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Stereoselective synthesis of a new enantiopure tricyclic β-lactam derivative via a tricarbonyl(η^6-arene)chromium(0) complex

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Abstract

The tricyclic β-lactam **5** has been synthesized both in racemic and enantiopure form starting from the enantiomerically pure tricarbonylchromium(0) complex **1**. The synthetic sequence involves the stereoselective [2+2] cycloaddition of **1** with acetoxyacetylketene, followed by intramolecular aromatic nucleophilic substitution of the fluorine atom. Mechanistic pathways leading to **5** are discussed.

1. Introduction

The resistance of pathogenic bacteria to β-lactam antibiotics has an important incidence in human infections. As a consequence, in the last few years many research groups have been actively involved in improving the microbiological activity of antibacterial agents, as well as finding β-lactamase inhibitors,[1] and exploring new β-lactam containing ring systems.

As part of our research aimed at the use of chiral arenechromium tricarbonyl derivatives for the stereoselective synthesis of heterocyclic systems with potential biological activity, we have recently reported the synthesis of enantiomerically pure azetidinones.[2–5] We therefore envisaged the opportunity of obtaining new chiral tricyclic β-lactams by exploiting the asymmetric induction, which could arise from *ortho*-substituted complexed arenes,[6] and the nucleophilic aromatic substitution[7] activated by the $Cr(CO)_3$ unit.

We report here our results on the synthesis of a new chiral tricyclic β-lactam **5**, 3,4-benzo-6-(4-methoxyphenyl)-2,6-oxazabicyclo[3.2.0]hept-3-en-7-one, both in racemic and enantiomerically pure form.

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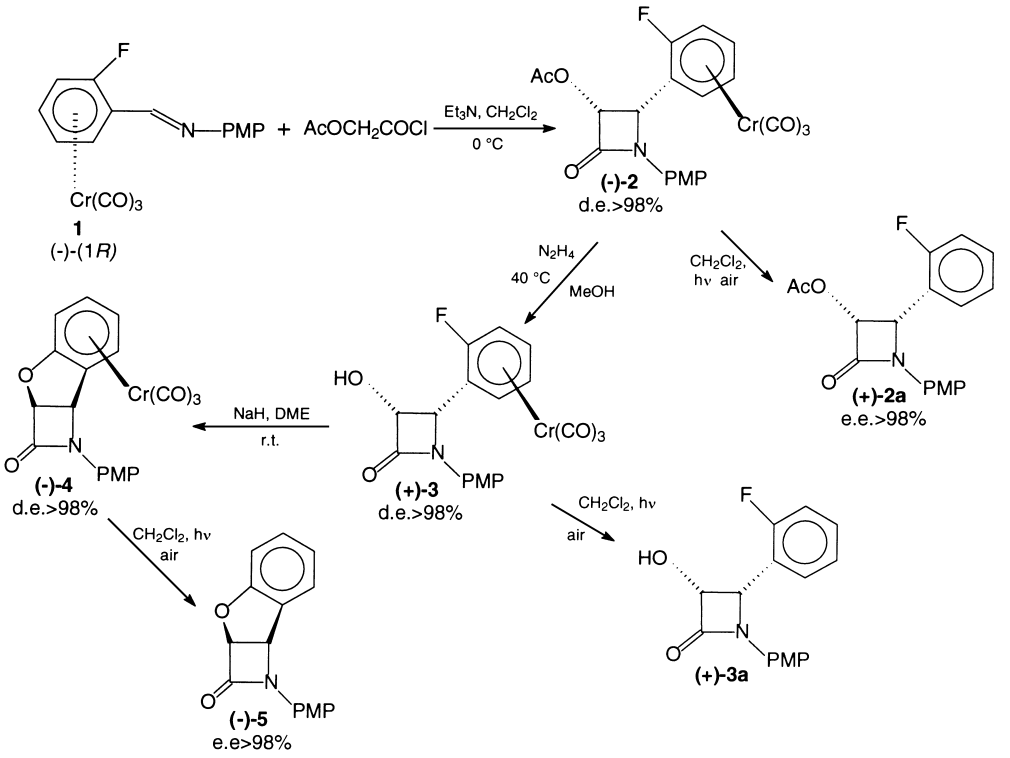
2. Results and discussion

The reaction sequence was first set up on racemic substrates and then repeated on enantiomerically pure complexes. In Scheme 1 the sequence for optically pure substrates starting from (–)-(1*R*) tricarbonyl[*N*-(2-fluorobenzylidene)-4-methoxyaniline]chromium **1** are reported. Imine **1** was obtained, in nearly quantitative yield, from the corresponding (–)-(1*R*) benzaldehyde complex.[8]



Scheme 1.

The [2+2] cycloaddition of imine (±)-**1** and acetoxyacetyl chloride at 0°C with Et_3N in CH_2Cl_2 afforded the *cis* β-lactam **2** as a single diastereoisomer in 94% yield (d.e. > 98%). Subsequent treatment of **2** with hydrazine in a methanolic solution gave, in 85% yield, the corresponding *cis* 3-hydroxy β-lactam **3**, the key intermediate for the tricyclic structure. The intramolecular displacement of the fluorine atom of **3** was carried out by treating the latter with an equimolar amount of NaH at room temperature.

Usual work-up of the reaction mixture, followed by chromatography and crystallization, gave rise to product **4** as a single diastereoisomer in 50% yield, whose spectroscopic and analytical data are consistent with the proposed tricyclic structure. Finally, uncomplexed **5** was obtained quantitatively by exposure of **4** to air and sunlight in CH_2Cl_2 solution.

A single crystal of racemic complex **4** was submitted to X-ray analysis[9] to confirm the proposed tricyclic structure. As it can be seen from Fig. 1, the $Cr(CO)_3$ unit lies on the opposite side to the C-3 and C-4 hydrogens of the β-lactam ring.

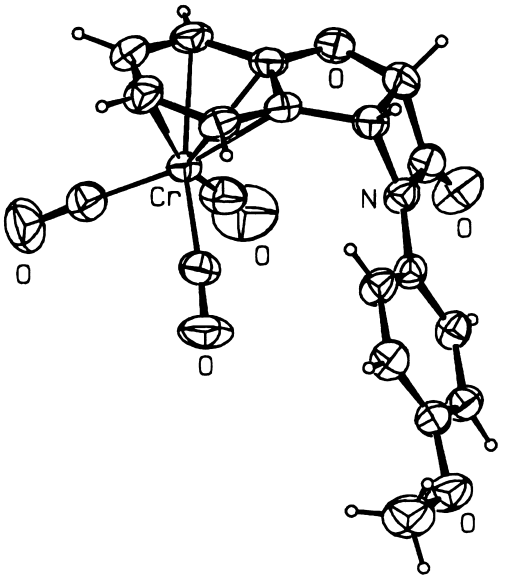
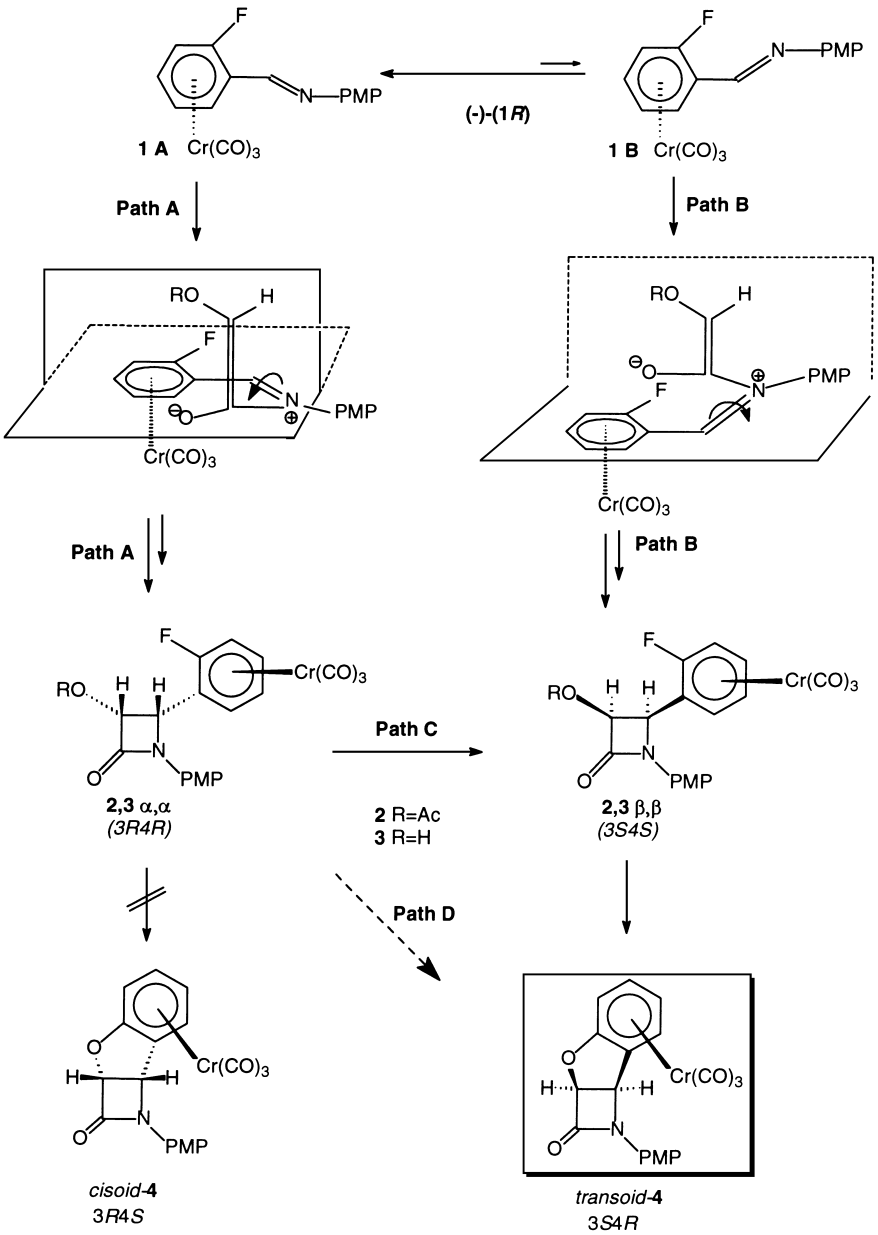


Figure 1. ORTOPEDII plot of **4**. Ellipsoids are at 50% of probability level; H atoms not to scale

Such a configuration is quite surprising on the basis of the accepted stereochemical model[10] for the chiral *ortho*-substituted benzaldehyde chromium complexes and for the imines[4] in the [2+2] cycloaddition. In fact, following the model, the complexed azetidinones **2** and **3** (Scheme 2, path A) should have the $Cr(CO)_3$ unit on the same side of the two hydrogens of the β-lactam ring when the fluorine atom is placed in front of the nucleophilic oxygen anion at the moment of tricyclic ring closure, giving rise therefore to *cisoid* **4** (*cisoid* with respect to the two hydrogens of the β-lactam ring versus the $Cr(CO)_3$ unit). We obtained instead *transoid* **4** that could arise either from the β-lactam **3**β,β (derived from the unfavourable conformation of the imine **1B**) (Scheme 2, path B), or from an inversion of the ring functions versus the $Cr(CO)_3$ unit during the ring closure of the β-lactam **3**α,α (Scheme 2, path D)

The absolute configuration of the new *ortho*-fluoro-substituted β-lactam (–)-**2**, obtained from the enantiomerically pure (–)-(1*R*) imine **1**, proves the validity of the stereochemical model. In fact from the conformer **1A** (the preferred one following the stereochemical model) the expected β-lactam **2** is α,α with the absolute configuration (3*R*,4*R*) for the complexed and (3*R*,4*S*) for the decomplexed one (Scheme 2, path A). On the contrary, the β-lactam **2** is β,β (Scheme 2, path B) with the absolute configuration (3*S*,4*S*) from the conformer **1B**. Therefore the same sequence of reactions was repeated starting from the enantiomerically pure (–)-(1*R*) imine **1** (see Scheme 1). The diastereomeric ratio found for the racemic **2** (d.e. > 98%) was confirmed by decomplexing a sample of optically active (–)-**2** by means of air and sunlight to the corresponding *N*-(4-methoxyphenyl)-3-acetoxy-4-(2-fluorophenyl)-azetidin-2-one (+)-**2a** which showed, by ^1H NMR in the presence of $Eu(hfc)_3$, an e.e. higher than 98%.

The determination of the absolute configuration of (+)-**2a** relies upon enzymatic hydrolysis experiments and the Cotton[11] effect. It is known that *Pseudomonas* lipase preferentially hydrolyzes the (3*S*,4*R*) enantiomer of 3-acetoxy-1,4-diphenyl β-lactam to the 3-hydroxy derivative,[12] confirmed as well by us for a series of 4-(*ortho*-substituted aryl) β-lactam.[5] Racemic **2a** (Scheme 1), submitted to kinetic resolution, gave rise to (+)-(3*R*,4*S*)-3-acetoxy derivative and (–)-(3*S*,4*R*)-3-hydroxy derivative, supporting the (3*R*,4*R*) absolute configuration for complexed (–)-**2**.

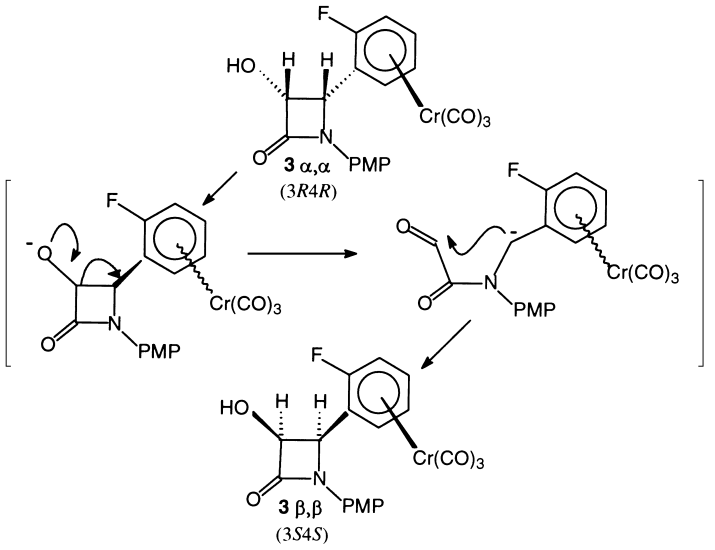


Scheme 2.

The positive Cotton effect in the CD curve[11] of (+)-**2a** is in good agreement with the (3*R*,4*S*) configuration finally confirming the validity of the adopted model.

After removal of the acetoxy group by means of hydrazine in methanolic solution, (+)-**3** was cyclized to (–)-**4** and decomplexed to (–)-**5**. The e.e. of tricyclic (–)-**5**, determined by ^{1}H NMR, was higher than 98%. Therefore, the step (+)-**3**→(–)-**4** was enantioselective but involved the inversion of the relative configuration between the $Cr(CO)_3$ group and the C3–C4 hydrogens, going from (+)-3α,α to *transoid* (–)-**4** (Scheme 2, path D).

Two reasonable mechanistic pathways leading to *transoid* **4** are hypothesized: (*a*) the aromatic nucleophilic substitution follows a *tele–meta* mechanism[13] rather than an *ipso* mechanism, involving the inversion of the stereochemistry of the complexed arene; (*b*) the oxy-anion generated from base treatment of **3**α,α (3*R*,4R) promotes an unusual ring opening across the C3–C4 bond to a benzylic carbanion (stabilized by $Cr(CO)_3$ unit) that regenerates the azetidinone ring by attack from the *Si*-face of the carbonyl group producing the enantiomeric hydroxy derivative **3**β,β (3*S*,4*S*) (see Scheme 3).

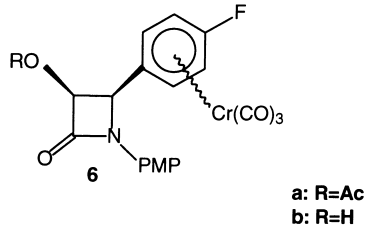


Scheme 3.

As regards to pathway (*a*), we have never found results different from the *ipso*-substitution mechanism[14] for the intermolecular aromatic nucleophilic substitution. Nevertheless, we considered it advisable to gain deeper insight about the plausibility of a *tele–meta* mechanism[13] in the case of sterically hindered intramolecular substitution.

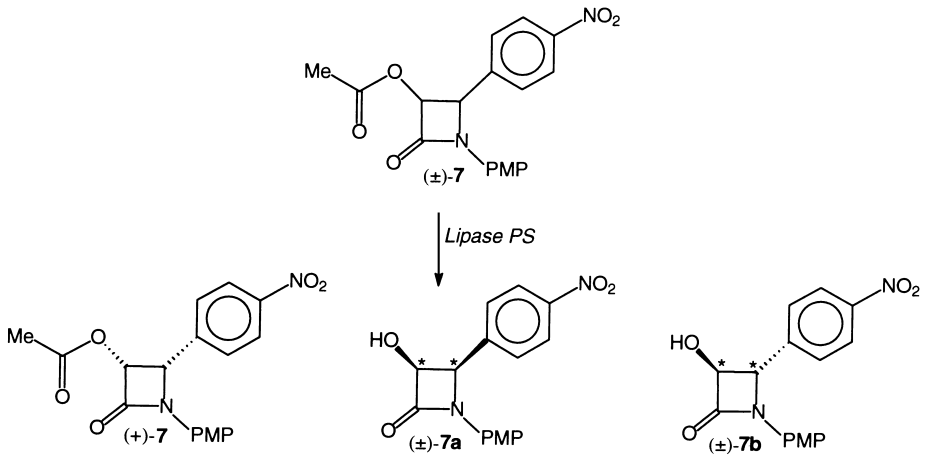
Therefore, we submitted the racemic *cis* **6b** (Scheme 4), synthesized in the usual way, to cyclization; no tricyclic product was detected even at longer reaction times. However, by changing the solvent from DME to DMF a 25% of *trans* 3-hydroxy derivative was obtained besides the recovery of starting *cis* **6b**. Such an isomerization may be due to azetidinone ring opening, similar to the one shown in Scheme 3, which could be favoured by structure strain. PM3[15] geometry calculation for a series of 3-hydroxy β-lactams (Fig. 2), such as 4-(2-fluorophenyl) **A**, 4-[2-fluoro-(η^6-tricarbonylchromium)phenyl] **B** and 4-(2-fluoro-4-nitrophenyl) **C** and their corresponding 3-oxy-anions was performed.[16] These calculations indicate that the C3–C4 bond length does not change in the series **A**–**C**, but strongly increases going from $\mathbf{A_1}$ to $\mathbf{B_1}$–$\mathbf{C_1}$. These observations could support the hypothesis that the oxy-anion formation promotes the unusual cleavage of the C3–C4 bond when the negative charge in the benzylic position may be stabilized due to the electron-withdrawing effect of the $Cr(CO)_3$ group, similar to the nitro group in the *para* position of the arene ring.

As a further support to the unusual C3–C4 bond breaking, racemic **7** was submitted to the lipase kinetic resolution (Scheme 5). At approximately 50% conversion, the (3*R*)-acetoxy-(4*S*)-(4-nitrophenyl) derivative **7** ($[\alpha]_D = +34.9$, c 1.2, $CHCl_3$, e.e. 49%) and a mixture of *cis* and



Scheme 4.

trans 3-hydroxy derivative (**7a** and **7b**) were recovered. After separation, both **7a** and **7b** show $[\alpha]_D \sim 0$; the racemization of the *cis* isomer must involve the double epimerization of both C3–C4 centres of the β-lactam, which can be explained only by ring opening.

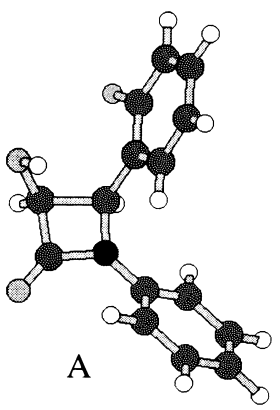


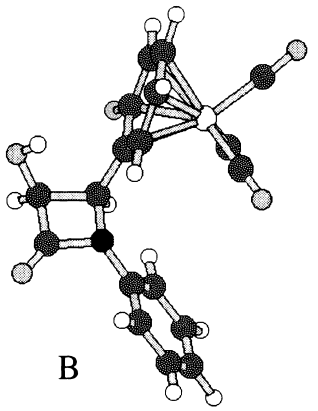
Scheme 5.

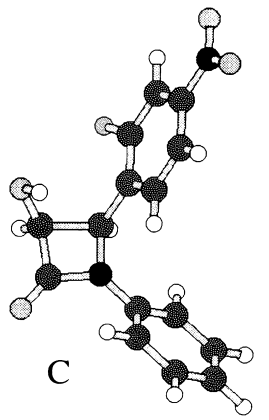
It is not surprising that during the ring closure (from **3**→**4**, Scheme 1) no *trans* isomer was detected, but, in contrast to the NO_2 group in **7**, the $Cr(CO)_3$ unit, bonded to the *ortho*-substituted arene, sterically hinders the formation of the *trans* isomer and directs stereoselectively the subsequent attack of benzylic carbanion on the opposite side of the starting configuration of the 3-hydroxy anion. Therefore, the *cis* hydroxy derivative (Scheme 2), which undergoes the ring closure to *transoid* **4**, is the geometrically favoured **3**β,β arising from **3**α,α through C3–C4 bond breaking (Scheme 2, path C). In fact, simulated geometries (PM3 level) show that the distance from the oxygen anion and the fluorine atom is 5.12 Å when the C3 and C4 hydrogens and $Cr(CO)_3$ are on the same side, and 4.87 Å when they are on the opposite side, making unfavourable the formation of tricyclic *cisoid* **4**.

Therefore, we state that the tricyclic product (–)-**5** (Scheme 1) has the C3 and C4 centres of the azetidinone ring with absolute configuration (1*S*,5*R*) opposite to the one of the precursor monocyclic β-lactam (+)-**3** (3*R*,4*R*).

Finally, to evaluate the ultimate scope of the procedure, the same reaction sequence outlined in Scheme 1 was repeated starting from the *ortho*-chloro-substituted tricarbonylchromium benzaldehyde, but the corresponding 3-hydroxy derivative does not undergo the cyclization, the only material recovered at longer reaction times being the decomplexed substrate.



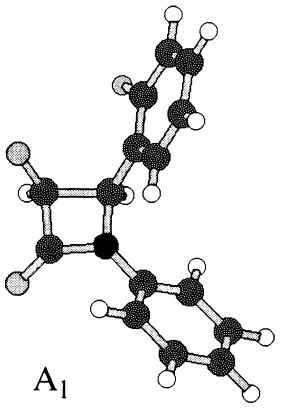


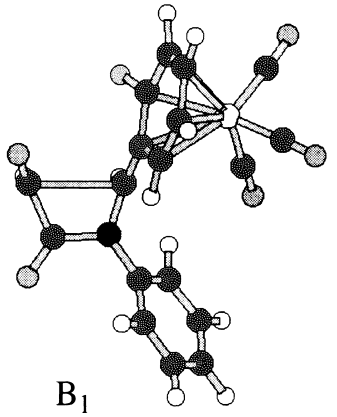


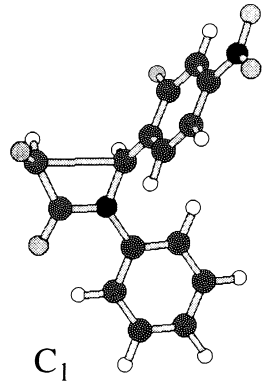
A: C3-C4=1.58 A°

B: C3-C4=1.58 A°

C: C3-C4=1.58 A°







A_1: C3-C4=1.696 A°

B_1: C3-C4=2.777 A°

C_1: C3-C4=2.754 A°

Figure 2.

3. Summary

A sample of **5** was submitted to microbiological screening to assess any activity as antibacterial or β-lactamase inhibitor.

We would like to emphasize that chiral *ortho*-substituted arenetricarbonylchromium derivatives are capable of controlling the absolute stereochemistry in the formation of the azetidinones and in further cyclization when benzylic anions are involved, these substrates being useful auxiliary tools for the diastereoselective synthesis of products with a potential biological activity. The synthesis of the new tryciclic **5** in enantiopure form supports further extension of the above method to additional compounds.

4. Experimental

All reactions were performed under a nitrogen atmosphere. Thermolysis with hexacarbonylchromium(0) were carried out in a round-bottomed flask, equipped with a Liebig air condenser and a water condenser on top. All chemicals were used as obtained from commercial sources. Column chromatography and TLC were carried out using, respectively, silica gel 60 and silica gel 60 F_{254} pre-coated plates. The melting points were measured using a Büchi 510 apparatus and are uncorrected. The IR spectra were recorded using a 1725X FTIR spectrometer. NMR spectra were recorded in $CDCl_3$ using Varian XL 300, Bruker AC 300 and AMX 300 spectrometers. Evaluation of enantiomeric excess was performed using Eu(hfc)$_3$, (tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) salt. The optical rotations were measured using a Perkin–Elmer 241 polarimeter, with a 1 dm pathlength at 25°C. The racemic compounds were prepared as previously reported. The enantiomerically pure complexed benzaldehydes were obtained by resolution of the corresponding racemic substrate using a known procedure.[8]

4.1. Preparation of (–)-tricarbonyl[N-(2-fluorobenzylidene)-4-methoxyaniline]chromium **1**

N-Methoxyaniline (284 mg, 2.31 mmol) was added under magnetic stirring to a solution of (–)-(1*R*) 2-fluorobenzaldehyde tricarbonylchromium {$[\alpha]_D = -1035$ (c 0.102, $CHCl_3$)} (600 mg, 2.31 mmol) in dry Et_2O (20 ml) and absolute EtOH (20 ml). The mixture was maintained at room temperature for 24 h, monitored by TLC (Et_2O/petroleum ether 3/1). After filtration and evaporation of the solvent under reduced pressure, the residue was dissolved in Et_2O (30 ml) and dried over Na_2SO_4. After filtration and evaporation, the red oil was crystallized by pentane (3–5 ml) and filtered. Yield 97%, orange solid, mp 114°C (pentane). $[\alpha]_D = -341$ (c 0.24, $CHCl_3$). $\nu_{(max)}$ (Nujol) 1985, 1934, 1897, 1616 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.8 (s, 3H, OMe); 5.0 (dt, 1H, J = 6.4, 2 Hz, arom. Cr(CO)$_3$); 5.4 (t, 1H, J = 6.2 Hz, arom. Cr(CO)$_3$); 5.6 (m, 1H, arom. Cr(CO)$_3$); 6.55 (m, 1H, arom. Cr(CO)$_3$); 6.9–7.2 (AB system, 4H, arom.); 8.4 (s, 1H, CH=N). Anal. calcd for $C_{17}H_{12}CrFNO_4$ (365.284): C, 55.90; H, 3.31; N, 3.83. Found C, 55.91; H, 3.32; N, 3.82.

4.2. Preparation of tricarbonyl[N-(4-methoxyphenyl)-3(R)-acetoxy-4(R)-(2-fluorophenyl)azetidin-2-one]chromium (–)-**2**

A solution of acetoxyacetyl chloride (0.41 ml, 3.82 mmol) in 5 ml of dry CH_2Cl_2 was carefully added to a solution of (–)-(1*R*) **1** (400 mg, 1.09 mmol) and Et_3N (0.91 ml, 6.53 mmol) in 8 ml of

dry CH_2Cl_2 cooled to 0°C. The reaction was maintained for 6 h at 0°C and overnight at room temperature. The reaction was quenched with 10 ml of H_2O and the organic layer dried over Na_2SO_4. After evaporation of the solvent at reduced pressure, the remaining brown solid was purified by chromatographic column (silica gel, eluent Et_2O/petroleum ether 3/1) The product was recovered as pale yellow solid, yield 93%, mp 199°C (dec.) (from petroleum ether); $[\alpha]_D = -25.5$ (c 0.133, $CHCl_3$). $\nu_{(max)}$ (Nujol) 1975, 1880, 1744 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.9 (s, 3H, COMe); 3.8 (s, 3H, OMe); 4.7 (m, 1H, arom. $Cr(CO)_3$); 5.22 (m, 1H, arom. $Cr(CO)_3$); 5.6 (d, 1H, J = 5 Hz, H_4); 5.6–5.5 (m, 2H, arom. $Cr(CO)_3$); 6.5 (d, 1H, J = 5 Hz, H_3); 7.0–7.5 (AB system, 4H, arom.). Anal. calcd for $C_{21}H_{16}CrFNO_7$ (465.36): C, 54.20; H, 3.47; N, 3.01. Found C, 54.18; H, 3.45; N, 2.99.

*4.3. Preparation of tricarbonyl[N-(4-methoxyphenyl)-3(R)-hydroxy-4(R)-(2-fluorophenyl)azetidin-2-one]chromium (+)-**3***

A solution of hydrazine monohydrate (0.047 ml, 0.97 mmol) in MeOH (3 ml) was added dropwise to a suspension of (–)-**2** (300 mg, 0.644 mmol) in 20 ml of MeOH cooled at 0°C. The reaction mixture was then warmed to 40°C until clear (about 2 h). The completion of the reaction was tested by TLC (eluent Et_2O/petroleum ether 1/1).The addition of water (20 ml) to the solution after cooling at room temperature afforded a yellow solid that was extracted with CH_2Cl_2 (3×20 ml), dried over Na_2SO_4 and, after evaporation of the solvent, filtered by addition of petroleum ether. Yield 85%, mp 184–185°C (dec.); $[\alpha]_D = +31.3$ (c 0.068 $CHCl_3$). $\nu_{(max)}$ (Nujol) 3267, 1969, 1918, 1731 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.1 (brs, 1H, OH); 3.8 (s, 3H, OMe); 4.8 (m, 1H, arom. $Cr(CO)_3$); 5.2–5.5 (m, 5H, arom. $Cr(CO)_3$ and H_3 and H_4); 7.0–7.5 (AB system, 4H, arom.). Anal. calcd for $C_{19}H_{14}CrFNO_6$ (423.322): C, 53.91; H, 3.33; N, 3.31. Found C, 53.93; H, 3.34; N, 3.30.

*4.4. Preparation of (–)-tricarbonyl[3,4-benzo-6-(4-methoxyphenyl)-2,6-oxazabicyclo[3.2.0]hept-3-en-7-one]chromium **4***

A solution of (+)-**3** (200 mg, 0.472 mmol) in DME (10 ml) was added to a suspension of NaH (0.519 mmol, oil suspension) in 8 ml of dry DME. The reaction was monitored by TLC (eluent Et_2O). When the reaction was complete (about 2 h), the mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3×20 ml). After evaporation of the solvent under reduced pressure, the residue was chromatographed (SiO_2, eluent Et_2O) and, together with small amounts of complexed (36 mg) and uncomplexed (28 mg) starting 3-hydroxy derivative **3** and a mixture of unidentified products, the tricyclic (–)-**4** was recovered in 50% yield as a single diastereoisomer. Pale yellow solid, mp 205°C (dec.) (from petroleum ether); $[\alpha]_D = -204.8$ (c 0.290, $CHCl_3$). $\nu_{(max)}$ (Nujol) 1958, 1889, 1751 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.8 (s, 3H, OMe); 4.58 (t, 1H, J = 6.1 Hz, arom. $Cr(CO)_3$); 5.1 (d, 1H, J = 6.6 Hz, arom. $Cr(CO)_3$); 5.4 (d, 1H, J = 4.6 Hz, H_5); 5.5 (t, 1H, J = 6.6 Hz, arom. $Cr(CO)_3$); 5.8 (d, 1H, J = 4.6 Hz, H_1); 6.0 (d, 1H, J = 6.1 Hz, arom. $Cr(CO)_3$); 6.9–7.4 (AB system, 4H, arom.); $M^{+1} = 403$. Anal. calcd for $C_{19}H_{13}CrNO_6$ (403.316): C, 56.58; H, 3.25; N, 3.47. Found C, 56.63; H, 3.24; N, 3.45.

*4.5. Preparation of (–)-3,4-benzo-6-(4-methoxyphenyl)-2,6-oxazabicyclo[3.2.0]hept-3-en-7-one **5** by decomplexation of (–)-**4***

A solution of (–)-**4** (200 mg, 0.496 mmol) in 15 ml of CH_2Cl_2 was exposed to air and sunlight for about 4–6 h (the reaction time was determined by TLC). The solvent was removed under

reduced pressure, the residue was taken up with Et_2O and filtered over a pad of Celite to remove the chromium salts. The ether solution was evaporated and the residue was crystallized by petroleum ether. Yield 98%, white solid, mp 169°C (from petroleum ether); $[\alpha]_D = -65.7$ (c 0.149, $CHCl_3$). $\nu_{(max)}$ (Nujol) 1734 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.8 (s, 3H, OMe); 5.65 (d, 1H, J = 4.5 Hz, H_5); 5.8 (d, 1H, J = 4.5 Hz, H_1); 6.9 (m, 4H, arom.); 7.3 (m, 1H, arom.); 7.5 (m, 3H, arom.). Anal. calcd for $C_{16}H_{13}NO_3$ (267.288): C, 71.90; H, 4.90; N, 5.24. Found C, 71.89; H, 4.91; N, 5.23. E.e. > 98%.

4.6. Decomplexation of (–)-**2** and (+)-**3**

The same procedure reported for the preparation of (–)-**5** was used. Product (+)-**2a**: yield 97%, white solid, mp 117°C (from petroleum ether); $[\alpha]_D = +26.3$ (c 0.114, $CHCl_3$). $\nu_{(max)}$ (Nujol) 1744 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.8 (s, 3H, Me); 3.8 (s, 3H, OMe); 5.68 (d, 1H, J = 4.9 Hz, H_3); 6.02 (d, 1H, J = 4.9 Hz, H_4); 6.8 (AB system, 2H, arom.); 7.1 (m, 2H, arom.); 7.25–7.4 (m, 4H, arom.). Anal. calcd for $C_{18}H_{16}FNO_4$ (329.331): C, 65.65; H, 4.90; N, 4.25. Found C, 65.70; H, 4.91; N, 4.23. E.e. > 98%. Product (+)-**3a**: yield 92%, white solid, mp 196–197°C (from petroleum ether). $[\alpha]_D = +180$ (c 0.1, $CHCl_3$). $\nu_{(max)}$ (Nujol) 3351, 1729 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.5 (d, 1H, J = 8.4 Hz, OH); 3.8 (s, 3H, OMe); 5.25 (dd, 1H, J = 5.1 and 8.4 Hz, H_3); 5.53 (d, 1H, J = 5.1 Hz, H_4); 6.85 (AB system, 2H, arom.); 7.1–7.4 (m, 6H, arom.). Anal. calcd for $C_{16}H_{14}FNO_3$ (287.293): C, 66.89; H, 4.91; N, 4.88. Found C, 66.91; H, 4.90; N, 4.86.

4.7. Enzymatic kinetic resolution of N-(4-methoxyphenyl)-3-acetoxy-4-(2-fluorophenyl)azetidin-2-one (±)-**2a**

To 200 mg of (±)-**2a** suspended in 9 ml of 0.1 M phosphate buffer solution (pH 7.5) and 1 ml of acetonitrile, 200 mg of *Lipase-P*[17] was added; the mixture was vigorously stirred at 37°C. After 24 h the reaction was quenched by extraction of the mixture with ethyl acetate (3×20 ml). Evaporation of the solvent afforded quantitatively a mixture that was separated by chromatography to give the 3-acetoxy derivative $[\alpha]_D = +25.8$ (c 0.12, $CHCl_3$), e.e. 97% and the corresponding 3-hydroxy derivative $[\alpha]_D = -182$ (c 0.23, $CHCl_3$).

4.8. Preparation of tricarbonyl[4-fluorobenzaldehyde]chromium

The complexation was performed as described for the corresponding *ortho*-substituted benzaldehyde to give the complexed diethylacetal, yellow solid, mp 34°C from pentane. ν_{max} (Nujol) 1974, 1892, 1102, 1056 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.3 (dt, 6H, J = 7, 0.9 Hz, Me); 3.65 (m, 4H, CH_2); 5.15 (s, 1H, CH); 5.45 (dt, 2H, J = 6.6, 1.02 Hz, arom. $Cr(CO)_3$); 5.8 (dd, 2H, J = 6.8, 3 Hz, arom. $Cr(CO)_3$). Anal. calcd for $C_{14}H_{15}CrFO_5$ (334.268): C, 50.31; H, 4.52. Found C, 50.52; H, 4.50. A solution of the complexed diethylacetal was dissolved in the minimum quantity of dioxane and, under vigorous stirring, treated at room temperature with a 10% aqueous solution of HCl. The colour of the solution changed from yellow to red; the progress was monitored by TLC (petroleum ether/Et_2O 3/1). A saturated solution of $NaHCO_3$ was added until pH 7 and then about 70% of the solvent was eliminated by reduced pressure and Et_2O was added. The solution was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed. Yield 26%, red solid, mp 89°C (from petroleum ether). ν_{max} (Nujol) 1975, 1885, 1682 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.4–6.0 (AB system, 4H, arom. $Cr(CO)_3$), 9.4

(s, 1H, CH=N). ^{19}F NMR ($CDCl_3$) δ –132.286. Anal. calcd for $C_{10}H_5FCrO_4$ (260.144): C, 46.17; H, 1.94. Found C, 46.22; H, 1.93.

4.9. Preparation of tricarbonyl[N-(4-fluorobenzylidene)-4-methoxyaniline]chromium

N-Methoxyaniline (378 mg, 3.07 mmol) was added to a solution of 4-fluorobenzaldehyde tricarbonylchromium (800 mg, 3.07 mmol) in dry Et_2O (25 ml) and absolute EtOH (25 ml) under magnetic stirring. The mixture was maintained at room temperature for about 24 h, monitored by TLC (Et_2O/petroleum ether 5/1). After evaporation of the solvent under reduced pressure, the residue was dissolved in Et_2O (35 ml) and dried over Na_2SO_4. Filtration and evaporation afforded a red oil that was made crystalline by pentane (3–5 ml). Yield 95%, orange solid, mp 116°C (from ether/pentane). ν_{max} (Nujol) 1970, 1893, 1622 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.9 (s, 3H, OMe); 5.6 (m, 2H, arom. $Cr(CO)_3$); 6.1 (m, 2H, arom. $Cr(CO)_3$); 6.9–7.1 (AB system, 4H, arom.); 7.9 (s, 1H, CH=N). ^{19}F NMR ($CDCl_3$) δ –134.27. Anal. calcd for $C_{17}H_{12}CrFNO_4$ (365.284): C, 55.90; H, 3.31; N, 3.83. Found C, 55.92; H, 3.30; N, 3.84.

4.10. Preparation of tricarbonyl[N-(4-methoxyphenyl)-3-acetoxy-4-(4-fluorophenyl)azetidin-2-one]-chromium (±)-6a

A solution of acetoxyacetyl chloride (0.21 ml, 1.95 mmol) in 5 ml of dry CH_2Cl_2 was carefully added to a solution of tricarbonyl[*N*-(4-fluorobenzylidene)-4-methoxyaniline]chromium (200 mg, 0.55 mmol) and Et_3N (0.35 ml, 2.5 mmol) in 8 ml of dry CH_2Cl_2 cooled to 0°C. The reaction was allowed to warm at room temperature and maintained for 6 h (TLC Et_2O). The reaction was quenched with 30 ml of saturated NH_4Cl, extracted with CH_2Cl_2 (3×25 ml) and the organic solvent was dried over Na_2SO_4. After evaporation of the solvent at reduced pressure, the remaining brown solid was purified by column chromatography (silica gel, eluent Et_2O/petroleum ether 4/1). The product was recovered in 96% yield as pale yellow solid, mp 116°C (dec.) (from petroleum ether). ν_{max} (Nujol) 1972, 1898, 1751 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.9 (s, 3H, COMe); 3.8 (s, 3H, OMe); 5.1 (d, 1H, J = 4.9 Hz); 5.2 (dt, 2H, J = 4.4, 1.8 Hz, arom. $Cr(CO)_3$); 5.3 (dt, 2H, arom. $Cr(CO)_3$); 5.85 (d, 1H, J = 4.9 Hz); 6.9–7.4 (AB system, 4H arom.). ^{19}F NMR ($CDCl_3$) δ –134.57. Anal. calcd for $C_{21}H_{16}CrFNO_7$ (465.36): C, 54.20; H, 3.47; N, 3.01. Found C, 54.25; H, 3.46; N, 3.00.

4.11. Preparation of tricarbonyl[N-(4-methoxyphenyl)-3-hydroxy-4-(4-fluorophenyl)azetidin-2-one]-chromium (±)-6b

A solution of hydrazine monohydrate (0.069 ml, 1.44 mmol) in MeOH (4 ml) was added dropwise to a suspension of **6a** (440 mg, 0.945 mmol) in MeOH (30 ml) cooled at 0°C. The reaction mixture was then warmed at 40°C until it became clear (about 3 h). The completion of the reaction was tested by TLC (eluent Et_2O/petroleum ether 5/1). The addition of water (30 ml) to the solution cooled at room temperature afforded a yellow solid, which was extracted with CH_2Cl_2 (3×20 ml), dried over Na_2SO_4 and, after evaporation of the solvent, filtered by addition of petroleum ether. Yield 81%, yellow solid, mp 165°C (dec.) (from CH_2Cl_2/pentane). ν_{max} (Nujol) 3295, 1965, 1894, 1723 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.1 (brs, 1H, OH); 3.7 (s, 3H, OMe); 4.9 (d, 1H, J = 5 Hz); 5.1–5.2 (m, 2H, arom. $Cr(CO)_3$); 5.3–5.4 (m, 2H, arom. $Cr(CO)_3$); 5.5 (m, 1H,); 6.8–7.3 (AB system, 4H, arom.). ^{19}F NMR ($CDCl_3$) δ –134.669. Anal. calcd for $C_{19}H_{14}CrFNO_6$ (423.322): C, 53.91; H, 3.33; N, 3.31. Found C, 53.94; H, 3.32; N, 3.30.

4.12. Reaction of **6b** with NaH in DMF

NaH (0.566 mmol, oil suspension) was added to a solution of **6b** (200 mg, 0.472 mmol) in 5 ml of DMF, under vigorous stirring. The reaction was monitored by TLC (eluent Et_2O). After 5 h, the mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3×20 ml). After evaporation of the solvent under reduced pressure, the crude material (150 mg) was directly decomplexed by exposing the solution in CH_2Cl_2 to air and sunlight for 4 h. The solvent was evaporated and the residue was taken up with Et_2O, filtered over Celite and evaporated. ^1H NMR ($CDCl_3$) show a 3:1 mixture of two diastereomeric 3-hydroxy derivatives. After chromatography (SiO_2, eluent Et_2O) the pure *cis* and *trans* isomers were recovered. Product **6b *cis*** decomplexed: 72 mg, white solid, mp 146°C (from pentane). ν_{max} (Nujol) 3339, 1723 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.08 (brs, 1H, OH); 3.74 (s, 3H, OMe); 5.16 (d, 1H, J = 5.2 Hz); 5.24 (d, 1H, J = 5.2 Hz); 6.7–7.1 (AB system, 4H, arom.); 7.3 (m, 4H, arom.). Anal. calcd for $C_{16}H_{14}FNO_3$ (287.293): C, 66.89; H, 4.91; N, 4.88. Found C, 66.92; H, 4.88; N, 4.89. Product **6b *trans*** decomplexed: 24.3 mg, white solid, mp 122°C (from pentane). ν_{max} (Nujol) 3391, 1719 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.55 (brs, 1H, OH); 3.75 (s, 3H, OMe); 4.70 (d, 1H, J = 1.6 Hz); 4.81 (d, 1H, J = 1.6 Hz); 6.75–7.1 (AB system, 4H, arom.); 7.2–7.4 (m, 4H, arom.). Anal. calcd for $C_{16}H_{14}FNO_3$ (287.293): C, 66.89; H, 4.91; N, 4.88. Found C, 66.90; H, 4.89; N, 4.86.

4.13. Preparation of N-(4-nitrobenzylidene)-4-methoxyaniline

4-Nitrobenzaldehyde (630 mg, 4.17 mmol) and 4-methoxyaniline (513 mg, 4.17 mmol) were heated in EtOH (40 ml) under reflux for 25 min. The mixture was cooled and the yellow solid filtered. Yield 90%, mp 132°C (from EtOH). ν_{max} (Nujol) 1568, 1504, 1338 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H, OMe); 6.95–7.3 (AB system, 4H, arom.); 8.05–8.3 (AB system, 4H, arom.); 8.6 (s, 1H, CH=N). Anal. calcd for $C_{14}H_{12}N_2O_3$ (256.264): C, 65.62; H, 4.72; N, 10.93. Found C, 65.68; H, 4.73; N, 10.95.

4.14. Preparation of N-(4-methoxyphenyl)-3-acetoxy-4-(4-nitrophenyl)azetidin-2-one (±)-7

A solution of acetoxyacetyl chloride (0.42 ml, 3.9 mmol) in 10 ml of dry CH_2Cl_2 was carefully added to a solution of tricarbonyl *N*-(4-nitrobenzylidene)-4-methoxyaniline (286 mg, 1.11 mmol) and Et_3N (0.7 ml, 5 mmol) in 10 ml of dry CH_2Cl_2 cooled to 0°C. The reaction was allowed to warm at room temperature and maintained for 3 h (TLC Et_2O). The reaction was quenched with 30 ml of saturated NH_4Cl, extracted with CH_2Cl_2 (3×25 ml) and the organic solvent was dried over Na_2SO_4. After evaporation of the solvent at reduced pressure, the remaining brown solid was purified by chromatographic column (silica gel, eluent Et_2O). Yield 85%, pale yellow solid, mp 165°C (from Et_2O). ν_{max} (Nujol) 1760, 1742, 1527, 1360 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.66 (s, 3H, COMe); 3.69 (s, 3H, OMe); 5.35 (d, 1H, J = 4.9 Hz); 5.91 (d, 1H, J = 4.9 Hz); 6.74–7.17 (AB system, 4H, arom.); 7.38–8.17 (AB system, 4H, arom.). Anal. calcd for $C_{18}H_{16}N_2O_6$ (356.340): C, 60.67; H, 4.53; N, 7.86. Found C, 60.71; H, 4.52; N, 7.83.

4.15. Enzymatic kinetic resolution of N-(4-methoxyphenyl)-3-acetoxy-4-(4-nitrophenyl)azetidin-2-one (±)-7

To 300 mg of (±)-**7** suspended in 14 ml of 0.1 M phosphate buffer solution (pH 7.5) and 1.5 ml of acetonitrile, 300 mg of *Lipase-P*[19] was added; the mixture was stirred vigorously at 37°C. After

24 h the conversion was about 50%; the reaction was quenched by extraction of the mixture with ethyl acetate (3×30 ml). Evaporation of the solvent afforded a mixture that was separated by chromatography. The resolved 3-acetoxy derivative was recovered in 46% yield (139 mg) $[\alpha]_D = +34.9$ (c 1.2, $CHCl_3$) and the two diastereomeric hydroxy derivatives *trans* and *cis* in 55:45 ratio. Product (+)-**7a** ***cis***: 44.4 mg; mp 154°C (from petroleum ether). ν_{max} (Nujol) 3306, 1728 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.75 (s, 3H, OMe); 4.0 (brs, 1H, OH); 5.30 (d, 1H, J = 5.2 Hz); 5.33 (d, 1H, J = 5.2 Hz); 6.8–7.2 (AB system, 4H, arom.); 7.5–8.2 (AB system, 4H, arom.). $[\alpha]_D = \sim 0$ (c 0.62 $CHCl_3$). Anal. calcd for $C_{16}H_{14}N_2O_5$ (314.302): C, 61.14; H, 4.49; N, 8.91. Found C, 61.10; H, 4.50; N, 8.91. $M^{+1} = 314$. Product **7b** ***trans***: 62 mg; mp 140°C (from petroleum ether). ν_{max} (Nujol) 3223, 1732 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.72 (s, 3H, OMe); 4.69 (d, 1H, J = 1.5 Hz); 4.98 (d, 1H, J = 1.5 Hz); 6.78–7.1 (AB system, 4H, arom.); 7.49–8.2 (AB system, 4H, arom.). $[\alpha]_D = \sim 0$ (c 0.88, $CHCl_3$). Anal. calcd for $C_{16}H_{14}N_2O_5$ (314.302): C, 61.14; H, 4.49; N, 8.91. Found C, 61.17; H, 4.51; N, 8.92. $M^{+1} = 314$.

*4.16. Preparation of tricarbonyl[*N-*(2-chlorobenzylidene)-4-methoxyaniline]chromium*

N-Methoxyaniline (133 mg, 1.08 mmol) was added to a solution of (±)-2-chlorobenzaldehyde tricarbonylchromium (300 mg, 1.08 mmol) in dry Et_2O (10 ml) and absolute EtOH (10 ml) under magnetic stirring. The mixture was maintained at room temperature for about 24 h and monitored by TLC (Et_2O/petroleum ether 3/1). After evaporation of the solvents under reduced pressure, the residue was dissolved in Et_2O (30 ml) and dried over Na_2SO_4. Filtration and evaporation afforded a red oil that was made crystalline by pentane (3–5 ml) and then filtered. Yield 96%, orange solid, mp 96°C (from pentane). ^1H NMR ($CDCl_3$) δ 3.8 (s, 3H, OMe); 5.2 (t, 1H, J = 7.2 Hz, arom. $Cr(CO)_3$); 5.45 (d, 1H, J = 6.5 Hz, arom. $Cr(CO)_3$); 5.55 (t, 1H, J = 6.5 Hz, arom. $Cr(CO)_3$); 6.55 (d, 1H, J = 7.2 Hz, arom. $Cr(CO)_3$); 6.9–7.25 (AB system, 4H, arom.); 8.5 (s, 1H, CH=N). Anal. calcd for $C_{17}H_{12}ClCrNO_4$ (381.736): C, 53.49; H, 3.17; N, 3.67. Found C, 53.51; H, 3.16; N, 3.69.

*4.17. Preparation of tricarbonyl[*N-*(4-methoxyphenyl)-3-acetoxy-4-(2-chlorophenyl)azetidin-2-one]-chromium*

A solution of acetoxyacetyl chloride (0.3 ml, 2.8 mmol) in 5 ml of dry CH_2Cl_2 was carefully added to a solution of tricarbonyl[*N*-(4-chlorobenzylidene)-4-methoxyaniline]chromium (300 mg, 0.79 mmol) and Et_3N (0.66 ml, 4.7 mmol) in 10 ml of dry CH_2Cl_2 cooled to 0°C. The reaction was allowed to warm at room temperature and maintained for 24 h (TLC Et_2O). The reaction was quenched with 30 ml of saturated NH_4Cl, extracted with CH_2Cl_2 (3×25 ml) and the organic solvent was dried over Na_2SO_4. After evaporation of the solvent at reduced pressure, the remaining brown solid was purified by chromatographic column (silica gel, eluent Et_2O/petroleum ether 3/1) The product was recovered in 65% yield, pale yellow solid, mp 195°C (from petroleum ether). ^1H NMR ($CDCl_3$) δ 1.9 (s, 3H, Me); 3.8 (s, 3H, OMe); 4.98 (t, 1H, J = 6.2 Hz, arom. $Cr(CO)_3$); 5.38 (d, 1H, J = 6.2 Hz, arom. $Cr(CO)_3$); 5.42–5.55 (m, 2H, arom. $Cr(CO)_3$); 5.65 (d, 1H, J = 5.1 Hz); 6.25 (d, 1H, J = 5.1 Hz); 7.0–7.5 (AB system, 4H, arom.). Anal. calcd for $C_{21}H_{16}ClCrNO_7$ (481.812): C, 52.35; H, 3.35; N, 2.91. Found C, 52.34; H,3.36; N, 2.90.

*4.18. Preparation of tricarbonyl[*N-*(4-methoxyphenyl)-3-hydroxy-4-(2-chlorophenyl)azetidin-2-one]-chromium*

A solution of hydrazine monohydrate (0.03 ml, 0.63 mmol) in MeOH (3 ml) was added dropwise to a suspension of 3-acetoxy derivative (200 mg, 0.42 mmol) in MeOH (20 ml) cooled at 0°C.

The reaction mixture was warmed to 40°C and maintained until it became clear (about 3 h). The completion of the reaction was tested by TLC (eluent Et_2O/petroleum ether 3/1). The addition of water (20 ml) to the solution cooled at room temperature afforded a yellow solid that was extracted with CH_2Cl_2 (3×20 ml), dried over Na_2SO_4 and, after evaporation of the solvent, filtered by addition of petroleum ether. Yield 78%, pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 3.0 (brs, 1H, OH); 3.8 (s, 3H, OCH_3), 5.1 (m, 2H, arom. $Cr(CO)_3$); 5.4 (d, 1H, J = 5.3 Hz), 5.6 (m, 2H, arom. $Cr(CO)_3$ and H_4); 6.5 (d, 1H, J = 7.1 Hz, arom. $Cr(CO)_3$); 6.85–7.5 (AB system, 4H, arom.). Anal. calcd for $C_{19}H_{14}ClCrNO_6$ (439.774): C, 51.89; H, 3.21; N, 3.19. Found C, 51.88; H, 3.20; N, 3.18.

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