Enantioselective synthesis of lactams and lactones
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CHAPTER 5

Determination of the Absolute Configuration of 3-Pyrrolin-2-ones

5.1 Introduction

Optically active 3-pyrrolin-2-ones have been shown to be important chiral synths for the preparation of a variety of biologically active compounds. These five-membered ring lactams have been used successfully in routes to various alkaloids and are suitable precursors for unusual γ-amino acids such as statine and its analogs. There are also many examples of pyrrolinone containing natural products with interesting pharmacological activities. Typical examples are the antitumor alkaloid Jatropha and the platelet aggregation inhibitor PI-091.

The chemistry of these versatile building blocks has been explored by a number of groups. Because of their multifunctional nature, these heterocycles can take part in several stereoselective transformations like conjugate additions, cycloadditions, acyliminium ion chemistry, and allylic substitutions.

The increasingly frequent use of these compounds as chiral intermediates makes it indispensable to have a fast, universal method for the determination of the absolute configuration. Classical methods to determine the absolute configuration are by chemical correlation or by the introduction of a heavy atom, followed by single crystal X-ray diffraction. The first method is rather time consuming; the second is dependent on the availability of crystals that are suitable for absolute configuration determination. Recently Gawronski et al. reported a simple circular dichroic method for determination of the absolute configuration of chiral 2(5H)-furanones. These butenolides are of a reactivity similar to the 3-pyrrolin-2-ones and have comparable structural features. This chapter describes how the CD method of Gawronski can be extended to the determination of the absolute configuration of 3-pyrrolin-2-ones.

5.2 Synthesis

As was already discussed in Chapter 2, several routes to enantiomerically pure 3-pyrrolin-2-ones are available. For the determinations of the absolute configuration described in this chapter three different types of pyrrolinones were used with N-alkyl or N-acyl groups that have been prepared by three different routes: 5-alkylpyrrolinones were prepared by Gawronski and Brzostowska, 5-acyloxypyrrolinones were prepared by us as described in detail in Chapters 2–4, and 5-alkoxypyrrolinones were prepared by Hiemstra and co-workers.
Route 1 is based on amino acids and provides the N-Boc protected 5-methyl pyrrolinone 5.5 (Scheme 5.1).\(^{3b}\) Following the procedure of Jouin\(^{3a}\) further improved by Ma\(^{3b}\) (5S)-N-tert-butoxycarbonyl-4-hydroxy-5-methyl-3-pyrrolin-2-one 5.3 was synthesized from N-Boc protected L-alanine and Meldrum’s acid. The synthesis of compound (+)-5.5 was accomplished by first reducing 5.3 with NaBH\(_4\),\(^{3b}\) followed by elimination of the hydroxyl group of 5.4 via the corresponding mesylate.\(^{11}\) N-Boc protected 3-pyrrolin-2-one 5.5 has been synthesized previously\(^{12}\) but apparently in partly racemized form (identical NMR spectrum but lower [\(\alpha\)]\(_D\) and oil instead of solid). Compound (+)-5.7 was obtained along with the isomer 5.6, by methylation of the hydroxy-substituted precursor 5.3\(^{3b}\), using diazomethane.

![Scheme 5.1](image)

Scheme 5.1  *Synthesis of 5-alkyl-pyrrolinones (route 1)*

Route 2 starts with a pyrrole or methoxyfuranone and includes an enantioselective enzymatic synthesis step (Scheme 5.2).\(^{13}\) N-Methylpyrrolinone 5.10 was synthesized by the photooxidation of N-methylpyrrole, followed by esterification. Subsequent enzymatic resolution by *Candida antarctica* mediated transesterification provided enantiopure (+)-5.10.\(^{13}\)

The N-acyl derivatives 5.13 and 5.14 were synthesized starting from commercially available 5-methoxy-3-furan-2-one and were obtained enantiomerically pure by an enzymatic transesterification using the same lipase (*Candida antarctica*) as applied in the preparation of 5.10. The enzyme specifically converted the (–)-enantiomer to the hydroxy derivative 5.15 or 5.16 and the unreactive (+)-enantiomer was obtained in >99% e.e.. In this way the maximum yield of 50% of enantiopure product in a kinetic resolution was obtained.\(^{13}\) Compounds (–)-5.14, (–)-5.17, and (–)-5.18 were obtained by the reverse reaction, the enzymatic esterification
Determination of the Absolute Configuration of 3-Pyrrolin-2-ones

of hydroxypyrrolinones 5.15 and 5.16. In this reaction the (–)-enantiomer of the hydroxypyrrolinone was converted to the (–)-acyloxypyrrolinones. Because the hydroxypyrrolinones 5.15 and 5.16 racemize under the reaction conditions (–)-5.14, (–)-5.17, and (–)-5.18 could be obtained enantiomerically pure in quantitative yield by a dynamic kinetic resolution.\(^\text{13}\)

\[\text{(–)-5.15} \quad \text{R} = \text{Et}\]
\[\text{(–)-5.16} \quad \text{R} = \text{Me}\]

\[\text{(–)-5.17} \quad \text{R} = \text{Me}, \text{R} = \text{Et}\]
\[\text{(–)-5.18} \quad \text{R} = \text{Et}, \text{R} = \text{Me}\]

Scheme 5.2 Synthesis of 5-acyloxy-pyrrolinones (route 2)

The 5-isopropoxy pyrrolinones 5.23 and 5.24 were obtained via a stereoselective synthesis route,\(^\text{7a,14}\) starting with (S)-malic acid (Scheme 5.3).
A method to independently establish the absolute configuration of 3-pyrrolin-2-ones is based on synthesis and characterization of the corresponding iron tetracarbonyl complexes (Scheme 5.4). Pyrrolinone (+)-5.14 was converted by reaction with Fe₂(CO)₉ into a 1:1 mixture of cis-(5.25a) and trans-(5.25b) Fe(CO)₄ complexes (Scheme 5.4.). The lack of π-face selectivity is in contrast with the selectivity observed in the synthesis of iron complexes with isopropoxy substituted pyrrolinones¹⁴,¹⁵ (in which case cis complex is formed predominantly, possibly because of precoordination of iron to the oxygen atom of the isopropoxy group). The isomers were distinguished on the basis of the coupling constants between H(4) and H(5) in the ¹H NMR spectra. For the cis complex 5.25a a value of 5 Hz was found, whereas for the trans complex 5.25b J < 0.5 Hz was observed. As in other pyrrolinone iron tetracarbonyl complexes¹⁴,¹⁵ the C(3)-C(4) bond is elongated from about 1.3 Å for a normal double bond to 1.414 (5) Å in the complex.

Scheme 5.4  Synthesis of pyrrolinone iron tetracarbonyl complexes

The cis-isomer was not isolated in pure form and was obtained by flash chromatography under nitrogen either as a mixture with the trans-isomer or contaminated with the starting material.
Pure trans-isomer 5.25b was isolated by flash chromatography and was recrystallized from pentane to give crystals suitable for X-ray crystal structure determination. The crystalline complex is stable in air.

5.3 CD Studies

In the case of simple 3-pyrrolin-2-ones bearing no substituents on the olefinic bond, the maximum of the $\pi-\pi^*$ Cotton effect is observed at $\lambda_{\text{max}}$ ca. 200 nm. The maximum of the n-$\pi^*$ Cotton effect is seen at longer wavelength, around 230 nm, where the UV spectrum displays a broad shoulder. CD/UV spectral data of all pyrrolinones investigated are shown in Table 5.1. The CD spectra of (+)-5.14 and (−)-5.14 are shown in Figure 5.1.

![CD spectra of (S)-(+) and (R)-(−) 5.14](image)

**Figure 5.1** CD spectra of (S)-(+) 5.14 (continuous) and (R)-(−)-5.14 (dashed) 10⁻³ M in acetonitrile

The 3-pyrrolin-2-ones with an oxygen substituent at C(5) generally display much stronger Cotton effects than those substituted with an alkyl group (e.g. compounds 5.5 and 5.7). A methoxy substituent at C(3) shifts the position of the $\pi-\pi^*$ band to ca. 230 nm (compound 5.7), as does tosyl substitution at N(1) (compound 5.24).

3-Pyrrolin-2-ones with an imide-type group ($R^2 = $ acyl) display an additional Cotton effect at ca. 280 nm, presumably due to a second n-$\pi^*$ transition. Such double n-$\pi^*$ Cotton
effects are observed at ca. 250 nm in saturated imides\textsuperscript{16} and result from the transitions involving combinations of the carbonyl n orbitals of opposite symmetry. This Cotton effect, however, is much smaller than the n-π* Cotton effect caused primarily by the α,β-unsaturated lactam chromophore.

![Diagram of 3-pyrrolin-2-ones]

Table 5.1 \textit{CD and UV data for chiral 3-pyrrolin-2-ones (in acetonitrile)}

<table>
<thead>
<tr>
<th>entry</th>
<th>compound</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>CD, Δγ (nm)/UV, γ (nm)</th>
<th>other CD bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (+)-5.5</td>
<td>Me Boc H</td>
<td>5300 sh (226)</td>
<td>9900 (205)</td>
<td>-0.8 (224)</td>
<td>+7.8 (200)</td>
<td>-</td>
</tr>
<tr>
<td>2 (+)-5.7</td>
<td>Me Boc MeO</td>
<td>12200 (228)</td>
<td>25300 (229)</td>
<td>-0.8 (251)</td>
<td>+2.8 (229)</td>
<td>-</td>
</tr>
<tr>
<td>3 (+)-5.10</td>
<td>AcO Me H</td>
<td>3400 sh (232)</td>
<td>-6 (250)</td>
<td>+25 (198)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4 (+)-5.13</td>
<td>EtCOO EtCO H</td>
<td>3600 sh (228)</td>
<td>10500 (203)</td>
<td>-5 (230)</td>
<td>+30.6 (206)</td>
<td>-0.6 (280)</td>
</tr>
<tr>
<td>5 (+)-5.14</td>
<td>AcO Ac H</td>
<td>3900 sh (228)</td>
<td>9600 (205)</td>
<td>-9.6 (230)</td>
<td>+28.1 (206)</td>
<td>-0.6 (280)</td>
</tr>
<tr>
<td>6 (-)-5.14</td>
<td>AcO Ac H</td>
<td>3600 sh (227)</td>
<td>10100 (203)</td>
<td>+9.7 (230)</td>
<td>-28.9 (205)</td>
<td>+0.9 (280)</td>
</tr>
<tr>
<td>7 (-)-5.17</td>
<td>AcO EtCO H</td>
<td>3400 sh (228)</td>
<td>9800 (203)</td>
<td>+9.0 (230)</td>
<td>-30.0 (206)</td>
<td>+0.6 (280)</td>
</tr>
<tr>
<td>8 (-)-5.18</td>
<td>EtCOO Ac H</td>
<td>3400 sh (228)</td>
<td>9500 (204)</td>
<td>+8.8 (230)</td>
<td>-31.0 (206)</td>
<td>+0.6 (280)</td>
</tr>
<tr>
<td>9 (-)-5.23</td>
<td>i-PrO Ac H</td>
<td>2000 sh (235)</td>
<td>2000 sh (235)</td>
<td>+6 (236)</td>
<td>-20 (212)</td>
<td>+1.0 (279)</td>
</tr>
<tr>
<td>10 (-)-5.24</td>
<td>i-PrO Ts H</td>
<td>12100 (229)</td>
<td></td>
<td>1.8 (271)</td>
<td>-6.0 (233)</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} No clear λ\textsubscript{max} down to 200 nm. \textsuperscript{b} Recorded in methanol solution.

The absolute configuration of chiral 3-pyrrolin-2-ones is readily determined from the sign of the Cotton effects associated with the α,β-unsaturated lactam chromophore (Figure 5.2). This is an extension of the configurational rule previously developed for α,β-unsaturated lactones (2(5H)-furanones).\textsuperscript{10} The extension is justified in view of the planarity of the α,β-unsaturated lactam ring, as demonstrated by the published X-ray data (vide infra),\textsuperscript{7a,17} and by
the isoelectronic nature of the unsaturated chromophore in 3-pyrrolin-2-ones and in 2(5H)-furanones.

The easiest assignment of absolute configuration is based on the sign of the $\pi-\pi^*$ Cotton effect (identified by the position of the $\text{UV}_{\text{max}}$): a positive $\pi-\pi^*$ Cotton effect arises from P-helicity of the C=C-C-R bond system whereas a negative $\pi-\pi^*$ Cotton effect reflects M-helicity of the same bond system. Although a detailed discussion of the observed relationship is not offered here, we note that coupling of the $\pi-\pi^*$ electric dipole transition moment of the planar (conjugated) chromophore with the $\sigma^*$ oscillator of the allylic carbon-carbon or carbon-heteroatom bond is a quite well-established mechanism of generating the rotational power.\(^{18}\) The observed Cotton effect associated with the n-$\pi^*$ transitions are opposite in sign compared to the $\pi-\pi^*$ transitions (Table 5.1, Figure 5.2).

\[
\begin{align*}
\text{P} & : n-\pi^* & \Delta \varepsilon < 0 \\
\text{M} & : \pi-\pi^* & \Delta \varepsilon > 0
\end{align*}
\]

**Figure 5.2** Correlation of the pyrrolinone Cotton effects with absolute configuration

Inspection of $[\alpha]_D$ data in the literature for chiral 3-pyrrolin-2-ones\(^{7,14,17,19}\) reveals that the sign of $[\alpha]_D$, with apparently no exception, corresponds to the sign of the $\pi-\pi^*$ \(\alpha,\beta\)-unsaturated lactam CD band: i.e. a positive $[\alpha]_D$ results from the contribution of the (strong) positive $\pi-\pi^*$ Cotton effect. The sign of rotation of 3-pyrrolin-2-ones can therefore be used for tentative assignment of its absolute configuration at C(5), but this assignment needs to be confirmed by the measurement of the CD spectrum.

### 5.4 Absolute Configuration by Chemical Correlation and X-ray Analysis

Compounds 5.5 and 5.7 were synthesized starting from enantiopure L-alanine and should therefore have the (S)-configuration. The synthesis of pyrrolinones 5.23 and 5.24 from enantiopure (S)-malic acid could only yield the (R)-enantiomer. This correlates with the absolute configuration of the iron tetracarbonyl complex of 5.24 recently reported by Hiemstra and co-workers.\(^{14}\) For compounds 5.10, 5.13, 5.14, 5.17, and 5.18 there is no chemical correlation because these compounds were synthesized from an achiral or racemic starting material. For compound 5.14 the absolute configuration was deduced from the crystal structure of the iron tetracarbonyl complex. The synthesis of this complex has been described above (Section 5.2). The crystal and molecular structure of 5.25b is shown in Figure 5.3. This establishes the trans-relative configuration of the complex as well as the (S)-absolute configuration at C(5). From the structure of this complex, the absolute configuration at C(5)
of (+) pyrrolinone 5.14 was unequivocally assigned to be S in accord with the assignment according to CD.

**Figure 5.3**  *ORTEP drawing (50% probability ellipsoids) of 5.25b*

### 5.5 Conclusions

By correlation of the signs of CD Cotton effects (Figure 5.2, Table 5.1) the absolute configurations of several pyrrolinones have been established. Since the results from chemical correlation or from X-ray crystal structure determination for a compound in each of the three classes of chiral pyrrolinones perfectly correlate with the absolute configurations determined by the sign of the Cotton effects for all studied pyrrolinones, we conclude that CD measurement is both a rapid and a reliable method to obtain the absolute configuration of chiral 3-pyrrolin-2-ones.

### 5.6 Experimental Section

**General information.** The CD spectra were recorded with a Jobin-Yvon Dichrograph III and the UV spectra were obtained on a Shimadzu UV 160 spectrophotometer. Pyrrolinones 5.10, 5.13, 5.14, 5.17, and 5.18\(^3\) were prepared as was described in Chapters 2 - 4. Pyrrolinones 5.23\(^7\) and 5.24\(^14\) were prepared by the group of Hiemstra\(^7a,14\) and 5.3 – 5.7 by the group of Gawronski.\(^3\) For other general remarks, see Chapter 2 and 3.
Determination of the Absolute Configuration of 3-Pyrrolin-2-ones

5(S)-N-tert-butoxycarbonyl-4-hydroxy-5-methyl-3-pyrrolin-2-one (5.3). Synthesized following the procedure of Jouin\(^2\)\(^a\), further improved by Ma\(^3b\). Compound 5.3 melts at 122-124°C; \([\alpha]_D^+77.8\) (c = 1, MeOH); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 1.51 (d, 3H, J = 6.9 Hz), 1.56 (s, 9H), 3.23 (m, 2H), 4.42 (dq, 1H, J = 6.9, 1.0 Hz), 5.00 (s, 1H); IR (KBr): 3419, 2976, 1718, 1678, 1568 cm\(^{-1}\).

5(S)-N-tert-butoxycarbonyl-4-hydroxy-5-methyl-3-pyrrolidine-2-one (5.4). The compound has m.p. 85-87°C; \([\alpha]_D^+48\) (c = 0.5, MeOH); \(^1\)H NMR (CDCl\(_3\), 300 MHz), major diastereomer: \(\delta\) 1.33 (d, 3H, J = 6.5 Hz), 1.53 (s, 9H), 2.24 (br, s, 1H), 2.58 (dd, 1H, J = 17.1, 8.9 Hz), 2.72 (dd, 1H, J = 17.1, 7.5 Hz), 4.25 (dq, 1H, J = 6.5, 6.5 Hz), 4.51 (dd, 1H, J ca. 7.5 Hz); IR (KBr): 3479, 2986, 2931, 1767, 1685 cm\(^{-1}\).

5(S)-N-tert-butoxycarbonyl-5-methyl-3-pyrrolin-2-one (5.5). The compound melts at 73-74°C; \([\alpha]_D^+145\) (c = 1, CHCl\(_3\)), (lit.\(^3b\) colorless oil, \([\alpha]_D^-9.6\), c = 1, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 1.44 (d, 3H, J = 6.7 Hz), 1.56 (s, 9H), 4.62 (dq, 1H, J = 6.7, 1.8 Hz), 6.07 (dd, 1H, J = 6.1, 1.8 Hz), 7.10 (dd, 1H, J = 6.1, 2.1 Hz); IR (KBr): 3076, 2985, 1765, 1688 cm\(^{-1}\).

5(S)-N-tert-butoxycarbonyl-4-methoxy-5-methyl-3-pyrrolin-2-one (5.6). Oil; \([\alpha]_D^+13.3\) (c = 1, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 300 MHz): 1.47 (d, 3H, J = 6.6 Hz), 1.54 (s, 9H), 3.83 (s, 3H), 4.38 (q, 1H, J = 6.6 Hz), 5.03 (s, 1H); IR (neat): 2960, 2873, 1729, cm\(^{-1}\).

5(S)-N-tert-butoxycarbonyl-2-methoxy-5-methyl-2-pyrrolin-4-one (5.7). The compound melts at 62-64°C; \([\alpha]_D^-12.7\) (c = 0.5, CHCl\(_3\)); \(^1\)H NMR (CDCl\(_3\), 300 MHz): 1.49 (d, 3H, J = 6.9 Hz), 1.53 (s, 9H), 4.02 (s, 3H), 4.09 (q, 1H, J = 6.9 Hz); 4.86 (s, 1H); IR (KBr): 2932, 2860, 1778, 1630 cm\(^{-1}\).

[5(S)-Acetic acid 1-acetyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl ester] tetracarbonyl iron (5.25). To a suspension of (+)-5.14 (1.00 g, 5.46 mmol) in diethylether (60 mL) was added Fe\(_2\)(CO)\(_9\) (4.00 g, 11.00 mmol) and the reaction mixture was stirred at room temperature for 20 h. The mixture was filtered over Celite (under an Ar atmosphere, using a connecting filter) and was washed with 20 mL of diethylether. The dark green solution was concentrated in vacuo, using a rotary evaporator equipped with a nitrogen inlet. The crude product was purified using flash chromatography under nitrogen pressure (pet.
ether/CH$_2$Cl$_2$/EtOAc 5:5:2). Dry degassed solvents and silica were used and fractions were stored under argon. Pure crystalline 5.25b, 0.363 g (1.03 mmol, 19%, $R_f$ 0.45) was obtained and recrystallized from pentane to provide light yellow prisms, mp 100°C (dec); $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 2.12 (s, 3H), 2.43 (s, 3H), 3.68 (d, $J = 5.4$ Hz, 1H), 3.87 (d, $J = 5.1$ Hz, 1H), 6.78 (s, 1H). $^{13}$C NMR (CDCl$_3$, 50.32 MHz): $\delta$ 20.9 (q), 24.6 (q), 43.6 (d), 51.2 (d), 84.2 (d), 205.7 (s). Anal. calcd for C$_{12}$H$_9$NO$_8$Fe: C 41.06, H 2.58, N 3.99, Fe 15.91, found: C 41.25, H 2.60, N 4.01, Fe 15.70. A mixture of 5.25b and 5.25a (0.667 g, 1.90 mmol, 35%) was obtained as a yellow solid and a mixture of 0.382 g 5.25a and 5.14 (6:4 ratio) was obtained as a light brown solid. For 5.25a: $^1$H NMR (CDCl$_3$): $\delta$ 2.11 (s, 3H), 2.41 (s, 3H), 3.89 (d, $J = 5.6$ Hz, 1H), 4.26 (dd, $J = 5.1$ Hz, 1H), 6.89 (d, $J = 4.6$ Hz, 1H).

Crystal data for 5.25b. C$_{12}$H$_9$NO$_8$Fe, orthorhombic, space group P2$_1$2$_1$2$_1$, $a = 7.2818$ (11), $b = 10.0953$ (14), $c = 19.1003$ (17)Å, $V = 1404.1$ (3)Å$^3$, $Z = 4$, MoK$_\alpha$, $\lambda = 0.71073$ Å, $\mu = 1.1$ mm$^{-1}$. X-ray data were collected on an Enraf-Nonius CAD4T diffractometer (Rotating Anode, Graphite Monochromator, $T = 150$ K, $\Theta_{\text{max}} = 27.5$E). The structure was solved with Patterson techniques using DIRDIF96 and refined by full matrix least-squares on $F^2$ using SHELXL97 (1918 reflections and 218 parameters). A final difference map showed no significant residual density. Hydrogen atoms of the methyl moieties were refined as rigid rotators riding on their carrier atoms. All other H-atoms were located from a difference map and their positions refined. Convergence was reached at $R = 0.0365$ for 1918 reflections with $I > 2\sigma(I)$ [$wR_2 = 0.0890$, $S = 1.04$]. The Flack parameter converged to 0.00 (3) for the absolute configuration shown in Figure 5.3. For full details see the supplementary material of the published article.\textsuperscript{1,20}

### 5.7 References

Determination of the Absolute Configuration of 3-Pyrrolin-2-ones

20 This material is available free of charge via the Internet at http://pubs.acs.org.