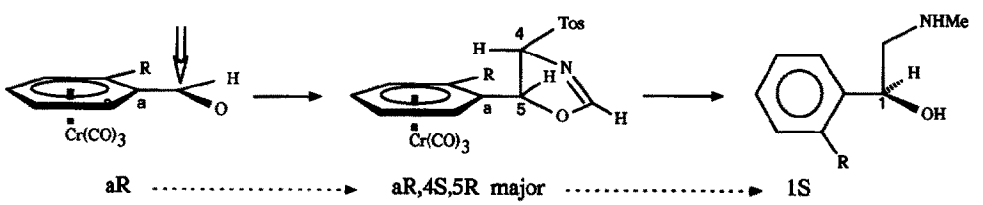
Because the 5.5Hz value found for the J_{45} was not indicative of either a trans or a cis structure, assignment of the trans-configuration on the oxazoline ring was made on the corresponding decomplexed oxazoline **4aI** by comparison with a mixture of the only two possible trans/cis oxazolines **4aI/4aII**[8,9] obtained in a different route.

Examination of the ^1H NMR spectrum of a 33/66 mixture of **4aI** and **4aII** respectively showed :

- a larger non-equivalence, Δν=240 Hz,in **4aI** (minor, 33%) than in **4aII** (major, 66%), Δν=60 Hz, between protons H4 and H5.
- a normal non-equivalence, Δν=85 Hz, between the ortho- and meta-protons of the tosyl-aromatic ring in **4aI** but an unusual equivalence between these protons in **4aII.**

A larger non-equivalence between protons H4 and H5 is expected in the trans-isomer due to two conjugated effects : a shielding-effect of the aromatic ring A on H4 and a deshielding-effect of the strongly polar SO_2 group on H5 (effects which are absent in the cis-isomer where H4 and H5 are in front of each other).

Scheme 3



Therefore the trans-configuration was assigned to isomer* 4aI *which had the larger non-equivalence and as a consequence also to* 3aI. *This trans complexed oxazoline* (-)-3aI, *obtained from optically pure aR complex* 2a, *could thus only be either aR,4S,5R or aR,4R,5S. However according to the S-configuration of the (+)-aminoalcohol* 5a *obtained, it could be concluded that the diastereomer obtained was aR,4S,5R*-3aI *which is in accord with our model of approach [1], scheme 3.

The unusual equivalence between ortho and meta protons of the tosyl-aromatic ring observed in the 4aII-cis-isomer could be understood upon examination of molecular-models, where it appeared clearly that the ortho-protons of ring B are situated in the shielding cone of ring A, Figure 1a, therefore the inductive deshielding effect of the SO_2 group on the ortho-protons is compensated by the shielding-effect of ring A on these protons.

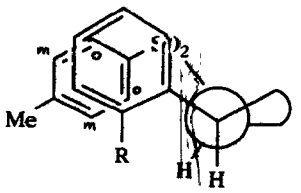


Figure 1a

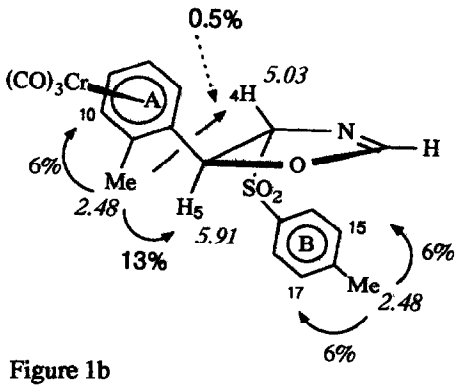


Figure 1b

A NOE difference study of the complexed trans oxazoline **3aI** showed a large (13%) effect on the δ5.91-signal versus a small (0.5%) effect on the δ5.03-signal upon irradiation of the δ2.48-singlet (corresponding to the 2 methyl-groups), Figure 1b. Therefore the signals at δ5.03 and δ5.91 were assigned respectively to protons H4 and H5 on the basis that the most populated conformation was the one shown on Figure 1b, where the $Cr(CO)_3$ tripod is directed away from the C4-ring-carbon and where ,as a consequence, H5 is closer to the o-methyl of ring A than H4. This conformation corresponds to the one found in the solid state for complex **3bI** (cf. below: Figure 2). Also of note are the identical 6% NOEs on ortho-protons H10 (ring A), and H15, H17(ring B).

X-ray structure of **3bI** *trans.*

It has not been possible to obtain a good crystal from optically pure complexed oxazoline **3aI**, however racemic complexed oxazoline **3bI**, also obtained as the only diastereomer but from racemic

complex **2b** in the same conditions[2], gave, by slow evaporation of CH_2Cl_2, a crystal suitable for X-ray analysis, Figure 2.

All bond-distances and bond-angles of complex **3bI** are in the usual range, Table 1. Some important torsional and dihedral angles are given in Table 2.

Table 1: *Bond Distances in Angstroms and Bond Angles in Degrees.*

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
CR	C6	2.209(2)	O7	C22	1.154(4)
CR	C7	2.202(2)	N3	C2	1.262(3)
CR	C8	2.228(3)	N3	C4	1.461(3)
CR	C9	2.198(3)	C4	C5	1.542(3)
CR	C10	2.226(3)	C5	C6	1.508(3)
CR	C11	2.250(3)	C6	C7	1.388(4)
CR	C20	1.818(2)	C6	C11	1.428(3)
CR	C21	1.832(3)	C7	C8	1.426(4)
CR	C22	1.830(3)	C8	C9	1.397(5)
S	O2	1.438(3)	C9	C10	1.365(6)
S	O3	1.437(2)	C10	C11	1.415(4)
S	C4	1.817(2)	C13	C14	1.372(4)
S	C13	1.765(3)	C13	C18	1.374(4)
O1	C2	1.355(3)	C14	C15	1.397(4)
O1	C5	1.440(3)	C15	C16	1.375(4)
O4	C11	1.342(4)	C16	C17	1.385(4)
O4	C12	1.438(4)	C16	C19	1.504(4)
O5	C20	1.155(3)	C17	C18	1.380(4)
O6	C21	1.150(3)			

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C6	CR	C7	36.7(1)	C9	CR	C10	35.9(1)
C6	CR	C8	67.2(1)	C9	CR	C11	65.8(1)
C6	CR	C9	79.3(1)	C9	CR	C20	135.1(2)
C6	CR	C10	67.16(9)	C9	CR	C21	89.1(1)
C6	CR	C11	37.34(9)	C9	CR	C22	138.0(2)
C6	CR	C20	102.2(1)	C10	CR	C11	36.8(1)
C6	CR	C21	167.8(1)	C10	CR	C20	165.4(1)
C6	CR	C22	98.1(1)	C10	CR	C21	101.1(1)
C7	CR	C8	37.54(9)	C10	CR	C22	104.2(2)
C7	CR	C9	66.8(1)	C11	CR	C20	137.0(1)
C7	CR	C10	77.9(1)	C11	CR	C21	133.4(1)
C7	CR	C11	65.8(1)	C11	CR	C22	86.7(1)
C7	CR	C20	87.7(1)	C20	CR	C21	88.7(1)
C7	CR	C21	140.5(1)	C20	CR	C22	86.7(1)
C7	CR	C22	131.1(1)	C21	CR	C22	87.9(1)
C8	CR	C9	36.8(1)	O2	S	O3	119.4(1)
C8	CR	C10	65.5(2)	O2	S	C4	106.5(1)
C8	CR	C11	78.0(1)	O2	S	C13	109.0(1)
C8	CR	C20	101.7(1)	O3	S	C4	106.8(1)
C8	CR	C21	105.5(1)	O3	S	C13	109.0(1)
C8	CR	C22	164.2(1)	C4	S	C13	105.3(1)
C2	O1	C5	105.8(2)	C8	C9	C10	121.5(3)
C11	O4	C12	118.0(3)	C9	C10	C11	120.8(3)
C2	N3	C4	105.3(2)	O4	C11	C6	115.3(3)
O1	C2	N3	119.5(2)	O4	C11	C10	125.3(3)
S	C4	N3	104.9(1)	C6	C11	C10	119.3(3)
S	C4	C5	112.8(2)	S	C13	C14	119.0(2)
N3	C4	C5	105.4(2)	S	C13	C18	120.2(2)
O1	C5	C4	102.6(2)	C14	C13	C18	120.8(3)
O1	C5	C6	108.7(2)	C13	C14	C15	118.7(2)
C4	C5	C6	113.9(2)	C14	C15	C16	121.3(3)
C5	C6	C7	122.1(2)	C15	C16	C17	118.5(3)
C5	C6	C11	119.4(3)	C15	C16	C19	120.2(3)
C7	C6	C11	118.4(2)	C17	C16	C19	121.2(3)
C6	C7	C8	121.7(3)	C16	C17	C18	120.7(3)
C7	C8	C9	118.1(3)	C13	C18	C17	119.8(3)

Table 2: *Selected torsional and dihedral angles.*

C5-C4-S-C13=	+67.4°
C4-S-C13-C18=	-110.9°
C4-C5-C6-C7=	-81.3°
C6-C11-O4-C12=	+165.8°
C11-phenylcentroid-Cr/phenylcentroid-Cr-C22=	5°

It confirmed, Figure 2, that the configuration at the oxazoline ring was trans as predicted from the NMR data[2] . It also confirmed that the *S*-configuration at C6 was associated with the *S*-configuration at C5 (*6S,4R,5S*) thus confirming our model of approach[1,2], see above, which stated that: upon nucleophilic additions, complexes of *aS* configuration (*6S* according to crystallographic numbering) lead mainly to the *S*-configuration at Cα (C5 according to crystallographic numbering) and of course that *aR* (=*6R*) complexes lead mainly to α*R* (=*5R*). Therefore changing a methyl group by a methoxy group on complexed ring A has a negligible effect and our previous conclusion that the single diastereomer of **3aI** obtained from (-)-*aR* complex **2a** had the *aR,4S,5R*-configuration is confirmed.

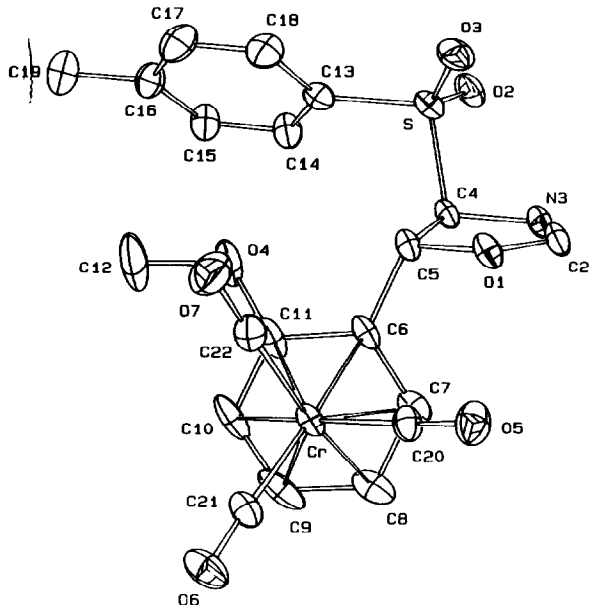


Figure 2: *Ortep plot of one molecule of* **3bI** *showing the labeling scheme used. Ellipsoïds are scaled to enclose 50% of the electronic density. Hydrogen atoms are omitted.*

It must also be pointed out that the conformation around C6-C5 found for complex **3bI** in the solid state corresponded to the conformation predicted above for complex **3aI** from our model of approach, schemes 2 and 3, and from the NOE experiment, Figure 1b.

Conclusion

Enantromerically pure (-)-*(aR)*-η^6-(o-tolualdehyde)chromium(0)tricarbonyl **2a** underwent completely diastereoselective addition of TosMic thus leading, after decomplexation and $LiAlH_4$ reduction, to optically the pure (+)-*S*-Halostachine analogue **5a**.

The single diastereomer of complexed oxazoline **3bI**, obtained from addition of TosMic onto racemic complex **2b**, was determined by X-ray to have the *6S,4R,5S/6R,4S,5R*-configuration thus confirming that complexes of configuration *aR* lead mainly to the *S*-configuration at Cα (and complexes of *aS* configuration to the *R*-configuration at Cα), in agreement with our model of approach[1] (see above).

This synthesis constitutes an easy entry to enantiomerically pure halostachine-like aminoalcohols.

Experimental section

Infrared have been recorded on a Perkin-Elmer 257 spectrometer (ν in cm-1). ^1H (200 MHz) and ^{13}C (50 MHz) have been recorded on a Bruker AC-200 (δ in ppm refered to TMS, Δν and J in Hz) Rotations have been measured on a Perkin-Elmer 241 MC. M.p. have been determined (uncorrected) on a Reichert Microscope. Flash-chromatographies were performed using silicagel 70-230 Mesh purchassed from Merck. Kieselgel 60 F_{254} (from Merck) have been used for TLC. All the solvents were distilled before use, THF over Na/benzophenone and CH_2Cl_2 over calcium hydride. All the compounds but toluylaldehyde, which was distilled before use, were reagent grade purchased from Aldrich and/or Janssen and used without further purification.

X-ray: One single crystal was cut out from a cluster of crystals and mounted on a rotation-free goniometer head. A systematic search in reciprocal space using a Enraf-Nonius CAD4-F automatic diffractometer showed that crystals of **3bI** belong to the triclinic system.

Quantitative data were obtained at room temperature. All experimental parameters used are given in table 3. The resulting dataset was transfered to a VAX computer, and for all subsequent calculations the Enraf-Nonius SDP/VAX package[10] was used. Three standard reflections measured every hour during the entire data collection period showed no significant trend. The data were corrected for Lorentz, polarisation and absorption factors, the latter calculated from psi scans of 4 reflections. The structure was solved using the heavy atom method. After refinement of the heavy atoms, a difference-Fourier map revealed maximas of residual electronic density close to the positions expected for hydrogen atoms; they were introduced in structure factor calculations by their computed coordinates

(C-H=0.95Å) and isotropic temperature factors such as B(H) = 1.3 Beqv(C) Å^2 but not refined. Full least-squares refinements ; $\sigma^2(F^2) = \sigma^2$counts + $(pI)^2$. A final difference map revealed no significant maxima. The scattering factor coefficients and anomalous dispersion coefficients come respectively from ref 11a and 11b.

Table 3: *X-ray experimental parameters.*

Formula	: $C_{20}H_{17}NO_7SCr$	Crystal size(mm)	: 0.23*0.28*0.30
Molecular weight	: 476.42	Temperature	: 20°C
Color	: yellow	Diffractometer	: Enraf-Nonius CAD4-F
Crystal system	: triclinic	Mode	: θ/2θ
a(Å)	: 10.134(3)	Scan speed	: variable
b(Å)	: 11.404(3)	Scan width(deg)	: 1.00 + 0.343tg(θ)
c(Å)	: 9.531(2)	Theta limits(deg)	. 2/27.5
α(deg)	: 98.51(2)	Octants	: ±h±k+l
β(deg)	: 96.50(2)	Number of data collected	: 4693
γ(deg)	: 70.81(2)	Number of data with	: 3163
U(Å^3)	: 1026.4	I > 3 σ (I)	
Z	: 2	Abs. min/max	: 0.97/1.00
Dcalc(gcm^{-1})	: 1.512	R(F)	: 0.040
Space group	: P-1	Rw(F)	: 0.059
Radiation	: MoK_α (graphite monochromate)	p	: 0.08
Wavelength(Å)	: 0.70930	GOF	: 1.267
μ(cm^{-1})	: 6.808		

(-)-*(aR)*-(o-toluylaldehyde)chromiumtricarbonyl: 2a

Complex **2a** was obtained following the usual method[1,4].

Red crystals, m.p. 100-101°C

Total yield from o-toluylaldehyde =23%. R_f= 0.26 (Et_2O/Hex.,1/1)

$[\alpha]_{579}$= -727 (C,0.72; $CHCl_3$)

IR ($CHCl_3$): $\nu_{C\,O}$ = 1970, 1895; $\nu_{C=O}$ = 1680

^{1}H NMR ($CDCl_3$): 2.55 (3H, s, CH_3-Ar); 5.05 (1H, d, J=6.5, H4); 5.23 (1H, t, J=6.5, H2); 5.73(1H, t, J=6.5, H3); 6.07 (1H, d, J=6.5, H1); 9.82(1H, s, CHO).

Anal. Calcd for $C_{11}H_8CrO_4$: C,51.57; H,3.15. Found: C,51.64; H,3.31.

***Condensation of TosMic with (-)-aR-Complex* 2a.**

To a mixture of (-)-*aR*-(o-toluylaldehyde)-chromium-tricarbonyl (128 mg, 0.5 mmol.) and TosMic (98 mg, 0.5 mmol) in MeOH (5 ml) at 0°C was added K_2CO_3 (69 mg, 0.5 mmol). After Stirring at 0°C for 30 mn. glacial-AcOH (58 ml, 0.5 mmol) was added dropwise. Then MeOH was evaporated under vacuum (without heating) and the residue dissolved in CH_2Cl_2 (20 ml). After washing with water (2 x 5 ml) the organic phase was dried over $MgSO_4$, the solvent evaporated and the crude compound analyzed by ^{1}H NMR before and after purification (by flash chromatography).

(-)-(*aR,4S,5R*)-5-[(o-tolyl)-chromium-tricarbonyl]-4-(p-toluene sulfonyl) oxazoline: 3a-trans
Yellow solid
Yield: 95% (isolated). R_f=0.23 (Et_2O/Hex. 8/2)
$[\alpha]_D$ = -299 (C,2.9; $CHCl_3$)
IR ($CHCl_3$): $\nu_{C=O}$ = 1975, 1900; $\nu_{C=N}$ = 1620
^1H NMR ($CDCl_3$): 2.48 (6H, s, p-CH_3 and o-CH_3); 5.03 (1H, dd, J_{45}= 5.5, J_{24}= 1.7, H4); 5.13 (3H, m, Harom.); 5.44 (1H, td, J= 6, J= 2, Harom.); 5.91 (1H, d, J_{54}= 5.5, H5); 7.22 (1H, d, J_{24}= 1.7, H2); 7.41 (2H, d, J=8.5, Harom.); 7.83 (2H, d, J=8.5, Harom.).
^{13}C NMR ($CDCl_3$): 19.7 (CH_3); 22.4 (CH_3); 76.2 (CH-O); 89.3 (CHarom.); 90.1 (S-CH-N); 93.0 (CHarom); 93.1 (CHarom.); 94.7 (CHarom.); 104.5 (Carom.); 108.6 (Carom.); 130.2 (2CHarom.); 130.6 (2CHarom.); 132.9 (Carom.); 160.0 (O-CH=N); 235.5 (3 C O).

Decomplexation

The complexed oxazoline **3a** (480 mg, 1.06 mmol.) was dissolved in CH_2Cl_2 (50 ml) and the solution placed in day light for 3 days. Every day the chromium oxide which precipitated was filtered out. Then, when the yellow colour had desappeared, the solvent was evaporated under vacuum and the crude compound purified by flash chromatography on silicagel treated with NEt_3.

(-)-(*4S,5S*)-5-[(o-methyl)phenyl]-4-(p-toluenesulfonyl) oxazoline: 4a-trans
Uncoloured oil.
Yield : 60%. R_f=0.54 (Et_2O/Hex 8/2)
$[\alpha]_D$= -170 (C,3.1; $CHCl_3$)
IR ($CHCl_3$): $\nu_{C=N}$ = 1620
^1H NMR ($CDCl_3$): 2.46 (3H, s, CH_3); 2.55 (3H, s, CH_3); 5.08(1H, dd, J_{45}= 5.5, J_{42}= 1.5, H4); 6.27 (1H, d, J_{54}= 5.5, H5); 7.20 (5H, m, 4Harom.+ H2); 7.40 (2H, d, Harom.); 7.85 (2H, d, Harom.).

***Reduction of oxazoline* 4a-trans**

$LiAlH_4$ (53 mg, 1.45 mmol) in anhydrous THF (10 ml) was refluxed for 1h. After cooling down to r.t., oxazoline (-)-4a-trans (158 mg, 0.5 mmol) dissolved in THF (5 ml) was added dropwise, the mixture was then stirred at r.t. for 3 more hours. After cooling at 0.C° in an ice-bath, a saturated solution of Na_2SO_4 (0.4 ml) was added dropwise and the mixture stirred at r.t. until the precipitate was powdered and white. After addition of $MgSO_4$ the mixture was heated to reflux and filtered. The precipitate was heated in THF (25 ml) and filtrered twice. The combined organic phases are concentrated under vacuum.

(+)-(*S*)-N-methyl-2-hydroxy-2-[(2-methyl)phenyl] ethylamine: 5a.
Uncolored oil.
Yield : 100%

$[\alpha]_D$= +42 (C, 3.8; $CHCl_3$)
IR ($CHCl_3$) : ν_{NH} and ν_{OH} 3600, 3350
^1H NMR ($CDCl_3$): 2.33 (3H, s, CH_3); 2.46 (3H, s, CH_3); 2.72 (2H, AB part of an ABX system; $\Delta\nu_{AB}$ = 16, J_{AB} = 13, J_{AX} = 4, J_{BX} = 8.5, CH_2); 3.12 (2H, broad s, NH and OH); 5.00 (1H, X part of the ABX, J_{AX} = 4, J_{BX} = 8.5, CH-O); 7.08-7.27 (3H, m, Harom.); 7.51(1H, d, J = 7.5, Harom.).
^{13}C NMR ($CDCl_3$): 18.8 (CH_3); 35.7 (CH_3-N); 57.8 (CH_2); 68.1 (CH-O); 125.4 (CHarom.); 126.1 (CHarom); 127.1 (CHarom.); 134.2 (Carom.); 140.7 (Carom.).
Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.45; H, 9.08; N, 8.22.

Supplementary material : Table S1: temperature factors for anisotropic atoms, table S2: positionnal parameters, table S3: observed and calculated structure factors amplitudes (*10) for all observed reflections (17 pages).

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References and notes.

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9) ^1H NMR ($CDCl_3$/TMS). Bruker AC 200, δ ppm, J Hz. *Oxazoline cis*, **4aII**: 2.39 (3H, s, p-CH_3); 3.54 (3H, s, o-CH_3); 5.12 (1H, dd, J_{45} = 4.5, $^4J_{42}$ = 1, H4); 5.41 (1H, d, J_{45} = 4.5, H5);7.20 (9H, broad singlet, 4H of ring B, overlapped with a multiplet, 4H of ring A + H2)
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