Electronic Supplementary Information (ESI)

An Iron Carbonyl Approach to the Influenza Neuraminidase Inhibitor Oseltamivir

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Contents:

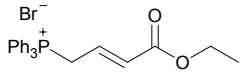
Also available is a separate ESI file containing selected NMR spectra.

General Experimental Procedures

Commercially available reagents were used without further purification. Dry THF was obtained through distillation from sodium/benzophenone ketyl and dry CH_2Cl_2 was obtained through distillation from calcium hydride. All syntheses using dry solvents were performed in oven-dried glassware. Analytical TLC was performed on MERCK silica gel, grade 60 F_{254}. Flash chromatography was performed on MERCK silica gel SI-60 Å (35-70). Analytical high performance liquid chromatography (HPLC) was performed on a Waters system with Waters 600E system controller, Waters 717 auto sampler, Waters 996 Photodiode Array Detector and a reverse phase Genesis C8 (4 µ 4.6 mm) column. Preparative HPLC was performed on a Waters system with Waters 600E system controller, Waters Model 441 Absorbance Detector and a reverse phase Modcol CER#3900 column. Melting points were obtained using a Mettler FP90 central processor with a Mettler FP82HT hot stage and are reported uncorrected. Optical rotations were measured on a Perkin Elmer 341 LC digital polarimeter with a sodium lamp (D-line, λ=589 nm) and are reported in 10^{-1} deg cm^2 g^{-1} in the form $[\alpha]_D^T$ X^o (c g/100 mL, solvent). Elemental analyses were undertaken at H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Infrared spectra were obtained on a Perkin Elmer 1600 Series Fourier Transform Spectrophotometer. NMR spectra were recorded on a Varian UNITY-VXR 5000 or a JEOL Eclipse+ spectrometer (^1H, 400 MHz; ^{13}C, 100 MHz). The spectra were run at ambient temperature in the reported deuterated solvent with all chemical shifts referenced with respect to the residual solvent peak ($CHCl_3$, δ_H 7.26 ppm and δ_C 77.16 ppm; MeOH, δ_H 3.31 ppm and δ_C 49.00 ppm; ACN, δ_H 1.94 ppm and δ_C 118.26 ppm). *J* values are given in Hz. All LCMS were obtained on an Agilent 1100 series module (column, Phenomenx Synergi MAX-RP C12 50 x 3 mm 4µm; eluent, 10 mM ammonium acetate in acetonitrile/water gradient); flow, 1.25 mL/min; temperature, 50 °C with a Waters ZQ 2000 mass spectrometer with pos/neg switch using DAD as the primary detector and ELS as secondary detector.

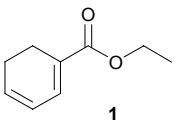
Experimental Details for the Synthesis of Oseltamivir

(*trans*-3-Ethoxycarbonylallyl)triphenylphosphonium bromide:



(*trans*-3-Ethoxycarbonylallyl)triphenylphosphonium bromide was prepared from ethyl 4-bromocrotonate and triphenylphosphine according to Howe,[1] with the use of toluene instead of benzene as the solvent. Increasing the reaction time from 4 h to 2 days, increased the yield to 90% compared with the 45% originally reported. Spectral data for this compound were in accordance with that previously published.

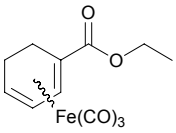
Ethyl 1,3-Cyclohexadien-1-carboxylate (1):



1

The synthesis of **1** was undertaken following the previously published procedure for that of the closely related methyl ester, utilizing (*trans*-3-ethoxycarbonylallyl)triphenylphosphonium bromide and acrolein.[2] Spectral data were in accordance with published data for this compound.[3]

Tricarbonyl(1-carboethoxycyclohexa-1,3-dienyl)iron ((±)-2):

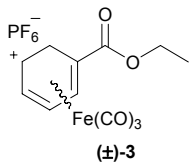


(±)-2

Ethyl 1,3-cyclohexadien-1-carboxylate (**1**) (1.29 g, 8.5 mmol) was dissolved in degassed toluene (10 mL) and to this was added a slurry of iron nonacarbonyl* (10 g, 27.5 mmol) in degassed toluene (10 mL). The reaction mixture was stirred at 55 ^{o}C under an argon atmosphere for 19 h, after which, it was allowed to cool to room temperature. Absorption onto silica and flash column chromatography washing with petroleum ether, followed by elution with 5% EtOAc in petroleum ether, gave **(±)-2** (2.15 g, 86%) as a yellow oil; Anal. Calc. for $C_{12}H_{12}FeO_5$: C, 49.35; H, 4.14. Found: C, 49.46; H, 4.20; ν_{max}(thin film)/cm^{-1} 2053, 1989, 1703; δ_H(400 MHz, $CDCl_3$) 6.05 (1H, dd, *J* = 0.8, 4.4), 5.35 (1H, ddd, *J* =0.8, 4.4, 6.8), 4.19 (1H, dq, *J* = 7.0, 10.8), 4.12 (1H, dq, *J* = 7.0, 10.8), 3.39-3.34 (1H, m), 2.18 (1H, dddd, *J* = 0.8, 3.6, 12.0, 15.2), 1.92 (1H, app ddt, *J* = 3.6, 3.6, 11.6), 1.74-1.65 (1H, m), 1.43 (1H, dddd, *J* = 0.8, 3.6, 8.4, 14.8), 1.27 (3H, t, *J* = 7.2); δ_C(100 MHz, $CDCl_3$) 210.4, 172.3, 88.7, 85.2, 65.2, 63.3, 60.8, 25.3, 23.1, 14.3; MS (ES) *m/z* 293.00 (M^+, 100%).

* Treated with 1M HCl to remove any pyrophoric free metallic iron and then washed successively with ethanol and toluene.

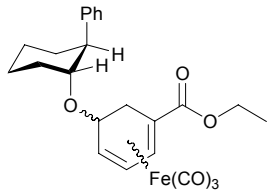
Tricarbonyl(1-carboethoxycyclohexa-1,3-dienyl)iron Hexafluorophosphate ((±)-3):



(±)-3

Tricarbonyl(1-carboethoxycyclohexa-1,3-dienyl)iron (**(±)-2**) (2.15 g, 7.4 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and triphenylcarbenium hexafluorophosphate (3.72 g, 9.6 mmol) was added portionwise. The reaction mixture was stirred at ambient temperature under an atmosphere of nitrogen for 6 h. Addition of Et_2O (50 mL), gave a precipitate that was isolated by filtration, washed with Et_2O and dried under vacuum affording racemic **(±)-3** (3.03 g, 94%) as a pale yellow powder; Anal. Calc. for $C_{12}H_{11}F_6FeO_5P$: C, 33.06; H, 2.54. Found: C, 32.87; H, 2.41; ν_{max}(KBr)/cm^{-1} 2119, 2077, 1708; δ_H(400 MHz, CD_3OD) 6.29 (1H, d, *J* = 4.4), 5.68 (1H, t, *J* = 6.0), 4.20-4.07 (2H, m), 3.98 (1H, dt, *J* = 3.2, 10.0), 3.38-3.35 (1H, m), 2.68 (1H, dd, *J* = 9.6, 15.2), 1.34 (1H, dd, *J* = 12.8, 5.6), 1.27 (3H, t, *J* = 7.2); δ_C(100 MHz, CD_3CN) 167.2, 104.7, 102.7, 90.9, 71.4, 63.5, 55.6, 23.8, 13.7.

Tricarbonyl[1-carboethoxy-5-[[(1*R*,2*S*)-*trans*-2-phenylcyclohexyl]oxy]cyclohexa-1,3-diene]iron (4a,b):



4a,b

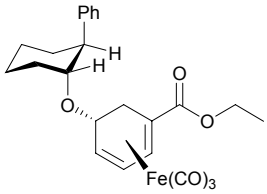
A suspension of the racemic cationic iron complex **(±)-3** (1.24 g, 2.8 mmol) and (-)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol (1.02 g, 5.7 mmol) in dry CH_2Cl_2 (20 mL) under argon was cooled on an ice bath to 0 ^oC. Diisopropylethyl amine (0.61 mL, 3.4 mmol) was added dropwise and the reaction mixture stirred on ice for 20 min before allowing it to warm to room temperature over 30 min. The reaction mix was concentrated and the addition of petroleum ether (60 mL) resulted in a precipitate that was removed by filtration and the eluant was concentrated under vacuum. Crude ^1H NMR indicated a 50:50 ratio of two diastereomers. The residue underwent flash column chromatography (5% EtOAc in petroleum ether) to give a diastereomeric mix of **4a,b** (0.99 g, 75%) as a yellow oil; Anal. Calc. for $C_{24}H_{26}FeO_6$: C, 61.82; H, 5.62. Found: C, 61.96; H, 5.60; ν_{max}(neat)/cm^{-1} 2930, 2055, 1984, 1705, 1244, 1064; δ_H(400 MHz, $CDCl_3$) 7.36-7.30 (2H$_b$, m), 7.29-7.21 (2H$_a$ and 3H$_b$, m), 7.20-7.13 (3H$_a$, m), 6.05 (1H$_a$, d, *J* = 4.3) and 6.00 (1H$_b$, d, *J* = 4.4), 5.36 (1H$_a$, t, *J* = 5.2) and 4.87 (1H$_b$, t, *J* = 5.5), 4.15-4.00 (2H$_b$ and 2H$_a$, m), 3.66-3.60 (1H$_b$ and 1H$_a$, m), 3.29-3.18 (1H$_b$ and 1H$_a$, m), 3.07-3.02 (1H$_a$, m) and 2.57 (1H$_b$, dd, *J* = 9.8, 15.3), 2.47-2.35 (2H$_b$ and 1H$_a$, m) and 2.15-2.08 (1H$_a$, m), 2.08-2.01 (1H$_a$, m) and 2.00-1.93 (1H$_b$, m), 1.90-1.77 (2H$_a$ and 2H$_b$, m), 1.76-1.68 (1H$_b$ and 1H$_a$, m), 1.60-1.50 (1H$_b$ and 1H$_a$, m), 1.39-1.18 (6H$_a$ and 7H$_b$, m), 0.65 (1H$_a$, dd, *J* = 2.9, 15.4); δ_C(100 MHz, $CDCl_3$) 209.6, 172.0, 171.7, 144.9,

144.2, 128.3, 128.2, 128.1, 128.0, 126.3, 90.0, 89.8, 84.9, 84.8, 82.6, 82.4, 76.9, 76.5, 62.3, 61.4, 60.7, 60.6, 58.6, 58.3, 51.5, 51.4, 34.3 33.7, 33.2, 33.2, 30.9, 29.6, 25.9, 25.4, 25.3, 14.2.

A further fraction containing slight product and the excess chiral alcohol underwent recrystallisation to afford pure (–)-(1*R*,2*S*)-*trans*-2-phenylcyclohexanol (0.37 g, 75% of excess).

The diastereomeric pair **4a,b** was separated by preparative HPLC with isocratic solvent conditions of 80% ACN:20% buffer (5% ACN, 0.1 M ammonium acetate) to give a small amount of mixture (8% recovered), along with the individual diastereomers **4a** (36% recovered) and **4b** (47% recovered) as yellow oils for which the diastereomeric purity was confirmed by analytical HPLC.[†]

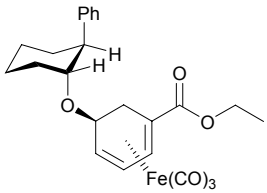
First fraction off HPLC column, **(+)-4a**.



(+)-4a

$[\alpha]_D^{20}$ +42° (c 2.3, $CHCl_3$); Anal. Calc. for $C_{24}H_{26}FeO_6$: C, 61.82; H, 5.62. Found: C, 61.94; H, 5.70; ν_{max}(neat)/cm^{-1} 2930, 2055, 1981, 1705, 1243, 1063; δ_H(400 MHz, $CDCl_3$) 7.29-7.23 (2H, m), 7.20-7.12 (3H, m), 6.05 (1H, d, *J* = 4.3), 5.36 (1H, t, *J* = 5.2), 4.15-3.99 (2H, m), 3.63 (1H, td, *J* = 3.1, 9.8), 3.26-3.18 (1H, m), 3.07-3.02 (1H, m), 2.44-2.35 (1H, m), 2.15-2.08 (1H, m), 2.08-2.01 (1H, m), 1.90-1.81 (2H, m), 1.73 (1H, bd, *J* = 11.8), 1.53 (1H, dq, *J* = 3.4, 13.1), 1.39-1.20 (3H, m), 1.21 (3H, t, *J* = 7.1), 0.65 (1H, dd, *J* = 2.9, 15.4); δ_C(100 MHz, $CDCl_3$) 171.8, 144.3, 128.2, 128.0, 126.4, 90.0, 84.8, 82.7, 76.9, 62.3, 60.7, 58.7, 51.4, 34.4, 33.2, 29.7, 26.0, 25.4, 14.2.

Second fraction off HPLC column, **(-)-4b**.



(-)-4b

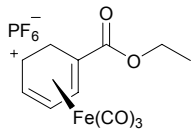
$[\alpha]_D^{20}$ -39° (c 2.7, $CHCl_3$); Anal. Calc. for $C_{24}H_{26}FeO_6$: C, 61.82; H, 5.62. Found: C, 62.00; H, 5.68; ν_{max}(neat)/cm^{-1} 2930, 2054, 1980, 1705, 1243, 1064; δ_H(400 MHz, $CDCl_3$) 7.35-7.30 (2H, m), 7.28-7.21 (3H, m), 6.00 (1H, d, *J* = 4.4), 4.87 (1H, t, *J* = 5.5), 4.15-4.00 (2H, m), 3.64 (1H, td, *J* = 3.0, 9.9), 3.29-3.20 (1H, m), 2.57 (1H, dd, *J* = 10.0, 15.1), 2.47-2.37 (2H, m), 2.00-1.93 (1H, m), 1.90-1.77 (2H, m), 1.75-1.68 (1H, m), 1.55 (1H, dq, *J* = 3.4, 12.8), 1.38-1.20 (4H, m), 1.22 (3H, t, *J* = 7.1); δ_C(100 MHz, $CDCl_3$) 172.0,

[†] The shown absolute stereochemistry was inferred by comparison of the subsequent products (**(–)-3b, (–)-6b** and **(–)-11**) with literature compounds.

144.9, 128.3, 128.2, 126.4, 89.8, 84.9, 82.5, 76.5, 61.5, 60.7, 58.3, 51.5, 33.7, 33.3, 30.9, 25.9, 25.3, 14.2.

Tricarbonyl(1-carboethoxycyclohexa-1,3-dienyl)iron Hexafluorophosphate ((+)-3a and (–)-3b):

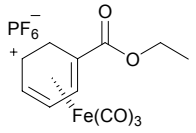
Tricarbonyl(1-carboethoxycyclohexa-1,3-dienyl)iron Hexafluorophosphate **(+)-3a**.



(+)-3a

A solution of **(+)-4a** (0.77 g, 1.7 mmol) in Et_2O (30 mL) was cooled on an ice bath to 0 °C and hexafluorophosphoric acid (60 wt% aq, 295 µL, 2.0 mmol) was added dropwise. This resulted in the immediate formation of a precipitate which was isolated by filtration, washed with Et_2O and dried under vacuum affording the enantiopure cation **(+)-3a** (0.68 g, 94%) as a pale yellow powder;[‡] $[\alpha]_D^{20}$ +159° (c 1.8, acetone); Anal. Calc. for $C_{12}H_{11}F_6FeO_5P$: C, 33.06; H, 2.54. Found: C, 33.14; H, 2.61; ν_{max}(KBr)/cm^{-1} 3098, 3082, 2125, 2078, 1708, 1522, 1461, 1389, 1285, 1270, 1182, 1114, 1106; δ_H(400 MHz, CD_3OD) 6.29 (1H, d, *J* = 3.6), 5.69 (1H, t, *J* = 5.0), 4.23-4.05 (2H, m), 3.98 (1H, d, *J* = 10.1), 3.39-3.34 (1H, m), 2.68 (1H, dd, *J* = 9.9, 15.0), 1.34 (1H, d, *J* = 14.9), 1.27 (3H, t, *J* = 7.0); δ_C(100 MHz, CD_3CN) 167.6, 105.1, 103.0, 91.2, 71.8, 64.0, 56.2, 24.2, 14.1.

Tricarbonyl(1-carboethoxycyclohexa-1,3-dienyl)iron Hexafluorophosphate **(–)-3b**.



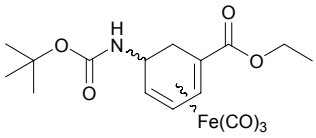
(–)-3b

The other diastereomer **(–)-4b** (0.69 g, 1.5 mmol)**,** was treated identically to give enantiopure cation **(–)-3b** (0.62 g, 94%) as a pale yellow powder;[§] $[\alpha]_D^{20}$ -156° (c 2.0, acetone), literature for methyl ester analogue $[\alpha]_D^{25}$ -162° (c 0.3, acetone)[4]; Anal. Calc. for $C_{12}H_{11}F_6FeO_5P$: C, 33.06; H, 2.54. Found: C, 32.88; H, 2.50; ν_{max}(KBr)/cm^{-1} 3098, 3082, 2124, 2084, 1708, 1522, 1461, 1389, 1285, 1271, 1182, 1114, 1106; δ_H(400 MHz, CD_3OD) 6.29 (1H, d, *J* = 3.9), 5.68 (1H, t, *J* = 4.8), 4.22-4.05 (2H, m), 3.98 (1H, d, *J* = 9.6), 3.39-3.34 (1H, m), 2.68 (1H, dd, *J* = 10.1, 14.9), 1.34 (1H, d, *J* = 15.2), 1.27 (3H, t, *J* = 7.0); δ_C(100 MHz, CD_3CN) 167.6, 105.1, 103.0, 91.2, 71.8, 63.9, 56.2, 24.2, 14.1.

[‡] Absolute stereochemistry was inferred by comparison of other enantiomer (**(–)-3b**) to literature.
[§] Absolute stereochemistry was inferred by comparison of the sign of rotation to literature for the corresponding methyl ester cationic complex

Tricarbonyl[5-(*tert*-butoxycarbonylamino)-1-carboethoxycyclohexa-1,3-diene]iron (5):

Racemic **(±)-5**.

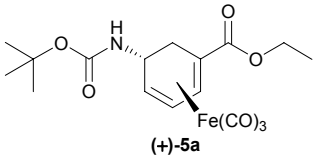


(±)-5

A suspension of the racemic cationic iron complex **(±)-3** (1.97 g, 4.5 mmol) and *tert*-butylcarbamate (1.16 g, 9.9 mmol) in dry CH_2Cl_2 (25 mL) under argon, was cooled on an ice bath to 0 ^oC. Diisopropylethyl amine (1.58 mL, 9.0 mmol) was added dropwise and the reaction mixture stirred on ice for 10 min before allowing it to warm to room temperature over 30 min. The addition of petroleum ether (40 mL) resulted in a precipitate that was removed by filtration and the eluant was concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (40 mL) and washed with 10% w/v citric acid (3x40 mL). The aqueous phase was back extracted with CH_2Cl_2 (40 mL) and the combined organic phases dried over $MgSO_4$, filtered and concentrated. The residue was distilled at reduced pressure to remove remaining *tert*-butylcarbamate, followed by flash column chromatography (15% EtOAc in petroleum ether) to give racemic **(±)-5** (1.58 g, 86%) as a yellow oil that partially crystallized on standing; Anal. Calc. for $C_{17}H_{21}FeNO_7$: C, 50.14; H, 5.20; N, 3.44. Found: C, 50.10; H, 5.11; N, 3.40; ν_{max}(neat)/cm^{-1} 2057, 1986, 1706, 1684; δ_H(400 MHz, $CDCl_3$) 6.19 (1H, d, *J* = 4.0), 5.39 (1H, dd, *J* = 4.8, 6.0), 4.45-4.38 (1H, br m), 4.35-4.24 (1H, br m), 4.21-4.06 (2H, m), 3.27 (1H, s), 2.84 (1H, dd, *J* = 11.2, 15.2), 1.41 (9H, s), 1.25 (3H, t, *J* = 7.2), 1.16 (1H, dd, *J* = 3.2, 15.6); δ_C(100 MHz, $CDCl_3$) 171.9, 155.1, 90.1, 84.2, 79.9, 62.7, 61.0, 59.7, 49.6, 31.1, 28.6, 14.3.

Tricarbonyl[5-(tert-butoxycarbonylamino)-1-carboethoxycyclohexa-1,3-diene]iron

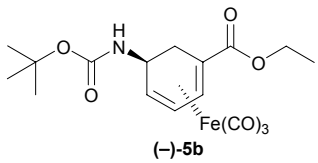
(+)-(*5R*)-5a.



(+)-5a

The procedure for the racemic synthesis and purification of **(±)-5** was undertaken on enantiomerically pure cationic iron complex **(+)-3a** to give **(+)-5a** as a yellow oil that partially crystallized on standing; $[\alpha]_D^{20}$ +58^o (c 2.3, $CHCl_3$); Anal. Calc. for $C_{17}H_{21}FeNO_7$: C, 50.14; H, 5.20; N, 3.44. Found: C, 50.20; H, 5.14; N, 3.35; ν_{max}(neat)/cm^{-1} 3357, 2980, 2057, 1988, 1694, 1514, 1367, 1270, 1248, 1171, 1098; δ_H(400 MHz, $CDCl_3$) 6.20 (1H, d, *J* = 4.0), 5.39 (1H, dd, *J* = 4.6, 6.0), 4.39 (1H, br s), 4.31 (1H, br s), 4.22-4.06 (2H, m), 3.27 (1H, br s), 2.85 (1H, dd, *J* = 10.6, 15.1), 1.42 (9H, s), 1.26 (3H, t, *J* = 7.1), 1.16 (1H, dd, *J* = 3.3, 15.7); δ_C(100 MHz, $CDCl_3$) 209.3, 171.7, 155.0, 90.0, 84.1, 79.7, 62.6, 60.9, 59.6, 49.5, 30.9, 28.4, 14.1.

Tricarbonyl[5-(tert-butoxycarbonylamino)-1-carboethoxycyclohexa-1,3-diene]iron **(–)-(*5S*)-5b**.

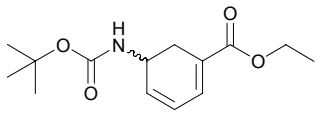


(–)-5b

The procedure for the racemic synthesis and purification of **(±)-5** was undertaken on enantiomerically pure cationic iron complex **(–)-3b** to give **(–)-5b** as a yellow oil that partially crystallized on standing; $[\alpha]_D^{20}$ -61° (c 2.2, $CHCl_3$); Anal. Calc. for $C_{17}H_{21}FeNO_7$: C, 50.14; H, 5.20; N, 3.44. Found: C, 50.24; H, 5.36; N, 3.32; ν_{max}(neat)/cm^{-1} 3352, 2978, 2057, 1987, 1694, 1682, 1514, 1366, 1270, 1247, 1171, 1098; δ_H(400 MHz, $CDCl_3$) 6.17 (1H, d, *J* = 4.1), 5.37 (1H, t, *J* = 5.4), 4.49 (1H, br d, *J* = 6.6), 4.27 (1H, br s), 4.19-4.02 (2H, m), 3.25 (1H, s), 2.81 (1H, dd, *J* = 11.5, 14.6), 1.38 (9H, s), 1.23 (3H, t, *J* = 7.1), 1.14 (1H, dd, *J* = 3.4, 15.5); δ_C(100 MHz, $CDCl_3$) 209.2, 171.7, 155.0, 90.0, 84.1, 79.7, 62.6, 60.9, 59.6, 49.5, 30.9, 28.2, 14.1.

Ethyl 5-(*tert*-Butoxycarbonylamino)-cyclohexa-1,3-diene-1-carboxylate (6):

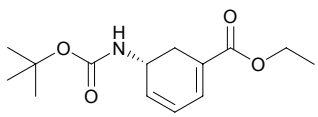
Racemic **(±)-6**.



(±)-6

To a solution of the iron complex **(±)-5** (2.13 g, 5.2 mmol) in EtOH (100 mL) on an ice bath at 0 ºC was added aqueous hydrogen peroxide (30%, 36 mL, 408 mmol), followed by the dropwise addition of 1 M NaOH (31.5 mL, 31.5 mmol) and the reaction mixture was stirred on ice under a nitrogen atmosphere for 5 min. The reaction was diluted with brine (200 mL) and the product extracted with CH_2Cl_2 (3x200 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated, affording **(±)-6** as a light yellow oil (1.33 g, 95%) of sufficiently high purity to be used directly in the next step. An analytically pure sample was prepared by flash chromatography eluting with a gradient of 5-10% EtOAc in petroleum ether to give an oil that partially crystallized on standing; Anal. Calc. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.98; H, 7.84; N, 5.28; NMR data for this racemic compound is in agreement with a recent enantiopure synthesis.[5]

Ethyl 5-(*tert*-Butoxycarbonylamino)-cyclohexa-1,3-diene-1-carboxylate **(+)-(*5R*)-6a**.

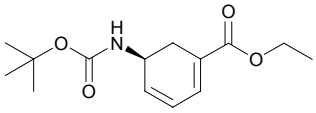


(+)-6a

The procedure for the decomplexation of racemic **(±)-5** was undertaken on the enantiomerically pure complex **(+)-5a** to give crude **(+)-6a** as a light yellow oil which was shown by crude ^{1}H NMR to contain less than 5% impurities and was used directly in

the next step; crude $[\alpha]_D^{20}$ +214° (c 1.1, $CHCl_3$); crude ^1H NMR data for this enantiomer corresponds to that reported for the opposite enantiomer.[5]

Ethyl 5-(*tert*-Butoxycarbonylamino)-cyclohexa-1,3-diene-1-carboxylate **(–)-(*5S*)-6b**.

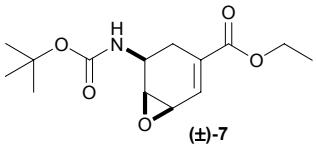


(–)-6b

The procedure for the decomplexation of racemic **(±)-5** was undertaken on the enantiomerically pure complex **(–)-5b** to give crude **(–)-6b** as a light yellow oil which was shown by crude ^1H NMR to contain less than 5% impurities and was used directly in the next step; crude $[\alpha]_D^{20}$ -217° (c 1.1, $CHCl_3$), literature of unknown purity $[\alpha]_D^{25}$ -141.2° (c 1.0, $CDCl_3$); crude ^1H NMR data is in agreement with the literature.[5]

Ethyl 5-(*tert*-Butoxycarbonylamino)-3,4-epoxy-cyclohexa-1-ene-1-carboxylate (7):

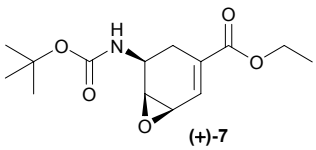
Racemic **(±)-7**.



(±)-7

The diene **(±)-6** (1.33 g, 5.0 mmol) was dissolved in CH_2Cl_2 (60 mL) and cooled to -78 ºC. *m*-CPBA (77%, 1.90 g, 8.5 mmol) was added in portions and the reaction mixture was stirred at -78 ºC under a nitrogen atmosphere for 30 min and then at ambient temperature for 4 h. The solution was cooled to -78 ºC and the resulting precipitate was removed by filtration, washing with cold CH_2Cl_2. The combined filtrates were washed with saturated Na_2SO_3 (2x100 mL), brine (1x100 mL) and saturated $NaHCO_3$ (2x100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated by rotary evaporation, affording a pale yellow oil (1.35 g, 95% crude yield); Due to the instability of the epoxide **(±)-7**, it was used as such directly in the next step. Crude δ_H(400 MHz, $CDCl_3$) 7.04 (t, *J* = 3.6 Hz, 1 H), 4.71 (br d, *J* = 8.8 Hz, 1 H), 4.21 (2H, q, *J* = 7.2), 4.14-4.06 (1H, m) 3.63 (1H, br s), 3.49 (1H, t, *J* = 4.2), 2.86 (1H, ddd, *J* = 2.0, 6.2, 16.6), 1.93 (1H, ddd, *J* = 3.2, 11.2, 16.4), 1.47 (9H, s), 1.29 (3H, t, *J* = 7.0).

Ethyl 5-(*tert*-Butoxycarbonylamino)-3,4-epoxy-cyclohexa-1-ene-1-carboxylate **(+)-(*3R,4S,5S*)-7**.



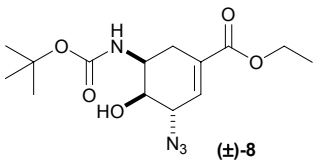
(+)-7

The diene **(–)-6b** underwent epoxidation following the procedure for the racemic compound **(±)-6**. The resulting epoxide **(+)-7** was shown by crude ^1H NMR data to contain less than 10% impurities and was used directly in the next step; crude $[\alpha]_D^{37}$ +33° (c 0.69, CH_2Cl_2); crude ν_{max}(neat)/cm^{-1} 3356, 2976, 1714, 1687, 1519, 1497, 1367, 1257, 1170, 1081; crude δ_H(400 MHz, $CDCl_3$) 7.02 (dd, *J* = 3.3, 4.1 Hz, 1 H), 4.80 (br d, *J* = 8.6 Hz, 1 H), 4.19 (2H, q, *J* = 7.1), 4.14-4.03 (1H, m) 3.63-3.60 (1H, m), 3.47 (1H, t, *J* = 4.2), 2.83 (1H, ddd, *J*

= 1.9, 6.5, 16.5), 1.92 (1H, ddd, *J* = 3.3, 11.3, 16.5), 1.45 (9H, s), 1.27 (3H, t, *J* = 7.1); crude δ_C(100 MHz, $CDCl_3$) 165.5, 155.3, 134.2, 132.8, 80.1, 61.2, 57.9, 48.7, 46.6, 28.5, 27.1, 14.3.

Ethyl 3-Azido-5-(*tert*-butoxycarbonylamino)-4-hydroxy-cyclohexa-1-ene-1-carboxylate (8):

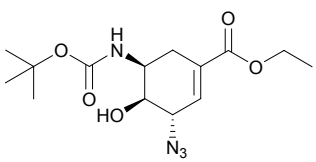
Racemic **(±)-8**.



(±)-8

A solution of epoxide **(±)-7** (0.92 g, 3.3 mmol) in DME (9 mL), water (4.5 mL) and EtOH (4.5 mL) was cooled on an ice bath to 0 ºC under a nitrogen atmosphere. Sodium azide[**] (1.33 g, 19.6 mmol) was added in portions, followed by NH_4Cl (1.05 g, 19.6 mmol). The reaction mixture was stirred on ice for 1 h and then at ambient temperature for a further 2 h. The solution was concentrated by rotary evaporation, diluted with water (25 mL) and extracted with EtOAc (3x35 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to afford **(±)-8** as a brown oil (1.01 g, 95%) of sufficiently high purity to be used directly in the next step. An analytically pure sample was prepared by flash chromatography on deactivated silica gel (pretreated with 10% Et_3N in petroleum ether, followed by extensive washing with 20% EtOAc in petroleum ether), eluting with 20-30% EtOAc in petroleum ether to give a white powder; Anal. Calc. for $C_{14}H_{22}N_4O_5$: C, 51.52; H, 6.79; N, 17.17. Found: C, 51.68; H, 6.71; N, 17.26; δ_H(400 MHz, $CDCl_3$) 6.75 (1H, s), 4.78 (1H, br s), 4.21 (2H, br q, *J* = 7.1), 4.19-3.96 (2H, m), 3.93-3.88 (1H, m), 2.76-2.65 (1H, m), 2.49 (1H, br d, *J* = 14.3), 1.45 (9H, s), 1.30 (3H, t, *J* = 7.2); δ_C(100 MHz, $CDCl_3$) 165.7, 157.4, 133.1, 131.4, 81.1, 72.7, 61.4, 61.2, 49.3, 29.0, 28.4, 14.3; MS (ES) *m/z* 327.05 (M^+, 10%), 227.04 (100, M^+-BOC).

Ethyl 3-Azido-5-(*tert*-butoxycarbonylamino)-4-hydroxy-cyclohexa-1-ene-1-carboxylate **(*3S,4S,5S*)-8**.



(*3S,4S,5S*)-8

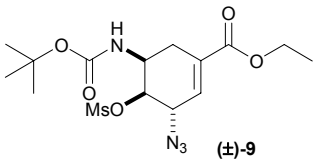
The crude epoxide **(+)-7** was converted to the corresponding azido alcohol using the same protocol as for the racemic compound **(±)-6**. The azido alcohol **8** was a brown oil and obtained as a single enantiomer with the crude ^1H NMR showing 90% purity (excluding residual solvent) which was sufficient to be used directly in the next step; crude δ_H(400 MHz, $CDCl_3$) 6.74 (1H, br s), 4.91 (1H, br s), 4.25-4.16 (2H, m), 4.16-3.95 (2H, m), 3.94-3.86 (1H, m), 2.69 (1H, br d, *J* = 18.4), 2.46 (1H, br d, *J* = 17.1), 1.44 (9H, s), 1.29 (3H,

[**] Caution! NaN_3 is highly toxic and should be handled with care.

t, *J* = 7.1); crude δ_C(100 MHz, $CDCl_3$) 165.7, 157.2, 132.8, 131.6, 80.9, 72.3, 61.3, 61.1, 48.9, 28.8, 28.4, 14.3.

Ethyl 3-Azido-5-(*tert*-butoxycarbonylamino)-4-[(methylsulfonyl)oxy]-cyclohexa-1-ene-1-carboxylate (9):

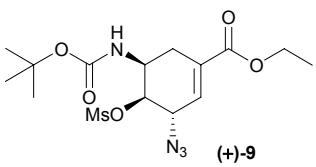
Racemic **(±)-9**.



(±)-9

To a solution of the azido alcohol **(±)-8** (0.79 g, 2.4 mmol) in dry CH_2Cl_2 (30 mL) on an ice bath at 0 ºC, was added Et_3N (1.11 ml, 7.9 mmol) followed by the dropwise addition of methanesulfonyl chloride (490 µl, 6.3 mmol). The reaction mixture was stirred on ice for 1 h, then diluted with CH_2Cl_2 (40 mL) and washed with water (80 mL) followed by brine (2x80 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. This crude material was absorbed to silica and purified by flash chromatography, eluting with 20-30% EtOAc in petroleum ether affording **(±)-9** as a white powder (0.65 g, 62%); Anal. Calc. for $C_{15}H_{24}N_4O_7S$: C, 44.55; H, 5.98; N, 13.85. Found: C, 44.61; H, 5.86; N, 13.50; δ_H(400 MHz, $CDCl_3$) 6.83 (1H, br s), 4.90 (1H, br s), 4.77 (1H, br s), 4.39 (1H, t, *J* = 3.9), 4.25 (2H, dq, *J* = 2.4, 7.1), 4.16-4.05 (1H, m), 3.08 (3H, s), 2.79 (1H, dd, *J* = 5.5, 18.0), 2.28 (1H, dd, *J* = 9.7, 18.1), 1.46 (9H, s), 1.32 (3H, t, *J* = 7.1); δ_C(100 MHz, $CDCl_3$) 165.2, 155.1, 133.6, 129.7, 80.7, 61.6, 58.1, 45.5, 45.5, 38.3, 28.4, 27.1, 14.3; MS (ES) *m/z* 304.98 (M^+-BOC, 100%).

Ethyl 3-Azido-5-(*tert*-butoxycarbonylamino)-4-[(methylsulfonyl)oxy]-cyclohexa-1-ene-1-carboxylate **(+)-(*3S,4S,5S*)-9**.



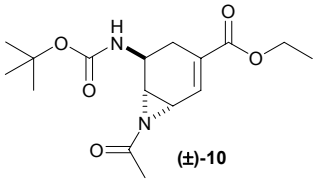
(+)-9

The crude azido alcohol **(*3S,4S,5S*)-8** (0.33 g, 1.0 mmol) underwent mesylation following the procedure for the racemic synthesis of **(±)-9**. The crude material was recrystallised from warm EtOAc affording **(+)-9**. The mother liquor was then purified by flash chromatography and the appropriate fraction recrystallised from warm EtOAc to give further **(+)-8** (combined yield 0.28 g, 68%) as a crystalline solid; $[\alpha]_D^{25}$ +164º (c 0.8, $CHCl_3$); mp 140-142 ºC (from EtOAc); Anal. Calc. for $C_{15}H_{24}N_4O_7S$: C, 44.55; H, 5.98; N, 13.85. Found: C, 45.49; H, 6.31; N, 11.58; ν_{max}(KBr)/cm^{-1} 3394, 2979, 2117, 1726, 1692, 1519, 1354, 1293, 1248, 1175; δ_H(400 MHz, $CDCl_3$) 6.83 (1H, br s), 4.90 (1H, br s), 4.85-4.77 (1H, m), 4.44-4.37 (1H, m), 4.30-4.20 (2H, m), 4.18-4.06 (1H, m), 3.09 (3H, s), 2.79

(1H, dd, J = 5.6, 17.9), 2.29 (1H, dd, J = 9.7, 18.1), 1.46 (9H, s), 1.32 (3H, t, J = 7.1); δ_C(100 MHz, $CDCl_3$) 165.1, 155.1, 133.5, 129.6, 80.5, 61.5, 58.0, 45.9, 45.4, 38.2, 28.4, 27.0, 14.2.

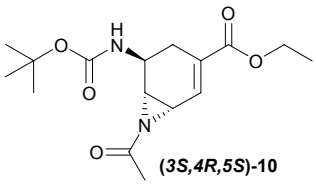
Ethyl 3,4-(*N*-Acetylaziridinyl)-5-(*tert*-butoxycarbonylamino)-cyclohexa-1-ene-1-carboxylate (10):

Racemic **(±)-10**.



The azido mesylate **(±)-9** (0.22 g, 0.6 mmol) was dissolved in THF (11 mL) under a nitrogen atmosphere and triphenylphosphine (0.16 g, 0.6 mmol) was added. The solution was stirred at room temperature for 80 min, whereupon water (1 mL) and Et_3N (230 µL, 1.64 mmol) were added. The reaction mixture was stirred for 15 h, then concentrated and redissolved in CH_2Cl_2 (11 mL). The solution was cooled on an ice bath to 0 ºC and pyridine (400 µL, 4.9 mmol) was added, followed by the dropwise addition of acetic anhydride (230 µL, 2.5 mmol). The reaction was stirred on ice for 10 min and then diluted with EtOAc (20 mL) and washed with water (2x20 mL) and brine (2x20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography, eluting with 20-30% EtOAc in petroleum ether, yielding **(±)-10** as an oil that partially crystallized on standing (0.12 g, 65%); Anal. Calc. for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.18; H, 7.42; N, 8.57; δ_H(400 MHz, $CDCl_3$) 7.19 (1H, t, J = 3.8), 4.58-4.51 (1H, m), 4.48-4.40 (1H, m), 4.20 (2H, dq, J = 0.7, 6.2), 3.15-3.06 (2H, m), 2.74 (1H, br d J = 17.2), 2.33 (1H, br d, J = 16.8), 2.14 (3H, s), 1.43 (9H, s), 1.29 (3H, t, J = 7.1); δ_C(100 MHz, $CDCl_3$) 181.4, 166.0, 155.2, 133.9, 130.4, 80.2, 61.2, 42.1, 41.2, 32.0, 28.5, 26.8, 23.3, 14.3; MS (ES) *m/z* 325.04 (M^+, 30%).

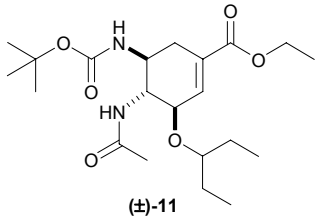
Ethyl 3,4-(*N*-Acetylaziridinyl)-5-(*tert*-butoxycarbonylamino)-cyclohexa-1-ene-1-carboxylate ***(3S,4R,5S)*-10**.



The procedure for the racemic synthesis and purification of **(±)-10** was undertaken on azido mesylate **(+)-9** to give the acetylated aziridine ***(3S,4R,5S)*-10**; δ_H(400 MHz, $CDCl_3$) 7.14 (1H, t, J = 3.8), 4.57 (1H, d, J = 8.7), 4.52-4.45 (1H, m), 4.14 (2H, dq, J = 1.2, 7.2), 3.11-3.03 (2H, m), 2.69 (1H, d, J = 17.1), 2.28 (1H, d, J = 17.0), 2.09 (3H, s), 1.38 (9H, s), 1.24 (3H, t, J = 7.1); δ_C(100 MHz, $CDCl_3$) 181.3, 165.9, 155.1, 133.8, 130.3, 80.0, 61.1, 42.0, 41.1, 31.9, 28.3, 26.7, 23.2, 14.2.

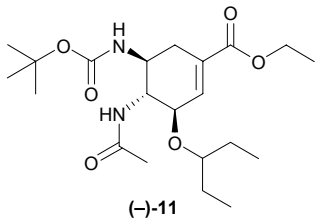
Ethyl 4-Acetylamino-5-(*tert*-butoxycarbonylamino)-3-(1-ethylpropoxy)-cyclohexa-1-ene-1-carboxylate (11):

Racemic **(±)-11**.



Prepared form acylated aziridine **(±)-10** using the procedure reported by Corey et al.,[5] affording **(±)-11** as a white powder (56.4 mg, 48%); spectral data for this compound was in agreement with the published data; Anal. Calc. for $C_{21}H_{36}N_2O_6$: C, 61.14; H, 8.80; N, 6.79. Found: C, 61.06; H, 8.72; N, 6.85.

Ethyl 4-Acetylamino-5-(*tert*-butoxycarbonylamino)-3-(1-ethylpropoxy)-cyclohexa-1-ene-1-carboxylate **(–)-(*3R,4R,5S*)-11**.



As for racemic **(±)-10,** the acetylated aziridine **(*3S,4R,5S*)-10** was subjected to the procedure reported by Corey et al.,[5] affording **(–)-11**; $[\alpha]_D^{25}$ -92° (c 0.6, $CHCl_3$), literature of unknown purity $[\alpha]_D^{25}$ -68.9° (c 1.0, $CHCl_3$); mp 149.9-151.9 °C (from pet. ether); Anal. Calc. for $C_{21}H_{36}N_2O_6$: C, 61.14; H, 8.80; N, 6.79. Found: C, 61.28; H, 8.70; N, 6.67; IR, ^{1}H NMR, ^{13}C NMR and MS data for this compound was in agreement with published data.[5]

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4 B. M. R. Bandara, A. J. Birch and L. F. Kelly, *J. Org. Chem.*, 1984, **49**, 2496.
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