Supporting Information:

Synthesis of (-) Lasubine (I) *via* a Planar Chiral [(η^6-Arene Cr(CO)$_3$] Complex.

by

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General

All manipulation involving organometallics compounds were carried out in an atmosphere of dry nitrogen. Standard Schlenk tube techniques were used to perform reactions of chromium complexes. All preparations were carried out in glass Schlenk ware, on a vacuum line. Degassing procedure consisted of repeated freeze-pump-thaw cycles. Solvents were freshly distilled from appropriate drying agents under a nitrogen atmosphere prior to use:

- Hexane/pentane: calcium hydride (CaH_2).
- Diethylether/tetrahydofuran: sodium/benzophenone.
- Dichloromethane: phosphorus pentoxide (P_2O_5).
- Toluene/benzene: sodium.

The reaction were followed by analytical thin-layer chromatography (TLC) using pre-coated plastic silica gel 60 F_{254} (Merck, 0.2 mm thick) sheets. Compounds were visualized by ethanolic phosphomolybdic acid spray or U.V.

Column flash chromatography (FC): SiO_2 (Merck 60).

NMR spectra were recorded as follows:

- ^{1}H: at 200 MHz on a Varian XL 200 or 400 MHz on a Bruker 400.
- ^{13}C: at 50 MHz on a Varian XL 200 or 100 MHz on a Bruker 400.

Chemical shifts are reported in ppm downfield from tetramethylsilane. Multiplicity is abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Spin-spin coupling constants are given in Hertz (Hz).

NMR data are tabulated in the order: multiplicity, number of protons, coupling constants. The solvent used is deuterated benzene or chloroform, unless otherwise stated.

Infrared spectra were recorded on a Perkin-Elmer 1650 FT-IR instrument. Relative intensities are abbreviated as follows: strong (s), medium (m), weak (w), broad (br).

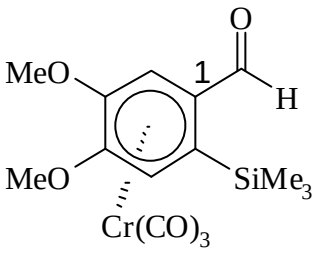
Mass spectra were measured on a Varian CH-4 spectrometer. Relative intensities are given in parenthesis.

Optical rotation was measured on a Perkin-Elmer 241 polarimeter using a cell of 10 cm length. Concentration is expressed in mg/ml.

Analysis by gas chromatography (GC) was performed on a perkin-Elmer 900 instrument.

The following abbreviations are used in the text: tetrahydrofuran (THF), ether (Et_2O), benzene (C_6H_6), chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), carbon tetrachloride (CCl_4).

***h*^{6}*-(4,5-dimethoxy-2-TMS-benzaldehyde)-Cr(CO)$_3$* (1*S*)-(+)-3a**



The veratraldehyde (12.10 g, 0.051 mol, 1 eq.) was dissolved in MeOH (250 ml). Trimethylorthoformate (11.06 ml, 0.102 mol, 2 eq.), *p*-TsOH (0.0.475 g, 0.0025 mol, 5%) and molecular sieve 4Å (15 g) were added. The solution was brought to reflux (70°C, 15 h). The solution was cooled, solvent evaporated and the residue was taken up in ether, washed with $NaHCO_3$, brine, dried on $MgSO_4$ to afford the protected aldehyde compound as a white solid (14.15 g, 98%). A deoxygenated mixture of this compound (12.80 g, 0.045 mol, 1 eq.), *n*-Bu_2O-THF (250 ml, 9/1) and hexacarbonylchromium (10.90 g, 0.0495 mol, 1.1 eq.) was heated at reflux (155°C, 18 h) until the first trace of green precipitate was observed. The cooled solution was then filtered through celite and the solvent evaporated. The residue was then dissolved in THF

(200 ml) and HCl (60 ml, 1N, 60 mmol) was added and stirring continued (rt, 15 h). Work-up and chromatography gave complex (±)-**(3a)** as a red solid (13.47 g, 80%).

^{1}H NMR: (C_6D_6, 200 MHz) δ 9.56 (*s*, 1H, CHO), 5.28 (*s*, 1H, H_{aro}), 4.96 (*s*, 1H, H_{aro}), 3.08 (*s*, 3H, CH_3), 3.01 (*s*, 3H, CH_3), 0.28 (*s*, 9H, TMS).

^{13}C NMR: (C_6D_6, 50 MHz) δ 232.7, 190.1, 134.3, 134.2, 97.0, 96.5, 83.0, 77.0, 56.7, 56.1, 0.69.

IR (CH_2Cl_2): 1969.1 (s), 1896.7 (s), 1685.1 (w).

MS (m/z): 374 (9), 318 (5), 290 (49), 245 (13), 223 (100), 126 (7), 52 (6).

HR-MS: calc. 374.02777 found 374.02919 formula $C_{15}H_{18}O_6SiCr$.

Resolution of h^6*-(4,5-dimethoxy-2-TMS-benzaldehyde)-Cr(CO)$_3$ (±)-**3a**

L-Valinol (2.30 g, 0.022 mol) was added to an Et_2O (50 ml) solution of [(4,5-dimethoxy-2-TMS-benzaldehyde) $Cr(CO)_3$] (±)-**(3a)** (6.6 g, 0.017 mol) containing an excess of 4Å molecular sieves (10 g). The mixture was stirred for 24 h, and then filtered through Celite and evaporated to give an orange oil. Addition of hexane and cooling precipitated orange crystals. Column chromatography (SiO_2, Ethylacetate-Hex 1/3, 3% Et_3N) gave two fractions.

Fraction 1 was dissolved in THF (30 ml) containing HCl (10 ml, 1N). After the mixture had been stirred for one hour, extraction, evaporation of the solvent and column chromatography (SiO_2, Et_2O) gave the product as a red solid which was identified as [η^6-(4,5-dimethoxy-2-TMS-benzaldehyde)-$Cr(CO)_3$] ((1*R*)-(-)-**3a**). (ee > 99%).

Fraction 2 was dissolved in THF (30 ml) containing HCl (10 ml, 1N). After the mixture had been stirred for one hour, extraction, evaporation of the solvent and column chromatography (SiO_2, Et_2O) gave the product as a red solid which was identified as [η^6-(4,5-dimethoxy-2-TMS-benzaldehyde)-$Cr(CO)_3$] ((1*S*)-(+)-**3a**). (ee > 99%).

The C.D. spectra of (+)-(1*S*)-**(3a)** measured in chloroform gives a negative Cotton effect at λ=326 nm (Δε -5.75) and a positive Cotton effect at λ=442.5 nm (Δε +6.58).

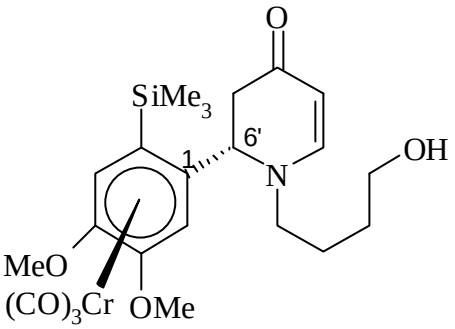
$[\alpha]_D^{20} = +924$ (c = 0.265, $CHCl_3$).

The enanatiomeric excess was determined by chiral HPLC using:

HPLC (chiracel OD-H, hexane / *i*-PrOH = 98 : 2, 1 ml / min): 15.2 min, 21.1 min.

1'-butan-4-ol-6'-(4,5-dimethoxy-2-TMS-phenyl-Cr(CO)$_3$)-2',3'-dihydro-1H-pyridin-4'-one

(1*S*, 6'*S*)-(+)-(7a)



The imine complex was prepared by the condensation of 4-amino-butan-1-ol with complexed benzaldehyde. The amine (0.51 ml, 5.5 mmol, 1 eq.) was added to a Et_2O (20 ml) solution of [η^6-(4,5-dimethoxy-2-TMS-benzaldehyde) $Cr(CO)_3$] ((1*S*)-(+)-**3a**) (2.00 g, 5.5 mmol, 1 eq.) containing an excess of 4Å molecular sieves and the mixture was stirred overnight. The initially red solution turned orange. The mixture was filtered through Celite and evaporated to give an orange oil. The crude product was used in the next step without purification. The aldimine complex, in the presence of $SnCl_4$, reacted smoothly the Danishefsky's diene to give the $Cr(CO)_3$ complex of 2-aryl-2,3-dihydro-4-pyridinone. $SnCl_4$ (1.02 ml, 8.80 mmol, 1.6 eq.) was added dropwise to a cooled (-78°C) THF (15 ml) solution of the imine complex and the mixture stirred (-78°C, 15 min.). The diene (2.09 ml, 11 mmol, 2 eq.) was added and stirring continued (-78°C to 0°C, 18h). Work-up and column chromatography (SiO_2, Ethylacetate) gave the title complex (1*S*, 6'*S*)-(+)-**7a** as an orange solid (1.35 g, 48%) and a single diastereomer.

^{1}H NMR: (C_6D_6, 200 MHz) δ 6.35 (*d*, 1H, *J*=7.4, H-C(1)), 5.68 (*s*, 1H, H_{aro}), 5.10 (*d*, 1H, *J*=7.4, H-C(2)), 4.91 (*s*, 1H, H_{aro}), 4.30 (*d*, 1H, *J*=8.5, H-C(3)), 3.50 (*m*, 1H, H-C(5), H-C(4)), 3.35 (*s*, 3H, CH_3), 3.30 (*m*, 2H, H-C(6)), 3.20(*s*, 3H, CH_3), 2.90 (*m*, 2H, H-C(5), H-C(4)), 2.45 (*d*, 1H, *J*=15.5, H-C(4)), 1.40 (*m*, 2H, H-C(7)), 1.35 (*m*, 2H, H-C(8)), 0.7 (*br t*, 1H, OH), 0.21 (*s*, 9H, TMS).

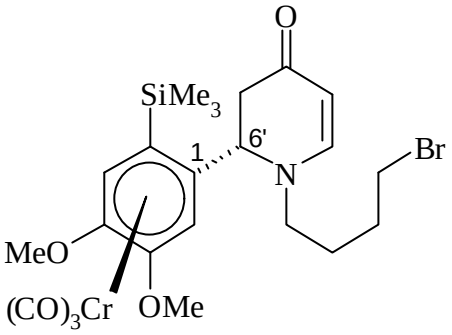
^{13}C NMR: (C_6D_6, 50 MHz) δ 233.7, 187.6, 153.7, 133.5, 130.9, 107.4, 97.9, 93.9, 83.4, 79.1, 62.0, 57.4, 57.2, 55.6, 54.9, 43.6, 29.3, 26.8, 0.91.

IR (CH_2Cl_2): 1955.2 (s), 1877.1 (s), 1642.9 (w), 1593.0 (w).

MS (m/z): 513 (10), 429 (78), 377 (20), 362 (11), 304 (100), 262 (53), 221 (35), 168 (9), 100 (7), 73 (15), 52 (10).

$[\alpha]_D^{20}$: + 152 (c = 0.530, $CHCl_3$).

***1'-(4-bromobutane)-6'-(4,5-dimethoxy-2-TMS-phenyl-Cr(CO)$_3$)-2',3'-dihydro-1H-pyridin-4'-one* (1*S*, 6'*S*)-(+)-(8a)**



MsCl (0.15 ml, 1.93 mmol, 1.4 eq.) and Hünig's base (0.476 ml, 2.72 mmol, 2 eq.) were added to a CH_2Cl_2 (20 ml) solution of complex (+)-**7a** (700 mg, 1.36 mmol, 1 eq.) at 0°C. Stirring was continued for 30 min. After extraction and solvent evaporation, the resulting complex was then dissolved in aceton (25 ml). LiBr (250 mg, 2.89 mmol, 2.1 eq.) was added and stirring continued overnight. Work-up and column chromatography gave the title complex (+)-**8a** as a yellow solid (720 mg, 92%).

^{1}H NMR: (C_6D_6, 200 MHz) δ 6.22 (*d*, 1H, *J*=7.6, H-C(1)), 5.65 (*s*, 1H, H_{aro}), 5.06 (*d*, 1H, *J*=7.6, H-C(2)), 4.89 (*s*, 1H, H_{aro}), 4.26 (*d*, 1H, *J*=8.2, H-C(3)), 3.47 (*m*, 1H, H-C(5)), 3.36 (*s*, 3H, CH_3), 3.20 (*s*, 3H, CH_3), 2.85 (*m*, 4H, H-C(5), H-C(6), H-C(4)), 2.44 (*d*, 1H, *J*=15.8, H-C(4)), 1.33 (*m*, 4H, H-C(7), H-C(8)), 0.20 (*s*, 9H, TMS).

^{13}C NMR: (C_6D_6, 50 MHz) δ 234.3, 185.7, 151.7, 132.1, 107.9, 98.6, 93.2, 84.4, 80.2, 69.9, 57.1, 56.3, 55.8, 53.6, 43.9, 32.5, 29.2, 28.2, 0.4.

IR (CH_2Cl_2): 1956.2 (s), 1877.2 (s).

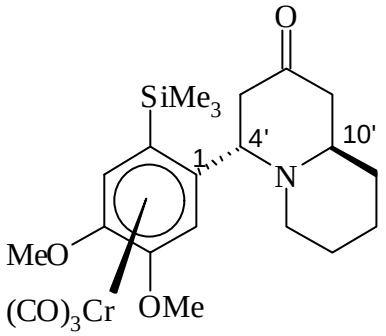
MS (m/z): 577 (12), 574 (12), 493 (21), 491 (21), 413 (58), 411 (48), 368 (42), 366 (44), 288 (36), 221 (64), 205 (35), 152 (25), 73 (100), 52 (51).

HR-MS: calc. 577.04102 found 577.03938 formula $C_{23}H_{30}O_6NSiCrBr^{81}$.

calc. 575.04309 found 575.04104 formula $C_{23}H_{30}O_6NSiCrBr^{79}$.

$[\alpha]_D^{20}$: + 139 (c = 0.200, $CHCl_3$).

***4'-(η⁶-4,5-dimethoxy-2-TMS-phenyl-Cr(CO)₃)-octahydro-quinolizidin-2'-one* (1*S*, 4'*S*, 10'*R*)- (-)-(9a)**



The complex (1S, 6'S)-(+)-**8a** (610 mg, 1.06 mmol, 1 eq.) was dissolved in benzene (120 ml). AIBN (20 mg) and tributyltin hydride (0.420 ml, 1.59 mmol, 1.5 eq.) were added. The solution was heated to reflux (100°C, 2h). The solution was cooled, solvent was evaporated and the complex (-)-**9a** isolated by column chromatography on silica gel as a yellow solid and a single diastereomer (475 mg, 90%).

^{1}H NMR: (C_6D_6, 200 MHz) δ 5.59 (*s*, 1H, H_{aro}), 5.02 (*s*, 1H, H_{aro}), 3.60 (*dd*, 1H, *J*=10.7, *J*=6.0, H-C(6')), 3.45 (*s*, 3H, CH_3), 3.28 (*s*, 3H, CH_3), 3.10 (*m*, 1H), 2.85 (*m*, 1H), 2.47 (*m*, 3H), 2.05 (*dd*, 1H, *J*=14.5, *J*=10.78), 1.75 (*m*, 2H), 1.55 (*m*, 1H), 1.40 (*m*, 1H), 1.28 (*m*, 1H), 1.15 (*m*, 2H), 0.33 (*s*, 9H, TMS).

^{13}C NMR: (C_6D_6, 50 MHz) δ 234.1, 206.2, 88.8, 84.1, 78.4, 74.3, 60.5, 56.9, 56.6, 52.8, 49.4, 47.7, 39.4, 28.6, 24.7, 19.8, 0.75.

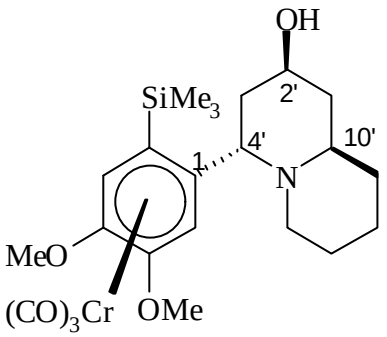
IR (CH_2Cl_2): 1953 (s), 1870 (s), 1715 (w).

MS (m/z): 497 (14), 414 (39), 413 (100), 361 (96), 346 (75), 279 (55), 236 (57), 221 (65), 152 (65), 110 (20), 52 (25).

HR-MS: calc. 497.13257 found 497.12929 formula $C_{23}H_{31}NO_6SiCr$.

$[\alpha]_D^{20}$: - 126 (c = 0.170, $CHCl_3$).

***4'-(η⁶-4,5-dimethoxy-2-TMS-phenyl-Cr(CO)₃)-octahydro-quinolizidin-2'-ol* (1*S*, 2'*S*, 4'*S*,10'*R*)-(-)-(10a)**



To a stirred solution of complex (-)-**9a** (380 mg, 0.76 mmol, 1 eq.) in THF (15 ml) was added at -78°C *L*-Selectride (0.83 ml, 1N/THF, 0.83 mmol, 1.1 eq.). Stirring was continued for 10 min. Work-up and column chromatography gave the title complex (-)-**10a** as a yellow solid and a single diastereomer (352 mg, 93%).

^{1}H NMR: (C_6D_6, 200 MHz) δ 5.68 (*s*, 1H, H_{aro}), 5.25 (*s*, 1H, H_{aro}), 4.15 (*m*, 1H, H-C(4')), 3.57 (*m*, 1H), 3.50 (*s*, 3H, OMe), 3.40 (*s*, 3H, OMe), 3.30 (*m*, 1H), 3.10 (*m*, 1H), 2.90 (*m*, 1H), 1.2-1.8 (serie of *m*, 10H), 0.70 (*br d*, 1H, OH), 0.38 (*s*, 9H, TMS).

^{13}C NMR: (C_6D_6, 50 MHz) δ 235.0, 133.8, 131.4, 119.3, 91.4, 87.8, 81.2, 65.0, 58.8, 58.0, 57.4, 53.3, 50.9, 42.3, 37.8, 32.5, 26.0, 22.9, 1.1.

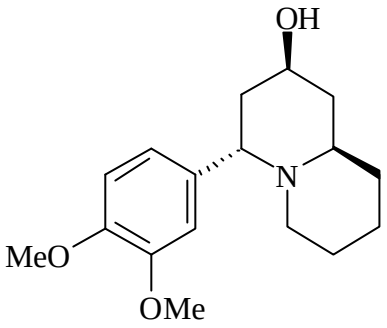
IR (CH_2Cl_2): 3624 (m), 2943 (m), 1952 (s), 1871 (s).

MS (m/z): 499 (3), 443 (3), 415 (50), 363 (14), 290 (16), 221 (14), 154 (100), 73 (38), 52 (31).

HR-MS: calc. 499.14822 found 499.14561 formula $C_{23}H_{33}NO_6SiCr$.

$[\alpha]_D^{20}$: -78 (c = 0.105, $CHCl_3$).

(-) Lasubine (I)



To a stirred solution of complex (-)-**10a** (200 mg, 0.400 mmol, 1 eq.) in THF (5 ml) at -78°C, was added a TBAF solution in THF (0.44 ml, 1N, 0.44 mmol, 1.1 eq.) and stirring was continued for 30 minutes. Extraction and column chromatography gave the desilylated complex (158 mg, 93%) as a yellow solid. This complex was dissolved in CH_3CN and then exposed to sunlight for 30 minutes. The decomplexation was monitored by TLC ($CHCl_3$/MeOH 9/1). After filtration on celite to remove chromium salt and flash chromatography, (-)-lasubine (I) was obtained as a slightly yellow oil in 84% yield. (ee > 98%, determined following conversion to the Mosher ester).

^{1}H NMR: (C_6D_6, 400 MHz) δ 6.89 (*m*, 3H, H_{aro}), 4.10-4.22 (*m*, 2H), 3.88 (*s*, 3H, OMe), 3.87 (*s*, 3H, OMe), 3.02 (*br s*, 1H), 2.75 (*br d*, 1H, *J*=12), 2.30 (*m*, 1H), 2.05 (*m*, 3H), 1.6-1.9 (*m*, 6H), 1.2 (*m*, 2H).

^{13}C NMR: (C_6D_6, 50 MHz) δ 149.1, 148.1, 135.4, 119.6, 112.3, 110.2, 64.1, 61.7, 55.1, 53.9, 52.1, 50.2, 40.4, 39.9, 33.1, 24.0, 23.2.

IR ($CHCl_3$): 3391 (w), 2960 (m), 2473 (w), 1678 (w), 1596 (w), 1519 (m), 1219 (s).

MS (m/z): 291 (77), 246 (21), 191 (24), 164 (100), 154 (98), 149 (11), 126 (31), 110 (39), 96 (29), 84 (41), 55 (25).

HR-MS: calc. 291.18344 found 291.18540 formula $C_{17}H_{25}NO_3$.

$[\alpha]_D^{20}$: -8.0 (c= 0.200, $CHCl_3$).

This is in agrement with reported data.[1]

[1] (a) Iida, H.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 1909. (b) Bardot, V.; Gardette, D.; Gelas-Mialhe, Y.; Gramain, J. C. Remuson, R. *Heterocycles*, **1998**, *48*, 507.