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# Synthesis and Structural Study of piperazine-2,5-diones derived from (R)-cysteine

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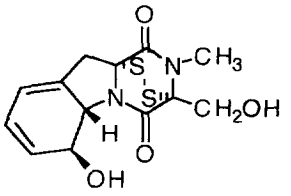
**Abstract:** Coupling Leuch´s anhydrides obtained from (R)-thiazolidine-4-carboxylic acids **1** and **3** with one equivalent of the corresponding ethyl ester derivative of **1** or **3**, leads to the formation of chiral piperazine-2,5-diones **2**, **4**, **5**, **6**, and **7**, on thermal treatment of the intermediate dipeptides. The configuration of the products was established by nOe experiments.

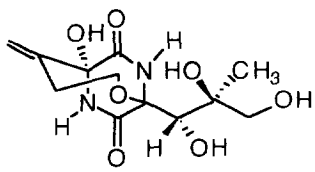
## Introduction

Piperazine-2,5-diones (diketopiperazines, DKPs) are amongst the most numerous and common of the cyclic dipeptides found in nature and the first examples of synthetic derivatives go back to the early days of Organic Chemistry[2]. Recently, there has been a growing interest in this group of natural products. The study of piperazine-2,5-diones has played an important role, in basic organic[3], structural[4] and medicinal chemistry[5]. Although a number of compounds have been discovered which catalyse the asymmetric addition of cyanide to aldehydes, giving optically active cyanohydrins, the most widely studied and effective catalyst (30-100% ee depending on the aldehyde) for this reaction is the cyclic dipeptide *cyclo*[(S)-phenylalanyl-(S)-histidyl][6]. Furthermore, *cyclo*[(S)-Val-Gly] and related compounds have played an important role in the asymmetric synthesis of a wide variety of chiral compounds (Schöllkopf´s methodology)[7]. Some DKPs show antiviral properties (for example **gliotoxin**[8]) and others are powerful antibiotics (for example **bicyclomycin**[9]).

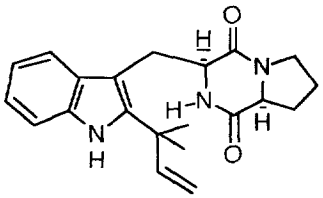
It is interesting to note the relatively large number of proline derivatives within this class of compounds (for example **desoxybrevianamide E**[10]), which have the characteristic fused *5,6* ring system. Among the sulphur-bridged piperazine-2,5-diones that contain the fused *5,5,6* skeleton, **Aranotin**[11] and related compounds have considerable resemblance to gliotoxin and also possess antiviral activity.



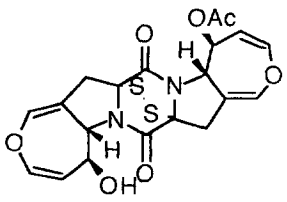
gliotoxin



bicyclomycin



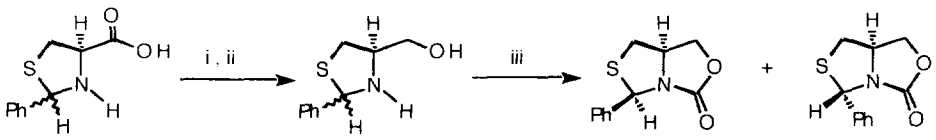
Desoxybrevianamide E



Aranotin

In the context of our efforts to obtain new protected forms of (R)-cysteine , we first developed a three step protocol for the conversion of (R)-thiazolidine-4-carboxylic acids, prepared from (R)-cysteine, to *bicyclic* thiazolidine derivatives[12] (Scheme 1). This procedure gives access to enantiomerically pure compounds after flash chromatography in a diastereoisomeric cis :trans ratio of 4.5:1.The generality of the process was demonstrated by preparation of the *tert*-butyl derivatives in moderate yields using the same procedure.

We wish to report herein the synthesis and characterisation of *tricyclic* piperazine-2,5-diones based on (R)-cysteine.



3 cis trans

**Scheme 1**

(i) EtOH, $SOCl_2$ (ii) $CaCl_2$, $NaBH_4$, EtOH ; (iii) $COCl_2$, toluene, 2N NaOH, $CH_2Cl_2$

## Results and discussion

### Synthesis

Both the *cyclo*[(S)-Pro-(S)-Pro] and *cyclo*[(S)-Pro-(R)-Pro] have been prepared by cyclisation of N-protected dipeptide methyl esters, obtained using DCCI coupling, by treatment with methanolic ammonia[13].

A survey of the literature revealed that little information on the formation of piperazine-2,5-diones derived from thiazolidine-4-carboxylic acid derivatives was available. Several *tricyclic* piperazine-2,5-diones were obtained from penicillamine in early investigations of the structure of penicillin[14]. Later, Györgydeák et al., reported that (R)-thiazolidine-4-carboxylic acid **1** could be dimerized to

diketopiperazine **2** (Scheme 2) using methane sulphonyl chloride at room temperature[15]. However, neither the yield nor the NMR data were mentioned and only the infra-red spectrum and the melting point (mp=290°C) were reported (we found mp=170-72°C). Korytnyk et al., reported the preparation of a *tricyclic* piperazine-2,5-dione obtained unexpectedly by treatment of (R)-2-(p-tolil)thiazolidine-4-carboxylic acid with DCCI and diazomethane[16].

A convenient method for the preparation of symmetrically substituted piperazine-2,5-diones involves refluxing the corresponding α-aminoacid (also the ethyl ester or the unprotected dipeptide) in phenol[17]. First, we examined the reaction of (R)-thiazolidine-4-carboxylic acid **1** under standard reaction conditions (heating under $N_2$ atmosphere in phenol at 140-50°C) without success. Second, treatment of (R)-2-phenylthiazolidine-4-carboxylic acid **3** under identical conditions did not yield the expected dimer either. In light of these preliminary results, we turned our attention to a stepwise synthesis of piperazine-2,5-diones[18].

The general features of the procedure involve : (i) preparation of the N-carboxy-α-aminoacid anhydride (Leuchs' anhydride) of the (R)-thiazolidine-4-carboxylic acid derivative, (ii) coupling the anhydride with the ethyl ester of the corresponding (R)-thiazolidine-4-carboxylic acid derivative to generate the first amide bond, and (iii) thermal treatment of the open dipeptide to form the second amide bond and release the *tricyclic* dipeptide .

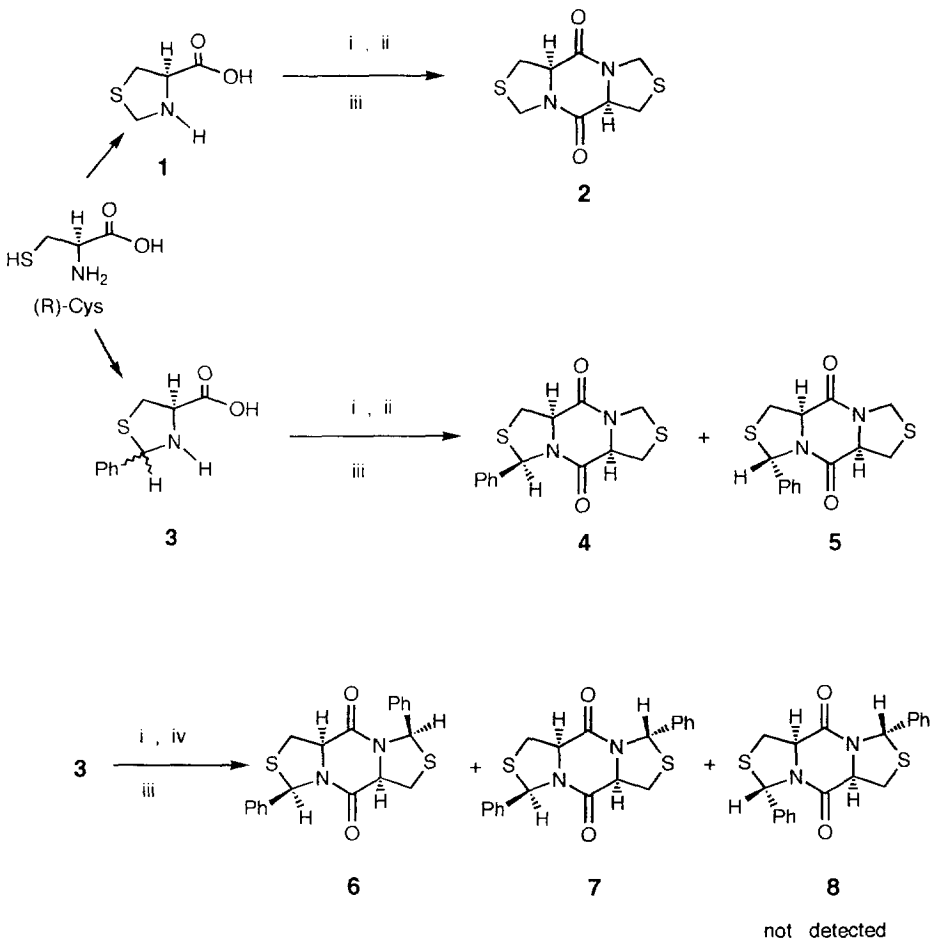
A simple synthesis of the DKP **2** in good overall yield was achieved from the known thiazolidine **1**[19]. This was reacted with phosgene in toluene at -30°C to room temperature overnight to afford Leuchs' anhydride[20]. Treatment of the anhydride with ethyl (R)-thiazolidine-4-carboxylic acid at -60°C to room temperature overnight , furnished an intermediate amide, which was immediately treated without purification to give DKP **2** upon stirring at reflux in toluene (Scheme 2). This synthesis from **1** proceeded in a good 80 % overall yield.

Compound **3**, in turn, could be readily transformed to the DKPs **4** and **5**. The known thiazolidine **3** [21] ( a 1:1 mixture of two epimers at C-2) reacted with phosgene to give Leuchs' anhydride. This was converted to the intermediate amide, which was cyclized to give a 72% yield of the separable diastereoisomeric DKPs **4** and **5** in a 1.5:1 ratio. After separation by flash chromatography , these DKPs were individually studied by NMR spectroscopy.

Thiazolidine **3** (two epimers), upon treatment with phosgene and ethyl (R)-2-phenylthiazolidine-4-carboxylic acid (also two epimers) afforded only two DKPs **6** and **7** (Scheme 2) in 64% yield in a 1.5:1 ratio (note that the statistical **6**:**7**:**8** ratio should be 1:2:1). The final composition of the mixture was determined by 200 MHz $^1H$ NMR spectral analysis of the crude sample and the results reflected the diastereoselection dictated by the thiazolidine ring opening-ring closure[12,22]. Proof of the structure of **6** and **7** follows from detailed NMR studies.

**NMR**

The individual isomers **4** and **5** (Scheme 2) were separated by chromatography and characterised by their analytical and spectroscopic properties. However, the structure of both epimers could not be assigned unambiguously solely on the basis of their $^1H$ and $^{13}C$ NMR chemical shifts. Instead, identification was made with the aid of differential n.O.e. experiments[23] (300MHz). Thus, for the major isomer, irradiation of the DKP ring proton at 4.71 ppm , enhanced




**Scheme 2**

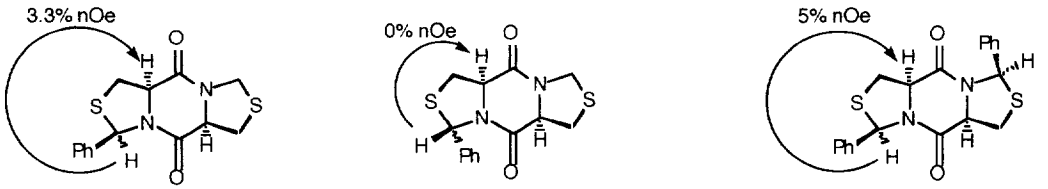
(i) $COCl_2$, toluene, THF, -30°C to room temp., overnight ; (ii) , $CH_2Cl_2$ , -60°C to room temp.,overnight

(iii) toluene at reflux, 2.5 h; (iv) , $CH_2Cl_2$ , -60°C to room temp., overnight

(3.3%) the benzylic proton signal at 6.2 ppm (cis **4**) (Figure 1). On the other hand, for the minor isomer, irradiation of the DKP ring proton at 4.71 ppm had no effect on the benzylic proton signal at 6.4 ppm (trans **5**) (Figure 1).

In the last example, ring closure (Scheme 2) may generate two new stereogenic centres and consequently might be expected to allow the formation of four possible diastereoisomers. However, only the three diastereoisomers **6**, **7** and **8** are possible, due to considerations of symmetry. Both **6** and **8** have a $C_2$ symmetry element whilst **7** is devoid of this feature.

The point may be further discussed if we consider the configurations of the two phenyl-substituted stereogenic centres on the five-membered rings. If the four asymmetric centres are listed, with those of the DKP ring in the middle, **6** has the configuration (R,R,R,R) , **8** is (S,R,R,S) and **7** corresponds to (S,R,R,R) which is the same as (R,R,R,S).




**4** **5** **6**

**Figure 1**

The identity of the two isolated diastereoisomers was established due to the simple NMR spectra of the $C_2$ symmetric diastereoisomer **6** (or **8**) compared with those of compound **7**. The cis (**6**) or trans (**8**) stereochemistry of the former was unequivocally determined on the basis of n.O.e. difference $^1H$ NMR experiments. So, the signal due to the DKP ring proton at 4.8 ppm showed significant n.O.e. enhancement (5%) when the benzylic proton at 6.2 ppm was selectively irradiated (Figure 1). This result supports the assignment of structure **6** to the compound.

In conclusion, we have applied a convenient protecting method for the amino, thiol, and carboxylic acid funtions of (R)-cysteine by using the readily available thiazolidine-4-carboxylic acid derivatives which undergo diastereoselective ring-closure reactions to afford chiral piperazine-2,5-diones.

## EXPERIMENTAL PART

**General.** All solvents were dried by standard methods. All reagents were of commercial quality from freshly opened containers. Column chromatography was carried out on $SiO_2$ (silica gel 60, Merck 0.063-0.200 mm) . TLC was carried out on $SiO_2$ (silica gel 60F 254 Merck, 0.063-0.200 mm) and the spots located with UV light or iodine vapors. Melting points were taken using a Büchi apparatus and are uncorrected. Microanalyses were performed on a Carlo-Erba 1106 analyzer by Centro de Investigación y Desarrollo (CSIC) Barcelona. $^1H$ and $^{13}C$ NMR spectra were obtained using a Varian XL-200 instrument in $CDCl_3$ with TMS as an internal reference,

unless otherwise specified. The assignments of $^{13}C$ NMR signals were made with the aid of DEPT sequence. IR spectra were recorded on a Perkin Elmer 1600 series FTIR. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

**General Procedure**: Phosgene (10.4 mL, 1.93M solution in toluene, 0.02 mmoL) was added to a solution of the (R)-thiazolidine-4-carboxylic acid derivative (**1** or **3** ) (0.01 mmoL) in THF (50 mL) at -30°C.The reaction mixture was allowed to warm to room temperature overnight under stirring. The clear solution was evaporated under reduced pressure without heating (bath temp. below 40°C). The oily residue was dissolved in dichloromethane (35 mL) and cooled to -60°C. Then a solution of the ethyl ester derivative of the corresponding (R)-thiazolidine-4-carboxylic acid ( **1** or **3** ) (0.01 mmoL) in dichloromethane (35 mL) was added dropwise, followed by solid $K_2CO_3$ (2.76 g, 0.02 mmoL) and stirring was continued overnight at room temperature. The solid is removed by filtration and the filtrate was evaporated under vacuum. The resulting product was dissolved in toluene (50 mL) and refluxed under stirring for 2.5 h. Removal of the solvent afforded the crude *tricyclic* piperazine-2,5-dione .

**(5aR, 10aR)-tetrahydro-3H,5H,8H, 10H-bisthiazolo[3,4-a: 3´,4´-d]pyrazine-5,10-dione 2.-**

Purification of the crude sample by chrystallization in ethanol afforded 1.82g (80%)of **2** as a white solid. M.p.=170-72°C. IR(KBr): 1655, 1420, 1296, 1189, 1130, 780, 724, 622 $cm^{-1}$. $^1H$ NMR (DMSO): δ 4.69 (d, J=9.9Hz, 1H), 4.66 (t, J=7.0Hz, 1H), 4.39 (d, J=9.9Hz, 1H), 3.3 (dd, J=7.0Hz, J=2Hz, 2H). $^{13}C$ NMR (DMSO): δ164.1 (C=O), 61.9 (CH), 48.2 ($CH_2$), 31.8 ($CH_2$). $[\alpha]_D^{20}$=-35 (c=0.4, $CHCl_3$). MS: 230 ($M^+$, 71), 197 (15), 184 (100), 156 (17), 127 (15), 88 (41), 86 (43), 59 (43), 55 (83) . Anal. calc.for $C_8H_{10}N_2O_2S_2$: C, 41.72; H, 4.38; N, 12.17%; found: C, 41.82; H, 4.32; N, 12.02%.

**(3R,5aR,10aR)-3-phenyltetrahydro-3H,5H,8H,10H-bisthiazolo[3,4-a: 3´,4´-d]pyrazine-5,10-dione 4 and (3S,5aR,10aR)-3-phenyltetrahydro-3H,5H,8H,10H-bisthiazolo[3,4-a: 3´,4´-d]pyrazine-5,10-dione 5.-**

The diastereoisomeric DKPs were separated by flash chromatography. Hexane/ether (1:1) eluted first diastereoisomer **5** (0.8g, 26%), a small amount of mixture (0.2g, 7%), and second, ether/$CH_2Cl_2$ (1:1) eluted diastereoisomer **4** (1.2g, 39%), corresponding to a total yield of 72% from **3**.

Analytical data for diastereoisomer **5**: M.p.=oil. IR(KBr): 1670, 1401, 1298, 1204, 911, 726 $cm^{-1}$. $^1H$ NMR: δ 7.4-7.2 (m, 5H), 6.4 (s, 1H), 4.8 (d, J=10.5Hz, 1H), 4.71 ( t, J=6.5Hz, 1H), 4.52 (t, 6.0Hz, 1H), 4.50 (d, J=10.5Hz, 1H), 3.63-3.30 (m, 4H). $^{13}C$ NMR: δ 163.2, 162.7 (2C=O), 138.8, 128.5, 128.3, 126.4 (Ph), 65.2, 62.9, 62.2 (3CH), 48.4, 2.7, 32.5 ($3CH_2$). $[\alpha]_D^{20}$=-82 (c=0.2, $CHCl_3$). MS: 306 ($M^+$, 100), 273 (33), 260 (97), 222 (25), 193 (32), 191 (30), 162 (41),
122 (65), 121 (83), 88 (58), 86 (57), 77 (29), 55 (84) . Anal.calc.for $C_{14}H_{14}N_2O_2S_2$: C, 54.87; H, 4.61; N, 9.14%; found: C, 54.40; H, 4.20; N, 9.01%.

Analytical data for diastereoisomer **4**: M.p.=182-83°C (white solid). IR(KBr): 1655, 1417, 1240, 718 $cm^{-1}$.$^1H$ NMR: δ 7.4-7.1 (m, 5H), 6.2 (s,1H), 4.9 (d, J=10.1Hz, 1H), 4.71 (q, J=10.8Hz,

J=6.0Hz, 1H), 4.52 (q, J=11Hz, J=7.0Hz, 1H), 4.50 (d, J=10.1Hz, 1H), 3.54-3.29 (m, 4H). $^{13}C$ NMR: δ 164.4, 163.9 (2C=O), 140.9, 128.8, 128.1, 124.7 (Ph), 64.9, 64.6, 63.2 (3CH), 48.6, 32.5, 30.2 ($3CH_2$). $[\alpha]_D^{20}$=+16 (c=0.2, $CHCl_3$). MS: 306($M^+$, 100),272 (30), 260 (77), 222 (19),193 (18),191 (25), 162 (29), 122 (86), 121 (66), 88 (63), 86 (55), 77 (27), 55 (55) . Anal.calc.for $C_{14}H_{14}N_2O_2S_2$: C, 54.87; H, 4.61; N, 9.14%; found: C, 54.49; H, 4.28; N, 9.52%.

**(3R,5aR,8R,10aR)-3,8-diphenyltetrahydro-3H,5H, 8H,10H-bisthiazolo[3,4-a: 3´,4´-d]pyrazine-5,10-dione 6 and (3S,5aR,8R,10aR)-3,8-diphenyltetrahydro-3H,5H,8H,10H-bisthiazolo[3,4-a: 3´,4´-d]pyrazine-5,10-dione 7.-**

The diastereoisomeric DKPs were separated by flash chromatography. Ether/$CH_2Cl_2$ (8:2) eluted first diastereoisomer **6** (1.3g, 34%), a small amount of mixture (0.3g, 8%), and second, $CH_2Cl_2$ eluted the diastereoisomer **7** (0.85g, 22%), corresponding to a total yield of 64% from **3**.

Analytical data for diastereoisomer **6**: M.p.=172-74°C (amorph, white solid). IR(KBr): 1684, 1383, 715, 695 $cm^{-1}$. $^1H$ NMR: δ 7.4-7.1 (m, 10H), 6.22 (s,1H), 4.8 (q, J=10.6Hz, J=6.5Hz, 2H), 3.52(q, J=12.6Hz, J=10.6Hz, 2H), 3.3 (q, J=12.6Hz, J=6.5Hz, 2H). $^{13}C$ NMR: δ 164.4 (C=O), 141.5, 128.8, 128.2, 124.8 (Ph), 65.3 (CH), 64.2 (CH), 29.9 ($CH_2$). $[\alpha]_D^{20}$=+17 (c=0.2, $CHCl_3$). MS: 382 ($M^+$, 15), 349 (32), 336 (43), 295 (18), 230 (12), 162 (100), 130 (33),122 (52), 121 (77), 86 (44), 77 (33), 59 (52) . Anal.calc.for $C_{20}H_{18}N_2O_2S_2$: C, 62.80; H, 4.74; N, 7.33%; found: C, 62.66; H, 4.88; N, 6.98%.

Analytical data for diastereoisomer **7**: M.p.=219-20°C (crystal., white solid). IR(KBr): 1667, 1407, 1291, 717, 697 $cm^{-1}$. $^1H$ NMR: δ 7.5-7.1 (m, 10H), 6.6 (s,1H), 6.25 (s, 1H), 4.75 (m, 2H), 3.7-3.2 (m, 4H).$^{13}C$ NMR: δ 164.4, 163.9 (2C=O), 140.9, 138.7,128.8,128.7, 128.5, 128.2, 126.4, 124.9 (2Ph), 65.7, 64.9, 64.5, 63.7 (4CH), 32.4, 30.2 ($2CH_2$). $[\alpha]_D^{20}$=-15 (c=0.2, $CHCl_3$). MS: 382 ($M^+$, 11), 349 (28), 336 (37), 295 (15), 230 (10), 162 (100), 130 (38), 122 (61), 121 (91), 86 (53), 77 (43), 55 (81). Anal.calc.for $C_{20}H_{18}N_2O_2S_2$: C, 62.80; H, 4.74; N, 7.33%; found: C, 62.94; H, 4.58; N, 6.96%.

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