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Tetrahedron: *Asymmetry* 16 (2005) 1905–1912

Synthesis of 2,4,5-trisubstituted thiazoline via a novel stereoselective intramolecular conjugate addition

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Received 13 August 2004; revised 26 April 2005; accepted 26 April 2005

Abstract—A convenient stereoselective preparation of 2,4,5-trisubstituted thiazolines is reported. The procedure involves the cyclisation of an unsaturated thioamide under mildly acidic conditions, and proceeds with excellent stereocontrol. A range of substrates are presented, and an explanation of the stereochemical outcome discussed.

1. Introduction

Thiazoline, as an important functional group in natural products and medicines, plays a significant role in bioactivity, for example, curicin A,[1,2] tantazole[3,4] and thiangazole.[5] A new and important natural product containing a thiazoline ring is apratoxin A. Apratoxins (Fig. 1), displaying potent in vitro and in vivo cytotoxicities, were isolated by Moore et al. from *Lyngbya* sp. Finger's Reef, Apra Harbor, Guam.[6,7] Apratoxins possess a number of intriguing structural elements, including a *tert*-butyl group as the starter unit of the polyketide segment and a thiazoline ring attached to the β-carbon of an α,β-unsaturated amide.

There are a number of approaches for the construction of the thiazoline unit.[8–16] Among these, two widely used methods are the direct thermal intramolecular cyclisation of thiolesters derived from vicinal amino thiols (Fukuyama),[4] and the cyclisation of a serine-derived thioamide, with or without the presence of an activating reagent.[10–12]

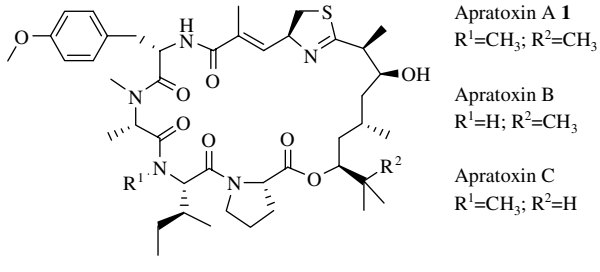

Figure 1. Apratoxins from *Lyngbya* sp.

It is well documented that the stereogenic centres adjacent to the thiazoline ring readily undergo epimerisation.[17,18] In the process of constructing the thiazoline motif towards the total synthesis of apratoxin A,[19,20] we initially chose the highly reliable and racemisation-free method: cyclodehydration of the corresponding δ-thioamide-α,β-unsaturated amide (Scheme 1). During the preliminary work, attempts to prepare thioamide **3** gave none of the desired product.[21,22] Instead, 2,4,5-trisubstituted thiazoline **4** was obtained as one single diastereoisomer, after purification of the crude reaction mixture.

The total synthesis of apratoxin A has been achieved by Forsyth's group.[23] As part of the effort we have made towards the total synthesis of apratoxin A, we herein report this unexpected intramolecular conjugate addition reaction of δ-thioamide-α,β-unsaturated esters or amides, producing 2,4,5-trisubstituted thiazolines with high diastereoselectivity.

2. Results and discussion

In the subsequent work, we found that when crude thioamide **3** was directly treated with Burgess' reagent, thiazoline **5** was isolated in 66% yield (Scheme 2).

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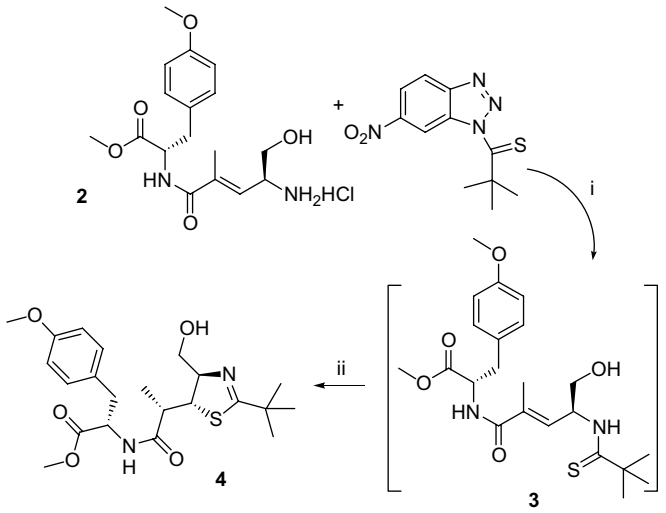
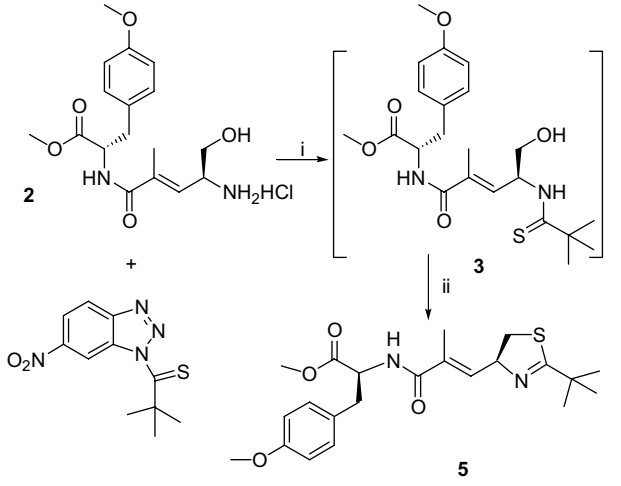
doi:10.1016/j.tetasy.2005.04.029



Scheme 1. Reagents and conditions: (i) **2**, DIPEA, DMF or DCM, 0 °C–rt; (ii) chromatography on silica gel, 75%.

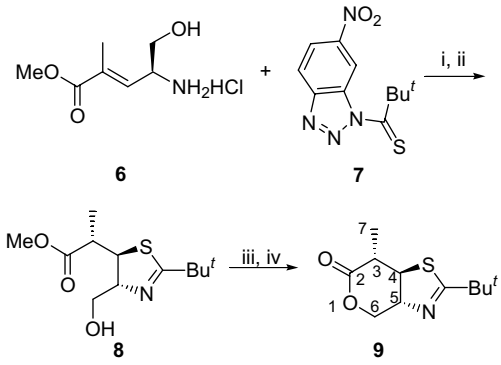


Scheme 2. Reagents and conditions: (i) **2**, DIPEA, DMF or DCM, 0 °C–rt; (ii) Burgess' reagent, THF, reflux, 66%.

This result clearly indicates that the thioacylation process is successful and provides the corresponding thioamide **3**, although this intermediate is unstable under acidic conditions and readily undergoes an intramolecular conjugate addition reaction. Lewis acids, even as weak as silica gel, can promote this reaction.

The structure of thiazoline **4** was confirmed by NMR and HRMS, but the configuration at the adjacent carbon was not. Extensive NMR techniques and further synthetic work were applied to determine the stereochemistry of the 2,4,5-trisubstituted thiazoline.

Thus, unsaturated ester **6**[24] was reacted with **7** under similar conditions as shown before (Scheme 3). Treatment of the crude thioamide with silica gel produced the corresponding thiazoline **8**. After saponification, lactonisation in the presence of EDCI and DMAP gave bicycle **9** in 41% yield (over three steps).[25,26] The ^{1}H NMR spectrum of compound **9** strongly suggests that protons H3–H4 and H4–H5 are in *trans*-relationships, with coupling constants of $J_{H3-4} = 12.4$ Hz and $J_{H4-5} = 13.5$ Hz, respectively. According to this assignment, the absolute stereochemistry of thiazoline **9** is (3*S*, 4*R*,5*R*). Further NOE experiments provided more conclusive support for this assignment; there are cross-peaks between the C3–C5 protons and the C4–C7 protons (see Fig. 2).



Scheme 3. Reagents and conditions: (i) DIPEA, DCM, 0 °C–rt, 12 h; (ii) silica gel column chromatography, 69%; (iii) LiOH, THF–H_2O–MeOH; (iv) EDCI, DMAP, CSA, 59%.

Regarding the mechanism of this stereoselective intramolecular conjugate addition reaction, it can be explained using the 1,3-allyl strain theory,[27,28] as shown in Figure 3. The proton attached to C4 lies on the plane of the conjugated portion in order to minimise steric hindrance, leaving the thiocarbonyl below the plane. This enables the nucleophilic sulfur atom to add to the double bond from the *Re* face, leading to an (*R*)-configuration at C-3. The stereochemical outcome at C-2 may have arisen from a concerted process, with the double bond picking up a proton from the top face, thus activating the C=C bond; or via a stepwise approach where the corresponding enolate was protonated from the top face. The two-step process is less attractive since the C-2 stereochemistry would be mainly determined by the stereochemistry at C-3, while freedom of rotation around

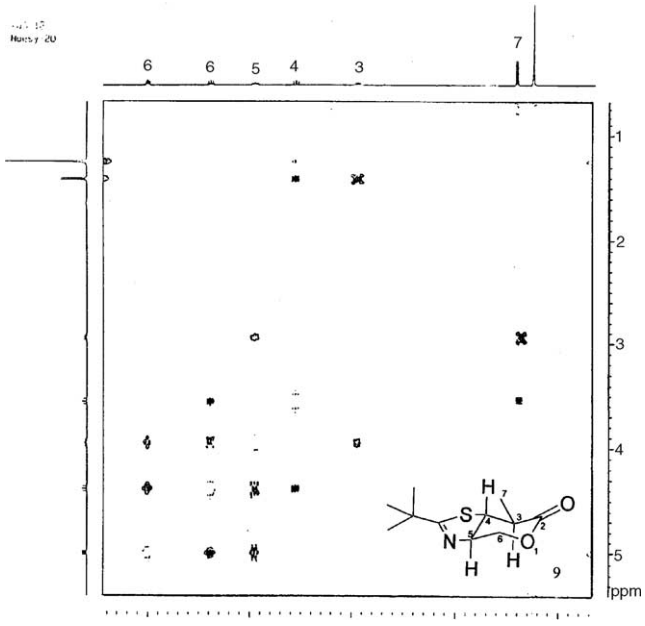


Figure 2. NOE spectrum of compound **9**.

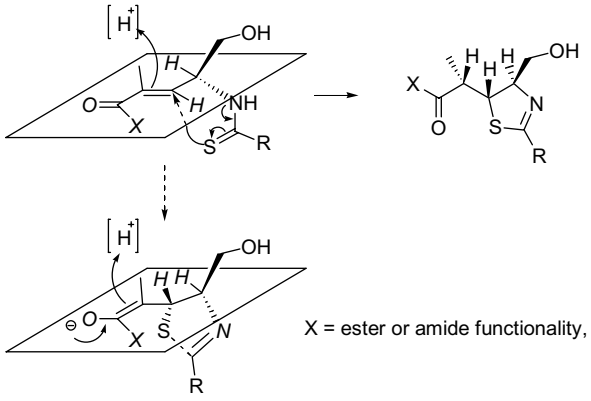


Figure 3. Mechanism of the stereoselective intramolecular Michael addition.

the C-2–C-3 bond would ensure a mixture of diastereoisomers.

In order to investigate the scope of this reaction for the highly stereoselective preparation of 2,4,5-trisubstituted thiazolines, different substrates were tested in the reaction. The results are listed in Table 1.

In the examples where the thioamide has a *tert*-butyl group attached, it can be seen that the cyclisation occurs readily, with no open chain material recovered (entries 1–3, 5, 7 and 9). The failure of the ring-closing step prevails in the instances where the thioamide has a phenyl group attached instead of the *tert*-butyl group (entries 4 and 6). This is most likely to be caused by the electronic effect that the phenyl group has on the sulfur atom, making it less nucleophilic. Stronger forcing conditions would need to be employed to encourage cyclisation, as shown in entries 4 and 6. These examples show poor diastereomer ratios after heating with CSA, but it is likely that this lack of stereocontrol is caused by acid-catalysed epimerisation of the labile C-2 centre. In contrast, when the Me-group on C-2 is absent, the cyclisation occurs readily even when the thioamide has a phenyl group attached (entries 7–10). The enhanced propensity towards cyclisation may again be explained in terms of electronic effects: the absence of the Me-group makes the C=C bond more electron deficient, hence more reactive towards the poorer nucleophile.

3. Conclusion

A novel intramolecular Michael addition reaction of a δ-thioamide-α,β-unsaturated ester or amide to produce the 2,4,5-trisubstituted thiazoline stereoselectively is disclosed.

4. Experimental

4.1. General experimental

All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents. All reaction vessels were oven-dried. Solvents were distilled prior to use: THF from Na/benzophenone, dichloromethane, DMF, triethylamine and diisopropylethylamine from CaH_2. NMR spectra were recorded on Bruker Advance DPX 300 MHz or AV400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm), relative to either a tetramethylsilane internal standard or the signals due to the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad), integration and coupling constants. Low- and high-resolution EI and FAB mass spectra were obtained using a Finnigan MAT 95 mass spectrometer, while ESI mass spectra were obtained using a Micromass Q-Tof-2™ spectrometer. IR spectra were recorded neat or as KBr discs on a Bio-Red FTS 165 Fourier transform spectrometer. Optical rotations were recorded on a Perkin Elmer 343 polarimeter. TLC was carried out using pre-coated sheets (Merck silica gel 60-F_{254}, 0.2 mm), which, after developing, were visualised at 254 nm, and/or staining in *p*-anisole, ninhydrin or phosphomolybdic acid solution followed by heating. Flash column chromatography was performed using the indicated solvents (with R_f = 0.15–0.20 for the desired component) on E. Merck silica gel 60 (230–400 mesh ASTM). Melting points were measured on Carl Zeiss melting point apparatus and are uncorrected.

4.2. Typical procedures

Method A: To a solution of unsaturated amino alcohol **6** (106.0 mg, 0.58 mmol, HCl salt) in DMF (0.5 mL) was added DIPEA (120 μL, 0.69 mmol) at 0 °C and after 5 min this was added to a solution of **7** (139.9 mg, 0.53 mmol) in DMF (0.5 mL) also at 0 °C. The mixture was stirred at room temperature for 12 h, diluted with saturated aqueous NH_4Cl (5 mL) and extracted with

Table 1. Stereoselective preparation of 2,4,5-trisubstituted thiazolines from different substrates

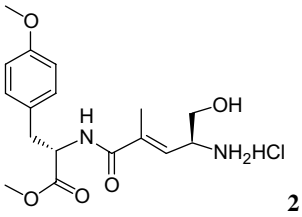
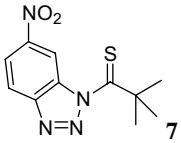
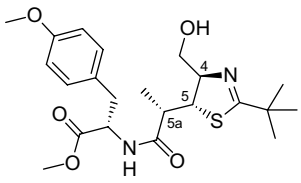
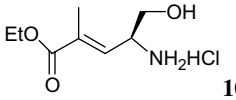
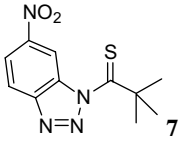
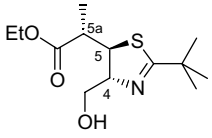
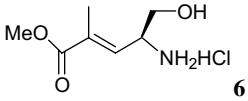
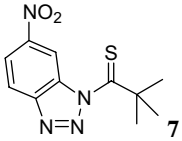
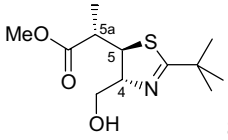
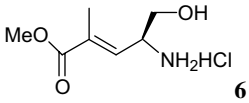
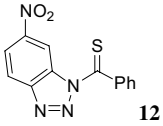
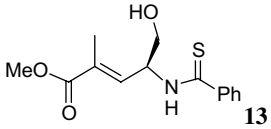
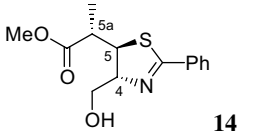
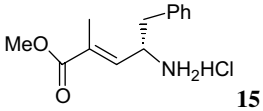
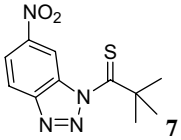
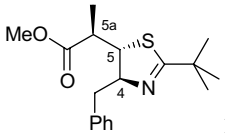
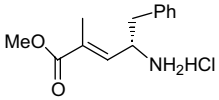
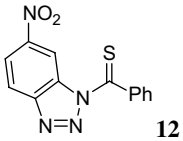
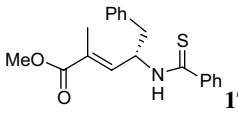
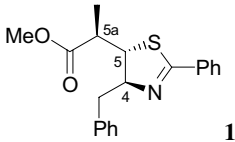
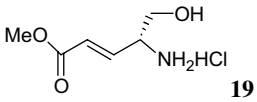
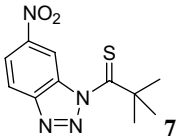
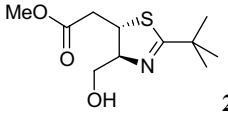
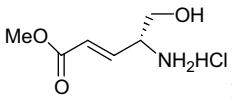
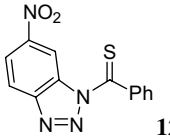
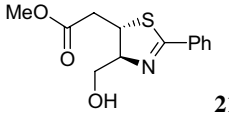
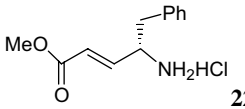
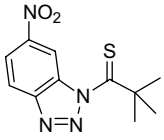
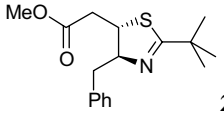
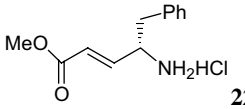
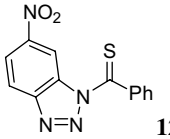
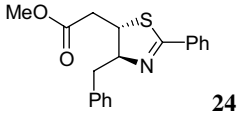
Entry	Substrates	Benzotriazole derivatives	Structures of product	Yield (%)	Diastereomer ratio[a]
1	 **2**	 **7**	 **4**	75	100:0:0:0[b]
2	 **10**	 **7**	 **11**	77	100:0:0:0[b]
3	 **6**	 **7**	 **8**	69	100:0:0:0[b]
4	 **6**	 **12**	 **13**  **14**	76 9	90:10:0:0[b,c]
5	 **15**	 **7**	 **16**	82	100:0:0:0[d]
6	 **15**	 **12**	 **17**  **18**	77	86:14:0:0[c,d]
7	 **19**	 **7**	 **20**	86	100:0

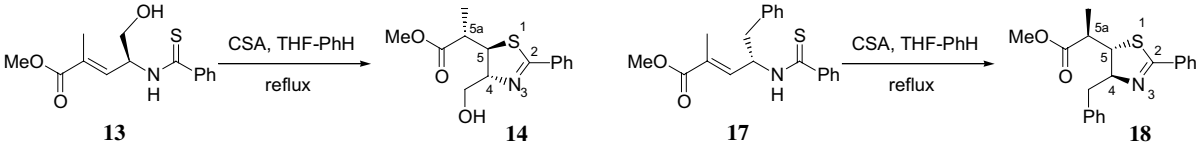
Table 1 (*continued*)

Entry	Substrates	Benzotriazole derivatives	Structures of product	Yield (%)	Diastereomer ratio[a]
8	 **19**	 **12**	 **21**	88	100:0
9	 **22**	 **7**	 **23**	88	100:0
10	 **22**	 **12**	 **24**	87	100:0

[a] Determined by ^{1}H NMR.

[b] The diastereomer ratio illustrated in the table corresponded to the following diastereoisomers: (4*R*,5*R*,5a*S*):(4*R*,5*R*,5a*R*):(4*R*,5*S*,5a*S*):(4*R*,5*S*,5a*R*).

[c] In entry 4, the crude product of the thioacylation reaction provided, after purification by chromatography on silica gel, thioamide **13** (76%) and thiazoline **14** (9%). Treatment of thioamide **13** in a benzene–THF solution with CSA under reflux (see scheme below) provided thiazoline **14** in 91% yield with relatively low de. Similarly, in entry 6, chromatographic purification of the crude product of thioacylation afforded thioamide **17** as the sole product. Treatment of **17** with CSA under identical conditions provided the corresponding thiazoline **18** (77% yield).



13 **14** **17** **18**

[d] The diastereomer ratio illustrated in the table corresponded to the following diastereoisomers: (4*S*,5*S*,5a*R*):(4*S*,5*S*,5a*S*):(4*S*,5*R*,5a*S*):(4*S*,5*R*,5a*R*).

ethyl acetate–benzene (3 × 25 mL, 3:1). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel using (ethyl acetate–hexane, 70:30) to give adduct **8** (95 mg, 69%) as an oil.

Method B: (applied to the situation where a stable thioamide was produced in Method A). To a solution of unsaturated amino alcohol **6** (86.5 mg, 0.47 mmol, HCl salt) in DMF (0.5 mL) was added DIPEA (122 μL, 0.71 mmol) at 0 °C and after 5 min added to a solution of **12** (133.9 mg, 0.47 mmol) in DMF (0.5 mL) also at 0 °C. The mixture was stirred at room temperature for 12 h, diluted with saturated aqueous NH_4Cl (5 mL) and extracted with ethyl acetate–benzene (3 × 25 mL, 3:1). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel using gradient elution (ethyl acetate–hexane, 50:50–70:30) to give **13** (100 mg, 76.0%) and **14** (12.1 mg, 9%) as oils.

Compound **13** was dissolved in benzene–THF (3 mL, 2:1), after which a catalytic amount of CSA was added and the mixture refluxed for 8 h. The solvents were removed in vacuo and the residue purified by chromatography on silica gel to yield the corresponding **14** (91 mg, 91%).

4.3. *N*-[(2*S*)-2-Methoxycarbonyl-3-(4′-methoxyphenyl) ethylamine]-2-*tert*-butyl-(4*R*)-4-hydroxymethyl-1,3-thiazoline-(5*R*)-5-(α*S*)-α-methyl-*E*-acrylamide 4

Method A: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02–7.05 (m, 2H), 6.81–6.86 (m, 2H), 6.10 (d, 1H, J = 7.98 Hz), 4.81–4.86 (m, 1H), 4.27–4.31 (m, 1H), 3.88 (dd, 1H, J = 2.94 Hz, 9.19 Hz), 3.79 (s, 3H), 3.74 (s, 3H), 3.63 (dd, 1H, J = 5.47 Hz, 10.75 Hz), 3.40 (dd, 1H, J = 7.36 Hz, 10.75 Hz), 3.08 (dd, 1H, J = 5.85 Hz, 14.05 Hz), 3.02 (dd, 1H, J = 5.85 Hz, 14.05 Hz), 2.64 (br, 1H), 2.31 (dd, 1H, J = 6.98 Hz, 9.19 Hz), 1.23 (s, 9H), 1.16 (d, 3H, J = 6.98 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.60, 173.75, 172.42, 158.76, 130.20, 127.54, 114.09, 82.30, 63.41, 55.20, 54.65, 53.13, 52.44, 47.16, 38.06, 37.14, 29.23, 16.53; IR (film) 3312.0 (br), 2966.7, 1641.6, 1613.5, 1513.6, 1460.4, 1365.5, 1249.3, 1179.4, 1042.8, 755.4 cm^{-1}; $[\alpha]_D^{20} = +161.5$ (c 1.0, $CHCl_3$); HR-EIMS (positive mode) calculated for $C_{22}H_{32}N_2O_5S$ 436.2023, found 436.2027.

4.4. *N*-[(2*S*)-2-Methoxycarbonyl-3-(4′-methoxyphenyl) ethylamine]-(4*S*)-2-*tert*-butyl-1,3-thiazoline-4-α-methyl-*E*-acrylamide 5

Reaction of compounds **2** and **7**, on a 0.2 mmol scale under the same conditions for 3 h, was diluted with ethyl acetate (70 mL) and washed with water (20 mL) and brine (20 mL). The solution was then dried over

Na_2SO_4 and concentrated in vacuo. The residue was dissolved in THF (0.5 mL) and transferred into a solution of Burgess reagent (52.4 mg, 0.22 mmol) in THF (1.5 mL) at 0 °C and the mixture heated to reflux for 3 h. After cooling to room temperature it was diluted with ethyl acetate (100 mL), washed with saturated NH_4Cl (30 mL) and brine (30 mL), dried over Na_2SO_4 and evaporated to leave a residue. Purification by chromatography on silica gel (ethyl acetate–hexane, 30:70) afforded the title thiazoline **5** (54.9 mg, 66%) as an oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.00–7.03 (m, 2H), 6.80–6.83 (m, 2H), 6.28–6.31 (m, 2H), 5.17 (m, 1H), 4.86–4.91 (m, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.43 (dd, 1H, J = 8.54 Hz, 10.97 Hz), 3.13 (dd, 1H, J = 5.84 Hz, 13.98 Hz), 3.09 (dd, 1H, J = 5.84 Hz, 13.98 Hz), 2.95 (dd, 1H, J = 8.78 Hz, 10.97 Hz), 1.93 (d, 3H, J = 1.27 Hz), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.85, 172.11, 168.45, 158.70, 134.88, 132.68, 130.20, 127.63, 114.00, 74.12, 55.14, 53.47, 52.31, 38.20, 38.10, 36.92, 29.23, 13.34; IR (film) 3345.94, 2964.95, 1739.04, 1666.82, 1613.68, 1513.64, 1249.01, 1045.80, 1000.32, 821.56 cm^{-1}; $[\alpha]_D^{20} = -14.1$ (c 2.0, $CHCl_3$); HR-EIMS (positive mode) calculated for $C_{22}H_{30}N_2O_4S$ 418.1926, found 418.1932.

4.5. (4*R*,5*R*)-2-*tert*-Butyl-4-hydroxymethyl-(α*S*)-α-methyl-1,3-thiazoline acetic acid ethyl ester 11

Method A: ^1H NMR ($CDCl_3$, 400 MHz) δ 4.40 (td, 1H, J = 3.35 Hz, 6.07 Hz), 4.11–4.22 (m, 2H), 3.98 (dd, 1H, J = 3.35 Hz, 7.22 Hz), 3.64 (dd, 1H, J = 6.07 Hz, 10.79 Hz), 3.58 (dd, 1H, J = 6.07 Hz, 10.79 Hz), 2.72 (br, 1H), 2.54–2.61 (m, 1H), 1.27 (t, 3H, J = 7.12 Hz), 1.24 (s, 9H), 1.21 (d, 3H, J = 7.22 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.35, 174.17, 82.03, 64.01, 60.86, 53.91, 45.05, 38.12, 29.19, 14.11 (2C); IR (film) 3390.2 (br), 2968.4, 1730.2, 1613.7, 1461.5, 1366.6, 1200.9, 1049.1, 979.3, 756.2 cm^{-1}; $[\alpha]_D^{20} = +156.2$ (c 4.2, $CHCl_3$); HR-EIMS (positive mode) calculated for $C_{13}H_{21}NO_2S$ (loss of H_2O) 255.1293, found 255.1292.

4.6. (4*R*,5*R*)-2-*tert*-Butyl-4-hydroxymethyl-(α*S*)-α-methyl-1,3-thiazoline acetic acid methyl ester, 8

Method A: ^1H NMR ($CDCl_3$, 400 MHz) δ 4.36 (td, 1H, J = 3.33 Hz, 6.07 Hz), 3.95 (dd, 1H, J = 3.33 Hz, 7.09 Hz), 3.67 (s, 3H), 3.60 (dd, 1H, J = 6.07 Hz, 10.81 Hz), 3.56 (dd, 1H, J = 6.07 Hz, 10.81 Hz), 3.22 (br, 1H), 2.53–2.60 (m, 1H), 1.20 (s, 9H), 1.17 (d, 3H, J = 7.09 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.50, 174.63, 81.96, 64.02, 53.86, 51.98, 44.92, 38.16, 29.20, 14.00; IR (film) 3377.3 (br), 2968.3, 2872.9, 1735.4, 1613.0, 1461.0, 1651.3, 1257.3, 1207.6, 1053.4, 981.9 cm^{-1}; $[\alpha]_D^{20} = +194.3$ (c 3.0, $CHCl_3$); HR-FABMS (positive mode) calculated for $C_{12}H_{22}NO_3S$ $[M+H]^+$ 260.1320, found 260.1324.

4.7. (3*R*,4*R*,7*S*)-2-*tert*-Butyl-7-methyl-3a,4,7,7a-tetrahydro-pyrano[3,4-*d*]thiazol-6-one 9

A solution of ester **6** (35.5 mg, 0.14 mmol) in THF–MeOH–H_2O (3 mL, 1:1:1) was chilled with an ice-water bath to which $LiOH{\cdot}H_2O$ (15.2 mg, 0.37 mmol) was added and stirred overnight at room temperature. The volatile components were removed under reduced pressure and the aqueous residue covered with Et_2O (5 mL) and acidified to pH 3.0 with 10% citric acid at 0 °C. The organic layer was separated and the aqueous phase was further extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and evaporated to dryness. This hydroxy acid intermediate was subsequently dissolved in DCM (2 mL) and cooled to 0 °C. To this solution was added EDCI (71.2 mg, 0.37 mmol), DMAP (45.4 mg, 0.37 mmol) and finally DIPEA (64.8 μL, 0.39 mmol). After final addition, the mixture was stirred at room temperature for 16 h, poured into saturated NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed (ethyl acetate–hexane, 1:4), to give the title bicyclic compound **9** (20.1 mg, 59%) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.98 (dd, 1H, J = 5.35 Hz, 10.39 Hz), 4.36 (dd, 1H, J = 10.39 Hz, 11.89 Hz), 3.93 (ddd, 1H, J = 5.35 Hz, 13.57 Hz, 11.89 Hz), 3.54 (dd, 1H, J = 12.41 Hz, 13.57 Hz), 2.92 (qd, 1H, J = 7.03 Hz, 12.41 Hz), 1.39 (d, 3H, J = 7.03 Hz), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.65, 170.25, 74.99, 72.25, 58.36, 42.58, 38.96, 28.88, 18.40; IR (KBr) 2969.8, 1750.4, 1598.3, 1320.8, 1168.4, 1094.8 cm^{-1}; $[\alpha]_D^{20} = +12.0$ (c 0.5, $CHCl_3$); mp: 145–146 °C; HR-EIMS (positive mode) calculated for $C_{11}H_{17}NO_2S$ 227.0980, found 227.0979.

4.8. (2*E*,5*S*)-5-Hydroxy-2-methyl-4-thiobenzoylamino-pent-2-enoic acid methyl ester, 13

To a solution of unsaturated amino alcohol **6** (86.5 mg, 0.47 mmol, HCl salt) in DMF (0.5 mL) was added DIPEA (122 μL, 0.71 mmol) at 0 °C. After 5 min this solution was transferred to a solution of **12** (133.9 mg, 0.47 mmol) in DMF (0.5 mL) also at 0 °C. The mixture was then stirred at room temperature for 12 h, diluted with saturated NH_4Cl (5 mL) and extracted with ethyl acetate–benzene (3 × 25 mL, 3:1). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by gradient chromatography (ethyl acetate–hexane, 50:50–70:30) to give **13** (100 mg, 76.0%) and **14** (12.1 mg, 9%) as oils. **13** ^1H NMR ($CDCl_3$, 300 MHz) 8.58 (d, 1H, J = 7.61 Hz), 7.68–7.73 (m, 2H), 7.27–7.38 (m, 3H), 6.77 (dd, 1H, J = 1.43 Hz, 8.86 Hz), 5.54–5.62 (m, 1H), 3.89 (dd, 1H, J = 4.11 Hz, 11.29 Hz), 3.81 (dd, 1H, J = 4.11 Hz, 11.29 Hz), 3.66 (s, 3H), 3.64–3.67 (br, 1H), 1.97 (d, 3H, J = 1.43 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.00, 168.22, 141.43, 136.82, 131.67, 131.06, 128.61, 126.91, 63.32, 56.13, 52.03, 13.39; IR (film) 3307.2 (br), 2952.8, 2363.8, 1717.6, 1531.8, 1448.2, 1351.2, 1270.6, 1063.1, 953.4, 769.3, 692.3 cm^{-1}; $[\alpha]_D^{20} = +78.3$ (c 2.0, $CHCl_3$); HR-FABMS (positive mode) calculated for $C_{14}H_{18}NO_3S$ $[M+H]^+$ 280.1007, found 280.1005.

4.9. (4*R*,5*R*)-4-Hydroxymethyl-2-phenyl-(α*R*)-α-methyl-1,3-thiazoline acetic acid methyl ester 14

Method B: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74–7.77 (m, 2H), 7.42–7.46 (m, 1H), 7.34–7.38 (m, 2H), 4.57–4.60 (m, 1H), 4.16 (dd, 1H, J = 3.87 Hz, 7.34 Hz), 3.71–3.79 (m, 2H), 3.70 (s, 3H), 3.68–3.70 (br, 1H), 2.65–2.72 (m, 1H), 1.25 (d, 3H, J = 7.04 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.58, 168.65, 132.61, 131.41, 128.41, 128.20, 82.62, 64.13, 54.31, 51.99, 44.72, 14.34; IR (film) 3363.2 (br), 2948.7, 1733.5, 1603.1, 1451.8, 1348.3, 1208.2, 1060.0, 952.8, 768.6, 691.2 cm^{-1}; $[\alpha]_D^{20} = +126.2$ (c 4.5, $CHCl_3$); HR-FABMS (positive mode) calculated for $C_{14}H_{18}NO_3S$ $[M+H]^+$ 280.1007, found 280.1000.

4.10. (4*S*,5*S*)-Benzyl-2-*tert*-butyl-(α*R*)-α-methyl-1,3-thiazoline-acetic acid methyl ester 16

Method A: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23–7.37 (m, 5H), 4.51 (ddd, 1H, J = 1.80 Hz, 5.05 Hz, 8.23 Hz), 3.83 (dd, 1H, J = 1.80 Hz, 7.13 Hz), 3.54 (s, 3H), 2.96 (dd, 1H, J = 5.05 Hz, 13.45 Hz), 2.63 (dd, 1H, J = 8.23 Hz, 13.45 Hz), 2.35 (dq, 1H, J = 7.04 Hz, 7.13 Hz), 1.26 (s, 9H), 1.11 (d, 3H, J = 7.04 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.34, 173.70, 137.47, 129.05, 127.86, 125.94, 80.83, 55.08, 51.27, 44.65, 38.98, 37.44, 28.68, 13.16; IR (KBr) 2938.8, 1732.8, 1447.3, 1372.4, 1225.6, 1043.2, 937.9, 846.8, 786.3, 634.0, 608.5 cm^{-1}; $[\alpha]_D^{20} = -152.4$ (c 1.6, $CHCl_3$); HR-ESIMS (positive mode) calculated for $C_{18}H_{26}NO_2S$ $[M+H]^+$ 320.1684, found 320.1680.

4.11. (2*E*,4*S*)-2-Methyl-5-phenyl-4-thiobenzoylamino-pent-2-enoic acid methyl ester 17

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63–7.65 (m, 2H), 7.46–7.47 (d, 1H, J = 5.64 Hz), 7.26–7.44 (m, 8H), 6.67 (dd, 1H, J = 1.34 Hz, 9.12 Hz), 5.73–5.80 (m, 1H), 3.74 (s, 3H), 3.22 (dd, 1H, J = 5.32 Hz, 13.50 Hz), 3.21 (dd, 1H, J = 7.68 Hz, 13.50 Hz), 1.81 (d, 3H, J = 1.34 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.49, 167.89, 141.81, 137.84, 136.03, 131.84, 131.23, 129.60, 128.78, 128.58, 127.16, 126.63, 55.14, 52.13, 39.49, 13.29; IR (film) 3312.2 (br), 2947.6, 2359.8, 1715.4, 1530.7, 1447.3, 1348.2, 1269.6, 1061.1, 954.4, 769.3, 692.3 cm^{-1}; $[\alpha]_D^{20} = -45.3$ (c 2.0, $CHCl_3$); HR-FABMS (positive mode) calculated for $C_{20}H_{22}NO_2S$ $[M+H]^+$ 340.1371 found 340.1375.

4.12. (4*S*,5*S*)-Benzyl-2-phenyl-(α*R*)-α-methyl-1,3-thiazoline acetic acid methyl ester 18

Method B: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84–7.86 (m, 2H), 7.40–7.50 (m, 3H), 7.2–7.35 (m, 5H), 4.75 (ddd, 1H, J = 2.02 Hz, 5.49 Hz, 8.09 Hz), 4.00 (dd, 1H, J = 2.02 Hz, 7.28 Hz), 3.56 (s, 3H), 3.08 (dd, 1H, J = 5.49 Hz, 13.50 Hz), 2.75 (dd, 1H, J = 8.09 Hz, 13.50 Hz), 2.47 (dq, 1H, J = 7.28 Hz, 7.06 Hz), 1.17 (d, 3H, J = 7.06 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.44, 166.48, 138.03, 133.21, 131.33, 129.62, 128.61, 128.55, 128.44, 126.59, 82.14, 56.37, 51.92, 45.16, 39.74, 13.99; IR (KBr) 2983.89, 2939.7, 1736.2, 1372.7, 1234.0, 1044.7, 946.3, 769.0 cm^{-1}; $[\alpha]_D^{20} = -94.3$ (c 3.6, $CHCl_3$); HR-EIMS (positive mode) calculated for $C_{20}H_{22}NO_2S$ $[M+H]^+$ 340.1371, found 340.1366.

4.13. (4*S*,5*S*)-2-*tert*-Butyl-4-hydroxymethyl-1,3-thiazoline-acetic acid methyl ester 20

Method A: ^{1}H NMR ($CDCl_3$, 300 MHz) 4.35 (m, 1H), 3.99 (ddd, 1H, J = 4.38 Hz, 8.29 Hz, 6.59 Hz), 3.70 (s, 3H), 3.65 (dd, 1H, J = 6.12 Hz, 10.90 Hz), 3.63 (dd, 1H, J = 8.29 Hz, 10.90 Hz), 2.71 (dd, 1H, J = 8.29 Hz, 16.77 Hz), 2.63 (dd, 1H, J = 6.59 Hz, 16.77 Hz), 2.38–2.44 (br, 1H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 181.52, 171.63, 82.95, 63.54, 51.95, 46.97, 41.05, 38.14, 29.22; $[\alpha]_D^{20} = -172.8$ (c 1.3, $CHCl_3$). IR (film) 3376.3 (br), 2964.8, 1739.3, 1610.2, 1439.1, 1348.3, 1214.3, 1049.5, 985.2 cm^{-1}. HR-ESIMS (positive mode) calculated for $C_{11}H_{20}NO_3S$ 246.1164, found 246.1165.

4.14. (4*S*,5*S*)-4-Hydroxymethyl-2-phenyl-1,3-thiazoline-acetic acid methyl ester 21

Method A: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.75–7.81 (m, 2H), 7.35–7.48 (m, 3H), 4.55 (m, 1H), 4.21 (ddd, 1H, J = 4.82 Hz, 8.43 Hz, 6.39 Hz), 3.84 (dd, 1H, J = 5.61 Hz, 11.10 Hz) 3.78 (dd, 1H, J = 8.36 Hz, 11.10 Hz), 3.72 (s, 3H), 2.82 (dd, 1H, J = 8.43 Hz, 16.87 Hz), 2.74 (dd, 1H, J = 6.39 Hz, 16.87 Hz), 2.70–2.82 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 171.57, 168.83, 132.72, 131.51, 128.48, 128.28, 83.60, 63.54, 51.99, 47.32, 40.93; $[\alpha]_D^{20} = -139.3$ (c 2.8, $CHCl_3$). IR (film) 3393.6 (br), 2949.5, 1733.9, 1600.2, 1441.7, 1345.6, 1216.8, 1062.4, 951.9, 768.1, 691.3 cm^{-1}; mp: 108.5–109.7 °C; HR-ESIMS (positive mode) calculated for $C_{13}H_{16}NO_3S$ $[M+H]^+$ 266.0851, found 266.0848.

4.15. (4*S*,5*S*)-4-Benzyl-2-*tert*-butyl-1,3-thiazoline acetic acid methyl ester 23

Method A: ^{1}H NMR ($CDCl_3$, 400 MHz) 7.19–7.31 (m, 5H), 4.46 (ddd, 1H, J = 2.17 Hz, 4.98 Hz, 8.71 Hz), 3.79 (ddd, 1H, J = 2.17 Hz, 6.52 Hz, 8.63 Hz), 3.55 (s, 3H), 2.96 (dd, 1H, J = 4.98 Hz, 13.53 Hz), 2.60 (dd, 1H, J = 8.71 Hz, 13.53 Hz), 2.45 (dd, 1H, J = 8.63 Hz, 16.32 Hz), 2.36 (dd, 1H, J = 6.52 Hz, 16.32 Hz), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 178.72, 171.19, 137.92, 129.39, 128.40, 126.44 82.00, 51.68, 48.59, 41.49, 38.73, 37.81, 29.12; $[\alpha]_D^{20} = -202.9$ (c 2.3, $CHCl_3$). IR (film) 2964.4, 2927.7, 1739.8, 1616.0, 1453.9, 1437.9, 1363.4, 1252.7, 1220.1, 1161.0, 1046.7, 978.0, 745.4, 701.4 cm^{-1}; HR-ESIMS (positive mode) calculated for $C_{17}H_{24}NO_2S$ $[M+H]^+$ 306.1528, found 306.1526.

4.16. (4*S*,5*S*)-4-Benzyl-2-phenyl-1,3-thiazoline acetic acid methyl ester 24

Method A: ^{1}H NMR ($CDCl_3$, 400 MHz) 7.82–7.85 (m, 2H), 7.39–7.50 (m, 3H), 7.23–7.35 (m, 5H), 4.72 (ddd, 1H, J = 2.50 Hz, 5.36 Hz, 8.75 Hz), 3.98 (ddd, 1H, J = 2.50 Hz, 6.20 Hz, 9.00 Hz), 3.60 (s, 3H), 3.11 (dd, 1H, J = 5.36 Hz, 13.60 Hz), 2.74 (dd, 1H, J = 8.75 Hz, 13.60 Hz), 2.60 (dd, 1H, J = 9.00 Hz, 16.48 Hz), 2.49 (dd, 1H, J = 6.20 Hz, 16.48 Hz); ^{13}C NMR ($CDCl_3$,

100 MHz) 171.21, 166.31, 137.92, 133.18, 131.30, 129.37, 128.54, 128.48, 128.38, 126.57, 82.80, 51.78, 49.24, 41.43, 39.01; $[\alpha]_D^{20} = -131.0$ (*c* 2.1, $CHCl_3$). IR (film) 3027.7, 2949.9, 2927.1, 1737.2, 1601.5, 1493.2, 1441.2, 1234.1, 1171.7, 944.1, 767.2, 693.7 cm^{-1}. HR-ESIMS (positive mode) calculated for $C_{19}H_{20}NO_2S$ $[M+H]^+$ 326.1215, found 326.1215.

Acknowledgments

We thank The University of Hong Kong and The Hong Kong Polytechnic University (PolyU5285 /02P, Project G-T628) for their support.

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