SYNTHESIS OF METHYL 2-(1',1'-DIMETHYL-2'-OXOPROPYL)THIAZOLE-4-CARBOXYLATE AND RELATED 2,4-DISUBSTITUTED THIAZOLES. KEY INTERMEDIATES IN THE SYNTHESIS OF ANTHelmINTIC AGENTS BASED ON MARINE NATURAL PRODUCT

Gloria Serra, Graciela Mahler, and Eduardo Manta*
Cátedra de Química Farmacéutica, Facultad de Química, Universidad de la República. Av. General Flores 2124. C.C. 1157, 11800 Montevideo, Uruguay

Abstract - Two methodologies, cyclodehydration of amides with TiCl₄ and cyclodehydration of β-hydroxy thioamides with PEG linked Burgess reagent were used in order to obtain 2,4-disubstituted thiazole rings (2) and (3) respectively. The scope and limitations of both methods were compared and contrasted.

In recent years, a wide range of novel 2,4-disubstituted thiazoline- and thiazole-containing secondary metabolites with interesting biological activity have been isolated and characterised from marine sources.¹ These compounds include the potent anthelmintic agent micothiazole (1),² the citotoxins patellazoles A-C³ and pateamine,⁴ and the antimitotic agent curacin A.⁵ Their structural features appear to be a consequence of a mixed biosynthetic origin, when a condensation between two polyketides residues and a cysteine derivative takes place.⁶

As part of our ongoing search of new compounds with anthelmintic activity,⁷ we are very interested to build simplified models of thiazolic structures like 1 for biological evaluation. In this sense we need a reliable and reproducible pathway for the synthesis of thiazoles (2), (3) and (15), which are suitably substituted for further elaboration to advanced precursors of new anthelmintic compounds. According to these goals, compounds (2), (3) and (15) are synthetic equivalents.

In the first approach, the compound (2) was synthesised from L-cysteine ethyl ester hydrochloride using
cyclodehydration of cysteine-amide derivatives with TiCl₄ and further oxidation of the resulting thiazoline (5) with activated MnO₂ to obtain the corresponding thiazole (Scheme 1).

L-Cysteine ethyl ester hydrochloride was converted to its S-benzyl derivative under standard benzylolation conditions. S-Benzyl-L-cysteine ethyl ester was condensed with 2,2-dimethylacetoacetic acid in CH₂Cl₂ at 0 °C using DCC and HOBT as condensing agents to afford amide (4) in 70 % yield. When 4 was treated with sodium in liquid ammonia at -78 °C, cleavage of thioether with concomitant reduction of ketone and ester groups to the corresponding diol took place. The diol obtained was directly submitted to cyclodehydration without further purification by refluxing it with solution of TiCl₄ in CH₂Cl₂, to give thiazoline (5) in 50% overall yield. Finally, 5 was oxidated to the thiazole (2) (60% yield) using activated MnO₂.

Even though the above synthetic sequence provides a concise route to the formation of thiazole (2), with yields according to those previously reported in the literature, when we intended to apply for multigram syntheses
significant deterioration in yield resulted. This is observed mainly in the cyclodehydration step, with yields ranging from 10 to 20% for multigram syntheses.

Thus, our efforts were directed towards the development of a synthetic route suitable to the preparation of multigram quantities of thiazoles like 2, 3 and 15.

Cyclodehydration of β-hydroxy thioamides using either Mitsunobu conditions,\textsuperscript{10} Burgess reagent\textsuperscript{11} or \textit{SOCl}\textsubscript{2}\textsuperscript{12} to give thiazolines, followed by oxidation to the corresponding thiazole, is a widely used methodology for the preparation of this kind of compounds.

\[
\begin{align*}
\text{MeO}_2\text{C} & \text{NH}_2\text{HCl} \quad \text{(i)} \quad \text{MeO}_2\text{C} & \text{NH} \quad \text{(ii)} \quad \text{MeO}_2\text{C} & \text{NH} \quad \text{(iii)} \\
\text{OH} & \quad \text{OH} & \quad \text{OTBDMS} & \quad \text{OTBDMS} \\
\text{10} & \quad 6 & \quad 7 \\
\text{MeO}_2\text{C} & \text{N} & \quad \text{MeO}_2\text{C} & \text{S} & \quad \text{MeO}_2\text{C} & \text{S} \\
\text{\textsuperscript{\textbullet}} & \quad \text{OH} & \quad \text{OH} & \quad \text{OTBDMS} & \quad \text{OTBDMS} \\
9 & \quad \text{8} & \quad \text{3}
\end{align*}
\]

i) 2,2-Dimethylacetoacetic acid, DIPA, DMAP, DCC, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C; ii) TBDMSCl, imidazole, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, rt; iii) Lawesson's reagent, Cs\textsubscript{2}H\textsubscript{4}, reflux; iv) TBAF, THF, rt; v) Burgess-PEG, Dioxane/THF, 85 °C; vi) MnO\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, reflux.

Scheme 2

Recently, a PEG-linked Burgess reagent has been developed by Wipf and co-workers\textsuperscript{13} and applied successfully to the cyclodehydration of β-hydroxy thioamides in good yields. This reagent is easily prepared and stable under
oxidative and wet conditions.

Following this approach, the thiazol (3) was obtained as shown in Scheme 2. First, L-serine methyl ester hydrochloride was condensed with 2,2-dimethylacetoacetic acid in CH₂Cl₂ at 0 °C using DCC as a condensing agent and a mixture of DIPA and DMAP as bases, affording 64% of amide (6). In order to improve the yield of the desired condensation product, many variations in the reaction conditions (solvent, condensing agents, bases, temperature) were performed. Neither of the conditions studied resulted in an increase of the yield of this reaction. Nevertheless, when 3,3-dimethylbutyric acid was used instead of 2,2-dimethylacetoacetic acid, the yield was improved to 95%. It seems to be clear that the low yield for the synthesis of amide (6) is due to the instability of the β-keto acid.

The hydroxy group of the amide (6) was protected ¹⁴ as its tert-butyldimethylsilyl ether, to give 7 (84% yield).

It is known that esters do no react with Lawesson's reagent in benzene at 80 °C.¹⁵ Under these conditions, the reactivity of the ketones is variable, being highly dependent on the steric hindrance at the carbonyl group, and even some simple ketones (i.e. octanone) do no react.¹⁶ It is worth mentioning that, when the keto amide (7) was treated with Lawesson's reagent in benzene at 80 °C, the methyl ketone moiety remained intact, and the keto thioamide (8) was obtained in 84% yield. Its structure was clearly established by spectroscopic data (Table 1).

![Chemical Structure](image)

<table>
<thead>
<tr>
<th></th>
<th>¹H-NMR (CDCl₃, ppm)</th>
<th>¹³C-NMR (CDCl₃, ppm)</th>
<th>IR (KBr, cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H₁</td>
<td>CH₂(-C₃)</td>
<td>C₁</td>
</tr>
<tr>
<td>7</td>
<td>O</td>
<td>6.56 d, J=7.6 Hz.</td>
<td>2.21 (s, 3H)</td>
</tr>
<tr>
<td>8</td>
<td>S</td>
<td>8.13 br s</td>
<td>2.17 (s, 3H)</td>
</tr>
</tbody>
</table>

* The thioamide I band falls in the fingerprint region which makes the assignments of this band difficult.¹⁷

Table 1

The NMR spectrum of 8 shows a single proton as a broad singlet at 8.13 ppm and a carbon signal at 205.8 ppm. These data, together with the 1508 cm⁻¹ IR absorption peak, are indicative of a thioamide function. At the same time, the signals corresponding to the methyl ketone moiety in compounds (7) and (8) do no change.
Deprotection of the silyl ether (8) and subsequent cyclodehydration of the β-hydroxy thioamide (9) with PEG-linked Burgess reagent, led to thiazoline (10). Oxidation of 10 (activated MnO₂, CH₂Cl₂, reflux) afforded the desired thiazole (3).

This last synthetic pathway provides 3 in an overall yield of 19% from L-serine methyl ester hydrochloride (seven steps). However, in contrast to the route summarised in Scheme 1, with an overall yield of 21%, that yield is maintained when multigram syntheses are performed (1-10 g).

From thiazole (3), a series of suitable 2,4-disubstituted thiazoles could be readily obtained through sequential reduction and monoprotection reactions as shown in Scheme 3. Treatment of 3 with sodium borohydride in MeOH afforded alcohol (11) (90% yield). In this reduction 6% of diol (12) was also obtained. Silylation of the hydroxyl group of 11 with tert-butylimethylsilyl trifluoromethanesulfonate (TBDMSTf) provided thiazole derivative (13), which by reduction with lithium aluminum hydride afforded 14 (82% yield). Acetylation under standard conditions of the primary hydroxyl group in 14, furnished compound (15).

![Chemical structure of the synthetic pathways](image)

**Scheme 3**

In conclusion, the synthetic equivalents compounds (2), (3) and (15) were prepared and fully characterised employing two methodologies. According to the results achieved, we suggest the use of the more efficient methodology shown in Scheme 1 when small amounts of product are needed (0.1-0.5 g). The cyclodehydration of
β-hydroxy thioamides with PEG-Burgess reagent (shown in Scheme 2), is more suitable for multigram synthesis (1-10 g). At the same time, we have proved that the oxygenated functions in 3, can be selectively and easily reduced and protected in good yields. Accordingly, a new series of synthetic intermediates of interest for our final objectives were obtained.

EXPERIMENTAL SECTION

General Methods
Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1310 and FTIR 8101A Shimadzu spectrophotometer. NMR spectra were recorded on Bruker AMX-400 and on Varian XL 100. Chemical shifts are related to TMS as internal standard. Low-resolution MS were obtained on a GCMS Shimadzu QP 1100-EX spectrometer. Elemental analyses were obtained from vacuum dried samples and performed on a Fisons EA 1108 CHN-O analyser. Flash column chromatography was carried out with Silica gel 60 (J. T. Baker, 40 µm average particle diameter). All reactions and chromatographic separations were monitored by TLC analyses, conducted on 0.25 mm Silica gel plastic sheets (Macherey - Nagel, Polygram® SIL G/UV 254). Spots were visualised under 254 nm illumination, by iodine vapour, p-hydroxybenzaldehyde spray or ninhydrine spray. All solvents were purified according to literature procedures. All reactions were carried out in dry, freshly distilled solvents under anhydrous conditions unless otherwise stated. Yields are reported for chromatographically and spectroscopically (1H and 13C-NMR) pure compounds.

Ethyl (S)-N-(2,2-Dimethylacetoacetyl)-S-benzyleysteine (4). To a stirred solution of L-cysteine ethyl ester chlorhydrate (20.0 g, 108 mmol) and Et3N (22 g, 216 mmol) in dry EtOH (160 mL), was added dropwise benzyl chloride (15.2 g, 136 mmol). The stirring, was continued at rt until monitoring by TLC indicated that all starting material has been consumed (ca. 12 h). The reaction mixture was concentrated in vacuo to yield a white residue. To this mixture suspended in dry CH2Cl2 (150 mL) at 0 °C were added 2,2-dimethylacetoacetic acid (15.5 g, 119 mmol), DCC (33.4 g, 162 mmol), and HOBT (14.6 g, 108 mmol) and was stirring overnight. The white precipitate was filtered and the filtrate was washed with 5% HCl. The organic layer was dried (MgSO4), filtered and concentrated. Purification by flash chromatography (silica gel, EtOAc/n-hexane, 1:2) afforded 26.5 g (70%) of
compound (4). Oil, Rf= 0.35 (silica gel, EtOAc/n-hexane, 1:2); IR (film) νmax 3340, 1720, 1650, 1020 cm⁻¹; ¹H-NMR (250 MHz, CDCl₃) δ 1.29 (t, J = 7 Hz, 3H), 1.44 (s, 6H), 2.24 (s, 3H), 2.83 (dd, J = 6.5, 14 Hz, 1H), 2.96 (dd, J = 4.8, 14 Hz, 1H), 3.73 (s, 2H), 4.21 (q, J = 7 Hz, 2H), 4.76 (m, 1H), 6.52 (d, J = 8 Hz, 1H), 7.32 (m, 5H); ¹³C-NMR (CDCl₃) δ 208.34, 172.37, 170.58, 137.53, 128.95, 128.67, 127.35, 61.86, 55.97, 51.56, 36.37, 33.19, 26.06, 20.73, 14.01; EIMS (70 eV); m/z (%) 351 (M⁺, 0.9), 260 (M⁺ - CH₂C₆H₅, 14.1), 131 (19.4), 91 (100.0), 85 (25.8), 70 (13.4), 57 (15.7), 43 (67.8).

(RS)-2-(1',1'-Dimethyl-2'-hydroxypropyl)-4-hydroxymethyl-Δ²-thiazoline (5). Compound (4) (0.50 g, 1.4 mmol) was dissolved in NH₃ (liq) (20 mL) at -78 °C. To this solution was added Na (0.97 g, 4.2 mmol) and the resulting dark blue solution was stirred for 5 h until monitoring of the reaction by TLC indicated that all starting material has been consumed and only one product was observed. Solid NH₄Cl (4.1 g, 82 mmol) was added in portions until the blue color disappeared. The -78 °C cooling bath was replaced with a bath of warm H₂O and the NH₃ allowed to evaporate under a stream of N₂. The resulting white solid was placed under a high-vacuum for 15 min before been dissolved in dry CH₂Cl₂ (20 mL). Then was added TiCl₄ (2.8 mL, 25.5 mmol) and the mixture was refluxed for 12 h. The reaction mixture was cooled and saturated aqueous Na₂CO₃ solution until pH 7 was added. The precipitate was filtered and the aqueous layer extracted with CH₂Cl₂ (6 x 20 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (silica gel, 3% MeOH in CHCl₃) afforded 0.25 g (50%) of compound (5). Oil, Rf= 0.45 (silica gel, 3% MeOH in CHCl₃); IR (KBr) νmax 3300, 1640 cm⁻¹; ¹H-NMR (250 MHz, CDCl₃) δ 1.16 (s, 6H), 1.18 (d, J = 10 Hz, 3H), 3.13 (dd, J = 8.5, 11 Hz, 1H), 3.26 (m, 1H), 3.78 (m, 3H), 4.66 (m, 1H); EIMS (20 eV), m/z (%) 159 (M⁺-CH₃CHO, 16.8), 128 (100.0), 113 (7.0), 96 (6.8), 86 (8.9), 70 (12.4), 57 (55.4), 44 (33.0).

Because the instability of compound (5), the stable trityl derivative was prepared.

(RS)-2-(1',1'-Dimethyl-2'-hydroxypropyl)-4-triphenylmethylmethoxymethyl-Δ²-thiazoline: Trityl derivative of 5: crystalline solid, mp 102.0-104.0 °C (EtOAc/n-hexane 1:10), Rf = 0.45 (silica gel, EtOAc/n-hexane 1:5); IR (KBr) νmax 3385, 1609, 1449, 1101, 1074, 702; ¹H-NMR (400 MHz , CDCl₃) δ 1.22 (m, 9H), 3.20 (m, 1H), 3.32 (m, 3H), 3.86 (m, 1H), 4.64 (br s, 1H), 4.68 (m, 1H), 7.29 (m, 9H), 7.47 (m, 6H); ¹³C-NMR (CDCl₃) δ 181.92, 144.27, 129.08, 126.29, 87.01, 73.64, 65.27, 45.87, 34.53, 25.72, 21.92, 17.78; EIMS (20 eV), m/z (%) 401 (M⁺-CH₃COH,
2-(1',1'-Dimethyl-2'-hydroxypropyl)thiazole-4-carboxaldehyde (2). To a stirred solution of compound (5) (50 mg, 0.25 mmol), in dry CHFCl₂ (15 mL), was added MnO₂ (1.30 g, 15 mmol) and the mixture was refluxed. When all starting material monitoring by TLC has been consumed (ca. 3 h), the mixture was cooled and filtered thorough Celite using CH₂Cl₂ to rinse the residual product from the oxidant. The solvent was removed in vacuo and the product was purified by flash chromatography (silica gel, 3% MeOH in CHCl₃) to yield 32 mg (60%) of 2. Oil, Rₜ = 0.30 (silica gel, EtOAc/n-hexane 1:2); IR (film) ν max 1703, 1255, 1053; ¹H-NMR (400 MHz, CDCl₃) δ 1.17 (d, J = 6.3 Hz, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 3.52 (brs, 1H), 4.02 (q, J = 6.3 Hz, 1H), 8.11 (s, 1H) 10.05 (s, 1H); ¹³C-NMR (CDCl₃) δ 185.1 1, 181.2 2, 154.6 3, 126.8 4, 74.4 5, 46.0 6, 27.1 7, 24.1 8, 18.3 9; EIMS (70 eV), m/z (%) 199 (M⁺, 0.4), 198 (M⁺-1, 3.5), 185 (65.4), 170 (M⁺-1-CO, 3.0), 153 (86.1), 154 (9.8), 125 (100.0), 112 (4.0), 85 (23.1), 57 (34.6), 45 (76.4).

Methyl (2S)-2-(2',2'-Dimethylacetoacetylamino)-3-hydroxypropanoate (6). To a solution of 2,2-dimethylacetoacetic acid (4.6 g, 34 mmol) in dry CH₂Cl₂ (150 mL) was added at 0 °C diisopropylamine (3.2 g, 32 mmol), L-serine methyl ester hydrochloride (5.0 g, 32 mmol) and 4-dimethylaminopyridine (0.39 g, 3.2 mmol). After 30 min, 1,3-dicyclohexylcarbodiimide (7.27 g, 36 mmol) was added. The reaction mixture was stirred at 0 °C for three days. The white precipitate was filtered, the solvent was evaporated and the residue was purified by flash chromatography (silica gel, EtOAc/n-hexane, 2:1) to give 4.73 g (64%) of compound (6). Oil, Rₜ = 0.24 (silica gel, EtOAc/n-hexane, 2:1); IR (film) ν max 3393, 1748, 1717, 1653, 1522, 1225, 1184 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.44 (s, 3H), 1.45 (s, 3H), 2.24 (s, 3H), 3.80 (s, 3H), 3.92 (m, 1H), 4.01 (m, 1H), 4.65 (m, 1H), 6.74 (br d, J = 6.3 Hz, 1H); ¹³C-NMR (CDCl₃) δ 209.0 1, 173.2 2, 171.0 3, 154.6 4, 63.2 5, 56.4 6, 55.2 7, 53.1 8, 26.3 9, 22.7 10; EIMS (20 eV), m/z (%) 202 (M⁺-CH₃O, 2.1), 201 (21.1), 189 (M⁺+1-CH₃CO, 37.1), 120 (41.6), 113 (30.5), 86 (51.1), 85 (38.1), 70 (100.0), 60 (25.1), 43 (61.7).

Methyl (2S)-3-[(tert-Butyldimethylsilyl)oxy]-2-(2',2'-dimethylacetoacetylamino)propanoate (7). To a solution of 6 (4.2 g, 17 mmol) in dry CH₂Cl₂ (35 mL) were added tert-butyldimethylsilyl chloride (2.8 g, 18 mmol),
imidazole (1.6 g, 24 mmol) and 4-dimethylaminopyridine (0.21 g, 1.7 mmol). The reaction mixture was stirred overnight at rt, diluted with Et₂O, washed with 1 M HCl, H₂O, dried (MgSO₄) and filtered. The solvent was removed and the product was purified by flash chromatography (silica gel, EtOAc/n-hexane, 1:4) to give 3.0 g (84%) of compound (7). Oil, Rₕ = 0.38 (silica gel, EtOAc/n-hexane, 1:4); IR (film) ν max 1750, 1717, 1682, 1510, 1113, 837, 779 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.41 (s, 3H), 1.42 (s, 3H), 2.21 (s, 3H), 3.75 (s, 3H), 3.82 (dd, J = 10, 3.2 Hz, 1H), 4.07 (dd, J = 10, 2.8 Hz, 1H), 4.60 (m, 1H), 6.56 (d, J = 7.6 Hz, 1H); ¹³C-NMR (CDCl₃) δ 208.07, 172.29, 170.57, 63.05, 56.06, 54.41, 52.41, 25.99, 25.63, 22.26, 22.22, 18.08, 0.37, -5.59, -5.70; EIMS (20 eV), m/z (%) 303 (M⁺+1-CH₂FO, 4.9), 288 (M⁺-C₄H₉, 100.0), 171 (11.9), 159 (16.3), 89 (34.8), 75 (29.4), 73 (27.0), 43 (17.1).

Methyl (2S)-3-[(tert-Butyldimethylsilyl)oxy]-2-{[2',2'-dimethylacetothioacetyl]amino}propanoate (8). To a stirred solution of 7 (3.0 g, 8.7 mmol) in benzene (35 mL) was added Lawesson’s reagent (1.8 g, 4.4 mmol) and the mixture was refluxed until monitoring of the reaction by TLC indicated that all starting material has been consumed (ca. 6 h). The mixture was filtered and the filtrate was concentrated in vacuo. Flash chromatography (silica gel, EtOAc/n-hexane, 1:4) afforded 2.6 g (84%) of compound (8). Oil, Rₕ = 0.80 (silica gel, EtOAc/n-hexane, 1:3); IR (film) ν max 1748, 1713, 1508, 1109, 1022, 833, 779 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.06 (s, 3H), 0.89 (s, 9H), 1.53 (s, 3H), 1.55 (s, 3H), 2.17 (s, 3H), 3.79 (s, 3H), 4.04 (dd, J = 10.3, 3 Hz, 1H), 4.12 (dd, J = 10.3, 2.3 Hz, 1H), 5.24 (m, 1H), 8.13 (br s, 1H); ¹³C-NMR (CDCl₃) δ 207.50, 205.80, 170.06, 62.44, 61.59, 60.12, 52.96, 26.14, 25.97, 25.37, 25.09, 18.41, -5.22, -5.38; EIMS (20 eV), m/z (%) 361 (M⁺, 1.4), 318 (M⁺-CH₂CO, 7.4), 304 (M⁺-C₄H₉, 53.4), 275 (187), 218(37.8), 186 (46.6), 159 (100.0), 89 (46.4), 73 (31.7), 43 (22.0).

Methyl (2S)-2-{[2',2'-Dimethylacetothioacetyl]amino}-3-hydroxypropanoate (9). To silyl ether (8) (2.6 g, 7.3 mmol) was added a solution 1M of tetrabutylammonium fluoride in THF (14.4 mL, 14.4 mmol). After stirring 1 h at rt, the solvent was evaporated and the residue partitioned between Et₂O and H₂O. The aqueous layer was extracted three times with Et₂O and the combined organic layers dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography (silica gel, EtOAc/n-hexane, 2:1) afforded 1.7 g (94%) of compound (9). Yellow oil, Rₕ = 0.40 (silica gel, EtOAc/n-hexane, 2:1); IR (film) ν max 3376, 1744, 1717, 1518, 1053 cm⁻¹; ¹H-NMR δ 1.57 (s,
Methyl (4S) 2-(1',1'-Dimethyl-2'-oxopropyl)-1,2-thiazoline-4-carboxylate (10). To a stirred solution of thioamide (9) (1.7 g, 6.9 mmol) in dry THF (18 mL) was added a solution of PEG-Burgess13 (9.9 g, 10.1 mmol) in dry dioxane (18 mL). The reaction mixture was heated at 85 °C until monitoring by TLC indicated that all starting material had been consumed (ca. 3 h). The solvent was removed in vacuo and the residue partitioned between Et2O and aqueous saturated NaHCO3. The aqueous layer was extracted five times with Et2O and the combined organic layers dried (MgSO4), filtered and concentrated in vacuo. Flash chromatography (silica gel, CHCl3) afforded 1.01 g (64%) of compound (10). Oil, RF = 0.7 (silica gel, 3% MeOH in CHCl3); IR (film) νmax 1746, 1717, 1609, 1042 cm⁻¹; 1H-NMR (400 MHz, CDCl3) δ 1.43 (s, 3H), 1.44 (s, 3H), 2.20 (s, 3H), 3.53 (dd, J = 11.3, 9.6 Hz, 1H), 3.59 (dd, J = 11.3, 7.7, 1H), 5.17 (m, 1H); 13C-NMR (CDCl3) δ 207.16, 178.50, 171.44, 78.18, 54.97, 53.00, 36.05, 25.76, 24.25, 24.09; EIMS (20 eV), m/z (%) 230 (M'+1, 10.1), 216 (M'+1-CH3, 71.2), 187 (M'+1-CH2CO, 41.2), 128 (100.0), 86 (26.7), 59 (16.1), 43 (69.5). Anal. Calcd for C10H15N03S: C 52.28, H 6.59, N 6.11. Found: C 53.11, H 6.59, N 6.18.

Methyl 2-(1',1'-Dimethyl-2'-hydroxypropyl)thiazole-4-carboxylate (3). To a stirred solution of 10 (0.76 g, 3.3 mmol) in dry CH2Cl2 (70 mL) was added MnO2 (5.8 g, 66 mmol) and the mixture was refluxed during 3 h. The reaction mixture was cooled and filtered through a pad of Celite and concentrated in vacuo. Purification by flash chromatography (silica gel, CHCl3) afforded 0.53 g (70%) of thiazole (3). Crystalline solid, mp 56.5-57.5 °C (CHCl3/n-hexane 1:1), RF = 0.25 (1% MeOH in CHCl3); IR (KBr) νmax 1738, 1717, 1242, 1217 cm⁻¹; 1H-NMR (400 MHz, CDCl3) δ 1.68 (s, 6H), 2.14 (s, 3H), 3.94 (s, 3H), 8.16 (s, 1H); 13C-NMR δ 207.70, 175.16, 162.20, 147.20, 128.34, 54.40, 52.76, 26.01, 25.86; EIMS (20 eV), m/z (%) 196 (M'+-OCH3, 5.4), 185 (M'+-1-CH3CO, 100.0), 153 (76.0), 125 (56.0), 43 (28.0). Anal. Calcd for C10H15NO3S: C 52.84, H 5.76, N 6.16. Found: C 53.57, H 5.72, N 6.25.

Methyl (RS)-2-(1',1'-Dimethyl-2'-hydroxypropyl)thiazole-4-carboxylate (11) and (RS)-2-(1',1'-Dimethyl-2'-
hydroxypropyl)-4-hydroxymethylthiazole (12). To a stirred solution of 3 (0.42 g, 1.83 mmol) in MeOH (60 mL) was added in portions NaBH₄ (0.77 g, 2.0 mmol) at rt. After 30 min the solvent was evaporated and the residue partitioned between Et₂O and brine. The aqueous layer was extracted five times with Et₂O and the combined organic layers dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography (silica gel, 3% MeOH in CHCl₃) afforded 0.38 g (90%) of 11 and 23 mg (6%) of 12. 11: oil, Rf = 0.65 (6% MeOH in CHCl₃); IR (film) νmax 3503, 1725, 1227, 1103 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.16, (d, J = 6.3 Hz, 3H), 1.45 (d, J = 5 Hz, 6H), 3.93 (s, 3H), 4.03 (q, J = 6.3 Hz, 1H), 8.09 (s, 1 H); ¹³C-NMR (CDCl₃) δ 180.48, 162.21, 146.56, 126.94, 74.34, 52.68, 45.93, 27.10, 24.03, 18.20; EIMS (20 eV), m/z (%) 214 (M⁺-CH₃, 1.6), 198 (bf-0CH₃, 5.1), 185 (93.8), 153 (100.0), 125 (86.0), 85 (12.3), 57 (3.2), 45 (14.2). 12: oil, Rf = 0.50 (silica gel, 6% MeOH in CHCl₃); IR (film) νmax 3384, 1055, 1028 cm⁻¹; 'H-NMR (400 MHz, CDCl₃) δ 1.15 (d, J = 6.3 Hz, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 3.94 (q, J = 6.3 Hz, 1H), 7.11 (t, J = 1 Hz, 1H); ¹³C-NMR (CDCl₃) δ 180.62, 156.06, 113.69, 74.60, 61.50, 45.40, 27.26, 23.97, 18.17; EIMS (70 eV), m/z (%) 200 (M⁺-1, 0.1), 157 (M⁺-CH₂CHO, 44.1), 139 (100.0), 71 (25.1), 45 (22.1).

Methyl (RS)-2-((2'-tert-Butyldimethylsilyloxy-1',1'-dimethylpropyl)thiazole-4-carboxylate (13). To a stirred solution of 11 (0.23 g, 1.0 mmol) in dry CH₂Cl₂ (5 mL) at 0 °C were added triethylamine (0.20 g, 2 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (0.55 g, 2.0 mmol). The reaction mixture was stirred overnight at rt and CH₂Cl₂ (10 mL) and saturated aqueous NaHCO₃ (until pH = 7) were added. The aqueous layer was extracted three times with CH₂Cl₂ and the combined organic layers dried (MgSO₄). The solvent was removed in vacuo to afforded 0.33 g (96%) of compound (13) which was used without further purification. 13. Oil, Rf = 0.80 (1% MeOH in CHCl₃); IR (film) νmax 1742, 1248, 1115, 835, 775 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.06, (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.04 (d, J = 6.2 Hz, 3H), 1.41 (s, 3H), 1.48 (s, 3H), 3.95 (s, 3H), 4.07 (q, J = 6.2 Hz, 1H), 8.09 (s, 1H); ¹³C-NMR (CDCl₃) δ 179.33, 162.69, 146.12, 127.72, 75.49, 52.63, 46.93, 26.51, 26.21, 24.48, 19.21, 18.37, -3.84, -4.77; EIMS (20 eV), m/z (%) 342 (M⁺-1, 0.1), 328 (M⁺-CH₃, 5.1), 286 (M⁺-C₃H₆, 100.0), 242 (30.9), 227 (25.8), 185 (27.9), 159 (47.8), 115 (22.4), 73 (79.7).

(RS)-2-((2'-tert-Butyldimethylsilyloxy-1',1'-dimethylpropyl)-4-hydroxymethylthiazole (14). To a stirred solution of 13 (0.10 g, 0.3 mmol), in dry Et₂O (25 mL) was added LiAlH₄ (12 mg, 0.03 mmol). The stirring was
continued until monitoring of the reaction by TLC indicated that all starting material had been consumed (ca. 30 min). NaOH (20%) in H₂O was added until pH =10 and the mixture was extracted three times with Et₂O. The combined organic layers were dried (MgSO₄), filtered and the solvent removed in vacuo. Flash chromatography (silica gel, 3% MeOH in CHCl₃) afforded 75 mg (82%) of compound (14). Crystalline solid, mp 53.0-54.5°C (CHCl₃/n-hexane 2:1), Rₚ = 0.50 (3% MeOH in CHCl₃); IR (KBr) νmax 3360, 1256, 1115, 1059, 837, 775 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.07 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.02 (d, J = 6.2 Hz, 3H), 1.36 (s, 3H), 1.42 (s, 3H), 3.00 (br s, 1H), 4.68 (s, 2H), 7.05 (s, 1 H); ¹³C-NMR (CDCl₃) δ 179.69, 155.52, 114.00, 126.30, 75.56, 61.38, 46.55, 26.21, 25.37, 24.86, 19.20, 18.35, -3.82, -4.81; EIMS (20 eV), m/z (%) 315 (M⁺, 0.3), 258 (M⁺-C₄H₈, 45.2), 214 (30.2), 159 (68.8), 115 (28.2), 103 (24.1), 73 (100.0).

(RS)-2-(2'-tert-Butyldimethylsilyloxy-1',1'-dimethylpropyl)-4-acetoxymethylthiazole (15). To a stirred solution of 14 (60 mg, 0.18 mmol) in dry CH₂Cl₂ (6 mL) were added pyridine (28 mg, 0.48 mmol) and acetic anhydride (24 mg, 0.24 mmol) and the mixture was stirred for 1 h. The mixture was diluted with CH₂Cl₂ (20 mL) and washed with 5% aqueous HCl, saturated NaHCO₃ and brine. The organic layer was dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography (silica gel, EtOAc/n-hexane, 1:3) afforded 57 mg (90%) of 15. Oil, Rₚ = 0.73 (silica gel, AcOEt/n-hexane, 1:3), IR (film) νmax 1746, 1250, 1225, 1115, 837, 775 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.11 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.04 (d, J = 6.2 Hz, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 2.13 (s, 3H), 4.09 (q, J = 6.2 Hz, 1H), 5.20 (m, 2H), 7.14 (s, 1 H); ¹³C-NMR (CDCl₃) δ 179.70, 171.09, 150.45, 116.98, 75.56, 62.45, 46.53, 26.18, 25.68, 24.29, 21.36, 19.12, 18.33, -3.87, -4.88; EIMS (20 eV), m/z (%) 342 (M⁺-CH₃, 3.3), 300 (M⁺-C₄H₈, 96.3), 199 (18.0), 159 (83.0), 117 (60.9), 115 (30.8), 73 (100.0), 43 (2.0).

ACKNOWLEDGMENT

This work was supported by grants from SAREC (Swedish Agency for Research Cooperation with Developing Countries) and PEDECIBA (Programa de Desarrollo de las Ciencias Básicas, Project URU/84/002). We would like to thank R. Fernández for his cooperation in the realisation of IR spectra, Dr. S. Gordon for her help in the translation of the present work, and Dr. G. Seoane for helpful discussion of this manuscript.
REFERENCES AND NOTES


1996, 61, 6556.


Received, 1st June, 1998