Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 11, pp. 3193-3202, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00422-3

Resolution of Chiral (Trimethylenemethane) Iron (Tricarbonyl) Complexes

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Abstract : Reaction of (S)-(-)-ethyl lactate and (R)-(+)-α-methylbenzylamine with the racemic crystalline activated TMM ester **3**, obtained in 3 steps from β,β'-dimethylacrylic acid, provides the easily separable diastereomeric esters **2a/2b** and amides **10a/10b**. From the esters and the N-BOC amides **11a/11b**, simple reactions allow the synthesis of other optically active TMM $Fe(CO)_3$ complexes of high enantiomeric purity and known absolute configuration. Copyright © 1996 Elsevier Science Ltd

Organotransition metal complexes have received considerable attention in recent years for use in organic synthesis. The cheap and non toxic metal, iron, is, in particular, well suited for stoichiometric applications. Thus, as a result of planar chirality of complexes, diastereoselective transformations provide an easy access to optically active compounds. The resolution of the racemic starting complexes is very important in this context and several methods have been developed, for instance, from suitably substituted (diene)$Fe(CO)_3$ complexes[1] and the (cyclopentadienyl)$Fe(CO)(PPh_3)$ acetyl complex.[2] Furthermore, complexation by a transition metal has been shown to stabilize considerably unstable or highly reactive polyunsaturated organic ligands, as illustrated by the formation of stable complexes of cyclobutadiene[3] or cyclohexadienone,[4,5] to quote only these. (Trimethylenemethane) $Fe(CO)_3$ complexes[6] belong also to this category and their use for synthetic purposes.[7-9] makes the availability of such chiral complexes as pure enantiomers most desirable.

We could previously achieve the resolution of (formyl TMM) $Fe(CO)_3$ via relatively easily separable chiral diastereomeric semioxamazones.[7] However, the cleavage of the semioxamazones to the enantiomeric aldehydes proceeded with a slight racemization, even under the carefully controlled conditions used (pyruvic acid in acetic acid/water, temperature not exceeding 20°C) so that in routine preparation an enantiomeric purity of only ca. 90 % could be reached.

We report herein two more general methods of resolution of functionalized TMM complexes. They represent significant improvements with regard to the ease of chromatographic separations and absence of racemization, allowing the efficient and simple preparation of pure enantiomers on a multigram scale. Both procedures are based on the easy separation of chiral diastereomeric esters and amides of (TMM) $Fe(CO)_3$ carboxylic acid by simple silica gel column chromatography. From several tested chiral auxiliaries, the cheapest, (S)-(-)-ethyl lactate and (R)-(+)-α-methylbenzylamine, turned out to be the most efficient.[10] The choice of derivatives of the acid function for the resolution was motivated by the fact that almost all functionalized TMM complexes are obtained via the acid or its esters.[6,11-13] Thus, a broad range of optically active TMM complexes could be available by use of the conventional procedures.

Reaction of β,β'-dimethylacrylic acid with (S)-(-)-ethyl lactate in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) as catalyst gave the corresponding esters **1** (69 %, $[\alpha]_D$ = - 47 in MeOH). On radical bromination with *N*-bromosuccinimide (NBS), **1** led to a mixture of distillable brominated products (115 - 135°C, 0.5 Torr) which were directly reacted with $Fe_2(CO)_9$, to give the diastereomeric complexed esters **2a** and **2b** (40 % overall, ca. 1.4 : 1) (scheme 1).

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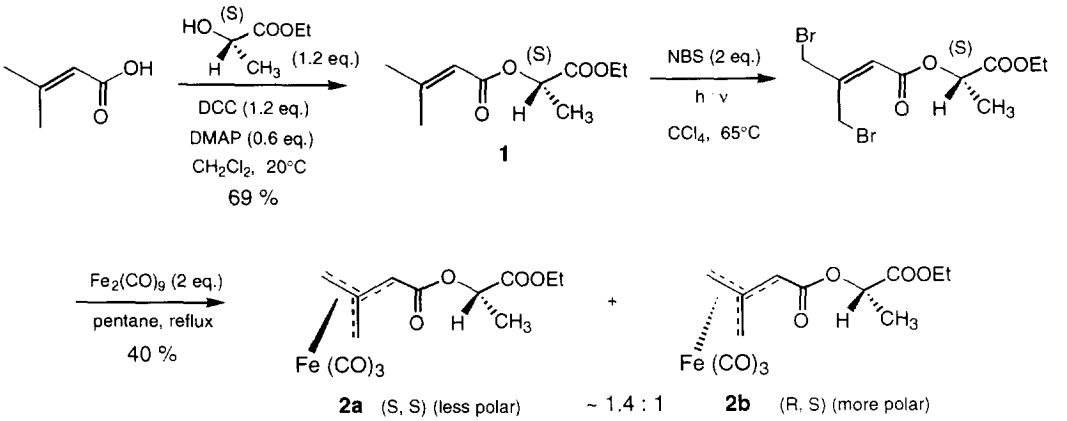
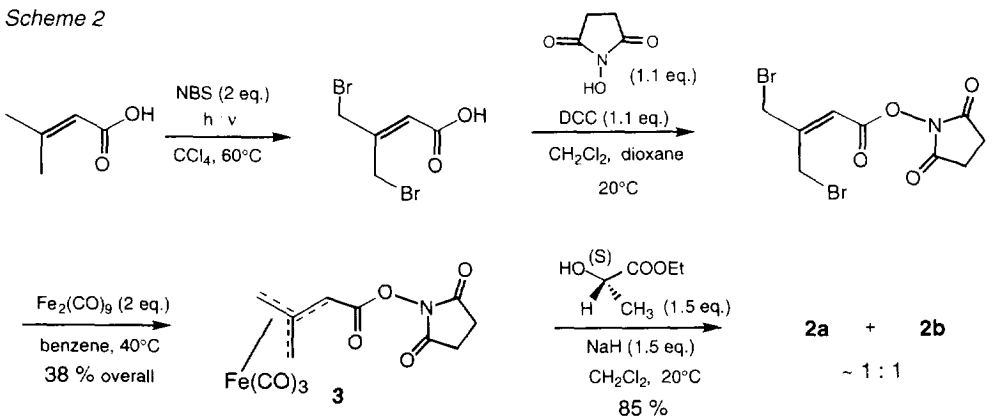
Scheme 1



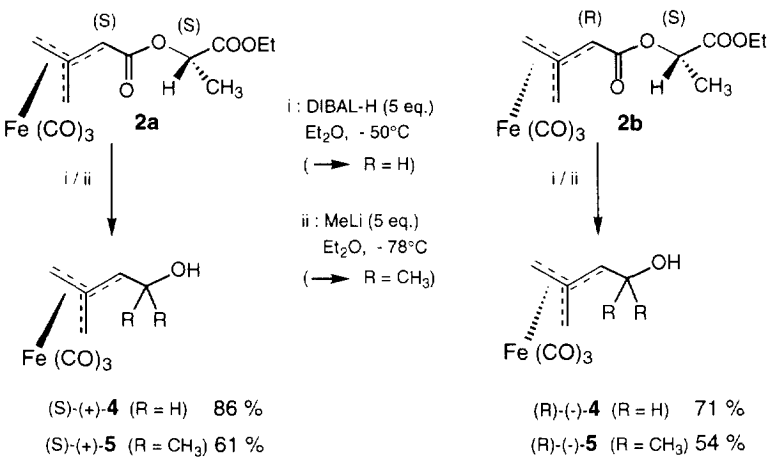
The separation of the esters **2a** and **2b** could be achieved by simple silica gel column chromatography, their difference in polarity being appreciable ($\Delta R_f \sim 0.08$ on a silica gel tlc plate with *n*-hexane/ether as eluent). However, **2b** was contaminated by small amounts of unbrominated ester **1** (same polarity). We therefore developed a modified procedure where the activated crystalline TMM ester **3**, liable to be a precursor for both the ethyl lactate-esters and the α-methylbenzylamides was prepared first.[14] For that purpose, β,β'-dimethyl acrylic acid was brominated with NBS,[15] and the crude radical dibromination product was esterified with *N*-hydroxysuccinimide in the presence of DCC. The resulting ester, again without purification, was reacted with two equivalents of $Fe_2(CO)_9$ to afford, after recrystallisation, the complexed activated ester **3** in 38 % overall yield. The transesterification gave rise, after chromatographic separation, to uncontaminated diastereomeric esters **2a** and **2b** in 85 % yield (scheme 2). Baseline separation is possible on a small scale, but on a routine preparative scale, roughly three fractions were isolated in order to economize time, solvent and adsorbant. Thus, respectively about 35 % of pure **2a** and **2b** are obtained, and the middle fraction, a mixture of **2a** and **2b** (~ 30 %), was simply recycled.

Scheme 2



The optically active primary TMM-alcohols (+)-**4** and (-)-**4** and the dimethylated tertiary TMM-alcohols (+)-**5** and (-)-**5** were obtained by reduction with DIBAL-H or reaction with MeLi, respectively from the less polar **2a** and the more polar **2b** esters (scheme 3). Oxidation of the primary alcohols (+)-**4** and (-)-**4** with manganese dioxide at room temperature provided in excellent yields the aldehydes (-)-**6** and (+)-**6** of high enantiomeric purity ($[\alpha]_D$ = - 268 and + 268 in $CHCl_3$, as compared to $[\alpha]_D$ = + 261, the highest previously measured $[\alpha]_D$ value, corresponding to an e.e. of ≥ 92 %).[7]

Scheme 3

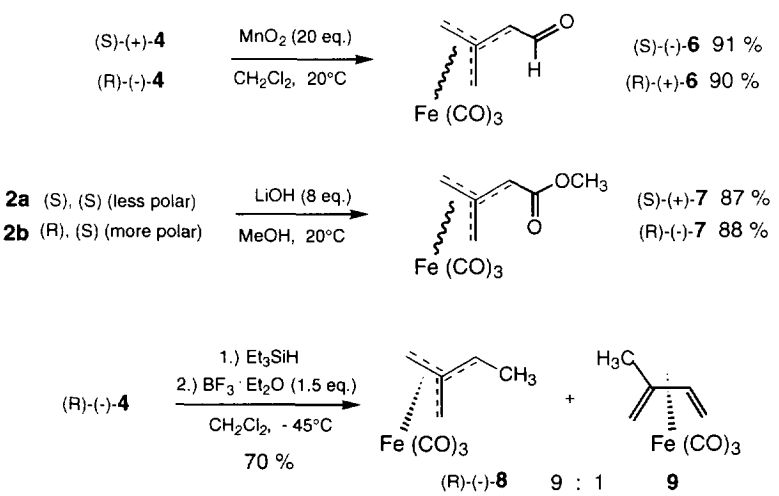


(S)-(+)-**4** (R = H) 86 %
(S)-(+)-**5** (R = CH_3) 61 %

(R)-(-)-**4** (R = H) 71 %
(R)-(-)-**5** (R = CH_3) 54 %

Treatment of the diastereomeric ester complexes **2a** and **2b** with lithium hydroxide in methanol afforded the enantiomeric TMM methyl ester complexes (+)-**7** and (-)-**7** and ionic hydrogenation (triethylsilane and $BF_3{\cdot}Et_2O$) of the primary alcohol (-)-**4** led in majority to the unfunctionalized chiral TMM complex (-)-**8** (scheme 4).

Scheme 4



Given an $[\alpha]_D$ of - 72 ($CHCl_3$), (-)-**8** must be of (R)-configuration as compared to - 68 mentioned in the literature and assigned as (R)-configuration by deduction from the X-ray diffraction of a crystalline dienic precursor molecule.[16,17] Consequently, we are now enabled to assign the absolute configuration to our chiral TMM complexes. The less polar diastereomeric TMM ester of ethyl-lactate **2a**, the primary alcohol (+)-**4**, the tertiary alcohol (+)-**5**, the aldehyde (-)-**6** and the methyl ester (+)-**7** have the (1S)-configuration (C1 being theTMM carbon bearing the functional chain), whereas the more polar diastereomeric TMM ester of ethyl lactate **2b**, the alcohols (-)-**4** and (-)-**5**, the aldehyde (+)-**6** and the methylester (-)-**7** are (1R).[18] This was confirmed by an X-ray structure analysis (vide infra).

An even more efficient chromatographic separation of diastereomeric TMM complexes was achieved when the activated ester **3** was reacted with (R)-(+)-α-methylbenzylamine in the presence of a catalytic amount of DMAP. A nearly 1 to 1 mixture of the amides **10a** and **10b** was obtained (80 %). They have very different polarities (**10a** less polar, **10b** more polar, $\Delta R_f \sim 0.15$) and were easily baseline separated by simple silica gel column chromatography. An X-ray analysis of **10b** revealed[19] the structure of the *like* diastereomer, i.e. the (R)-(+)-α-methylbenzylamine amide of (1R)-tricarbonyliron TMM carboxylic acid (Fig. 1).

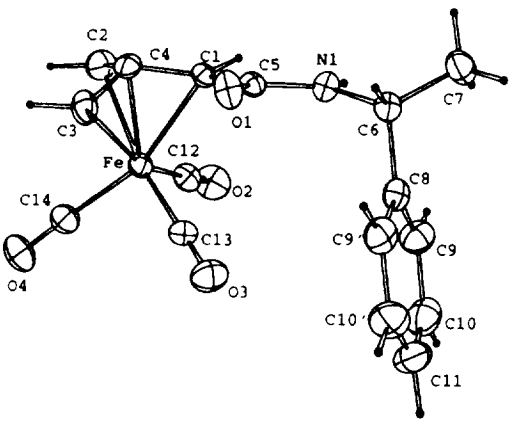
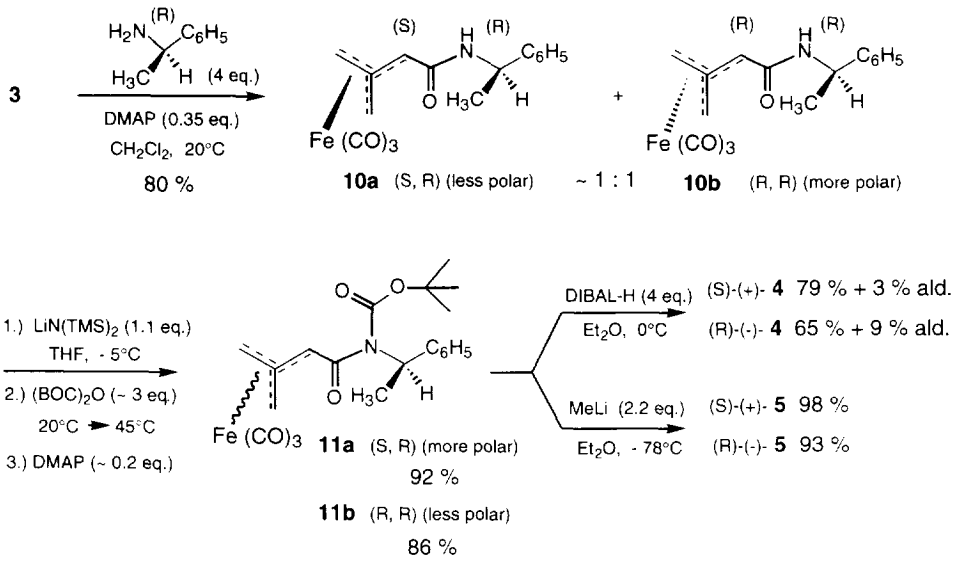


Figure 1 : ORTEP view of **10b**

The secondary amide function was not appropriate for further transformations and had to be activated by *N*-substitution. This was best achieved by formation, almost without racemization, of the *N*-BOC derivatives **11a** and **11b** (ca. 90 %, with inversion of polarities).[20] Having a similar reactivity to the esters, simple transformations provided in good yields the chiral TMM complexes (scheme 5).

Thus, from the *N*-BOC amides **11a** and **11b** both the primary alcohols (-)-**4** and (+)-**4** and the dimethyl TMM carbinols (-)-**5** and (+)-**5** are readily available in excellent yields. As for the absolute configuration, the measured optical rotations confirmed our previous deductions .

Scheme 5



In conclusion, by means of separation of diastereomeric complexes, we have developed an easy route to chiral TMM $Fe(CO)_3$ complexes of high enantiomeric purity and known absolute configuration. With a minimum loss, the chiral auxiliary could be introduced after formation of the TMM complex. For this purpose, the synthesis of the crystalline TMM ester of *N*-hydroxysuccinimide, precursor of both diastereomeric esters and amides, was crucial.

EXPERIMENTAL SECTION :

Elemental analyses were performed by the "Service de Microanalyse de la Fédération de Recherche Chimie de l'ULP de Strasbourg". IR spectra were recorded on a Perkin-Elmer IR-881 instrument. Optical rotations were determined on a Perkin-Elmer 241 MC polarimeter at the sodium D line at 22°C, concentrations are given in g/100 ml. ^1H (200 MHz) and ^{13}C (50.3 MHz) NMR spectra were recorded on a Bruker AC 200 spectrometer (δ in ppm referenced to $CHCl_3$ (7.27 ppm) as internal standard with chemical shifts referred to TMS; coupling constants J in Hz, multiplicities are designed as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Melting points were determined on a Reichert melting point apparatus and are uncorrected. Analytical thin layer chromatography was performed on Merck Kieselgel 60 F_{254} glass plates (0.25 mm), compounds were detected by UV light (254 nm) and by aspersion with an ethanol-vanilline-H_2SO_4 solution followed by heating. Column chromatography was carried out on Merck Kieselgel 60 (70 - 230 mesh ASTM). Photolyses were carried out with a Mazda 250 W medium pressure Hg lamp in a Pyrex glass reactor.

Reactions involving irontricarbonyl complexes were done under an argon atmosphere in dried glassware. Solvents were distilled before use : ether and THF over sodium/benzophenone, benzene over sodium and CH_2Cl_2 over P_2O_5. Methyllithium was purchased from Aldrich and titrated with diphenylacetic acid before use.

The crystal structure of **10b** was determined on a Mach 3 Nonius diffractometer by the "Service Commun de Rayons X de la Fédération de Recherche Chimie de l'ULP de Strasbourg".

3,3-Bis (bromomethyl) acrylic acid : 3,3-dimethylacrylic acid (5.0 g, 50 mmol) was dissolved in CCl_4 (300 ml). *N*-bromosuccinimide (NBS, 18.7 g, 105 mmol) was added and the mixture was irradiated for 3 h at 60°C with a medium pressure 250 W Hg lamp. After filtration the solution was concentrated (40°C, 15 Torr).

The resulting yellow oily product (13 g) containing about 75 % of dibrominated acid (^{1}H NMR) was used for the next reaction without purification.[15]

N-Succinimido-3,3-bis (bromomethyl) acrylate : The crude 3,3-bis (bromomethyl) acrylic acid (10.3 g, corresponding to ca. 30 mmol of pure staating material) was dissolved in a mixture of CH_2Cl_2 (170 ml) and dioxane (25 ml). *N*-hydroxysuccinimide (5.2 g, 45 mmol) was added and the solution cooled to 0°C. A solution of dicyclohexylcarbodiimide (9.3 g, 45 mmol) in CH_2Cl_2 (30 ml), cooled to 0°C, was then added and the reaction mixture was allowed to warm up to room temperature. Stirring was continued for 5 h. After filtration on a pad of celite and evaporation of the solvents (50°C, 15 Torr, then 20°C, 1 Torr), the crude viscous product was dissolved in ethyl acetate (75 ml) and cooled to - 10°C for 2 h. Filtration (~ 100 mg of dicyclohexylurea) and evaporation of the solvent yielded an oily product (16.5 g containing ca. 50 % of the title compound) which was used for the next reaction without further purification.

N-succinimido (TMM) Fe(CO)$_3$ carboxylate **3** : $Fe_2(CO)_9$ (30.0 g, 82.5 mmol) was added to a solution of the crude *N*-succinimido-3,3-bis (bromomethyl) acrylate (16.4 g, corresponding to ca. 23 mmol of pure dibromoacrylate) in benzene (350 ml). After 1.5 h refluxing, the mixture was filtered on a pad of celite which was washed with ether (3 x 50 ml). The solvents were evaporated (25°C, 15 Torr) and the crude product (13 g) filtered on a short column (Ø = 10 cm) of silica gel (160 g, eluent hexane/ether/CH_2Cl_2 1 : 1 : 1 v/v) to afford 6.4 g of nearly 90 % pure TMM complex **3** . By recrystallization from $CHCl_3$/EtOH (1 : 2 v/v, 80 ml) pure complex **3** was obtained as orange crystals (4.9 g, 38 % overall in three steps from 3,3-dimethylacrylic acid without intermediate purification), mp 140° C. – IR (CCl_4) : ν = 2080, 2022, 2007 (C≡O), 1804, 1766, 1745 (C=O). – ^{1}H NMR ($CDCl_3$) : δ = 2.13 (s, 1H), 2.23 (d, 1H, J = 4.3), 2.54 (d, 1H, J = 2.3), 2.77 (s, 4H), 2.85 (d, 1H, J = 2.3), 3.85 (d, 1H, J = 4.3). – ^{13}C NMR ($CDCl_3$) : δ = 25.6, 52.4, 53.9, 56.7, 109.7, 167.5, 169.3, 207.1, 208.7, 209.0. – Anal. calcd. for $C_{12}H_9FeNO_7$ (335.05) : C, 43.02; H, 2.71. Found : C, 42.94; H, 2.82.

Esters of (S)-(-)-ethyl lactate and (TMM) Fe(CO)$_3$ Carboxylic acid **2a** and **2b** : NaH (25 mg, 1.03 mmol) was added at 20°C in 3 fractions with ten minute intervals over 30 min to a solution of (S)-(-)-ethyl lactate (122 mg, 1.03 mmol) and *N*-succinimido (TMM) $Fe(CO)_3$ carboxylate **3** (230 mg, 0.69 mmol) in 10 ml of CH_2Cl_2. The reaction mixture was cooled to - 78°C and 10 ml of 0.1 N HCl were added slowly. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2 (15 ml). The combined organic phases were washed with water (2 x 30 ml) and saturated brine (30 ml) and dried over $MgSO_4$. After filtration and evaporation of the solvent (25°C, 15 Torr), 283 mg of the crude, roughly 1 : 1 mixture of diastereomeric esters were obtained. Although baseline separable by careful chromatography over silica gel they were usually partially fractioned with recycling of the middle fraction : chromatography (25g SiO_2, hexane/ether 10 : 1.5 v/v) gave pure **2a** (70 mg), a mixture fraction (88 mg) and pure **2b** (41 mg). Total yield 85 %, ratio ca. 1 : 1.

(S)-**2a** : less polar diastereomer, yellow oil, R_f = 0.47 (hexane/ether, 10 : 1.5 v/v), $[\alpha]_D$ = + 200 (c = 1, $CHCl_3$). – IR (CCl_4) : ν = 2073, 2001 (C≡O), 1757, 1719 (C=O). – ^{1}H NMR ($CDCl_3$) : δ = 1.28 (t, 3H, J = 7.1), 1.47 (d, 3H, J = 7.1), 1.98 (s, 1H), 2.02 (d, 1H, J = 4.3), 2.48 (d, 1H, J = 2.4), 2.83 (d, 1H, J = 2.4), 3.94 (d, 1H, J = 4.3), 4.18 (qd, 2H, J = 7.1, 5.8), 5.03 (q, 1H, J = 7.1). – ^{13}C NMR ($CDCl_3$) : δ = 14.1, 17.0, 52.9, 57.1, 59.5, 61.3, 68.4, 109.0, 170.7, 171.0, 208.4, 209.6, 210.0. – Anal. calcd. for $C_{13}H_{14}FeO_7$ (338.09) : C, 46.18; H, 4.17. Found : C, 46.36; H, 3.94.

(R)-**2b** more polar diastereomer, yellow oil, R_f = 0.39 (hexane/ether, 10 : 1.5 v/v), $[\alpha]_D$ = - 237 (c = 1, $CHCl_3$). – IR (CCl_4) : ν = 2070, 2002 (C≡O), 1755, 1720 (C=O). – ^{1}H NMR ($CDCl_3$) : δ = 1.28 (t, 3H, J = 7.1), 1.46 (d, 3H, J = 7.1), 2.02 (s, 1H), 2.07 (d, 1H, J = 4.3), 2.47 (d, 1H, J = 2.4), 2.93 (d, 1H, J = 2.4), 3.90 (d, 1H, J = 4.3), 4.21 (q, 2H, J = 7.1), 5.01 (q, 1H, J = 7.0). – ^{13}C NMR ($CDCl_3$) : δ = 14.1, 17.0, 53.5, 57.2, 59.5, 61.3, 68.6, 108.3, 170.7, 171.0, 209.6, 209.7, 209.8. – Anal. calcd. for $C_{13}H_{14}FeO_7$ (338.09) : C, 46.18; H, 4.17. Found : C, 46.00; H, 4.34.

(TMM Carbinol) Fe(CO)$_3$ (+)-**4** *and* (-)-**4** *from the esters* **2a/2b** : DIBAL-H (1 M in hexane, 2.5 ml, 2.5 mmol) was added dropwise at - 78°C to a solution of the less polar ester **2a** (170 mg, 0.5 mmol) in 10 ml of ether. After stirring for 30 min at - 78°C and additional 30 min between - 78°C and - 50°C, a saturated NH_4Cl solution in water was added to the cold mixture. The phases were separated and the aqueous layer was extracted twice with ether (15 ml). The formation of an emulsion was avoided by addition of a few drops of 2N HCl. The combined organic phases were washed with water (2 x 30 ml) and saturated brine (30 ml) and

dried over $MgSO_4$. After filtration and evaporation of the solvent (25°C, 15 Torr), the crude product (147 mg) was purified by silica gel chromatography (15 g, hexane/ether 10 : 5 v/v) : (S)-(+)-(TMM Carbinol) $Fe(CO)_3$ (+)-**4** (96 mg, 86 %, $[\alpha]_D$ = + 57, (c = 1, $CHCl_3$)). Similarly, from the more polar ester **2b** (170 mg, 0.5 mmol) one obtained (R)-(-)-(TMM carbinol) $Fe(CO)_3$ (-)-**4** (79 mg, 71 %, $[\alpha]_D$ = - 58, (c = 1, $CHCl_3$)). The ^1H NMR and IR spectra are in good accordance with those given in the literature[12] for (±)-**4** .

*(TMM dimethylcarbinol) $Fe(CO)_3$ (+)-**5** and (-)-**5** from the esters* **2a/2b** : MeLi (1.3 M in ether, 3.9 ml, 5.0 mmol) was added at - 78°C to a solution of the ester **2a** (400 mg, 1.18 mmol) in ether (30 ml). Stirring was continued for 1.5 h at - 78°C and then a saturated NH_4Cl solution in water (15 ml) was added to the cold mixture. The phases were separated and the aqueous layer was extracted twice with ether (20 ml). The combined organic phases were washed with water (2 x 30 ml) and saturated brine (30 ml) and dried over $MgSO_4$. After filtration and evaporation of the solvent (25°C, 15 Torr), the crude product (295 mg) was purified by silica gel chromatography (20 g, hexane/ether 10 : 1.5 v/v) : (S)-(+)-(TMM dimethylcarbinol) $Fe(CO)_3$ (+)-**5** (182 mg, 61 %, $[\alpha]_D$ = + 102, (c = 1, $CHCl_3$)). Similarly, from **2b** (170 mg, 0.5 mmol) and MeLi (1.5 M in ether, 1.67 ml, 2.5 mmol) one obtained (R)-(-)-(TMM dimethylcarbinol) $Fe(CO)_3$ (-)-**5** (68 mg, 54 %, $[\alpha]_D$ = - 96, (c = 1, $CHCl_3$)). – The ^1H NMR and IR spectra are in good accordance with those given in the literature[13] for (±)-**5** .

*Formyl - TMM) $Fe(CO)_3$ (-)-**6** and (+)-**6** :* The enantiomeric primary alcohols (+)-**4** (30 mg, 0.13 mmol) and (-)-**4** (47 mg, 0.21 mmol) were oxidized at room temperature with MnO_2 (20 eq., Mangan(IV)oxid gefällt aktiv, Merck 5958) in CH_2Cl_2 (5 - 8 ml), following the procedure given in the literature[11,13] for the racemic alcohol, to yield respectively the (TMM) $Fe(CO)_3$ aldehydes (S)-(-)-**6** (26 mg, 91 %, $[\alpha]_D$ = - 268 (c = 0.5, $CHCl_3$)) and (R)-(+)-**6** (42 mg, 90 %, $[\alpha]_D$ = + 268 (c = 0.5, $CHCl_3$)). – The ^1H NMR and IR spectra are in good accordance with those of the literature for (±)-**6** .

*(Methoxycarbonyl- TMM) $Fe(CO)_3$ (+)-**7** and (-)-**7** :* $LiOH{\cdot}H_2O$ (60 mg, 1.43 mmol) was added to a solution of the TMM complex **2a** (60 mg, 0.18 mmol) in MeOH (7 ml). After stirring for 3.5 h at 20°C, water (3 ml) was added and the pH was adjusted to ~ 7 with 0.5 N HCl. The mixture was extracted with CH_2Cl_2 (3 x 10 ml) and the combined organic phases were washed with H_2O (2 x 30 ml) and saturated brine (30 ml) and dried over $MgSO_4$. After filtration and evaporation of the solvents (25°C, 15 Torr), the nearly pure crude product was filtered through silica gel (10 g, eluent hexane/ether 10 : 5 v/v) to give (S)-(+)-(Methoxycarbonyl-TMM) $Fe(CO)_3$ (+)-**7** (39 mg, 87 %, $[\alpha]_D$ = + 323 (c = 1, $CHCl_3$)). Similarly, the TMM complex **2b** (50 mg, 0.15 mmol) afforded (R)-(-)-(Methoxycarbonyl-TMM) $Fe(CO)_3$ (-)-**7** (33 mg, 88 %, $[\alpha]_D$ = - 315 (c = 1, $CHCl_3$)). – The ^1H NMR and IR spectra are in good accordance with those given in the literature[6] for (±)-**7**. The enantiomeric excess, measured by ^1H NMR spectroscopy in the presence of a chiral shift reagent (the doublet at 2.46 ppm (1H, J = 2.4) of (±)-**7** splits into two doublets at 2.71 and 2.75 ppm when 0.35 equivalents of $Eu(hfc)_3$ is added), is ≥ 94 % for the ester (+)-**7** and ≥ 95 % for its enantiomer (-)-**7**.

*(R)-(-)-(methyl TMM) $Fe(CO)_3$ (-)-**8** :* $BF_3{\cdot}Et_2O$ (77 mg, 0.54 mmol) in CH_2Cl_2 (3 ml) was added at - 50°C to a solution of the primary TMM alcohol complex (-)-**4** (80 mg, 0.36 mmol) and triethylsilane (84 mg, 0.72 mmol) in CH_2Cl_2 (10 ml). After stirring for 45 min. at - 45°C, a saturated NH_4Cl solution in water (10 ml) was added to the cold mixture. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2 (10 ml). The combined organic phases were washed with water (2 x 20 ml), saturated brine (20 ml) and dried ($MgSO_4$). Filtration and evaporation of the solvent (20°C, 15 Torr) a crude product (67 mg) remained which was purified by silica gel chromatography (10 g, eluent hexane) to yield a mixture containing 90 % of (R)-(-)-(methyl TMM) $Fe(CO)_3$ (-)-**8,** along with 10 % (isoprene) $Fe(CO)_3$ (52 mg, 70 %, $[\alpha]_D$ = - 72 (c = 1, $CHCl_3$)). By careful silica gel chromatography these complexes are partially separable (R_f = 0.80 and 0.75 respectively, in hexane) in accordance with previous observations[16].

Amides of (R)-(+)-α-methylbenzylamine and (TMM carboxylic acid) $Fe(CO)_3$ **10a** *and* **10b** :

(R)-(+)-α-methylbenzylamine (363 mg, 3.0 mmol) and DMAP (31 mg, 0.26 mmol) were added to a solution of the *N*-succinimido (TMM) $Fe(CO)_3$ ester **3** (254 mg, 0.76 mmol) in CH_2Cl_2 (10 ml). Stirring was continued for 2.5 h at room temperature. The reaction mixture was washed with 0.05 N HCl (2 x 15 ml) and

the aqueous phases were extracted twice with CH_2Cl_2 (15 ml). The combined organic phases were washed with water (2 x 15 ml), saturated brine (15 ml) and dried over $MgSO_4$. After filtration and evaporation of the solvent (25°C, 15 Torr), the crude product (244 mg) was purified by silica gel chromatography (10 g, eluent hexane/ether 10 : 1.5 to 10 : 3 v/v) to yield the amides **10a** and **10b** (101 mg and 106 mg, 80 %).

(S)-(+)-(TMM amide of (R)-methylbenzylamine) $Fe(CO)_3$ **10a** : less polar diastereomer, yellow crystals, mp 167°C, R_f = 0.60 (hexane/ether 1 : 1 v/v), $[\alpha]_D$ = + 160 (c = 1, $CHCl_3$). – IR (CCl_4) : ν = 3453 (NH), 2067, 2003 (C≡O), 1665 (C=O). – ^1H NMR ($CDCl_3$) : δ = 1.45 (d, 3H, J = 6.9), 1.86 (d, 1H, J = 4.3), 1.88 (s, 1H), 2.46 (d, 1H, J = 2.2), 2.73 (d, 1H, J = 2.2), 4.10 (d, 1H, J = 4.3), 5.05 (dq, 1H, J = 7.1, 7.1), 5.61 (broad d, 1H, J = 7.4), 7.21 - 7.38 (m, 5H). – ^{13}C NMR ($CDCl_3$) : δ = 21.4, 48.7, 52.5, 58.1, 64.3, 107.0, 126.3, 128.7, 127.4, 143.1, 169.3, 209.4, 210.2, 210.7. – Anal. calcd. for $C_{16}H_{15}FeNO_4$ (341.14) : C, 56.33; H, 4.43; N, 4.11. Found : C, 56.40; H, 4.58; N, 3.99.

(R)-(-)-(TMM amide of (R)-methylbenzylamine) $Fe(CO)_3$ **10b** : more polar diastereomer, yellow crystals, mp 134°C, R_f = 0.45 (hexane/ether 1 :1 v/v) $[\alpha]_D$ = - 77 (c = 1, $CHCl_3$). – IR (CCl_4) : ν = 3447 (NH), 2068, 2006, 1992 (C≡O), 1665, 1640 (C=O). – ^1H NMR ($CDCl_3$) : δ = 1.48 (d, 3H, J = 6.9), 1.86 (d, 1H, J = 4.3), 1.87 (s, 1H), 2.45 (d, 1H, J = 2.2), 2.72 (d, 1H, J = 2.2), 4.12 (d, 1H, J = 4.3), 5.05 (dq, 1H, J = 7.1, 7.1), 5.61 (broad d, 1H, J = 7.1), 7.22 - 7.37 (m, 5H) – ^{13}C NMR ($CDCl_3$) : δ = 21.6, 48.8, 52.2, 58.0, 64.5, 107.3, 126.3, 127.4, 128.7, 143.0, 169.4, 208.8, 210.3, 211.1. – Anal. calcd. for $C_{16}H_{15}FeNO_4$ (341.14) : C, 56.33; H, 4.43; N,4.11. Found : C, 56.25; H, 4.44; N, 4.19.

N-BOC amides of (R)-(+)-α-methylbenzylamine and (TMM Carboxylic acid) $Fe(CO)_3$ **11a** *and* **11b** : $LiN(TMS)_2$ (0.5 M in THF, 5.6 ml, 2.8 mmol) was added dropwise over 45 min to a solution of the less polar amide **10a** (892 mg, 2.62 mmol) in THF (40 ml) cooled to - 5°C. After 15 min stirring at - 5°C, $(BOC)_2O$ (1250 mg, 5.73 mmol) in THF (5 ml) was added and stirring was continued for 1 h at 20°C and 1 h at 45°C (CO_2 evolution). DMAP (50 mg, 0.41 mmol) was added and after additional 30 min $(BOC)_2O$ (340 mg, 1.56 mmol) to complete the reaction. The solution was stirred at 45°C for 1 more h and then cooled to - 50°C. A saturated NH_4Cl solution in water (30 ml) was added. The phases were separated and the aqueous layer was extracted with ether (3 x 30 ml). The combined organic phases were washed with water (30 ml) and saturated brine (30 ml) and dried over $MgSO_4$. After filtration and evaporation of the solvents (25°C, 15 Torr), the crude product (1810 mg) was purified by silica gel chromatography (80 g, eluent hexane/ether 10 : 0.5 v/v) to afford a first fraction of di-*tert*-butyl carbonate (320 mg), followed by a mixture of the diastereomers **11a** and **11b** (8 mg, racemization ~ 0.3 %) and finally pure **11a** (1068 mg, 92 %).

(S, R)-*N*-BOC amide **11a** : more polar diastereomer, yellow crystals, mp 72°C, R_f = 0.48 (hexane/ether 10 : 1 v/v) $[\alpha]_D$ = +10 (c = 1, $CHCl_3$). – IR (CH_2Cl_2) : ν = 2067, 2001 (C≡O), 1728, 1651 (C=O). – ^1H NMR ($CDCl_3$) : δ = 1.10 (s, 9H), 1.61 (d, 3H, J = 6.9), 2.02 (s, 1H), 2.17 (d, 1H, J = 4.3), 2.43 (d, 1H, J = 2.1), 3.71 (d, 1H, J = 4.3), 4.24 (d, 1H, J = 2.1), 5.92 (q, 1H, J = 6.9), 7.15 - 7.35 (m, 5H). – ^{13}C NMR ($CDCl_3$) : δ = 16.7, 27.4, 51.0, 54.4, 57.1, 65.8, 83.0, 106.5, 126.4, 126.7, 128.2, 142.0, 153.1, 172.5, 209.6, 209.8, 210.8. – Anal. calcd. for $C_{21}H_{23}FeNO_6$ (441.26) : C, 57.16; H, 5.25; N, 3.17. Found : C, 57.43; H, 5.33; N, 3.06.

Similarly, from the more polar amide **10b** (440 mg, 1.29 mmol), $LiN(TMS)_2$ (0.5 M in THF, 3.0 ml, 1.5 mmol), $(BOC)_2O$ (920 mg, 4.2 mmol) and DMAP (40 mg, 0.33 mmol), one obtained a crude product (918 mg) which was purified by silica gel chromatography (60 g) to give di-*tert*-butyl carbonate (281 mg), followed by pure **11b** (489 mg, 86 %) and finally a mixture fraction of the diastereomers **11a** and **11b** (31 mg, racemization ~ 1 %)

(R, R)-*N*-BOC amide **11b** : less polar diastereomer, yellow crystals, mp 88°C, R_f = 0.55 (hexane/ether 10 : 1 v/v) $[\alpha]_D$ = + 65 (c = 1, $CHCl_3$). – IR (CH_2Cl_2) : ν = 2068, 2003 (C≡O), 1729, 1657 (C=O). – ^1H NMR ($CDCl_3$) : δ = 1.15 (s, 9H), 1.64 (d, 3H, J = 6.9), 1.97 (s, 1H), 2.12 (d, 1H, J = 4.4), 2.40 (d, 1H, J = 2.0), 3.67 (d, 1H, J = 2.0), 3.96 (d, 1H, J = 4.4), 5.92 (q, 1H, J = 6.9), 7.20 - 7.31 (m, 5H). – ^{13}C NMR ($CDCl_3$) : δ = 17.1, 27.5, 51.2, 53.7, 56.8, 66.0, 82.8, 107.9, 126.4, 126.6, 128.1, 142.0, 153.0, 173.0, 209.2, 210.2, 210.6. – Anal. calcd. for $C_{21}H_{23}FeNO_6$ (441.26) : C, 57.16; H, 5.25; N, 3.17. Found : C, 57.02; H, 5.01; N, 3.30.

(TMM Carbinol) $Fe(CO)_3$ (+)-**4** *from the N-BOC amide* **11a** : DIBAL-H (1 M solution in hexane, 1.0 ml, 1.0 mmol) was added dropwise at - 78 °C to a solution of the more polar *N*-BOC amide **11a** (107 mg, 0.24 mmol) in ether (10ml). After stirring for 30 min at - 78°C and additional 30 min at 0°C, the reduction to the alcohol was almost complete and a saturated NH_4Cl solution in water (10 ml) was added. The phases were separated and the aqueous layer was extracted twice with ether (15 ml), the formation of an emulsion being avoided by addition of a few drops of 2N HCl. The combined organic phases were washed with water (2 x 15 ml) and saturated brine (15 ml) and dried over $MgSO_4$. Filtration and evaporation of the solvent (25°C, 15 Torr) afforded a crude product (117 mg) which was purified by silica gel chromatography (10 g, eluent hexane/ether 10 : 3 v/v) to yield the (TMM) aldehyde (-)-**6** (2 mg, 3 %) and the primary (TMM) carbinol (+)-**4** (43 mg, 79 %, $[\alpha]_D$ = + 57 (c = 1, $CHCl_3$)).

(TMM dimethylcarbinol) $Fe(CO)_3$ (+)-**5** *and* (-)-**5** *from the N-BOC amides* **11a** *and* **11b** :

MeLi (1.3 M solution in ether, 6.0 ml, 7.85 mmol) was added at - 78°C to a solution of the more polar *N*-BOC amide **11a** (1575 mg, 3.57 mmol) in ether (80 ml). After stirring for 30 min. at - 78°C a saturated NH_4Cl solution in water was added to the cold mixture. The phases were separated and the aqueous layer was extracted twice with ether (50 ml). The combined organic phases were washed with water (2 x 50 ml), saturated brine (50 ml) and dried ($MgSO_4$). After filtration and evaporation of the solvent (25°C, 15 Torr), the crude product (1720 mg) was purified by silica gel chromatography (70 g, eluent hexane/ether 10 : 1.5 v/v)) : (S)-(+)-(TMM dimethylcarbinol)$Fe(CO)_3$ (+)-**5** (882 mg, 98 %, $[\alpha]_D$ = + 100 (c = 1, $CHCl_3$)). Similarly, from the less polar *N*-BOC amide **11b** (205 mg, 0.46 mmol) and MeLi (1.3 M in ether, 0.75 ml, 1.0 mmol) the (R)-(-)-(TMM dimethylcarbinol) $Fe(CO)_3$ (-)-**5** was obtained (107mg, 93 %, $[\alpha]_D$ = + 104 (c = 1, $CHCl_3$)).

Acknowledgement :

We are grateful to Dr. A. de Cian (Laboratoire de Cristallochimie et Chimie Structurale, associé au C.N.R.S., Institut Le Bel, ULP Strasbourg) for a crystal structure determination and to the BASF for repeated gifts of $Fe(CO)_5$.

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(*Received in UK* 19 *August* 1996; *accepted* 20 *September* 1996)