# SYNTHESIS OF ASPIROCHLORINE PRECURSORS

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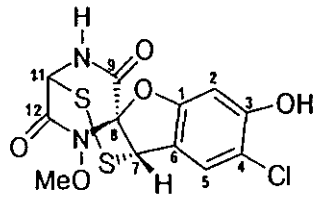
**Abstract**-Synthesis of key precursors of aspirochlorine (**1**) and related compounds has been achieved in 5 steps from 1,4-diacetyl-2,5-piperazinedione (**2**). MCPBA mediated oxidative cyclization of 1-acetyl-3-salicylidene-2,5-piperazinedione (**4**) yielded a spiro 3*H*-benzofuranol derivative (**6**) stereoselectively. Bromination of **6** by a 2-fluoropyridinium salt and sodium bromide, followed by NBS treatment yielded dibromide mixtures (**8**). Conversion of produced dibromides (**8**) to dithioacetates (**9**) by potassium thioacetate afforded all of four possible diastereomers. The ratio of the diastereomers was found to be solvent dependent.

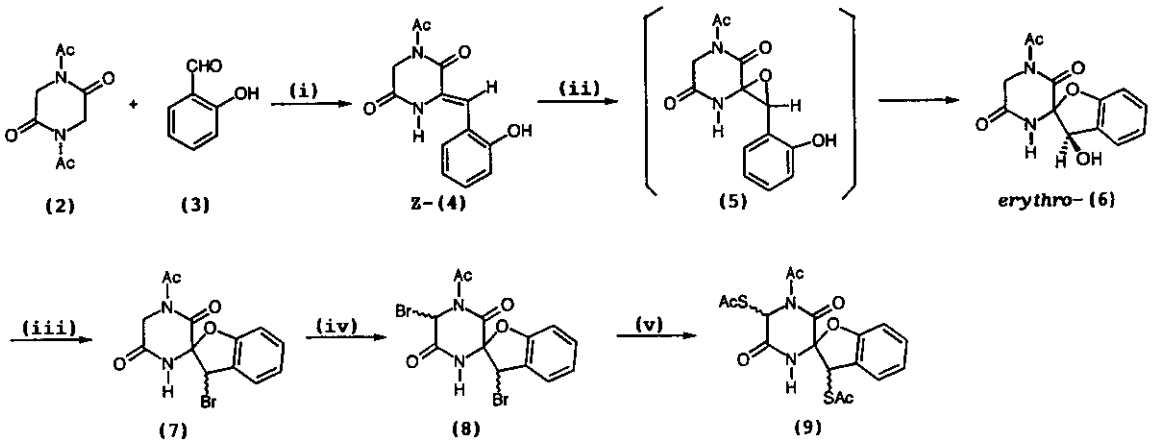
An antibiotic aspirochlorine (A 30641) was found in a culture of *Aspergillus tamari NRRL 8101* [1] and exhibited a good activity spectrum against Gram positive bacteria and fungi.[2] Although C-C bridged epidithio-2,5-piperazinedione moieties are common to the class of fungal metabolites including gliotoxins, aranotins, and others,[3] the structure of aspirochlorine (**1**) possesses an epidithio bridge which exceptionally locates across piperazinedione and furan rings of the spiro[3*H*-benzofuran-2,3'-

(2',5'-piperazinedione)] skeleton.[4] Its unique structure has made it the target of several synthetic studies.[5,6] Williams and Miknis[5] described an elegant synthesis of (±)-aspirochlorine. Coumarilic acid was selected by them as a starting material and after introduction of a side chain necessitated for construction of the piperazinedione part of the spiro ring, the tricyclic system was accomplished by means of an *N*-bromosuccinimide (NBS) mediated oxidative cyclization. Although Williams' approach is one of efficient methods to construct a spirobenzofuran structure, we have attempted synthesis of the aspirochlorine skeleton starting from 2,5-piperazinedione itself, because we have been investigating reactivity and synthetic applicability of 2,5-piperazinedione derivatives.[7] Here, we describe synthesis of spiro[3*H*-benzofuran-2,3'-(2',5'-piperazinedione)] derivatives by use of stereocontrolled formation of the quaternary center in a single step, which serve as synthetic intermediates of aspirochlorine and related compounds.



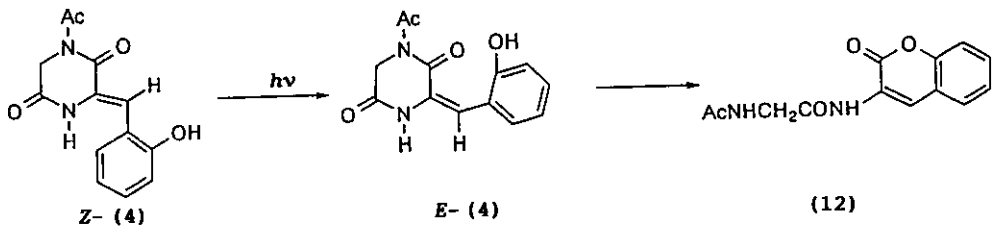
ASPIROCHLORINE(1)

The present synthetic pathway to a spirobenzofuran ring is shown in Scheme 1. A potassium *t*-butoxide (*t*-BuOK) catalyzed condensation of 1,4-diacetyl-2,5-piperazinedione (**2**) with salicylaldehyde (**3**) gave (*Z*)-1-acetyl-3-salicylidene-2,5-piperazinedione ((*Z*)-**4**).[8] Stereochemistry of (*Z*)-**4** was deduced by $^1$H NMR spectroscopy. (*Z*)-**4** isomerized under ambient light to give (*E*)-**4**, which was spontaneously converted into a 3-aminocoumarine derivative (**12**) as shown in Scheme 2.[6] NBS mediated cyclization of (*Z*)-4 to spirobenzofuran derivatives was examined under various conditions. However, products were found to be mixtures of brominated products which were too hard to separate by column chromatography. Peracid oxidation of **4** may give an oxiran (**5**)[9], from which a spirobenzofuran ring could be prepared through nucleo-



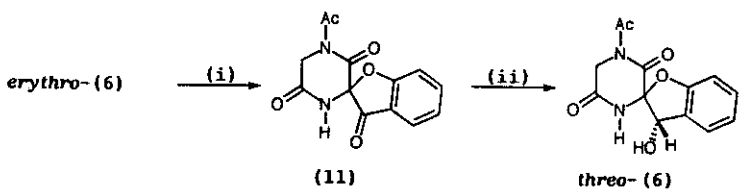

(i) *t*-BuOK, DMF (ii) MCPBA, $NaHPO_3$, $CH_2Cl_2$ (iii) (a) 1-Methyl-2-fluoropyridinium *p*-toluenesulfonate, $Et_3N$, MeCN (b) NaBr (iv) NBS, AIBN, $CCl_4$ (v) AcSK, MeCN

Scheme 1




Scheme 2

phlic displacement at the quarternary carbon center of **5** by the phenolic oxygen atom.[10] The epoxidation of **4** was achieved by *m*-chloroperbenzoic acid (MCPBA) in dichloromethane to give a single product. The IR and $^1H$ NMR spectra of this compound did not conform to those of the expected oxiran structure of **5**. Oxidation of this compound by $MnO_2$ yielded a carbonyl compound (**11**) (Scheme 3), and methylation gave a corresponding methoxy derivative, so that the presence of a secondary hydroxy group was suggested. $^{13}C$ NMR spectra of the methoxy com-




(i) $MnO_2$, $CHCl_3$ (ii) Pd/C, EtOH

Scheme 3

pound had quite similar NMR feature to that of aspirochlorine (**1**). Particularly, the $^{13}C$ spectra of this compound revealed the presence of a quarternary carbon atom signal (93.3 ppm), which corresponded to that (102.6 ppm) of aspirochlorine.[11] This and other spectral feature indicated the structure to be a 1-oxa-6,9-diaza-2,3-benzospiro[5,4]-decane system (an aspirochlorine skeleton) as depicted in Scheme 1. Thus, MCPBA oxidation of (*Z*)-**4** yielded an oxiran derivative (**5**), which was undergone spontaneous intramolecular nucleophilic oxiran ring opening by the phenolic hydroxy group. Because **4** possessed (*Z*)-configuration, the stereospecific oxygen atom insertion by MCPBA occurred evenly to the *re-re* and *si-si* faces of the double bond to give (*R*,S*)-**5** and (*S*,R*)-**5**, respectively.[12] Following nucleophilic displacement by the phenolic hydroxy group at the quarternary carbon center should produce (*4S*,5S*)-**6** from (*R*,S*)-**5** and (*4R*,5R*)-**6** from (*S*,R*)-**5**, respectively (the racemic **6** was called as *erythro*-**6**, hereafter). Then, the structure of **6** was unambiguously determined by single crystal X-Ray analysis. In order to obtain a fine single crystal, and a more likely model of aspirochlorine, the hydroxy group was acetylated and 3-methoxy and 4-chlorine substitutes were introduced. (Figure 1) 2,4-Dihydroxybenzaldehyde was methylated by methyl iodide and sodium hydride in DMF to give 2-hydroxy-4-methoxybenzaldehyde. Chlorination of this compound by *m*-chlorosuccinimide and hydrochloric acid in chloroform gave 5-chloro-2-hydroxy-4-ethoxyzenzaldehyde. The condensation of this benzaldehyde derivative with

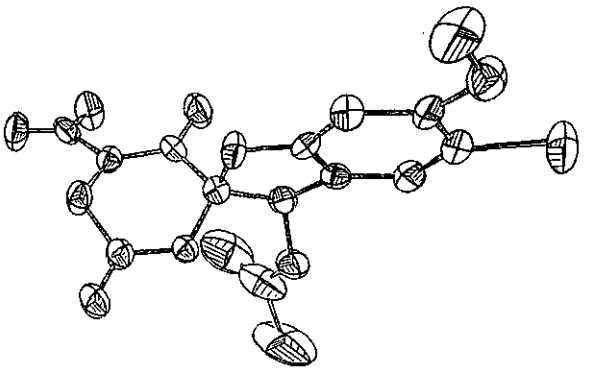


Figure 1 The ORTEP drawing of an *erythro*-(**6**) derivative.
The hydroxy function was protected by acetyl group and 3-methoxy and 4-chloro-substituents were introduced.

2,5-piperazinedione (60%), and following MCPBA oxidation (78%) were performed by the same procedures described above to give a derivative of **6** having 4-chloro-3-methoxy substituents on the phenyl ring. Next, in order to replace the hydroxy group of *erythro*-**6** with a bromine atom, *erythro*-**6** was successively treated with 1-methyl-2-fluoropyridinium *p*-toluenesulfonate and potassium or sodium bromide[15] under various conditions to give mixtures of *erythro* - and *threo* -**7** ( *erythro* : *threo* =2-3:1, Table 1) in 83-91%. In all cases, *erythro* -**7** was produced predominantly, although Mukaiyama[13] reported that this pyridinium salt-metal bromide mediated bromination of secondary alcohols proceeded through direct displacement to give clean inversion of configurations. The configuration at the benzylic positions of these monobromides (**7**) was determined by $^1$H NMR experiments. Irradiation of the benzylic proton (6.52 ppm) of the major bromide did not give NOE enhancement of the NH proton signal (9.83 ppm). On the other hand, similar irradiation of the minor bromide (6.22 ppm) resulted in significant enhancement of the NH proton signal (9.88 ppm). Thus the *erythro* stereochemistry was assigned to the major diastereomer. The down field parts (4.45 ppm) of an AB-type signal of the piperazinedione ring protons of *erythro*-**7** revealed double doublet splitting. This characteristic indi-

Table 1 Conversion of spirobenzofuranol (*erythro*-**6**) to monobromides (**7**) by 1-methyl-2-fluoropyridinium *p*-toluenesulfonate and metal bromides

| Metal bromide[a)] | Solvent | Product yield/%[b)] (*erythro* -**7** : *threo* -**7**) | |
|---|---|---|---|
| KBr | $CH_3CN$ | 83 | (59 : 24) |
| NaBr | $CH_3COCH_3$ | 88 | (60 : 28) |
| NaBr | $CH_3CN$ | 91 | (68 : 23) |

a) 3.0-3.1 equivalents of the reagents were used. b) Reaction was carried out for 24 h, and isolated yields are given.

cated that *erythro*-**7** holds a flattened chair shaped piperazinedione ring similar to that of *erythro*-**6**, so that the *equatorial* methylene proton is forced to be coplanar with the NH proton. In contrast, NOE experiments for *threo* -**7** revealed that it holds a flattened boat shaped piperazinedione ring, hence its flag-pole proton located in close proximity with the NH proton as well as with the benzylic proton. Bromination of *threo*-**6**, which was obtained from *erythro*-**6** by $MnO_2$ oxidation and Pd/C catalyzed hydrogenation (Scheme 3), gave rise to *erythro*-**7** predominantly ( *erythro;threo* =8:1). *Erythro*-**7** was treated with NBS in carbon tetrachloride to give a 1:1 diastereomer mixture of 3,6'-dibromides (**8**). Conversion to dithioacetate (**9**) was performed using the crude diastereomer mixture of **8**. Thus treatment of the mixture with potassium thioacetate in acetonitrile gave three (**9a**, **9b**, **9c**) of possible four diastereomeric dithioacetates in 29, 26, and 6 % yields, respectively. The reaction was highly solvent dependent as described in Table 2, and all four diasteromers could be obtained by changing reaction conditions. In addition, a 3-bromo-6'-acetylthio derivative (**10**) was produced in some cases. Stereochemistry of these dithioacetates was determined by $^1H$ NMR and X-Ray crystallography. The structure

Table 2 Conversion of monobromides (**7**) to dithioacetates (**9**)[a)]

| Monobromide(**7**) | Solvent | Reaction time/h | Product yields/%[b)] **9a** | **9b** | **9c** | **9d** | **10** | Recovered **7** |
|---|---|---|---|---|---|---|---|---|
| *Erythro*-**7** | $CH_3CN$ | 24 | 29 | 26 | 6 | | | |
| | $CH_3COCH_3$ | 0.5 | | | | 28 | | 25 |
| | $CH_3COCH_3$ | 24 | 58 | | | | 7 | 12 |
| | $CH_2Cl_2$ | 24 | 16 | | 4 | | 9 | 22 |
| *Threo*-**7** | $CH_3CN$ | 24 | 14 | | | | | 24 |
| | $CH_2Cl_2$ | 24 | 12 | | | | | 9 |

a) Bromination of **7** by NBS, followed by treatment with potassium thioacetate (see Exp.). b) Isolated yields.

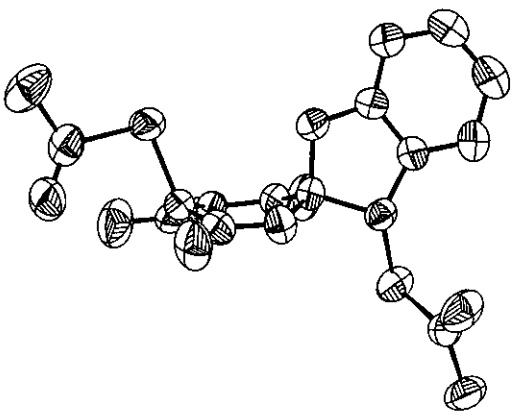
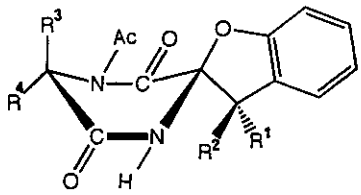


Figure 2

The ORTEP drawing of dithioacetate (9b)




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| 9a | H | SAc | SAc | H |
| b | SAc | H | SAc | H |
| c | H | SAc | H | SAc |
| d | SAc | H | H | SAc |

Figure 3 Configuration of 9a-d

The ORTEP drawing of 9b is given in Figure 2.

**9b** was first determined by single crystal X-Ray diffraction and the result is depicted in Figure 2, which indicates the piperazinedione ring to be a flattened boat form possessing an axial acethylthio group. Irradiation of the benzylic proton (5.60 ppm) resulted in significant NOE enhancement of the NH proton (7.50 ppm), and the piperazinedione ring protons (6.67 ppm) were splitted by the long ranged NH proton. Stereochemistry of other isomers (**9a**, **9c**, **9d**) was deduced by considering the NOE enhancement and the long rang coupling pattern. The piperazinedione ring protons were split to doublets in **9a** and **9b**, but were singlets in **9c** and **9d**. Irradiation of the benzylic protons of **9a** and **9c** resulted in slight enhancement of the corresponding NH protons, but those of **9b** and **9d** showed significant NOE enhancement of the NH protons. Chemical shifts of respective protons were also took into accounts to deduce the stereochemistry by comparing those of known piperazinedione derivatives,[14-17] and results are depicted in Figure 3. The synthesized stereoisomers of dithioacetylated spirobenzofuran derivatives may be employed for syntheses of aspirochlorine and related compounds[18] by the oxidative cleavage of the thioacetate.

## EXPERIMENTAL

The melting points were taken on a micro hot-plate melting point apparatus and are uncorrected. The IR spectra were recorded on a HITACHI I-2000 spectrophotometer. $^{1}H$ and $^{13}C$ NMR spectra were determined using JEOL JNM-60, FX-90Q and BRUCKER AC-250 spectrometers, and chemical shifts are given in ppm downfield from TMS. The mass spectra were recorded on ESCO EDM-05A and SHIMAZU GCMS-QP2000A spectrometers. Analytical thinlayer chromatography (TLC) was carried out using Merk Kieselgel 60F254 aluminum sheets. Column chromatography was performed using silica gel (200 mesh) purchased from Wako Pure Chemical Industries Ltd. Solvents were purified as usual.

**(*Z*)-1-Acetyl-3-salicylidene-2,5-piperazinedione (4)**

To a solution of 1,4-diacetyl-2,5-piperazinedione (**2**) (3.9 g, 19.8 mmol) and salicylaldehyde (**3**) (3 mL, 28.7 mmol) in anhydrous DMF (50 mL), *t*-BuOK (2.4 g, 21.4 mmol) in *t*-butyl alcohol (40 mL) was added slowly at 0°C with stirring. The mixture was kept in the dark at rt overnight. The reaction was quenched by adding a small amount of acetic acid, and the mixture was poured into 300 mL of icewater. The precipitates were collected, washed thoroughly with icewater, and pressed dry by squeezing the water. The crude product was recrystallized from acetonitrile to give 3.9 g of **4** (76%); mp 209.2-211.1°C ; $^{1}H$ NMR (60 MHz, DMSO-$d_6$): $\delta$ =2.46(3H, s), 4.26(2H, s), 6.6-7.5(5H, m), 9.83(1H, br s), and 10.38(1H, br s); IR (KBr):$\upsilon$ =3080, 1710, 1680, 1430, 1256 $cm^{-1}$; MS: m/z=260($M^+$), 259($M^+$-H), 218($M^+$-Ac), 201($M^+$-Ac and OH); Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found; C, 59.93; H, 4.87; N, 10.69.

**Spiro[3*H*-3-hydroxybenzofuran-2,3'-(1'-acetyl-2',5'-piperazinedione)] (*erythro*-6)**

To a solution of the salicylidene derivative (*Z*-**4**) (1.50 g, 5.8 mmol) in dry dichloromethane (200 mL), *m*-chloroperbenzoic acid (MCPBA) (2.24

g, 13.0 mmol) and $NaHPO_3$ (90 mg, 0.87 mmol) were added. The solution was refluxed in the dark for 24 h. The reaction mixture was cooled and filtered, and the filtrate was washed with a sat. $Na_2SO_3$ aq. solution and water, and evaporated under reduced pressure to give an yellowish oil, which solidified upon standing. The solid was purified by chromatography using benzene-acetone (8:1), and the collected solid was recrystallized from benzene to give *erythro* **-6** (850 mg, 53%). mp 177.1-177.8°C; $^1$H NMR (90 MHz, acetone-$d_6$): δ=2.50(3H, s), 4.27(1H, d, J=18 Hz), 4.72(1H, d, J=18 Hz), 5.85(1H, br s), 6.77(1H, br s), 6.7-7.4(4H, m), 7.8(1H, br s); $^{13}$C NMR (22.5 MHz, acetone-$d_6$): δ =27.0, 46.5, 72.5, 93.3, 110.8, 122.8, 126.6, 128.4, 131.3, 157.5, 164.9, 166.3, 171.9; IR (KBr): υ=3400, 1715, 1695, 1370, 1215, 970, 890 $cm^{-1}$; MS: m/z=276($M^+$), 234($M^+$-Ac), 217($M^+$-Ac and OH); Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.69; H, 4.36; N, 10.16.

**Spiro[3*H*-3-bromobenzofuran-2,3'-(1'-acetyl-2',5'-piperazinedione)] (7)**

To an acetonitrile solution (15 mL) of *erythro* **-6** (205 mg, 0.742 mmol) and 1-methyl-2-fluoropyridinium *p*-toluenesulfonate (252 mg, 0.890 mmol), triethylamine (0.07 mL, 0.52 mmol) in acetonitrile (5 mL) was added, and the solution was stirred at rt under an $N_2$ atmosphere. After 2 h sodium bromide (248 mg, 2.41 mmol) was added successively to the reaction mixture, which was stirred for 24 h at rt. The mixture was filtered and concentrated under reduced pressure to give a white solid, which was chromatographed using benzene-acetone (4:1) to give *erythro*-**7** (171 mg, 68%) and *threo*-**7** (58 mg, 23%). The both isomers were recrystallized from benzene-hexane.

***Erythro*-7** : Rf=0.75 (benzene-acetone, 4:1); mp 142.2-143.1°C; $^1$H NMR (250 MHz, DMSO-$d_6$):δ =2.41(3H, s), 4.15(1H, d, J=17.8 Hz), 4.44(1H, d, J=17.8 Hz), 6.52(1H, s), 6.96-7.08(2H, m), 7.30-7.41(2H, m), 9.83 (1H, br s); $^{13}$C NMR (62.7 MHz, DMSO-$d_6$): δ =26.8, 46.1, 54.3, 93.0,

110.0, 122.5, 126.1, 126.5, 131.3, 156.2, 163.6, 164.3, 171.1; IR (KBr): υ =3430, 1710, 1370, 1212, 878, 750 $cm^{-1}$; MS: m/z= 338, 340($M^+$), 241, 239, 217; Anal. Calcd for $C_{13}H_{11}N_2O_4Br$: C, 46.04; H, 3.27; N, 8.26. Found: C, 46.11; H, 3.33; N, 8.23.

***Threo*-7** : Rf=0.50 (benzene-acetone, 4:1); mp 165.4-166.9°C; $^1H$ NMR (250 MHz, DMSO-$d_6$): δ =2.48(3H, s), 4.29(1H, d, J=17.7 Hz), 4.45(1H, d, J=17.7 Hz), 6.22(1H, s), 6.98-7.11(2H, m), 7.27-7.42(2H, m), 9.88(1H, br s); $^{13}C$ NMR (62.7 MHz, DMSO-$d_6$): δ =26.7, 46.3, 53.7, 95.7, 110.3, 122.8, 124.9, 125.8, 131.2, 157.2, 163.0, 164.2, 171.1; IR(KBr): υ = 3100, 1695, 1370, 1212, 986, 760 $cm^{-1}$. MS: m/z=338, 340($M^+$), 241, 239, 217: Anal. Calcd for $C_{13}H_{11}N_2O_4Br$: C, 46.04; H, 3.27; N, 8.26. Found: C, 46.12; H, 3.15; N, 8.29.

**Spiro[3*H*-3-bromobenzofuran-2,3'-(1'-acetyl-6'-bromo-2',5'-piperazinedione)] (8)**

To a carbon tetrachloride solution (15 mL) of *erythro*-**7** (168 mg, 0.500 mmol) and azobisisobutyronitrile (AIBN) (5 mg), *N*-bromosuccinimide (NBS) (102 mg, 0.573 mmol) was added under an $N_2$ atmosphere, and the solution was heated at 77°C for 3 h. The reaction mixture was cooled, filtered, and the filtrate was concentrated under reduced pressure to give an orange solid. The solid was chromatographed using benzene-acetone (8:1) and the collected solid was recrystallized from benzene-hexane to give **8** as a 1:1 diastereomer mixture (136 mg, 65% combined yield): mp 241-242°C; $^1H$ NMR (250 MHz, $CDCl_3$): δ =2.59(3H, s), 6.27(1H, s), 6.81 and 6.82(1H, s), 6.92(1H, d, J=8.13 Hz), 7.10 and 7.11(1H, d, J=7.55 Hz), 7.30(1H, dd, J=7.55, 8.13 HZ), 7.36(1H, s), 7.44(1H, d, J=7.55 Hz); $^{13}C$ NMR (62.7 MHz, $CDCl_3$): δ =27.5, 47.9, 52.8, 90.4, 111.3, 123.6, 125.7, 126.1, 128.4, 132.0, 155.3, 162.4, 169.7 ; IR (KBr): υ=3452, 1730, 1710, 1380, 1210, 766 $cm^{-1}$; MS: m/z=337, 339($M^+$-Br), 297, 295, 215; Anal. Calcd for $C_{13}H_{10}N_2O_4Br_2$: C, 37.35; H, 2.41; N, 6.70. Found: C, 37.42; H, 2.34; N, 6.78.

**Spiro[3*H*-3-thioacetylbenzofuran-2,3'-(6'-thioacetyl-2',5'-piperazinedione)] (9)**

To a carbon tetrachloride solution (25 mL) of **7** (208 mg, 0.613 mmol) and AIBN (7 mg), NBS (168 mg, 0.944 mmol) was added under an $N_2$ atmosphere, and the solution was refluxed for 2 h. The reaction mixture was worked up as described above, and the product was used in the next step without further purification. Thus the yellow solid was taken up in 10 mL of a solvent given in Table 2 and potassium thioacetate (141 mg, 1.24 mmol) was added to the solution under stirring at rt. The reaction mixture was filtered after 24 h and the filtrate was concentrated to give a smelling solid. The solid was chromatographed using benzene-acetone (8:1) to give respective isomers successively, which were recrystallized from benzene-hexane. Yields of the isomers are shown in Table 2.

**9a:** Rf=0.40 (benzene-acetone, 4:1), mp 202-203°C; $^1$H NMR (250 MHz, acetone-$d_6$): δ=2.42(3H, s), 2.46(3H, s), 2.55(3H, s), 6.07(1H, s), 6.63(1H, s), 6.91(1H, d, J=7.7 Hz), 7.05(1H, t, J=7.5 Hz), 7.27-7.34(2H, m), 8.47(1H, br s); $^{13}$C NMR (22.5 MHz, acetone-$d_6$): δ =27.0, 30.0, 30.3, 50.7, 55.2, 92.0, 110.8, 123.0, 125.1, 128.4, 130.8, 155.9, 163.9, 165.3, 170.4, 193.7, 195.9; IR (KBr): υ =3450, 1730, 1366, 1240, 1220, 1130 $cm^{-1}$; MS: m/z=408($M^+$), 366($M^+$-Ac), 324($M^+$-2AcO); Anal. Calcd for $C_{17}H_{16}O_6N_2S_2$: C, 49.99; H, 3.95; N, 6.86. Found: C, 49.68; H, 3.97; N, 6.64.

**9b:** Rf=0.48 (benzene-acetone, 4:1), mp 190-193°C; $^1$H NMR (250 MHz, $CDCl_3$): δ = 2.45(3H, s), 2.47(3H, s), 2.52(3H, s), 5.59(1H, s), 6.69(1H, s), 6.89(1H, d, J=7.7 Hz), 7.01(1H, t, J=7.7 Hz), 7.137(1H, d, J=7.7 Hz), 7.24(1H, t, J=7.7 Hz), 7.36(1H, br s); $^{13}$C NMR (22.5 MHz, $CDCl_3$): δ=27.3, 30.0, 30.2, 51.6, 55.0, 96.7, 110.7, 123.4, 123.9, 128.4, 130.0, 156.6, 163.7, 165.0, 170.1, 190.5, 195.0; IR (KBr): υ= 3440, 1730, 1712, 1368, 1220, 1120 $cm^{-1}$; MS: m/z=408($M^+$),

366($M^+$-Ac), 324($M^+$-2Ac), 281; Anal. Calcd for $C_{17}H_{16}O_6N_2S_2$: C,49.99; H, 3.95; N, 6.86. Found: C, 50.08; H, 3.92; N, 6.64.

**9c:** Rf=0.30 (benzene-acetone, 4:1), mp 203-204°C, $^1$H NMR (250 MHz, $CDCl_3$): δ =2.31(3H, s), 2.35(3H, s), 2.61(3H, s), 6.19(1H, s), 7.10 (1H, s), 7.18(1H, d, J=7.9 Hz), 7.25-7.50(3H, m), 8.09(1H, br s); $^{13}$C NMR (22.5 MHz, $CDCl_3$): δ =26.7, 30.1, 30.2, 51.6, 56.9, 96.7, 114.8, 122.8, 123.5, 125.9, 126.9, 128.5, 159.5, 162.0, 169.0, 191.0, 194.5; IR (KBr): υ =3450, 1700, 1370, 1200, 1100 $cm^{-1}$; MS: m/z=408($M^+$), 366($M^+$-Ac), 324($M^+$-2Ac); Anal. Calcd for $C_{17}H_{16}O_6N_2S_2$: C, 49.99; H, 3.95; N, 6.86. Found: C, 49.93; H, 3.90; N, 6.97.

**9d:** Rf=0.56 (benzene-acetone, 4:1), mp 205-206°C; $^1$H NMR (250 MHz, acetone-$d_6$): δ =2.43(3H, s), 2.47(6H, s), 5.78(1H, s), 6.59(1H, s), 6.87(1H, d, J=8.0 Hz), 7.01(1H, t, J=7.6 Hz), 7.14(1H, d, J=7.6 Hz), 7.26(1H, dd, J=7.6, 8.0 Hz), 9.08(1H, s); $^{13}$C NMR (22.5 MHz, acetone-$d_6$): δ = 26.9, 28.8, 30.7, 52.0, 55.7, 97.9, 110.5, 123.1, 124.4, 129.0, 130.3, 157.6, 164.6, 166.1, 170.6, 190.4, 194.6 ; IR (KBr):υ = 3440, 1710, 1360, 1210 $cm^{-1}$; MS: m/z=408($M^+$), 248, 217, 187; Anal. Calcd for $C_{17}H_{16}O_6N_2S_2$: C, 49.99; H, 3.95; N, 6.86. Found: C, 49.90; H, 3.94; N, 6.90.

**10:** Rf=0.50 (benzene-acetone, 8:1), mp 201-202°C; $^1$H NMR (90 MHz, $CDCl_3$): δ =2.34(3H,s), 2.38(3H, s) 5.88(1H, s), 6.51(1H, s), 6.8-7.5(5H, m); $^{13}$C NMR (22.5 Hz, $CDCl_3$): δ =25.0, 30.5, 53.5, 58.0, 92.5, 110.6, 123.4, 125.9 128.0, 131.5, 155.4, 161.9, 163.3, 170.0, 197.6 ppm; IR (KBr): υ =3450, 1710, 1370, 1240, 1190 $cm^{-1}$; MS: m/z=414, 412($M^+$), 334($M^+$-Br), 330, 328($M^+$-2Ac); Anal. Cacld for $C_{15}H_{13}O_5N_2BrS$: C, 43.65; H, 3.17; N, 6.78. Found; C, 43.59; H, 3.12; N, 6.89.

**Spiro[3*H*-3-hydroxybenzofuran-2,3'-(1'-acetyl-2',5'-piperazinedione)] (*threo*-6)**

A suspension of *erythro*-**6** (50 mg, 0.18 mmol) and active manganese dioxide ($MnO_2$)(1.0 g) in chloroform (50 mL) was stirred at rt for 2 h.

Inorganic solid was removed by filtration and the filtrate was concentrated under reduced pressure to give a solid, which was chromatographed using benzene-acetone (5:1) to give *spiro*[*3H*-3-benzofuranone-2,3'-(1-acetyl-2',5'-piperazinedione)] (**11**) in a 28 mg (56%) yield. mp 69.5-70.0°C; $^1$H NMR (60 MHz, $CDCl_3$): δ = 2.47(3H, s) 4.12(2H, d, J=17.0 Hz), 4.56(1H, d, J=17.0 Hz), 6.90-7.70(4H, m), 8.03(1H, br s); IR (KBr): υ =3180, 1750, 1720, 1700 $cm^{-1}$; MS: m/z=274($M^+$), 232($M^+$-Ac).

Hydrogen gas was introduced to a stirred suspension of palladium oxide (PdO) (38 mg) and **11** (156 mg, 0.57 mmol) in anhydrous dioxane (10 mL). After all of **11** was exhausted (about 10 h), the catalyst was removed and the filtrate was concentrated under reduced pressure to give a solid. Chromatographic purification of the solid using benzene-acetone (9:1) gave pure *threo* -**6** in a 129 mg (82%) yield; mp 137-139°C; $^1$H NMR (90 MHz, acetone-$d_6$): δ =2.47(3H, s), 4.38(1H, d, J=18 Hz), 4.39(1H, d, J=18 Hz), 5.34(1H, d, J=8.4 Hz), 5.63(1H, d, J=8.4 Hz), 6.7-7.4(4H, m), 8.5(1H, br s); $^{13}$C NMR (22.5 MHz, acetone-$d_6$): δ =27.3, 47.2, 83.1, 97.1, 111.0, 123.1, 126.0, 128.7, 131.3, 159.2, 165.7, 165.9, 172.2; IR (KBr): υ = 3400, 3250, 1730, 1690 $cm^{-1}$; MS: m/z=276($M^+$), 234($M^+$-Ac), 217($M^+$-Ac and OH); Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.50; H, 4.34; N, 10.06.

**5-Chloro-2,4-dihydroxybenzaldehyde (3')**

To a solution of 2,4-dihydroxybenzaldehyde (2.3 g, 16.7 mmol) and *N*-chlorosuccinimide (2.3 g, 17.2 mmol) in 50 mL of chloroform, conc. hydrochloric acid (1 mL) was added slowly and the soution was refluxed for 4 h. Upon cooling solid mass was separated. The solid was washed with cold water, and recrystallized from water to give the aldehyde (1.93 g, 67 %): mp 158-159°C; $^1$H NMR (60 MHz, acetone-$d_6$): δ =6.37(1H, s), 7.53(1H, s), 9.59(1H, s), 9.73(1H, br s); IR (KBr): υ =3200, 1630, 1419, 1200, 1190 $cm^{-1}$; Anal. Calcd for $C_7H_5O_3Cl$: C, 48.72; H, 2.92.

Found; C, 48.56; H, 2.96.

**5-Chloro-2-hydroxy-4-methoxybenzaldehyde (3")**

To a mixture containing sodium hydride (190 mg, 7.9 mmol) in 5 mL of dry DMF solution, 5-chloro-2,4-dihydroxybenzaldehyde (900 mg, 5.2 mmol) in 20 ml of DMF was added slowly with stirring. After 2 h, methyl iodide (2.0 g, 14 mmol) was added to the reaction mixture. After addition of methyl acetate (100 ml), the reaction solution was washed with dil. HCl solution, a aq. 5% $NaHCO_3$ solution, water and a sat. aq. NaCl solution. The crude product was purified by column chromatography using benzene to give the aldehyde (650 mg, 67 %): mp 96-97°C; $^1$H NMR (90 MHz, acetone-$d_6$) $\delta$ =3.93(3H, s), 6.53(1H, s), 7.60(1H, s), 9.63(1H, s), 11.3(1H, s); $^{13}$C NMR (22.5 MHz, acetone-$d_6$) $\delta$=57.1, 101.2, 114.4, 115.8, 134.6, 162.4, 163.6, 195.0; IR (KBr): $\upsilon$=3088, 1635, 1605, 1480, 1275, 1200, 1175 $cm^{-1}$; Anal. Calcd for $C_8H_7O_3Cl$: C, 51.49; H, 3.78. Found; C, 51.53; H, 3.73.

**(*Z*)-1-Acetyl-3-(5-chloro-2-hydroxy-4-methoxy)benzylidene-2,5-piperazinedione (4')**

The similar procedure described for the synthesis of **4** was applied. The crude product was recrystallized from EtOH to give the piperazinedione (81%). mp 237-238°C; $^1$H NMR (90 MHz, DMSO-$d_6$) $\delta$ =2.44(3H, s), 3.77(3H, s), 4.26(2H, s), 6.62(1H, s), 6.87(1H, s), 7.35(1H, s), 10.13(2H, br); $^{13}$C NMR (22.5 MHz, DMSO-$d_6$) $\delta$ =26.7, 45.7, 100.4, 111.6, 113.5, 114.1, 124.7, 130.8, 153.3, 155.8, 161.5, 163.5, 171.9; IR (KBr): $\upsilon$ =3160, 1680, 1608, 1360, 1260 $cm^{-1}$; MS: m/z=326, 327($M^+$), 227, 225; Anal. Calcd for $C_{14}H_{13}O_5N_2Cl$: C, 51.77, H, 4.01, N, 8.63. Found: C, 51.86, H, 4.23, N, 8.46.

**Spiro[3*H*-5-chloro-3-hydroxy-6-methoxybenzofuran-2,3'-(1'-acetyl-2',5'-piperazinedione)] (6')**

The similar procedure described for the synthesis of *erythro*-**6** was applied to prepare the desired spirobenzofuranol (68% yield). mp 198-

199°C; $^{1}$H NMR (90 MHz, acetone-$d_6$) δ =2.50(3H, s), 4.25(1H, d, J=17.6 Hz), 4.72(1H, dd, J= 1.15, 17.6 Hz) 5.80(2H, s), 6.62(1H, s), 7.46(1H, s), 7.88(1H, br); $^{13}$C NMR (22.5 MHz, acetone-$d_6$) δ =27.0, 46.5, 56.7, 72.1, 94.3, 96.2, 115.8, 120.6, 127.2, 157.5, 157.9, 164.5, 166.3, 171.9; IR (KBr): υ =3430, 1700, 1680, 1430, 1360, 1190, 1150 $cm^{-1}$; MS: m/z=340, 342($M^+$), 298($M^+$-Ac), 252; Anal. Calcd for $C_{14}H_{13}O_6N_2Cl$: C, 49.35, H, 3.85, N, 8.22; Found, C, 49.42, H, 3.96, N, 8.15.

**CRYSTAL DATA**

The derivative of *erythro*-**6** prepared for X-Ray diffraction analysis exhibited the following characteristics: $C_{19}H_{21}O_8N_2Cl$, Formula weight =411.804: Crystal system,*Orthorhombic*, Space group, Pbca, Z=8, a=15.975 (4), b=24.306(3), c=9.999(2)Å, V=3882.6Å$^3$, d=1.415g/$cm^{-3}$. Of the 5002 reflections measured, 3246 were significantly greater than their back ground count.

**9b** exhibited the following characteristics: $C_{17}H_{16}O_6N_2S_2$, Formula weight=408.457: Crystal system, *Orthorhombic* ; Space group, Pccn, Z=8, a=10.270(2), b=23.549(3), c=17.897(3)Å; *V*=4306.8Å$^3$; *d*=1.380g/$cm^{-3}$. Of the 4381 reflection measured, 3094 were significantly greater than their background count.

The structure was solved by direct method using MULTAN and in the final refinement by the block-matrix least square methods. The refinement converged to R=0.0954 and Rw=0.1394 for *erythro*-**6**, and R=0.0928 and Rw=0.0642 for **9b**.

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