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The synthesis of *S*-(+)-2,2-dimethylcyclopropane carboxylic acid: a precursor for cilastatin

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Abstract

S-(+)-2,2-Dimethylcyclopropane carboxylic acid, a precursor for cilastatin, was prepared from 2-methylpropene and chiral iron carbene in three steps. Asymmetric cyclopropanation reaction of 2-methylpropene with iron carbene complex having chirality at the carbene ligand, followed by exhaustive ozonolysis, produced *S*-(+)-2,2-dimethylcyclopropanecarboxylic acid of up to 92% ee. The absolute configuration of complexed chiral cyclopropane (−)-**8** was determined by X-ray crystallographic analysis. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

The practical importance of *S*-(+)-2,2-dimethylcyclopropanecarboxylic acid (+)-**10** comes from the pharmaceutical field. Imipenem **1** (Fig. 1), one of the most promising β-lactam antibiotics, was found to be deactivated by renal dipeptidase (dehydropeptidase-I).[1] Cilastatin **2** (Fig. 1), an excellent inhibitor of dehydropeptidase-I which increases the in vivo stability of imipenem, has the desired pharmacological properties.[2] The *S*-(+)-2,2-dimethylcyclopropane carboxylic acid (+)-**10** is a key building block for the synthesis of cilastatin. Several methods recently reported for the asymmetric synthesis of (+)-**10** or its esters were mainly based on: (1) the cyclopropanation of chiral alkenes;[3,4] or (2) on the enantioselective cyclopropanation of alkenes in the presence of chiral copper carbenoid by means of ethyl diazoacetate.[5,6] Aratani[5] and Evans[6] have obtained the ethyl ester of (+)-**10** with an excellent ee by the second method. Recently, we developed a novel method for the synthesis of an iron carbene having chirality at the carbene ligand, and reported the first asymmetric cyclopropanation with styrene with 60% ee.[7] Here we report the asymmetric synthesis of *S*-(+)-2,2-dimethylcyclopropanecarboxylic acid via the same chiral iron carbene complex.

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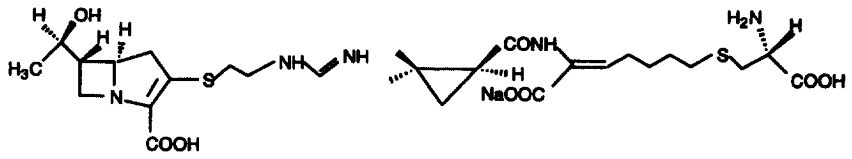
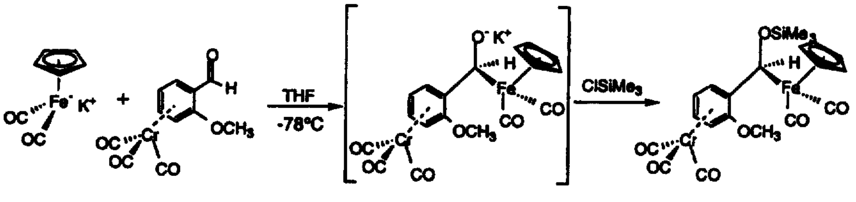


1 Imipenem **2** Cilastatin

Figure 1.

2. Results and discussion

The enantiomerically pure *O*-anisaldehyde(tricarbonyl)chromium complex (+)-**4**[8] was reacted with the Fp anion **3** in the presence of chlorotrimethylsilane, followed by extraction and column chromatography, providing an enantiomerically pure bimetallic complex (−)-**6** in 90% yield (Scheme 1).



3 S-(+)-**4** **5** SS-(-)-**6**

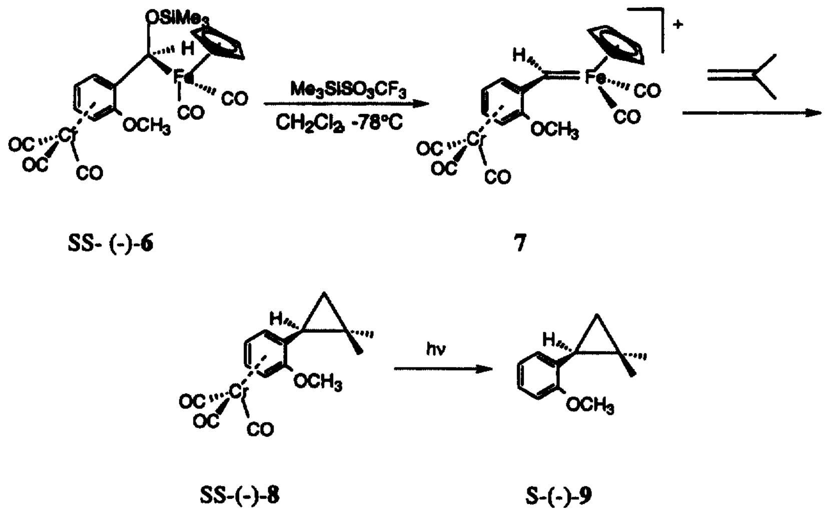
Scheme 1.

In order to carry out the asymmetric cyclopropanation reaction, one equivalent of the enantiomerically pure (−)-(α-siloxy-*O*-methoxybenzyl) bimetallic complex (−)-**6** was dissolved in dichloromethane and then treated with 1.1 equivalent of trimethylsilyl trifluoromethanesulfonate at −78°C in the presence of an excess of 2-methylpropene. The corresponding complexed cyclopropane (−)-**8** was obtained in 91% yield (Scheme 2). The absolute configuration of (−)-**8** was established by X-ray crystallographic analysis as *SS*-(−)-2,2-dimethyl-1-*O*-methoxyphenyl (tricarbonyl chromium) cyclopropane (Fig. 2).

Decomplexation of the Cr(CO)$_3$ moiety from (−)-**8** under a sun lamp or natural sunlight in a solution of pentane:ether provided the chiral cyclopropane (−)-**9** with 97% yield. A >95% ee was indicated for (−)-**9** as measured by the proton NMR spectrum, utilizing a chiral shift reagent of ytterbium D-3-heptafluorobutyrylcamphorate Yb(hfc)$_3$.

Ozonolysis of the cyclopropane (−)-**9** followed by oxidative workup with hydrogen peroxide and subsequent fractional distillation gave a clear oil of *S*-(+)-2,2-dimethylcyclopropane carboxylic acid (+)-**10** in 82% yield (Scheme 3). The enantiomeric excess of (+)-**10** was determined by the proton NMR spectrum of its *S*-methyl mandelate ester derivative.[9,10] The split mandelate methine proton of **11** indicated a 92% ee (Fig. 3a) when compared with the corresponding 1:1 diastereomeric mixture (Fig. 3b).

In conclusion, the asymmetric synthesis of *S*-(+)-2,2-dimethylcyclopropane carboxylic acid was carried out by using an iron carbene having a chiral carbene ligand in high yield with 92% ee. Extension of the chiral cyclopropanation to other olefins in order to prepare other building blocks for the synthesis of natural products and insecticides is being worked on.



Scheme 2.

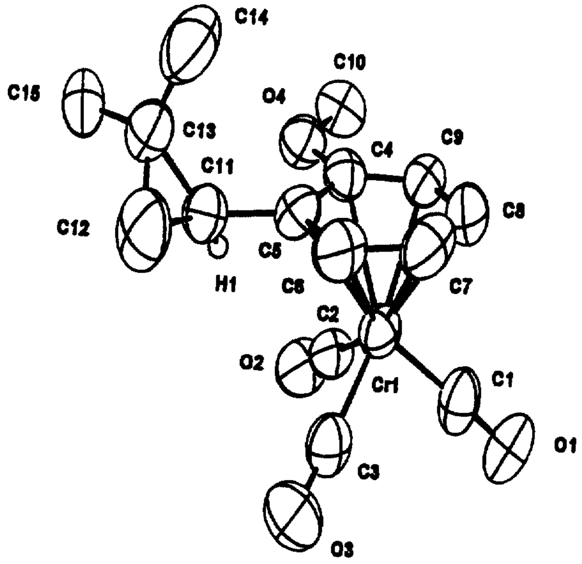
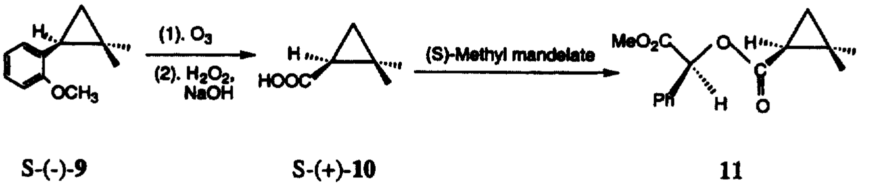


Figure 2. ORTEP drawing of *SS*-(−)-8. Ellipsoids are drawn at the 35% probability level



Scheme 3.

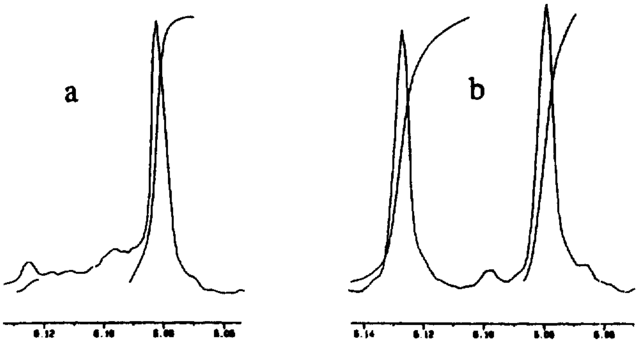


Figure 3. 300 MHz ^{1}H NMR spectrum of **11** (a) and the corresponding diastereomeric mixture (b)

3. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 250 or 300 MHz spectrometer, in deuterated chloroform using the solvent signal as internal reference unless otherwise stated. Chemical shifts are expressed in ppm. Optical rotations were recorded on a Jasco DIP-370 digital polarimeter at 20°C. Infrared spectra were taken with a Nicolet FT-IR spectrometer. The CHN analyses were carried out with a Perkin–Elmer 240C element analyzer. Mass spectra were obtained on a Hewlett Packard 5985B (H/P), GC/MS system, operated in DIP, CI or EI-70 eV. X-Ray diffraction analysis was performed on a Picker 4-circle autodiffractometer at 22(2)°C. The ozone in the ozonolysis was generated by a T-400 Welsbach ozonator.

All reactions and manipulations of transition metal complexes were performed under a dry nitrogen atmosphere using standard Schlenk line and/or dry box techniques. All glassware required for the above was either flamed under vacuum or dried in an oven prior to use.

Tetrahydrofuran, diethyl ether, dichloromethane, pentane and deuterated chloroform were purified according to our previous procedure.[11] Hydrogen peroxide was obtained from Mallinckrodt Co. Chlorotrimethylsilane, trimethylsilyl triflate ($CF_3SO_3SiMe_3$), L-(+)-valinol, *ortho*-anisaldehyde and ytterbium D-3-heptafluorobutyrylcamphorate $Yb(hfc)_3$ were obtained from Lancaster and used without treatment. *S*-(+)-Methyl mandelate, 1,3-dicyclohexylcarbodiimide, 4-dimethylaminopyridine and benzene-d_6 were obtained from Aldrich and used without further purification unless otherwise stated.

Potassium cyclopentadienyldicarbonylferrate, $K[(\eta^5\text{-}C_5H_5)Fe(CO)_2]$[12] and enantiomerically pure *S*-(+)-*O*-anisaldehyde(tricarbonyl)chromium complex[8] were prepared according to the literature methods.

3.1. SS-(−)-$(\eta^5\text{-}C_5H_5)(CO)_2FeCH(OSiMe_3)[(\eta^6\text{-O-}CH_3OC_6H_4)Cr(CO)_3]$ (−)-**6**

A 3.6–4.2 mmol (1.2 equiv.) sample of FpK **3** was dissolved in 40–45 ml of THF and cooled to −78°C, and a 3.0–3.5 mmol (1 equiv.) sample of *S*-(+)-*O*-anisaldehyde(tricarbonyl)chromium complex (+)-**4**, which had been dissolved in 20 ml of THF and degassed twice, was transferred via a cannula to this Fp anion solution under −78°C. After the reaction mixture was stirred for 4–4.5 h at −78°C, 3.6–4.2 mmol (1.2 equiv.) of chlorotrimethylsilane was added dropwise. Stirring was continued for 4 h, and the temperature was maintained at −78°C. After warming the reaction mixture for 20 min to ambient temperature, the solvent was removed under reduced pressure, and the crude product was separated with a water-jacked column on silica gel (40–140 mesh) using a 0–2% dichloromethane/pentane mixture. The precursor (−)-**6** was isolated as a brown solid in 90% yield. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 6.20 (s, 1H, CH), 5.82 (d, 1H, J=6.4 Hz, Ph), 5.39 (t, 1H, J=6.0 Hz, Ph), 5.01 (d, 1H, J=7.3 Hz, Ph), 4.95 (t, 1H, J=7.3

Hz, Ph), 4.69 (s, 5H, C_5H_5), 3.70 (s, 3H, OCH_3), 0.28 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 234.6 ($Cr(CO)_3$), 216.7, 215.2 ($Fe(CO)_2$), 135.2 ($COCH_3$), 120.1, 92.1, 89.5, 86.7 (C_5H_5), 85.7, 84.9, 73.7 (FeCH), 54.8 (OCH_3), 0.47 ($Si(CH_3)_3$). IR (CH_2Cl_2) ν_{CO}: 2007, 1953, 1872 cm^{-1}. Anal. calcd for $FeC_{21}H_{22}O_7CrSi$: C, 48.29; H, 4.24. Found: C, 48.12; H, 4.21. $[\alpha]_D^{20}$ −335 (c, 0.226, $CHCl_3$).

3.2. SS-(−)-2,2-Dimethyl-1-O-methoxyphenyl(tricarbonyl chromium)cyclopropane (−)-8

A 2.5–3.0 mmol (1 equiv.) sample of the bimetallic complex (−)-**6** was dissolved in 25 ml of CH_2Cl_2 and cooled to −78°C, and an excess of 2-methylpropene, which had been condensed to liquid at −78°C, was introduced. After adding 3.0–3.6 mmol (1.1 equiv.) of trimethylsilyl triflate, the solution was stirred for 4 h at −78°C and warmed to room temperature over 0.5 h. The color of the reaction mixture changed to purple after several minutes of stirring. After the treatment of the reaction mixture with a short-wash column of neutral alumina (activity IV) under nitrogen, the solvent was removed under reduced pressure. The crude product was then separated with a chromatography column on neutral alumina (activity IV) and a bright yellow solid of (−)-**8** was isolated in 91% yield. ^1H NMR ($CDCl_3$, 250 MHz) δ: 5.36–5.42 (m, 2H, Ph), 5.13 (d, 1H, J=6.6 Hz, Ph), 4.90 (t, 1H, J=6.2 Hz, Ph), 3.77 (s, 3H, OCH_3), 1.85 (t, 1H, J=7.2 Hz, CH), 1.19 (s, 3H, CH_3), 0.82 (s, 3H, CH_3), 0.81 (t, 1H, J=5.4 Hz, CH_2), 0.64 (t, 1H, J=5.5 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 232.4 ($Cr(CO)_3$), 163.9, 142.2, 95.7, 92.7, 85.8, 74.8 (Ph), 56.0 (OCH_3), 26.7, 19.8, 20.2 (cyclopropane), 24.8 (CH_3), 18.2 (CH_3). Anal. calcd for $C_{15}H_{16}O_4Cr$: C, 57.69; H, 5.16. Found: C, 57.74; H, 5.25. m/z: 312 (22%, M^+). $[\alpha]_D^{20}$ −191 (c, 0.273, $CHCl_3$).

3.3. S-(−)-2,2-Dimethyl-1-O-methoxyphenylcyclopropane (−)-9

A 2.2–2.8 mmol sample of (−)-**8** was dissolved in 200–250 ml solvent (pentane:ether, 50:50), and stirred under a sun lamp or natural sunlight for 3 days while air was bubbled through the solution. The solution became colorless. After gravity filtration, the solvent was removed by a rotavapor and a clear oil of (−)-**9** was obtained in 97% yield. The enantiomeric excess of the product was determined by adding 40 mg of $Yb(hfc)_3$ into 4 mg of (−)-**9** in 0.5 ml $CDCl_3$ and the split peaks of the methoxy proton in ^1H NMR spectrum were used to determine the ee of (−)-**9**. A >95% ee of (−)-**9** was indicated. ^1H NMR ($CDCl_3$, 250 MHz) δ: 7.16 (t, 1H, J=7.7 Hz, Ph), 7.01 (d, 1H, J=6.4 Hz, Ph), 6.86 (t, 1H, J=7.4 Hz, Ph), 6.83 (d, 1H, J=8.0 Hz, Ph), 3.83 (s, 3H, OCH_3), 1.83 (t, 1H, J=7.3 Hz, CH), 1.24 (s, 3H, CH_3), 0.75 (d, 2H, J=7.3 Hz, CH_2), 0.70 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 250 MHz) δ: 159.7, 129.4, 129.0, 126.7, 120.1, 110.0 (Ph), 55.5 (OCH_3), 27.1 (CH_2), 25.6 (CH), 20.1 ($C(CH_3)_2$), 18.2 (CH_3), 17.8 (CH_3). Anal. calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.80; H, 9.46. m/z: 176 (46%, M^+), 161 (94, M−Me) and 146 (16, M−2Me). $[\alpha]_D^{20}$ −51 (c, 0.548, $CHCl_3$).

3.4. S-(+)-2,2-Dimethylcyclopropane carboxylic acid (+)-10

A 2.0–2.5 mmol sample of (−)-**9** was dissolved in 60 ml of CH_2Cl_2 and cooled to −78°C, and a stream of ozone was bubbled through the solution for 0.5 h. Bubbling was continued for 8 h, and the temperature was maintained at −20 to −30°C. The reaction mixture was then poured into a solution of 20 ml 30% H_2O_2 in 60 ml 10% NaOH, and stirred overnight at room temperature. After acidifying the solution to pH 3, the reaction mixture was extracted with CH_2Cl_2, and dried over $MgSO_4$. After fractional distillation the final product of *S*-(+)-2,2-dimethylcyclopropane carboxylic acid (+)-**10** was obtained in 82% yield. ^1H NMR ($CDCl_3$, 250 MHz) δ: 1.51 (dd, 1H), 1.24 (s, 3H), 1.15 (s, 3H), 1.11 (dd, 1H), 0.93 (dd, 1H);

^{13}C NMR ($CDCl_3$, 250 MHz) δ: 179.2 (COOH), 27.0 (CH), 26.6 (CH_3), 24.5 ($C(CH_3)_2$), 22.9 (CH_2), 18.6 (CH_3). $[\alpha]_D^{20}$ +114 (c, 1.13, $CHCl_3$).

3.5. *Determination of enantiomeric excess of (+)-**10***

S-methyl mandelate (0.2 mmol) and dicyclohexylcarbodiimide (0.2 mmol) were added to a solution of acid (+)-**10** (0.2 mmol) and 4-dimethylaminopyridine (0.04 mmol) in 5 ml CH_2Cl_2 at −10°C, and the mixture was stirred for 3 h at −10°C. After filtration of the precipitated urea, the solvent was removed with a rotavapor. Without further purification, ^1H NMR was obtained in C_6D_6 and the split peak (around δ 6.1) of mandelate methine proton was used to calculate the ee of (+)-**10**. The corresponding diastereomeric mixture of *S*-methyl mandelate ester derivative was prepared from the racemic 2,2-dimethylcyclopropane carboxylic acid in the same way.

3.6. *X-Ray structure determination of* SS-*(−)-2,2-dimethyl-1-*O*-methoxyphenyl (tricarbonyl chromium)cyclopropane*

(−)-**8** A yellow crystal (0.3×0.15×0.15 mm) of compound (−)-**8**, which was obtained by slow evaporation of an ethyl ether solution, was anchored with epoxy in a quartz capillary tube and mounted on the autodiffractometer for data collection. A summary of crystallographic data (collected at room temperature) and structure refinement is given in Table 1. Cell constants were determined by least-squares refinement of 10 reflections. Data were sorted and collected using PCXTL.[13] Orientation and crystal decay were monitored by measuring the intensities of three standard reflections at intervals of 120 min. Minimal intensity losses were observed. Data reduction, handling and analysis were performed using NRCVAX.[14] The locations of non-hydrogen atoms were determined by direct methods using SHELXS-86.[15] The structure was refined against *F* using SHELX-76.[16] All heavy atoms were refined anisotropically. Hydrogen atoms were allowed to ride on the heavy atom to which they were attached, with hydrogen atom thermal parameters fixed at 1.2 times the equivalent isotropic thermal parameter of the heavy atom. The Flack *x* parameter was 0.019 with an esd of 0.042. The expected value is 0 (within 3 esds) for the correct enantiomer, and +1 for the inverted enantiomer.

Acknowledgements

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Table 1
Crystallographic data for *SS*-(−)-2,2-dimethyl-1-*O*-methoxyphenyl(tricarbonyl chromium)cyclopropane (−)-**8**

Formula	$C_{15}H_{16}O_4Cr$
Molar mass	312.28
Cryst syst	orthorhombic
Space group	$P2_12_12_1$
a, Å	6.5929(7)
b, Å	9.8258(14)
c, Å	23.076(4)
V, Å^3	1494.9(4)
Z	4
d_{calc}, g cm^{-3}	1.388
μ, mm^{-1}	6.48
T, °C	22(2)
Radiation	Ni-filtered Cu Kα, λ=1.54178 Å
2θ range, deg	4-100
Index ranges	$0\leq h\leq 6$; $0\leq k\leq 9$; $0\leq l\leq 22$
Scan type	θ/2θ
No. of data collected	948
No. of unique data	820 ($I>3\sigma(I)$)
No. of parameters	182
GOF[a]	1.91
R, R_w[b]	.062, .065
$(\Delta\rho)_{max}$, eÅ^{-3}	-.38, +.26
Flack x parameter	.019(.042)

[a] $GOF=[\Sigma[w(F_o^2-F_c^2)^2]/(M-N)]^{1/2}$, where M is the number of reflections and N is the number of parameters refined. [b] $R=\Sigma|F_c|/\Sigma|F_o|$; $R_w=\Sigma[w^{1/2}|(F_o-F_c)|]/\Sigma[w^{1/2}|F_o|]$.

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