Holzapfel–Meyers–Nicolaou Modification of the Hantzsch Thiazole Synthesis

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Abstract: Modified conditions for Hantzsch thiazole synthesis provides valine- and threonine-derived thiazoles without significant loss of optical purity. This two- or three-step procedure proceeds by the cyclocondensation of the corresponding thioamide under basic conditions, according to modified methods of Meyers and Holzapfel. The hydroxythiazoline intermediate is then dehydrated by treatment with trifluoroacetic anhydride–pyridine, followed by triethylamine, according to Nicolaou’s procedure. Solvolysis of the trifluoroacetamide derivative produced in this process can be affected with sodium ethoxide in ethanol to give a reliable method for the stereoselective synthesis of functionalised thiazole building blocks in high yield.

Key words: Hantzsch, thiazoles, heterocycles, amino acids

Amino acid derived thiazoles are a common motif in many families of biologically active natural products such as the thiopeptide antibiotics (1 and 2, Figure 1),1 patellamides such as 3,2 and nostocyclamide (4).3 The successful total synthesis of such natural products is dependent upon the ability to prepare amino acid derived thiazoles in high yield and enantiomeric purity. The Hantzsch synthesis of thiazoles by reaction of an amino acid derived thioamide with an α-bromocarbonyl compound at reflux in ethanol is known to result in epimerisation at the α-stereogenic centre as a result of the concomitant formation of one equivalent of hydrogen bromide (Scheme 1).

Figure 1 Thiopeptide antibiotics and other heterocyclic natural products containing amino acid derived thiazoles
Recent years have seen a number of attempts to adapt the Hantzsch thiazole synthesis for use with substrates prone to racemisation. In 1990, Holzapfel et al. reported a modification of the standard reaction conditions and successfully prepared amino acid derived thiazoles in high enantiomeric purity by using a lower reaction temperature and basic reaction conditions. A key feature of the modified Hantzsch thiazole synthesis is the formation of the hydroxythiazoline intermediate and addition of reagents to activate, facilitating the necessary elimination to furnish thiazole 7 (Scheme 2). Further studies by Meyers et al. examined the effect of using different reagents to eliminate the intermediate hydroxythiazoline to form the desired thiazole product. The reaction was conducted at \(-40^\circ C\) to \(-20^\circ C\) and the experimental procedure differed significantly from the Holzapfel method in the isolation of 6 and removal of the heterogeneous base prior to the elimination step. These conditions have been successfully utilized in the landmark synthesis of several heterocyclic natural products and their analogues in recent years, including nostocyclamide, the promothiocins, and the \textit{Lissoclinum} cyclic peptides and more recently, GE2270A. However, it is apparent from a study by Pattenden et al. that whilst these modified Hantzsch procedures constitute an extremely valuable route to optically pure thiazoles, the conditions of Meyers can prove to be problematic, in particular when larger quantities of products are required.

![Scheme 2 Formation of valine-derived thiazoles 7 and 8](image)

Valine-derived thiazole 7 was a key building block in our synthetic efforts towards micrococcin P1 (1) and so, with a number of different literature procedures available to effect the desired transformation, an investigation into the most reliable method for its synthesis was undertaken. To this end, thiovalinamide 5 was prepared according to established methods and submitted, in turn, to the reported conditions for modified Hantzsch thiazole synthesis, examining in each case the yield and optical purity of the product 7 (Scheme 2, Table 1). The acidic reaction conditions of the traditional Hantzsch reaction (entry 1) were clearly inappropriate for substrate 5, whereas the Holzapfel (entry 2) and Meyers (entries 3 and 4) modifications did provide the product 7, but either in low yield on a small scale (entries 2 and 3) or compromised optical purity (entry 4) when 1.0 g of 5 was used. These findings are in agreement with Pattenden’s previous observations. Nicolau’s modified conditions (entry 5), whilst not being investigated previously for the synthesis of 7, did deliver the product, but without complete stereocontrol and only after solvolysis of the trifluoroacetamide 8, which was the sole product of this procedure.

As the three methods given in Table 1 failed to provide a satisfactory and reproducible route to thiazole 7 both in terms of yield and enantiomeric excess, it was decided that further modifications to the reaction conditions should be investigated. The Meyers and Nicolau conditions were the main focus of these subsequent studies. Modification of Nicolau’s conditions by changing the base used for dehydration of intermediate 6, led to the iso-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Quantity of 5 (g)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Reagents</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hantzsch</td>
<td>0.050</td>
<td>EtOH</td>
<td>reflux</td>
<td>–</td>
<td>reflux</td>
<td>–</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Holzapfel</td>
<td>0.050</td>
<td>DME</td>
<td>0</td>
<td>KHCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0</td>
<td>TFAA, 2,6-Lu</td>
<td>33</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>Meyers</td>
<td>1.0</td>
<td>DME</td>
<td>–40 to –20</td>
<td>KHCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>–40 to –20</td>
<td>TFAA, 2,6-Lu</td>
<td>9</td>
<td>&gt;98</td>
</tr>
<tr>
<td>4</td>
<td>Meyers</td>
<td>0.050</td>
<td>DME</td>
<td>–40 to –20</td>
<td>KHCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>–40 to –20</td>
<td>TFAA, 2,6-Lu</td>
<td>59</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>Nicolau</td>
<td>0.3</td>
<td>DME</td>
<td>r.t.</td>
<td>NaHCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0</td>
<td>TFAA, py, Et,N</td>
<td>85&lt;sup&gt;a&lt;/sup&gt;</td>
<td>88&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>The ee values were determined by HPLC on a chiral stationary phase, using a ChiralPac AD column, flow rate 1 mL min<sup>−1</sup>; t-PrOH:hexane, 5:95; detected at 269 nm.

<sup>b</sup>No product was isolated, probably as a consequence of HBr-catalysed Boc deprotection and subsequent loss of the product during work-up and purification.

<sup>c</sup>Only 8 was isolated; ee value was determined following subsequent solvolysis to 7.
loration of a 1:4 mixture of the desired product 7 and the N-
trifluoroacetyl derivative 8 (Table 2, entry 1), both in 91% ee. The Meyers modification of the Hantzsch thiazole synthesis was then performed at –18 °C rather than –40 °C, and resulted in a dramatic increase in yield from 59% to 97% but curiously delivered the trifluoroacet-
trifluoroacetyl derivative

With a method in hand for the synthesis of chiral thiazoles in excellent yield and enantiomeric purity, the reagents used to dehydrate the intermediate hydroxythiazoline 6 were varied in order to circumvent the formation of racemisation in the Hantzsch thiazole synthesis occurs in the elimination step of the procedure. Addition of methanesulfonyl chloride and triethylamine to 6 at room temperature, gave hydroxythiazoline 6, which was then treated with methanesulfonyl chloride and triethylamine as described in Table 3. It is worthy of note that thiazole 7 can be prepared as a single enantiomer following dehydration, even when 6 is prepared at room temperature. This finding demonstrates that, under basic conditions, racemisation in the Hantzsch thiazole synthesis occurs in the elimination step of the procedure. Addition of methanesulfonyl chloride and triethylamine to 6 at room temperature and stirring for one hour, afforded 7 in 70% yield and 38% ee (entry 1). The probable cause of the observed racemisation was the exothermic reaction, which occurred on addition of methanesulfonyl chloride and triethyl-

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>DME</td>
<td>r.t.</td>
<td>NaHCO₃</td>
<td>TFAA, 2,6-Lu, Et₃N</td>
<td>88ᵇ</td>
</tr>
<tr>
<td>2</td>
<td>DME</td>
<td>–18</td>
<td>KHCO₃</td>
<td>TFAA, 2,6-Lu</td>
<td>97ᶜ</td>
</tr>
</tbody>
</table>

* The ee values were determined by HPLC. See Table 1 footnote a, for conditions.
* Isolated 7 (18% yield, 91% ee) and 8 (70% yield, 91% ee); the ee value for 8 was determined following subsequent solvolysis to 7.
* Only 8 was isolated; the ee value was determined following subsequent solvolysis to 7.

Scheme 3 Reagents and conditions: (i) ethyl bromopyruvate, KHCO₃, DME, r.t., 2 h; (ii) See Table 3.

Table 3 Reaction Conditions for the Methanesulfonyl Chloride–Triethylamine Mediated Synthesis of Thiazole 7 from Hydroxythiazoline 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>MsCl (equiv)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Work-up</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>r.t.</td>
<td>1</td>
<td>no</td>
<td>70</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>0–r.t.</td>
<td>2</td>
<td>no</td>
<td>33</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>1.1</td>
<td>0–r.t.</td>
<td>2</td>
<td>yes</td>
<td>15</td>
<td>&gt;98</td>
</tr>
<tr>
<td>4</td>
<td>1.1</td>
<td>0–r.t.</td>
<td>48</td>
<td>no</td>
<td>21</td>
<td>&gt;98</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>0</td>
<td>3.5</td>
<td>no</td>
<td>35</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>0–r.t.</td>
<td>60</td>
<td>no</td>
<td>28</td>
<td>&gt;98</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>r.t.</td>
<td>2+1</td>
<td>no</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>r.t.</td>
<td>2+1</td>
<td>no</td>
<td>68</td>
<td>36</td>
</tr>
<tr>
<td>9ᵇ</td>
<td>10</td>
<td>–½</td>
<td>0.5</td>
<td>no</td>
<td>68</td>
<td>12</td>
</tr>
<tr>
<td>10ᵇ</td>
<td>10</td>
<td>–½</td>
<td>0.5</td>
<td>no</td>
<td>26</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

* Reaction conducted using a CEM Discover® Coolmate apparatus, with concurrent irradiation and cooling.
* Reaction conducted under thermal conditions.

of methanesulfonyl chloride and prolonged reaction times (60 h, entry 6), afforded a slight improvement in yield over those described in entry 4. Addition of five equivalents of methanesulfonyl chloride, stirring for two hours, then addition of triethylamine resulted in a poor yield and low optical purity (entry 7); increasing to 10 equivalents methanesulfonyl chloride, gave a moderate yield of 7, also with low optical purity. Having limited success with improving the yield of the reaction by increasing the reaction time, the effect of microwave irradiation at low temperature with concurrent heating and cooling was investigated. Hydroxythiazoline 6 was formed by irradiation of a mixture of 5, ethyl bromopyruvate and potassium hydrogen carbonate in 1,2-dimethoxyethane (DME) for 20 min-
utes at −20 °C with an initial power of 300 W, using a CEM Discover® CoolMate Sub-Ambient microwave synthesizer. The mixture was then treated as shown in Table 3 (entry 9). Irradiation at −1 °C for 30 minutes, afforded thiazole 7 in 68% yield, however, the enantiomeric excess was only 12%. Finally, the CoolMate reaction was repeated under thermal conditions (entry 10) and furnished 7 as a single enantiomer in 26% yield. As no suitable method for the synthesis of enantiopure thiazoles in high yield had been discovered, the reaction was attempted using p-toluenesulfonyl chloride as the activating agent. However, no thiazole was formed under any of the conditions investigated. Reactions utilizing triflic anhydride also failed due to polymerisation of the solvent. On the basis of these findings it was concluded that the most efficient route to enantiopure valine-derived thiazole 7 was via trifluoroacetamide 8, using the conditions shown in Table 2, entry 2.

During our work towards the synthesis of the central heterocyclic domain of micrococcin P1 (2), it was necessary to prepare threonine-derived thiazole 13 (Scheme 4). The formation of 13 from thioamide 12 was investigated under a range of conditions (Table 4). Meyers’ original conditions failed to give the desired product (entry 1); the methanesulfonyl chloride–triethylamine conditions furnished 13 in only 21% yield (entry 2). Nicolaou’s original conditions afforded thiazole 13 as a single diastereoisomer in good yield (entry 3). The lack of a free NH in thiazole 13 eliminates the possibility of formation of an N-trifluoroacetyl derivative, as observed in the valine example (Scheme 2), making Nicolaou’s reaction conditions particularly useful for such substrates and our adopted method of choice.

### Table 4 Synthesis of Thiazole 13 from Thioamide 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Meyers</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>MeCl₂–Et₃N</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>Nicolaou</td>
<td>74</td>
</tr>
</tbody>
</table>

Reagents and conditions: Ethyl bromopyruvate, NaHCO₃, DME, r.t., 24 h; then MeCl₂ (10 equiv, r.t., 16 h), Et₃N (r.t., 4 h).

In conclusion, a range of conditions have been investigated for the conversion of amino acid derived thioamides into thiazoles without racemisation. While previously reported conditions for this transformation have been found to be unreliable, modifications to the temperature and reagents used have provided insight into the causes of racemisation in the Hantzsch thiazole synthesis and enabled the preparation of chiral thiazole building blocks with complete stereocontrol and in excellent yield.

Commercially available reagents were used without further purification; solvents were dried by standard procedures. Petroleum ether (PE), where used, had a boiling range of 40–60 °C. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Meratex silica 60. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF₂₅₄, that were visualised under UV light (at 254 and/or 360 nm). Melting points (mp) were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded in CHCl₃ for solid samples or as a thin film between NaCl plates for liquid samples, in the range 4000–600 cm⁻¹ on a Perkin–Elmer 1600 series FTIR spectrometer and are reported in cm⁻¹. ¹H NMR spectra were recorded at 400 MHz in CDCl₃ at 25 °C, unless otherwise stated, using a Bruker DPX 400, Bruker DRX 500 or Bruker Avance 250 instrument and are reported in ppm. In vacuo refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

### (5)-N-tert-(Butoxycarbonyl)valinamide

To a stirred solution of N-Boc-(5)-valine (3.00 g, 13.81 mmol) and Et₃N (1.94 mL, 1.41 g, 13.94 mmol, 1.01 equiv) in anhydrous THF (120 mL) at 0 °C, was added ethyl chloroformate (1.33 mL, 1.51 g, 13.94 mmol, 1.01 equiv) and the mixture stirred for 1 h. Aqueous NH₂SO₄ (35%, 10 mL) was added and the solution was allowed to warm to r.t. and stirred for 1 h. The organic solvent was removed in vacuo and the resulting aqueous solution was diluted with H₂O (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed sequentially with sat. aq NaHCO₃ (50 mL), citric acid (1 M, 50 mL), brine (50 mL), dried (Na₂SO₄) and evaporated in vacuo to yield the title compound.

Yield: 2.83 g (95%); colourless solid; mp 159–161 °C (EtOAc) (Lit.¹ 160–161 °C); [α]D₂⁰ 17.0 (c 1.00, MeOH) (Lit.17 ± 7.7 (c 1.33, DME)).

HRMS: m/z [M + H⁺] calcd for C₁₀H₁₄N₂O₂: 217.1547; found: 217.1546.

IR (CHCl₃): 3385, 3342, 3191, 2921, 1681, 1657, 1519, 1461, 1377, 1245, 1170, 1044, 899, 878, 775, 722 cm⁻¹.

¹H NMR (250 MHz, CDCl₃): δ = 6.05 (1 H, br s, exch. D₂O, NH), 5.72 (1 H, br s, exch. D₂O, NH), 5.05 (1 H, br d, exch. D₂O, NH), 3.90 (1 H, dd, J = 7.9, 7.9 Hz, o-CH), 2.08 (1 H, m, (CH₃)₂CH), 1.38 (9 H, s, (CH₃)₃), 0.92 (3 H, d, J = 6.8 Hz, CH₂(CH₃)₂), 0.88 (3 H, d, J = 6.8 Hz, CH₂(CH₃)₂).

¹C NMR (100 MHz, CDCl₃): δ = 175.0 (C), 156.1 (C), 80.1 (C), 59.4 (CH), 30.8 (CH), 28.3 (CH₃), 19.3 (CH₃), 17.8 (CH₄).

MS (APCI): m/z (%): 217 (90) [M + H⁺], 161 (100), 151 (15), 149 (57), 139 (10), 129 (22).

### (5)-N-tert-(Butoxycarbonyl)thiovalinamide (5)

(5)-N-tert-(Butoxycarbonyl)valinamide (2.00 g, 9.25 mmol, 1 equiv) was dissolved in anhydrous CH₂Cl₂ (120 mL). Lawesson’s reagent (1.87 g, 4.62 mmol, 0.5 equiv) was added and the resulting solution was heated at reflux for 16 h. The solvent was evaporated...
in vacuo and the residue was dissolved in EtOAc (100 mL) and washed with sat. aq NaHCO3 (100 mL). The organic layer was dried (Na2SO4) and evaporated in vacuo and the residue was purified by column chromatography (PE–Et2O, 3:7) to give the title compound.

Yield: 1.33 g (62%); yellow foam; mp 84–85 °C (PE–Et2O) (Lit.13 112–113 °C); [α]D23 +46.7 ([c 0.3, CHCl3]) [Lit.13 +45.5 ([c 0.7, CHCl3])]; Rf = 0.30 (PE–Et2O, 3:7).

HRMS: m/z [M + H+] calcd for C10H23N2O4S: 313.1319; found: 313.1319.

2. Ethyl 2-[(tert-butoxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylate (7); Meyers Method4b

KHO3 (1.72 g, 17.2 mmol, 4 equiv) was added to a solution of (S)-N-(tert-butoxycarbonyl)thiazol-4-amine (1.00 g, 4.3 mmol) in anhydrous DME (10 mL) and the solution was stirred at –18 °C. A solution of TFAA (125 μL, 0.89 mmol, 4 equiv) and 2,6-lutidine (3.09 mL, 2.84 g, 26.50 mmol, 9 equiv) in anhydrous DME (4 mL) was added and the reaction mixture was stirred at –18 °C for 30 min. The solvent was evaporated in vacuo and the residue was dissolved in CHCl3 (20 mL) and washed with H2O (20 mL). The aqueous layer was further extracted with CHCl3 (20 mL) and the combined organic extracts were washed with H2O (20 mL) and brine (20 mL), dried (Na2SO4) and evaporated in vacuo. Purification of the residue by column chromatography (PE–EtOAc, 3:1) afforded the title compound.

Yield: 1.21 g (97%); yellow oil; Rf = 0.30 (PE–EtOAc, 3:1).

HRMS: m/z [M + H+] calcd for C17H26N2O4S: 345.1361; found: 345.1361.

IR (CH2Cl2): 3300, 2922, 2853, 1713, 1649, 1508, 1369, 1207, 1168, 1097, 1017 cm–1.

1H NMR (400 MHz, CDCl3): δ = 8.02 (1 H, s, 5-H), 5.39 (1 H, d, J = 10.9 Hz, CH2CH3), 4.34 (2 H, q, J = 7.1 Hz, OCH2CH3), 2.78 [1 H, m, (CH3)2CH], 1.43 [9 H, s, C(CH3)3], 1.31 [3 H, t, J = 7.1 Hz, OCH2CH2], 0.95 (3 H, d, J = 6.6 Hz, CH2CH3CH), 0.92 (3 H, d, J = 6.6 Hz, CH2CH2CH). 13C NMR (125 MHz, CDCl3): δ = 173.2 (C), 161.4 (C), 155.2 (C), 147.4 (C), 126.8 (CH), 68.9 (CH), 61.4 (CH), 58.0 (CH), 33.3 (CH), 28.3 (CH), 27.4 (CH), 19.4 (CH), 14.4 (CH). Signals for F3C and F3COCO not observed.

MS (ES+): m/z (%) = 425 (3) [M+H], 325 (58), 273 (100), 196 (30), 180 (8).

(5)-Ethyl 2-[(tert-butoxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylate (8) (5)-Ethyl 2-[(tert-butoxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylate (700 mg, 1.65 mmol) was dissolved in EtOH (16.5 mL) and EtOAc (0.336 mg, 4.95 mmol, 3 equiv) was added. The solution was stirred at r.t. for 4 h then evaporated in vacuo. The residue was partitioned between EtOAc (20 mL) and H2O (20 mL) and the aqueous layer was further extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (Na2SO4) and evaporated in vacuo. Trituration of the residue with PE afforded the product.

Yield: 440 mg (81%); colourless solid; ee >98%.

(5)-Ethyl 2-[(tert-butoxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylate (8); Nicolaou Method7

NaHCO3, (868 mg, 10.33 mmol, 8 equiv) was added to a solution of (S)-tert-butyl 1-amino-3-methyl-1-thioxobutan-2-ylcarbamate (300

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mg, 1.29 mmol) in anhydrous DME (15 mL). Ethyl bromopyruvate
(0.49 mL, 755 mg, 3.87 mmol, 3 equiv) was added and the solution
was stirred at rt for 16 h. The mixture was evaporated in vacuo and
the residue was partitioned between H2O (30 mL) and Et2O (15 mL).
The aqueous layer was further extracted with Et2O (15 mL) and
the combined organic extracts were washed with brine (15 mL),
dried (Na2SO4) and evaporated in vacuo. The residue was dissolved
in anhydrous DME (15 mL) and cooled to 0 °C. Pyridine (0.94 mL,
919 mg, 11.61 mmol, 9 equiv) was added slowly, followed by drop-
wise addition of TFAA (0.73 mL, 1.09 g, 5.16 mmol, 4 equiv), and
the solution was stirred at 0 °C for 2 h. Et3N (0.36 mL, 261 mg, 2.58
mmol, 2 equiv) was added and the reaction mixture was warmed to
rt. and evaporated in vacuo. The residue was dissolved in CHCl3
(20 mL), washed with H2O (20 mL) and brine (10 mL), dried
(Na2SO4) and evaporated in vacuo. Purification of the residue by
column chromatography (PE–EtOAc, 3:1) afforded the title com-
ound.
Yield: 467 mg (85%); yellow oil; ee 88% after conversion into (S)-
ethyl 2-[1-tert-butoxycarbonylaminol)-2-methylpropylthiazole-4-
carboxylic acid (7) by the method outlined above.

(4S,SR)-3-(tert-Butyloxycarbonyl)-2,2,5-trimethyloxazolidine-4-carboxylic Acid (9)
N-Boc-3-oxo-threonine (7.50 g, 34.2 mmol) was dissolved in THF
(200 mL) and 2,2-dimethoxypropane (42.07 mL, 35.64 g, 342.2 mmol,
10 equiv) and PPTS (2.58 g, 10.3 mmol, 0.3 equiv) was added. The
solution was heated at reflux for 16 h then allowed to cool and evap-
orated in vacuo. The residue was partitioned between EtOAc (200
mL) and 2,2-dimethoxypropane (42.07 mL, 35.64 g, 342.2 mmol,
10 equiv) and the resulting aqueous solution was extracted with
EtOAc (200 mL) and H2O (200 mL), and the aqueous layer was fur-
ther extracted with EtOAc (200 mL). The combined organic extracts
were washed with brine (100 mL), dried (Na2SO4) and evaporated in vac-
uo to give the title compound.
Yield: 8.81 g (99%); off-white solid; mp 91–92 °C (CHCl3); [α]D22
−60.0 (c 1.00, CHCl3).
HRMS: m/z [M + H+] calcld for C12H22NO5: 260.1492; found:
260.1491.

(4S,SR)-3-tert-Butyl 4-Cyano-2,2,5-trimethyloxazolidine-3-carboxylic Acid (11)
(4S,SR)-tert-Butyl 4-carbamoyl-2,2,5-trimethyloxazolidine-3-carboxylic acid
(6.70 g, 25.9 mmol) was dissolved in pyridine (150 mL) and
the solution was cooled to 0 °C. Phosphorus oxychloride (6.04
mL, 9.94 g, 64.9 mmol, 2.5 equiv) was added and the solution
was stirred at 0 °C for 3 h. The mixture was poured over ice then diluted
with H2O (150 mL) and extracted with EtOAc (3 × 100 mL). The
combined organic extracts were washed sequentially with HCl (2
M, 150 mL), H2O (3 × 150 mL) and brine (100 mL), dried (Na2SO4)
and evaporated in vacuo to afford the title compound.
Yield: 4.88 g (78%); colourless solid; mp 44–47 °C (CHCl3); [α]D22
−69.4 (c 1.00, CHCl3).
HRMS: m/z [M + H+] calcld for C12H23N2O5S: 275.1424; found:
275.1417.

(4S,SR)-tert-Butyl 4-Carbamothioyl-2,2,5-trimethyloxazolidine-3-carboxylic Acid (12)
(4S,SR)-tert-Butyl 4-cyano-2,2,5-trimethyloxazolidine-3-carboxylic acid
(6.70 g, 25.9 mmol) was dissolved in pyridine (150 mL) and
the solution was cooled to 0 °C. Phosphorus oxychloride (6.04
mL, 9.94 g, 64.9 mmol, 2.5 equiv) was added and the solution
was stirred at 0 °C for 3 h. The mixture was poured over ice then diluted
with H2O (150 mL) and extracted with EtOAc (3 × 100 mL). The
combined organic extracts were washed sequentially with HCl (2
M, 150 mL), H2O (3 × 150 mL) and brine (100 mL), dried (Na2SO4)
and evaporated in vacuo to afford the title compound.
Yield: 4.88 g (78%); colourless solid; mp 44–47 °C (CHCl3); [α]D22
−69.4 (c 1.00, CHCl3).
HRMS: m/z [M + H+] calcld for C12H23N2O4S: 259.1654; found:
259.1654.

(4S,SR)-tert-Butyl 4-Carboxamoyl-2,2,5-trimethyloxazolidine-3-carboxylic Acid (10)
To a stirred solution of (4S,SR)-3-(tert-butoxycarbonyl)-2,2,5-tri-
methyloxazolidine-4-carboxylic acid (8.80 g, 33.9 mmol) and Et3N
(4.97 mL, 3.61 g, 35.63 mmol, 1.05 equiv) in anhydrous THF (200
mL) at 0 °C was added ethyl chloroformate (3.41 mL, 3.87 g, 35.63
mmol, 1.05 equiv) and the mixture stirred for 1 h. Aqueous NH3
(0.49 mL, 755 mg, 3.87 mmol, 3 equiv) was added and the solution
was allowed to warm to rt. and stirred for 24 h. The solution
was evaporated in vacuo and the resulting aqueous solution was extracted with
EtOAc (3 × 100 mL). The combined organic extracts were washed sequen-
tially with H2O (100 mL) and brine (100 mL), dried (Na2SO4) and
evaporated in vacuo to yield the title compound.
Yield: 5.40 g (99%); pale-yellow solid; mp 106–108 °C (EtOAc);
[α]D22 −8.2 (c 1.00, CHCl3) [Lit.7 –9.8 (c 0.19, CHCl3)].
HRMS: m/z [M + H+] calcld for C12H23N2O4S: 275.1424; found:
275.1424.

IR (CHCl3): 3197, 3067, 2925, 1762, 1619, 1434, 1368, 1265, 1139, 1090, 978, 940, 855, 736 cm–1.
HRMS: m/z [M + H+] calcld for C12H23N2O4: 259.1652; found:
259.1654.
13C NMR (100 MHz, CDCl3): δ = 205.6 (C), 152.2 (C), 125.5 (CH), 94.8 (C), 81.6 (C), 73.9 (CH), 30.3 (CH3), 28.3 (CH3), 26.2 (CH3), 19.2 (CH3).

MS (ES+): m/z (%) = 297 (7) [M + Na+], 219 (12), 161 (100), 133 (27), 116 (40).

(4S,5R)-tert-Butyl 4-[4-(Ethoxycarbonyl)thiazol-2-yl]-2,2,5-trimethyloxazolidine-3-carboxylate (13)

NaHCO3 (13.23 g, 157.4 mmol, 8 equiv) was added to a solution of (4S,5R)-tert-butyl 4-carboxamido-2,2,5-trimethyloxazolidine-3-carboxylate (5.40 g, 19.7 mmol) in anhydrous DME (100 mL). Ethyl bromopyruvate (7.41 mL, 11.51 g, 59.0 mmol, 3 equiv) was added and the reaction mixture was stirred at 0 °C for 2 h. Et3N (5.49 mL, 3.98 g, 39.4 mmol, 2 equiv) and pyridine (14.32 mL, 14.01 g, 177.1 mmol, 9 equiv) were added slowly, followed by dropwise addition of TFAA (11.13 mL, 16.56 g, 78.7 mmol, 4 equiv) to the mixture and the solution was warmed to r.t. and evaporated in vacuo. The residue was dissolved in CHCl3 (200 mL) and E2O (100 mL). The aqueous layer was further extracted with E2O (100 mL) and the combined organic extracts were washed with brine (100 mL), dried (Na2SO4) and evaporated in vacuo. The residue was dissolved in CHCl3 (200 mL) and Et2O (100 mL), and the combined organic extracts were washed with brine (100 mL), dried (Na2SO4) and evaporated in vacuo. The residue was dissolved in anhydrous DME (100 mL) and the solution was cooled to 0 °C. Pyridine (14.32 mL, 14.01 g, 177.1 mmol, 9 equiv) was added slowly, followed by dropwise addition of TFAA (11.13 mL, 16.56 g, 78.7 mmol, 4 equiv) and the solution was stirred at 0 °C for 2 h. Et3N (5.49 mL, 3.98 g, 39.4 mmol, 2 equiv) was added and the reaction mixture was warmed to r.t. and evaporated in vacuo. The residue was dissolved in CHCl3 (200 mL), washed with H2O (200 mL) and brine (100 mL), dried (Na2SO4) and evaporated in vacuo. Purification of the residue by column chromatography (PE–EtOAc, 3:1) afforded the title compound. Yield: 5.37 g (74%); off-white solid; mp 97–100 °C (PE–EtOAc); [α]D 25 (c 1.00, CHC13) [Lit.7 –51.0 (c 0.33, CHCl3)].


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