Stereoselective Epoxidation and Bromoalkoxylation with 3-Ylidenepyrazine-2,5-diones

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Abstract: 3-Ylidenepyrazine-2,5-diones **1** were stereoselectively epoxidsed by dimethyldioxirane giving access to spirooxiranes **2** and diols **3**. Bromohydroxylation and bromoalkoxylation of 3-ylidenepyrazine-2,5-diones **1** produced high yields of optically active 3-(1-bromoalkyl)pyrazine-2,5-diones **4** with a 3-hydroxy or 3-alkoxy function, respectively. Whereas direct hydrogenation of epoxides **2** afforded epimeric mixtures of 3-(1-hydroxyalkyl)pyrazine-2,5-diones **5** and **6**, the highly stereoselective transformation into **5** was possible by primary acid cleavage of the oxirane ring followed by hydrogenation of the resulting keto-enol mixtures **7**/**8**.

Key words: epoxidation, pyrazine-2,5-diones, hydrogenations, amino acid derivatives

3-Ylidenepyrazine-2,5-diones (3-ylidene-2,5-diketopiperazines) have found wide application in the synthesis of derivatives of non-natural amino acids.[1] Their dehydroamino acid motif allows a variety of additions to the C–C double bond. Our preliminary investigations into the possibility of epoxidation of 3-ylidenepyrazine-2,5-diones **1** revealed that the powerful reagent dimethyldioxirane allowed the synthesis of the corresponding spirooxiranes **2**, which represent configurationally stable α-keto acid derivatives.[2] Full experimental details, investigation of alternative routes and some reactions of the spirooxiranes **2** are reported in the present paper.

Prior to our investigations, MCPBA had been applied for the epoxidation of achiral 3-ylidenepyrazine-2,5-diones.[3–5] Thus 3,6-bis-ylidenepyrazine-2,5-diones could be epoxidised by MCPBA.[4] Remarkably, this reaction stopped after the first epoxidation, i.e. a further epoxidation of the resulting 3-ylidenepyrazine-2,5-dione moiety did not occur. We also found the 3-ylidenepyrazine-2,5-diones **1** to be resistant to MCPBA. The more powerful dimethyldioxirane, however, epoxidised 3-ylidenepyrazine-2,5-diones **1** at room temperature (Scheme 1). The resulting oxiranes **2** (Tables 1 and 2) could only be isolated if an electron-withdrawing acyl group (R^2 = Ac or Bz) was attached to the adjacent nitrogen atom. Otherwise (R^2 = H, Me) diols **3** were obtained, which were obviously formed by hydrolytic ring-opening of the expected dioxiranes **2** by traces of water found in the solution of the dimethyldioxirane. The higher susceptibility to ring-opening can be explained by the facile formation of *N*-acyliminium salts **11** (Figure 1), if no electron-withdrawing group R^2 is attached to the nitrogen atom. The stereochemical mode of formation of epoxides **2** was proved by X-ray crystal analysis of compound **2c**.[2] All compounds **2**

Table 1 Yields of Products **2**–**8**

Product	R^1	R^2	R^3	Yield (%)
2a	Me	PhCO	–	95
2b	*i*-Pr	PhCO	–	95
2c	Ph	MeCO	–	56
2d	3-Cl,4-$MeOC_6H_3$	MeCO	–	84
3a	*i*-Pr	H	–	80
3b	Ph	H	–	55
3c	Ph	Me	–	62
4a	Ph	H	H	98
4b	Ph	H	Me	99
4c	Ph	H	Et	83
4d	Ph	H	*i*-Pr	86
4e	Ph	Me	H	98
4f	Ph	Me	Me	99
4g	Ph	Me	Et	96
4h	Ph	Me	*i*-Pr	90
5a	Me	PhCO	–	60
5b	*i*-Pr	PhCO	–	50
5c	Ph	H	–	46
6	Ph	H	–	–
7a/8a	Me	PhCO	–	53
7b/8b	*i*-Pr	PhCO	–	53
7c/8c	Ph	H	–	38

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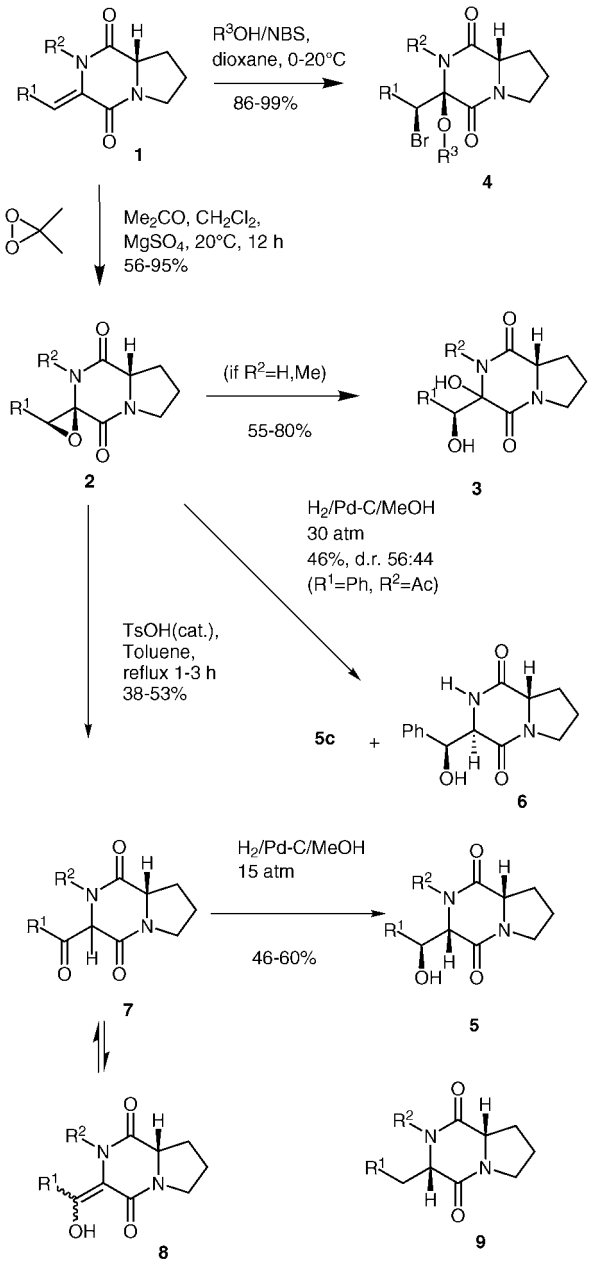

Scheme 1

exhibit the same sign of optical rotation (Table 2). The configuration at the hemiaminal carbon atom of diols **3** remains unknown.

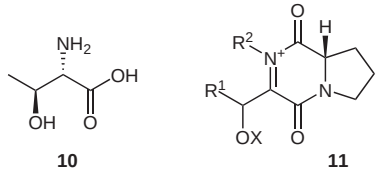

Figure 1 Structures of *allo*-threonine (**10**) and *N*-acyliminium salts **11**

We also tried to synthesise epoxides **2** by intramolecular nucleophilic substitution at bromohydrins **4** (R^3 = H). The bromohydroxylation and bromoalkoxylation of **1** with NBS in the presence of water or alcohol, respectively, afforded excellent yields of adducts **4** (Scheme 1, Table 1). The stereoselectivity, however, was low in particular in the case of bromohydroxylation (R^3 = H) where the attacking water is less voluminous as compared with alcohols (R^3 = alkyl) in bromoalkoxylations. As could be proved by X-ray crystal analysis of compound **4f** (Figure 2), the attack of the bromine occurred preferably from the same side as the epoxidation, i.e. *anti* with respect to the trimethylene bridge between positions 1 and 6 of the pyrazine-2,5-dione ring of **1**. Additions of bromine and alkoxides to 3-ylidenepyrazine-2,5-diones had been reported before, but achiral or racemic starting materials were used and the stereochemical mode of addition could not fully be determined.[3–6] Attempts to convert **4a** into the corresponding oxirane **2** under basic conditions, as successfully used in the 3,5-bisbenzylidenepyrazine-2,5-dione or in the racemic series,[3,4] gave low yields and modest stereoselectivity (70:30) and thus the intramolecular oxirane formation starting from **4** cannot compete with the epoxidation of **1** with dimethyldioxirane.

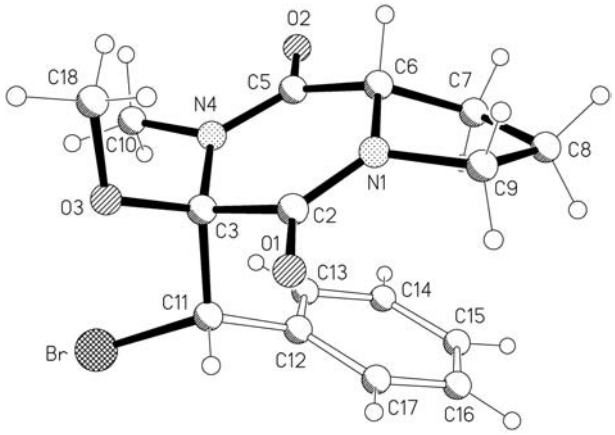

Figure 2 X-ray crystal structure of compound **4f** (radii are arbitrary)

We further investigated the reduction of the oxirane ring of the spiropyrazine-2,5-diones **2** in order to obtain 3-(1-hydroxyethyl)pyrazine-2,5-diones **5** as precursors for α-amino-β-hydroxycarboxylic acids such as *allo*-threonine **10** (Figure 1). As reported by Marcuccio et al.,[4] Pd/C-catalysed hydrogenation of oxiranes derived from 3,6-bisylidenepyrazine-2,5-diones under basic conditions opened the oxirane by maintaining the hemiaminal moiety, i. e. by forming 3-benzyl-3-hydroxypyrazines. In contrast, hydrogenation of **2c** with Pd/C at 30 atm in methanol gave an epimeric mixture of the deacetylated ring-opened products **5c** and **6**, while the hemiaminal structure was erased and the acetyl group was split off. Epimers **5c** and **6** could not be separated by column chromatography. In order to achieve a more stereoselective transformation of oxiranes **2** into 3-(1-hydroxyethyl)-pyrazine-2,5-diones **5**, we chose a detour applied by Marcuccio in the racemic

series.[4] At first, the oxirane ring of the spiro compounds **2** was opened by refluxing in toluene in the presence of catalytic amounts of *p*-TsOH, followed by hydrogenation. Interestingly, mixtures of keto/enol forms **7** and **8** (see Table 2) were obtained after the first step, rather than just ketones as found by Marcuccio. Conditions of hydrogenation of **7**/**8** to 3-(1-hydroxyethyl)pyrazine-2,5-diones **5** (see Table 2) must be controlled since extended reaction times gave rise to the formation of 3-alkylpyrazine-2,5-diones **9**, which are probably formed by elimination of water from **5** to give 3-ylidenepyrazine-2,5-diones **1**, followed by further hydrogenation. The diastereomeric ratios of the hydrogenation products **5** are high (Table 2). The stereochemical outcome of the hydrogenation implies that the keto form **7** rather than the enol **8** was reduced. Attack at the latter would have led to the opposite configurations of the hydrogenation product. For proving the absolute configuration, a sample of 3-(1-hydroxyethyl)pyrazine-2,5-dione (**5a**) was hydrolysed with 6 N aqueous HCl at 120 °C for 20 hours. As could be determined by capillary GC-MS (L-Chirasil-Val), *allo*-threonine **10** (Figure 1) was formed in 88% ee.

In summary, epoxidation of the C–C double bond of 3-ylidenepyrazine-2,5-diones **1** with dimethyldioxirane and bromine/alcohol or bromine/water addition occur in the same stereochemical mode providing spirooxiranes **2**, corresponding diols **3** or 3-(1-bromoalkyl)pyrazine-2,5-diones **4**, respectively. These products represent new optically active and configurationally stable α-keto acid derivatives. Rearrangement and reduction of spirooxiranes **2** give access to the synthesis of optically active 3-(1-hydroxyalkyl)pyrazine-2,5-diones **5** as new derivatives of α-amino-β-hydroxy acids.

Table 2 Spirooxiranes **2,** Diols **3**, 5-(1-Bromoalkyl)pyrazine-2,4-diones **4**, Hydroxyalkylpyrazindiones **5**, Acylpyrazindiones **7** and Enols **8** Prepared

Product	dr	Mp (°C)	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
2a	>95:5[a]	169–170	1.20 (d, *J* = 5.8, 3 H, CH_3), 1.91 (m, 2 H, CH_2), 2.16–2.24 (m, 2 H, CH_2), 3.48–3.53 (m, 2 H, CH_2N), 4.08 (q, *J* = 5.8, 1 H, CH), 4.56 (t, *J* = 7.7, 1 H, 3-H) 7.39–7.74 (m, 5 H, C_6H_5)	15.2 (CH_3), 23.4(CH_2), 26.4 (CH_2), 45.2 (CH_2N), 58.9 (CH), 59.0 (CH), 71.3 (C), 128.6 (CH), 130.2 (CH), 133.5 (C), 134.1 (CH), 161.7 (C), 170.2 (C), 170.6 (C)
2b	>95:5[b]	179–189	0.85 (d, *J* = 6.4, 3 H, CH_3), 0.99 (d, *J* = 6.5, 3 H, CH_3), 1.90 (m, 1 H, CH), 2.15–2.23 (m, 4 H, 2 × CH_2), 3.50 (m, 2 H, CH_2N), 3.62 (d, *J* = 5.9, 1 H, CHO), 4.55 (t, *J* = 7.7, 1 H, 6-H), 7.50–7.70 (m, 5 H, C_6H_5)	18.5 (CH_3), 20.3 (CH_3), 23.4 (CH_2), 26.4 (CH), 27.9 (CH_2), 45.2 (CH_2N), 59.0 (CH), 67.4 (CH), 73.0 (C), 128.6 (CH), 130.4 (CH), 133.4 (CH), 134.2 (C), 161.9 (C), 170.3 (C), 170.8 (C)
2c	>95:5[c]	137–138	1.90–1.94 (m, 2 H, CH_2), 1.97 (s, 3 H, CH_3), 2.21–2.35 (m, 2 H, CH_2), 3.48 (m, 2 H, CH_2N), 4.61 (t, *J* = 7.9, 1 H, 6-H), 4.93 (s, 1 H, CH), 7.25 (s, 5 H, C_6H_5)	23.4 (CH_2), 26.3 (CH_3), 27.0 (CH_2), 44.8 (CH_2N), 60.3 (CH), 62.7 (CH), 71.7 (C),126.6 (CH), 128.2 (CH), 128.9 (CH), 132.5 (C), 161.3 (C), 169.8 (C), 171.5 (C)
2d	>95:5[d]	150–154	1.95–2.01 (m, 2 H, CH_2), 2.06 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 2.29–2.36 (m, 2 H, CH_2), 3.47–3.53 (m, 2 H, CH_2N), 4.61 (t, *J* = 7.9, 1 H, 6-H), 4.93 (s, 1 H, CH), 7.01–7.20 (m, 3 H_{arom})	20.6 (CH_3), 23.5 (CH_2), 26.5 (CH_3), 27.1 (CH_2), 45.0 (CH_2N), 60.1 (CH), 61.7 (CH), 71.7 (C), 123.7 (CH), 126.6 (CH), 127.1 (C),128.0 (CH), 131.9 (C), 147.4 (C), 160.9 (C), 168.2 (C), 169.9 (C), 171.3 (C)
3a	>95:5[e]	155–157	0.81 (d, *J* = 6.6, 3 H, CH_3), 0.92 (d, *J* = 6.6, 3 H, CH_3), 1.82–1.92 (m, 2 H,CH_2), 1.97 (m, 1 H, CH), 2.33–2.38 (m, 2 H, CH_2), 3.38 (m, 2 H, CH_2N), 4.22 (dd, ^1J = 6.5, ^2J = 10.2, 1 H, CHN), 5.57 (br, 1 H, OH), 5.85 (d, *J* = 10.4, 1 H, CHO)	18.2 (CH_3), 20.1 (CH_3), 21.9 (CH_2), 28.7 (CH_2), 30.0 (CH), 45.4 (CH_2N), 58.6 (CHN), 77.3 (CHO), 83.0 (CO), 164.4 (C), 170.5 (C)
3b	>90:10[f]	158	1.35–1.65 (m, 2 H, CH_2), 1.82–2.32 (m, 2 H, CH_2), 3.21–3.33 (m, 2 H, CH_2N), 3.65 (dd, ^1J = 5.7, ^2J = 11.3, 1 H, CHN), 5.38 (s, 1 H, CHO), 7.19–7.29 (m, 5 H, C_6H_5)	20.7 (CH_2), 28.5 (CH_2), 44.9 (CH_2N), 58.6 (CHN), 77.7 (CHO), 88.9 (CO), 127.8 (CH), 128.2 (CH), 128.7 (CH), 135.4 (C), 163.3 (C), 167.7 (C)
3c	92:8	160–161.5	1.50 (m, 2 H, CH_2), 1.84 (m, 2 H, CH_2), 3.20 (s, 3 H, CH_3N), 3.42–3.53 (m, 2 H, CH_2N), 3.70 (dd, ^1J = 5.7, ^2J = 11.8, 1 H, CHN), 5.32 (s, 1 H, CHO), 6.00 (br, 1 H, OH), 7.23–7.28 (m, 5 H, C_6H_5)	20.8 (CH_2), 28.2 (CH_2), 30.2 (CH_3), 44.9 (CH_2N), 58.9 (CHN), 80.2 (CHO), 88.0 (CO), 127.0 (CH), 128.0 (CH), 128.6 (CH) 137.4 (C), 164.7 (C), 165.9 (C)

Table 2 Spirooxiranes **2,** Diols **3**, 5-(1-Bromoalkyl)pyrazine-2,4-diones **4**, Hydroxyalkylpyrazindiones **5**, Acylpyrazindiones **7** and Enols **8** Prepared (continued)

Product	dr	Mp (°C)	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
4a	58:42	148–150	1.03–2.02 (m, 4 H, 2 × CH_2), 3.15–3.42 (m, 2 H, CH_2N), 4.07 (dd, ^1J = 6.3, ^2J = 6.1, 1 H, H), 5.58 (s, 1 H, CH), 7.23–7.48 (m, 5 H, C_6H_5), 8.44 (s, 1 H, NH)[g]	21.0 (CH_2), 28.3 (CH_2), 44.6 CH_2N), 58.2 (CH), 60.4 (CH), 83.6 (C), 127.7 (CH), 128.4 (CH), 130.1 (CH), 136.9 (C), 162.1 (C), 168.2 (C)
4b	60:34:6	127–128	1.15 (m, 1 H, CH_2), 1.35–2.14 (m, 3 H, CH_2), 3.30 (m, 2 H, CH_2N), 3.37 (s, 3 H, OCH_3), 3.89 (m, 1 H, 6-H), 5.54 (s, 1 H, CH), 7.27–7.45 (m, 5 H, C_6H_5), 8.57(s, 1 H, NH)[h]	20.9 (CH_2), 28.5 (CH_2), 45.0 (CH_2N), 51.9 (CH_3), 58.7 (CH), 59.4 (CH), 89.1 (C), 127.9 (CH), 128.9 (CH), 129.8 (CH), 135.0 (C), 159.8 (C), 167.5 (C)
4c	88:12	121–124	0.71–0.81 (m, 1 H, CH_2), 1.18 (t, *J* = 2.7, 3 H, CH_3), 1.42–2.07 (m, 3 H, CH_2), 3.14–3.21 (m, 2 H, OCH_2), 3.44 (dd, ^1J = 7.1, ^2J = 7.0, 1 H, CH_2N), 3.59 (dd, ^1J= 7.1, ^2J = 7.2, 1 H, CH_2N), 3.90 (dd, ^1J = 6.0, ^2J = 6.1, 1 H, 6-H), 5.57 (s, 1 H, CH), 6.80 (s, 1 H, NH), 7.19–7.37 (m, 5 H, C_6H_5)	14.8 (CH_3), 21.0 (CH_2), 28.6 (CH_2), 45.0 (CH_2N), 58.8 (CH), 59.7 (CH), 60.3 (CH_2O), 88.6 (C), 128.0 (CH), 128.9 (CH), 129.9 (CH), 135.1 (C), 160.3 (C), 167.4 (C)
4d	79:12:9	116–119	1.08 (d, *J* = 6.2, 3 H, CH_3), 1.12 (d, *J* = 6.1, 3 H, CH_3), 1.04–2.00 (m, 4 H, 2 × CH_2), 3.11 (m, 2 H, CH_2N), 3.85 (t, *J* = 6.1, 1 H, 6-H), 4.09 (m, 1 H, OCH), 5.52 (s, 1 H, CH), 7.26–7.34 (m, 5 H, C_6H_5), 8.55 (s, 1 H, NH)	20.6 (CH_2), 23.0 (CH_3), 23.1 CH_3), 28.4 (CH_2), 44.9 (CH_2), 58.2 (CH), 60.0 (CH), 67.8 (CH), 88.6 (C), 127.8 (CH), 128.7 (CH), 130.1 (CH), 135.9 (C), 160.7 (C), 167.5 (C)
4e	58:42	125–127	0.61 (m, 1 H, CH_2), 1.61–1.69 (m, 2 H, CH_2), 2.00–2.05 (m, 1 H, CH_2), 2.69 (s, 3 H, CH_3), 3.23 (m, 1 H, CH_2N), 3.65 (m, 1 H, CH_2N), 5.52 (s, 1 H, CH), 7.28–7.43 (m, 5 H, C_6H_5)[i]	28.3 (CH_2), 29.1 (CH_3), 29.4 CH_2), 44.7 (CH_2N), 58.9 (CH), 59.0 (CH), 86.1 (C), 128.1(CH), 129.0 (CH), 129.6(CH), 134.8 (C), 162.8 (C), 165.7 (C)
4f	72:28	105–106	0.07–0.14 (m, 1 H, CH_2), 1.23–1.57 (m, 2 H, CH_2), 1.76–1.89 (m, 1 H, CH_2), 2.67 (s, 1 H, CH_3N), 3.24 (s, 3 H, CH_3O), 3.33–3.56 (m, 2 H, CH_2N), 3.76 (dd, ^1J = 5.6, ^2J = 5.8, 1 H, 6-H), 5.58 (s, 1 H, CH), 7.20–7.42 (m, 5 H, C_6H_5)[j]	20.7 (CH_2), 28.6 (CH_2), 30.6 (CH_3N), 45.4 (CH_2N), 52.6 (OCH_3), 57.5 (CH), 58.8 (CH), 91.9(C), 128.5 (CH), 129.2 (CH), 129.7 (CH), 135.8 (C), 166.9 (C)
4g	83:17	104–105	0.07 (m, 1 H, CH_2), 1.24 (t, *J* = 7.0, 3 H, CH_3), 1.38–1.51 (m, 2 H, CH_2), 1.81–1.96 (m, 1 H, CH_2), 2.65 (s, 3 H, CH_3N), 3.32–3.53 (m, 4 H, CH_2N, CH_2O), 3.73 (dd, ^1J = 5.7, ^2J = 5.8, 1 H, 6-H), 5.57 (s, 1 H, CH), 7.21–7.50 (m, 5 H, C_6H_5)	14.5 (CH_3), 20.5 (CH_2), 28.4 (CH_2), 30.5 (CH_3N), 45.1 (CH_2N), 57.5 (CH), 58.6 (CH), 60.8 (O CH_2), 92.0 (C), 128.1 (CH), 128.8 (CH), 129.5 (CH), 135.7 (C), 160.7 (C), 166.6 (C)
4h	82:12	117–118	0.27 (m, 1 H, CH_2), 1.12 (d, *J* = 4.6, 6 H, 2 × CH_3), 1.45–1.59 (m, 2 H, CH_2), 1.87–2.07 (m, 1 H, CH_2), 2.62 (s, 3 H, CH_3N), 3.18–3.30 (m, 2 H, CH_2N), 3.78 (m, 1 H, 6-H), 4.01 (m, 1 H, CH), 5.56 (s, 1 H, CH), 7.19–7.47 (m, 5 H, C_6H_5)	20.3 (CH_2), 22.5 und 22.7 (CH_3), 29.2 (CH_2), 31.1 (CH_3N), 45.1 (CH_2N), 58.1 (CH), 58.2 (CH), 70.2 (CHO), 91.9 (C), 127.7 (CH), 128.4 (CH), 129.4 (CH), 135.5 (C), 160.7 (C), 166.2 (C)
5a	92:8	200–220	1.36 (d, *J* = 6.4, 3 H, CH_3), 1.84–2.06 (m, 2 H, CH_2), 2.30–2.47 (m, 2 H, CH_2), 3.50–3.64 (m, 2 H, CH_2N), 4.04–4.13 (m, 1 H, CH), 4.54 (t, *J* = 2.3, 1 H), 5.89 (qd, ^qJ = 6.4, ^dJ = 3.1, 1 H, CHO), 7.32–7.41 (m, 3 H, C_6H_5), 8.00–8.15 (m, 2 H, C_6H_5)	14.0 (CH_3), 22.2 (CH_2), 28.5 (CH_2), 45.3 (CH_2N), 58.1 (CH), 58.8 (CH), 70.2 (CHO), 128.3 (CH), 129.7 (C), 130.0 (CH), 133.2 (CH), 162.6 (C), 165.3 (C), 170.5 (C)
5b	70:30	–	1.25 (d, *J* = 5.7, 3 H, CH_3), 1.28 (d, *J* = 5.8, 3 H, CH_3), 1.84–1.97 (m, 3 H, CH, CH_2), 2.16–2.19 (m, 2 H, CH_2), 3.61–3.79 (m, 2 H, CH_2N), 4.12 (m, 1 H, CH), 4.59 (d, *J* = 4.2, 1 H, 3 H), 5.25 (dd, ^1J = 2.9, ^2J = 8.6, 1 H, CHO), 7.18–7.53 (m, 3 H, C_6H_5), 7.86–7.95 (m, 2 H, C_6H_5)	21.0 (2 × CH_3), 21.2 (CH_2), 26.2 (CH), 32.0 (CH_2), 47.7 (CH_2N), 52.3 CH), 61.4 (CH), 68.6 (CHO), 126.2 (CH), 128.5 (CH), 129.8 (C), 130.3 (CH), 133.7 (CH), 161.9 (C), 163.5 (C),171.2 (C)
5c	>90:10	–	1.50–2.15 (m, 4 H, 2 × CH_2), 3.17–3.54 (m, 2 H, CH_2N), 4.23 (m, 1 H, CH), 4.38 (d, *J* = 8.0, 1 H, 3-H), 5.18 (d, *J* = 8.0, 1 H, CHO), 7.18–7.50 (m, 5 H, C_6H_5)	21.3 (CH_2), 28.6 (CH_2), 44.8 (CH_2N), 57.3 (CH), 59.0 (CH), 74.5 (CHO), 128.2 (CH), 128.5 (CH), 129.9 (CH), 133.1 (C), 163.4 (C), 169.7 (C)

Table 2 Spirooxiranes **2,** Diols **3**, 5-(1-Bromoalkyl)pyrazine-2,4-diones **4**, Hydroxyalkylpyrazindiones **5**, Acylpyrazindiones **7** and Enols **8** Prepared (continued)

Product	dr	Mp (°C)	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ
7a/**8a**	1:7[k]	80–81	**7a**: 1.62–1.74 (m, 2 H, CH_2), 1.84–1.93 (m, 2 H, CH_2), 2.41 (s, 3 H, CH_3), 3.46–3.89 (m, 2 H, CH_2N), 3.87 (dd, ^1J = 6.6, ^2J = 9.8, 1 H, CH), 5.47 (s, 1 H, 3-H), 7.41 (m, 3 H, CH), 8.03 (m, 2 H)	14.2 (CH_3), 22.6 (CH_2), 29.4 (CH_2), 45.8 (CH_2N), 60.1 (CH), 60.4 (CH_3), 128.5 (CH), 128.9 (C), 130.4 (CH), 133.8 (CH), 159.0 (C), 163.4 (C), 168.8 (C), 198.6 (C)
			8a: 1.62–1.74 (m, 2 H, CH_2), 1.84–1.93 (m, 2 H, CH_2), 2.41 (s, 3 H, CH_3), 3.46–3.89 (m, 2 H, CH_2N), 3.87 (dd, ^1J = 6.6, ^2J = 9.8, 1 H, CH), 7.41 (m, 3 H, C_6H_5), 8.03 (m, 2 H, C_6H_5), 8.90 (s, 1 H, OH)	17.0 (CH_3), 21.9 (CH_2), 28.3 (CH_2), 45.5 (CH_2N), 58.7 (CH), 119.3 (C), 128.5 (CH), 128.9 (C), 130.4 (CH), 133.8 (CH), 141.5 (COH), 157.9 (C), 163.4 (C), 166.7 (C)
7b/**8b**	2:3[k]	–	**7b**: 1.03 (d, *J* = 6.6, 3 H, CH_3), 1.27 (d, *J* = 7.1, 3 H, CH_3), 1.58–2.28 (m, 5 H, 2 × CH_2, CH), 3.34–3.55 (m, 2 H, CH_2N), 3.98 (m, 1 H, CH), 5.61 (s, 1 H, 3-H), 7.27–7.54 (m, 3 H, C_6H_5), 8.05 (m, 2 H, C_6H_5)	17.2 (CH_3), 19.2 (CH_3), 22.6 (CH_2), 29.4 (CH_2), 38.2 (CH), 45.9 (CH_2), 60.0 CH, 68.6 (CH), 128.1 (CH), 128.6 (CH), 128.9 (C), 132.5 (CH), 159.3 (C), 162.9 (C), 169.2 (C), 204.8 (C)
			8b: 0.90 (d, *J* = 6.9, 3 H, CH_3), 1.10 (d, *J* = 6.8, 3 H, CH_3), 1.58–2.28 (m, 5 H, 2 × CH_2, CH), 3.34–3.55 (m, 2 H, CH_2N), 3.98 (m, 1 H, CH), 7.27–7.54 (m, 3 H, C_6H_5), 8.05 (m, 2 H, C_6H_5), 9.20 (s, 1 H, OH)	18.9 (CH_3), 20.6 (CH_3), 22,6 (CH_2), 28.1 (CH_2), 29.1 (CH), 45.5 (CH_2N), 58.3 (CH), 119.0 (C) 128.5 (CH), 128.9 (C), 130.4 (CH), 133.5 (CH), 148.4 (C), 158.1 (C), 162.9 (C), 167.8 (C)
7c/**8c**[l]	3:1[k]	–	**7c**: 1.69–2.11 (m, 4 H, 2 × CH_2),), 3.47–3.65 (m, 2 H, CH_2N), 4.14 (m, 1 H, CH), 5.64 (d, *J* = 4.1, 1 H, 3-CH), 7.24–7.68 (m, 5 H, C_6H_5)	22.0 (CH_2), 28.7 (CH_2), 46.1 (CH_2N), 58.9 (CH), 64.0 (CH), 128.7 (CH), 130.0 (CH), 133.4 (C), 134.5 (CH), 160.1 (C), 172.2 (C), 191.4 (C)
			8c: 1.69–2.11 (m, 4 H, 2 × CH_2), 3.47–3.65 (m, 2 H, CH_2N), 4.14 (m, 1 H, CH), 7.24–7.68 (m, 5 H, C_6H_5)	21.0 (CH_2), 28.5 (CH_2), 45.6 (CH_2N), 56.1 (CH), 119.5 (C), 128.6 (CH), 130.2 (CH), 132.2 (C), 134.5 (CH) 139.7 (C), 156.9 (C), 169.7 (C)

[a] $[\alpha]^{546}$ –279.3 (*c* = 1, $CHCl_3$).
[b] $[\alpha]^{546}$ –247.3 (*c* = 1, $CHCl_3$).
[c] $[\alpha]^{546}$ –206.2 (*c* = 1, $CHCl_3$).
[d] $[\alpha]^{546}$ –68.3 (*c* = 1.35, $CHCl_3$).
[e] $[\alpha]^{546}$ –124.6 (*c* = 1, $CHCl_3$).
[f] $[\alpha]^{546}$ –62.4 (*c* = 0.7, $CHCl_3$).
[g] Major isomer. Minor isomer: ^{1}H NMR (DMSO-d_6): δ = 1.03–2.02 (m, 4 H, 2 × CH_2), 3.31 (m, 2 H, CH_2N), 4.19 (dd, 1 H, 6-H, ^1J = 6.3 Hz, ^2J = 6.5 Hz), 5.35 (s, 1 H, CH), 7.24–7.61 (m, 5 H, C_6H_5), 8.56 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6): δ = 21.4 (CH_2), 28.7 (CH_2), 38.9 (CH_2N), 59.1 (CH), 60.0 (CH), 84.3 (C), 128.0 (CH), 129.9 (CH), 130.5 (CH), 135.1 (C), 163.1 (C), 168.5 (C).
[h] Major isomer. Minor isomer: ^{1}H NMR (DMSO-d_6): δ = 1.15 (m, 1 H, CH_2), 1.35–2.14 (m, 3 H, CH_2), 3.22 (s, 3 H, OCH_3), 3.30 (m, 2 H, CH_2), 4.10 (dd, 1 H, 6-H, ^1J = 6.0 Hz, ^2J = 6.0 Hz), 5.54 (s, 1 H, CH), 7.27–7.45 (m, 5 H, C_6H_5), 8.5 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ = 21.4 (CH_2), 28.5 (CH_2), 44.7 (CH_2N), 52.1 (CH_3), 57.3 (CH), 59.3 (CH), 89.5 (C), 128.0 (CH), 128.3 (CH), 129.9 (CH), 133.6 (C), 161.5 (C), 168.0 (C).
[i] Major isomer. Minor isomer: ^{1}H NMR ($CDCl_3$): δ = 0.61 (m, 1 H, CH_2), 1.61–1.69 (m, 2 H, CH_2), 2.00–2.05 (m, 1 H, CH_2), 2.88 (s, 3 H, CH_3), 3.23 (m, 1 H, CH_2N), 3.65 (m, 1 H, CH_2N), 5.40 (s, 1 H, CH), 7.28–7.43 (m, 5 H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ = 28.2 (CH_2), 29.4 (CH_2), 30.3 CH_3), 44.8 (CH_2N), 57.8 (CH), 59.4 (CH), 87.1 (C), 128.1(CH), 128.9 (CH), 129.7 (CH), 135.5 (C), 162.8 (C), 165.7 (C).
[j] Major isomer. Minor isomer: ^{1}H NMR ($CDCl_3$): δ = 0.07–0.14 (m, 1 H, CH_2), 1.23–1.57 (m, 2 H, CH_2), 1.76–1.89 (m, 1 H, CH_2), 2.54 (s, 3 H, CH_3N), 3.19 (s, 3 H, CH_3O), 3.33–3.56 (m, 2 H, CH_2N), 3.97 (dd, 1 H, 6-H, ^1J = 5.7 Hz, ^2J = 5.8 Hz), 5.55 (s, 1 H, CH), 7.20–7.47 (m, 5 H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ = 21.2 (CH_2), 29.3 (CH_3N), 29.6 (CH_2), 45.8 (CH_2N), 53.0 (OCH_3), 57.6 (CH), 59.1 (CH), 92.4 (C), 127.9 (CH), 128.8 (CH), 130.6 (CH), 134.7 (C), 167.3 (C).
[k] Ratio of isomers **7**:**8**, determined by NMR spectroscopy.
[l] Obtained from **2c**.

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, on a Bruker AC-300 with TMS as internal standard. Mass spectra (HP 5995 A) were measured at 70 eV. Optical rotations were determined with a Perkin-Elmer Polarimeter 241. Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatography. If not otherwise mentioned, chemicals were purchased from Aldrich. Starting materials 1[7] and solutions of dimethyldioxirane in acetone[8] were obtained following literature procedures.

Spirooxiranes 2 and Diols 3 by Epoxidation of 3-Ylidenepyrazine-2,5-diones 1; General Procedure

Anhyd $MgSO_4$ (500 mg) and ca. 0.1 M solution of dimethyldioxirane in acetone (ca. 20 mL) were added to a solution of 3-ylidenepyrazine-2,5-dione **1** (0.7 mmol for **2a**, 0.26 mmol for **2b**, 0.6 mmol for **2c**, 0.82 mmol for **2d**, 0.41 mmol for **3a**, 0.33 mmol for **3b**, 0.78 mmol for **3c**) in anhyd CH_2Cl_2 (20 mL). The mixture was stirred under argon overnight. Eventually, (TLC check) additional dimethyldioxirane solution (5 mL portions) was added. After all starting material had disappeared, the $MgSO_4$ was filtered off

and the filtrate was submitted to column chromatography (**2a**: EtOAc–hexane, 10:1, R_f 0.8; **2b**: EtOAc–hexane, 6:1, R_f 0.8; **2c**: EtOAc–hexane, 10:1, R_f 0.7; **2d**: EtOAc–hexane, 6:1, R_f 0.8; **3a**: $CHCl_3$–MeOH, 6:1, R_f 0.4; **3b**: $CHCl_3$–MeOH, 6:1, R_f 0.5; **3c**: $CHCl_3$–MeOH, 6:1, R_f 0.5). The products were purified by recrystallisation.

Hydrolysis of Spirooxiranes 2 to 3-Acylpyrazine-2,5-diones 7 and Enols 8; General Procedure

A mixture of spirooxirane **2** (1.3 mmol), *p*-TsOH (22 mg, 0.13 mmol), $MgSO_4$ (500 mg) and anhyd toluene (30 mL) was refluxed for 1–3 h. The yellow colour of the solution disappeared as the reaction came to completion. $MgSO_4$ was filtered off and the filtrate was washed with H_2O (2 × 15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$), concentrated and submitted to column chromatography (EtOAc–hexane, 10:1, R_f 0.45/0.40 for **7a**/**8a**; 0.5 for **7b**/**8b**; 0.5 for **7**/**8c**). Products were obtained as isomeric mixtures which were submitted to reduction (see below).

Hydrogenation of Spirooxirane 2b to 3-(2-Hydroxyethyl)pyrazine-2,5-diones 5c and 6

10% Pd/C (about 30 mg) was added to a solution of **2b** (100 mg, 0.33 mmol) in anhyd MeOH (10 mL). The mixture was placed under H_2 at 30 atm for 14 h. After filtration through Celite, the solution was concentrated and the remainder was purified by column chromatography (EtOAc–hexane 10:1, R_f 0.5) affording an epimeric mixture of **5c** and **6** (40 mg, 46%) as a colourless oil.

^{1}H NMR (DMSO-d_6): δ (major isomer) = 1.69–1.89 (m, 2 H, CH_2), 2.14–2.24 (m, 2 H, CH_2), 3.30–3.59 (m, 2 H, CH_2N), 3.91 (dd, ^1J = 7.0 Hz, ^2J = 9.1 Hz, 1 H, CH), 4.53 (t, *J* = 7.9 Hz, 1 H, CH), 5.31 (dd, ^1J = 3.6 Hz, ^2J = 9.2 Hz, 1 H, C*H*OH), 7.23–7.31 (m, 5 H, C_6H_5).

^{13}C NMR (DMSO-d_6): δ (major isomer) = 22.7 (CH_2), 27.7 (CH_2), 44.8 (CH_2N), 57.2 (CHN), 58.6 (CHN), 78.6 (CHOH), 127.1 (CH), 128.2 (CH), 129.5 (CH), 137.1 (C), 164.3 (C), 168.0 (C).

^{1}H NMR (DMSO-d_6): δ (minor isomer) = 1.69–1.89 (m, 2 H, CH_2), 2.14–2.24 (m, 2 H, CH_2), 3.30–3.59 (m, 2 H, CH_2N), 4.23 (dd, ^1J = 3.5 Hz, ^2J = 8.2 Hz, 1 H, CH), 4.53 (t, *J* = 7.9 Hz, 1 H, CH), 4.96 (dd, ^1J = 5.2 Hz, ^2J = 7.9 Hz, 1 H, C*H*OH), 7.23–7.31 (m, 5 H, C_6H_5).

^{13}C NMR (DMSO-d_6): δ (minor isomer) = 21.6 (CH_2), 28.5 (CH_2), 44.9 (CH_2N), 55.8 (CHN), 58.6 (CHN), 81.2 (CHOH), 128.1 (CH), 128.5 (CH), 129.6 (CH), 135.5 (C), 163.4 (C), 168.0 (C)

Reduction of 3-Acylpyrazine-2,5-diones 7 and Enols 8 to 3-(1-Hydroxyalkyl)pyrazine-2,5-diones 5; General Procedure

A mixture of Pd/C (ca. 30 mg), **7/8** (0.5 mmol) and anhyd MeOH (20 mL) was hydrogenated at 15 atm. The resulting mixture was filtered through Celite and the filtrate was submitted to column chromatography (EtOAc–hexane, 10:1, R_f 0.35 for **5a**, 0.5 for **5b**, 0.5 for **5c**. In the case of **5a**, the 3-alkyl product **9a** (R^1 = Me, R^2 = PhCO) was obtained as a byproduct in 40% yield.

NBS Addition to 3-Ylidenepyrazine-2,5-diones 1; 3-(1-Bromoalkyl)pyrazine-2,5-diones 4; General Procedure

R^3OH (2 mL) or H_2O (2 mL) was added to a solution of 3-ylidenepyrazine-2,5-dione **1** (3 mmol) in anhyd dioxane (20 mL). A solution of NBS (0.534 g, 3 mmol) in anhyd dioxane (20 mL) was slowly added under stirring. After the reaction had gone to completion (about 3 h, TLC check) and the yellow colour had disappeared, the solvent was removed under vacuum. The remainder was dissolved in EtOAc (50 mL) and the resulting solution was washed with H_2O (3 × 20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and the solvent was stripped off. The remaining solid was purified by recrystallisation affording the product as colourless crystals.

X-Ray Crystal Analysis of 4f[9]

Crystal Data: Triclinic, space group *P*–1, *a* = 7.999(4), *b* = 8.110(3), *c* = 12.567(5) Å, *α* = 105.27(3), *β* = 91.69(3), *γ* = 101.34(3)°, *V* = 768.3 Å^3, *Z* = 2, D_c = 1.588 Mg m^{-3}, *F*(000) = 376, μ = 2.7 mm^{-1}, *T* = –100 °C. *Data Collection*: A crystal of ca. 0.5 × 0.5 × 0.4 mm was used to register 4557 intensities (Mo-*K*α radiation, $2\theta_{max}$ 55°) on a Stoe STADI-4 diffractometer. *Structure Refinement*: The structure was refined anisotropically against F^2 (program SHELXL-97, G.M. Sheldrick, Univ. of Göttingen) to *wR*2 = 0.088, *R*1 = 0.036 for 201 parameters and 3525 independent reflections; max. Δρ = 0.51 eÅ^{-3}, *S* = 1.05. Hydrogen atoms were included using a riding model or rigid methyl groups.

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(9) Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC-187708. Copies can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: Int. +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].