ARTICLE

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Tandem oxidation processes for the preparation of nitrogen-containing heteroaromatic and heterocyclic compounds

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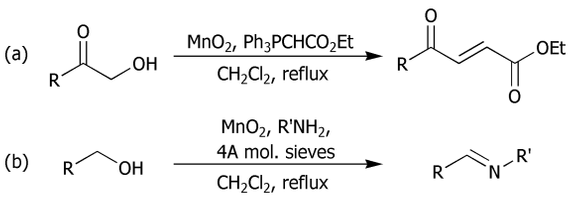
α-Hydroxy ketones undergo manganese dioxide-mediated oxidation followed by *in situ* trapping with aromatic or aliphatic 1,2-diamines to give quinoxalines or dihydropyrazines, respectively, in a one-pot procedure which avoids the need to isolate the highly reactive dicarbonyl intermediates. The scope and limitations of these procedures are outlined and modifications to this procedure are discussed in which reduction is carried out in the same reaction vessel, generating piperazines, or oxidation, leading to pyrazines.

Introduction

Nitrogen-containing heteroaromatic and heterocyclic compounds are indispensable structural units for both the chemist and the biochemist. Quinoxalines constitute the basis of many insecticides, fungicides, herbicides and anthelmintics, as well as being important in human health and as receptor antagonists.[1,2] There are numerous methods of preparing quinoxalines but the double condensation of a 1,2-dicarbonyl compound and a 1,2-diaminoaromatic is commonly employed.[1–3] Similarly, dihydropyrazines, piperazines and pyrazines are of great importance in natural products and as chemotherapeutic agents[2b,4] and can be prepared from the corresponding 1,2-dicarbonyl compound and an aliphatic 1,2-diamine,[3a,4,5] followed by reduction or oxidation of the resulting dihydropyrazines, if required.

We have recently developed a number of manganese dioxide-mediated tandem oxidation processes (TOPs) for the elaboration of alcohols.[6–8] As part of this programme, we established that α-hydroxyketones undergo *in situ* oxidation-trapping when treated with manganese dioxide in the presence of stabilised Wittig reagents, giving γ-ketocrotonates (Scheme 1a).[7] In addition, we have also developed a TOP-amine trapping sequence leading to imines (Scheme 1b).[8] We therefore decided to extend these procedures and investigate the conversion of α-hydroxyketones **1** into diamino heterocycles.[9]

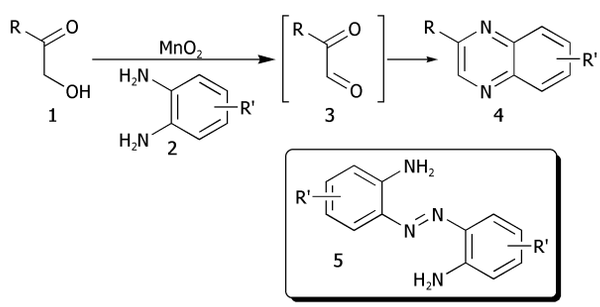


Scheme 1 TOP approaches to γ-ketocrotonates and imines.

Results and discussion

We first studied the preparation of quinoxalines **4** and related heterocycles employing a manganese dioxide-mediated TOP with suitable 1,2-diaminoaromatics **2** avoiding the need to isolate the "hyper-reactive"[10] 1,2-dicarbonyl intermediate **3** (Scheme 2).

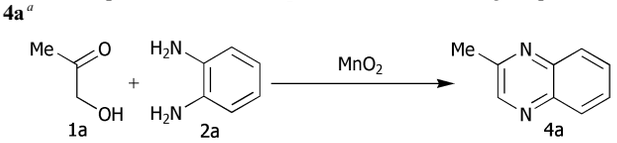
Preliminary studies were carried out using hydroxyacetone **1a** (R=Me) and *o*-phenylenediamine **2a** (R′=H), and are summarised in Table 1. On the first attempt we were delighted to observe the formation of 2-methylquinoxaline **4a**[11a] but the



Scheme 2 Proposed TOP synthesis of quinoxalines.

yield of 43% was disappointing (Table 1, entry i). Addition of acid or base (entries ii and iii), or changing the solvents (entries iv and v) gave no improvement. The major by-product was isolated and identified as the known[12] diazobenzene **5a** resulting from oxidative coupling of **2a**. We therefore investigated batchwise addition of the reagents and the use of different stoichiometries (entries vi and vii). The optimum conditions involved the use of a two fold excess of diamine **2a** (entry vii); in this case the reaction was complete in just one hour and 2-methylquinoxaline **4a** was isolated in 79% yield (after

Table 1 Optimisation of MnO_2-mediated TOP leading to quinoxaline **4a**[a]



Entry	Reagents	Conditions	Time/h	Yield (%)
i	15 eq. MnO_2, 1.1 eq. **2a**	CH_2Cl_2, Δ	20	43
ii	15 eq. MnO_2, 1.1 eq. **2a**, 1% AcOH	CH_2Cl_2, Δ	20	10
iii	15 eq. MnO_2, 1.1 eq. **2a**, 1% K_2CO_3	CH_2Cl_2, Δ	20	10
iv	15 eq. MnO_2, 1.1 eq. **2a**	Et_2O, Δ	20	12
v	15 eq. MnO_2, 1.1 eq. **2a**	THF, Δ	20	15
vi	15 eq. MnO_2, 3.0 eq. **1a**, 1.0 eq. **2a**	CH_2Cl_2, Δ	20	51[b]
vii	10 eq. MnO_2, 2.0 eq. **2a**, 4 Å mol. sieves	CH_2Cl_2, Δ	1	79[c]

[a] Based on 1 eq. alcohol **1a** unless otherwise stated; the diazo compound **5a** was also formed (up to 15%). [b] Yield based on diamine **2a**. [c] The isolated yield of diazo compound in this case was 6% based on **2a**.

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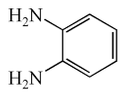
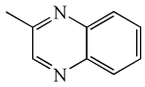
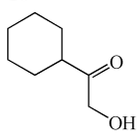
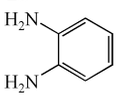
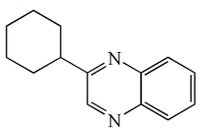
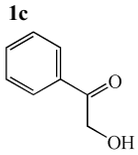
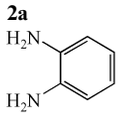
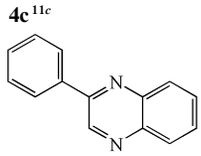
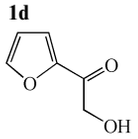
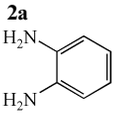
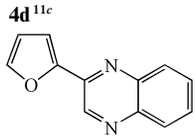
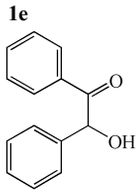
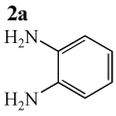
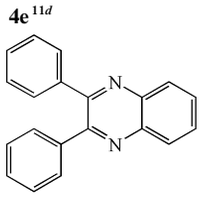
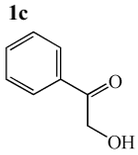
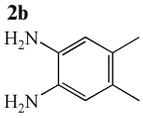
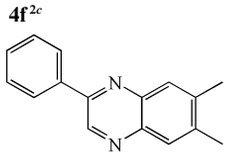
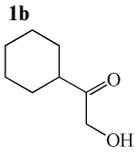
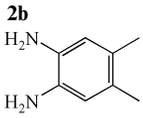
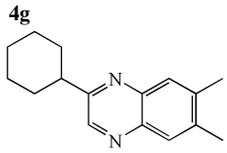
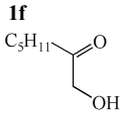
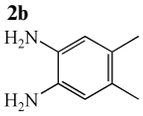
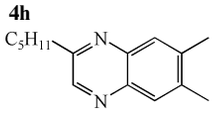
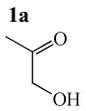
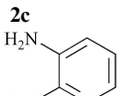
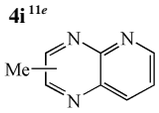
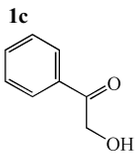
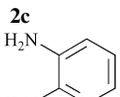
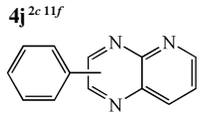
Table 2 MnO_2-mediated TOP quinoxaline formation[a]

Entry	α-Hydroxy ketone **1**	Amine **2**	Product **4**	Yield (%)
i	**1a** 	**2a** 	**4a**[11a] 	79
ii	**1b** 	**2a** 	**4b**[11b] 	78
iii	**1c** 	**2a** 	**4c**[11c] 	79
iv	**1d** 	**2a** 	**4d**[11c] 	89
v	**1e** 	**2a** 	**4e**[11d] 	75
vi	**1c** 	**2b** 	**4f**[2c] 	66
vii	**1b** 	**2b** 	**4g** 	89
viii	**1f** 	**2b** 	**4h** 	62
ix	**1a** 	**2c** 	**4i**[11e] 	66[b]
x	**1c** 	**2c** 	**4j**[2c 11f] 	69[c]

[a] Using 10 eq. MnO_2 and 2 eq. diamine in CH_2Cl_2 at reflux; diazo and polymeric byproducts were removed during chromatography. Yield refers to isolated, chromatographically and spectroscopically pure product. [b] Isolated as a mixture of regioisomers, ~7 : 1 in favour of the 3-methylpyrido[2,3-*b*]pyrazine as determined by ^{1}H NMR spectroscopy [c] Isolated as a mixture of regioisomers, ~2 : 1 in favour of the 3-phenylpyrido[2,3-*b*]pyrazine as determined by ^{1}H NMR spectroscopy.

chromatography to remove **5a** and polymeric by-products). The operational simplicity of this process is noteworthy: after the reaction is complete the remaining oxidant and its by-products are removed by filtration and concentration *in vacuo* followed by chromatography gives the pure product.

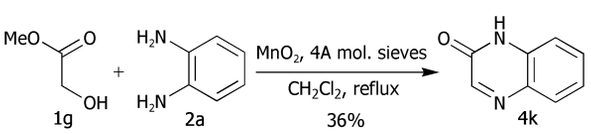
With the successful optimisation results in hand, we moved on to investigate the scope of the process (Table 2), first in terms of α-hydroxyketone substrate (entries i–v). As can be seen, in addition to α-hydroxyacetone **1a**, the related 1-cyclohexyl-2-hydroxyethanone **1b**[13] also gave an excellent yield of the corresponding quinoxaline **4b** on treatment with manganese dioxide and 1,2-diaminobenzene. Substrates **1a** and **1b** were of particular interest as the intermediate α-keto aldehydes are often problematic in terms of the "hyper-reactivity" of

the aldehyde function.[10] We next moved on to examine aryl substituted α-hydroxyketones (entries iii and iv), both hydroxyacetophenone **1c** and the related furyl system **1d**[13] giving the expected adducts **4c** and **4d**, respectively. The secondary alcohol benzoin **1e** was also shown to react well under these oxidative-trapping conditions with 1,2-diaminobenzene **2a** giving 2,3-diphenylquinoxaline **4e** in 75% yield (entry v).

We next studied the use of other diamines (entries vi–x). Thus, 1,2-diamino-4,5-dimethylbenzene **2b** was also shown to work well in these reactions giving the desired 2,6,7-trisubstituted quinoxalines **4f**, **4g** and **4h** in good to excellent yields with α-hydroxyketones **1c**, **1b** and **1f**, respectively (entries vi–viii). Finally, 2,3-diaminopyridine **2c** was investigated as a coupling partner with **1a** and **1c**, giving the corresponding 2/3-substituted pyrido[2,3-*b*]pyrazines **4i** and **4j** as mixtures of regioisomers (entries ix and x).

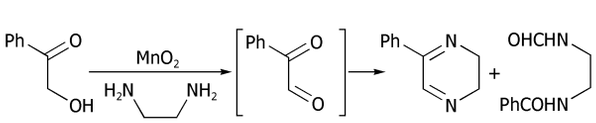
Finally in this section of the research, we attempted to apply this methodology to the synthesis of quinoxalin-2-ones. Hence, methyl glycolate (1.20 equivalents) and 1,2-phenylene diamine **2a** were reacted under the standard conditions. Unfortunately, oxidation of the glycolate is much slower than for the α-hydroxyketones and therefore, production of diazobenzene is much faster than formation of the quinoxalinone **4k**, which was isolated in a disappointing yield of 36% (Scheme 3). Even when the glycolate was used in two-fold excess with respect to phenylene diamine **2a**, ^{1}H NMR spectroscopy of the crude product, after complete consumption of **2a**, showed the molar ratio of diazobenzene **5a** to quinoxaline **4k** to be ~1.1 : 1.

With a facile and technically straightforward synthesis of quinoxalines and related heteroaromatic compounds from the corresponding α-hydroxyketones to hand, our attention turned to the development of related procedures for the preparation of pyrazines, dihydropyrazines and piperazines.

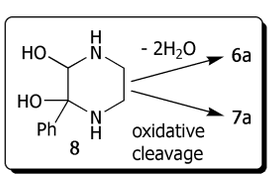


Scheme 3 Synthesis of quinoxalin-2-ones.

Initial studies concentrated on the preparation of dihydropyrazines, using α-hydroxyacetophenone **1c** as the model α-hydroxyketone with ethylenediamine **5a** (Scheme 4). We quickly established that the process was viable under the optimum conditions as used for quinoxaline synthesis. The expected 2-phenyl-5,6-dihydropyrazine **6a** was produced in 28% yield without contamination by diazo byproducts. However, somewhat surprisingly, the major product from this reaction was *N*-benzoyl-*N′*-formyl 1,2-diaminoethane **7a**, obtained in a yield of 50%.



Solvent:Additive	Ratio 6a:7a
CH_2Cl_2	1:1.8
CH_2Cl_2-amberlyst 15	1:1
CH_2Cl_2-1 eq. HCl	2.5:1
MeCN-1 eq. HCl	2:1



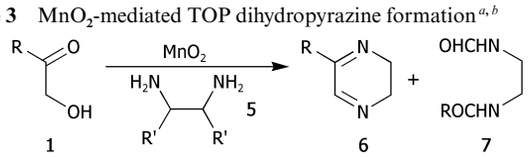
Scheme 4 TOP approach to dihydropyrazines.

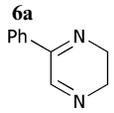
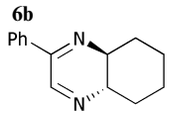
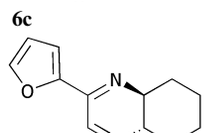
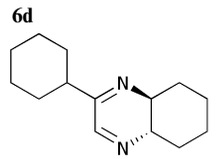
We assume that a bis-hemi-aminal intermediate, such as **8**,[5a] which would give adduct **6a** after dehydration, can also undergo oxidative cleavage in the presence of manganese dioxide giving bis-amide **7a**. The oxidative cleavage of 1,2-diols using MnO_2 is well known[14] but, to our knowledge, it has not been reported with hemi-aminals before. An isolated example of the oxidative cleavage of a bis-hemiaminal using sodium perbromate has however been reported.[15] By varying the reaction conditions and solvent (Scheme 4), we found that it was possible to minimise formation of bis-amide **7a** by the addition of 2.0 M HCl in Et_2O (1 equivalent with respect to the diamine) to the reaction mixture. Using this optimised procedure, dihydropyrazine **6a** was obtained in 53% yield. The dihydropyrazines produced in this manner are fairly sensitive, particularly in unpurified form, and were therefore chromatographed immediately after work up using deactivated, neutral alumina.

We then went on to determine the scope of this procedure, particularly in terms of the α-hydroxyketone substrate (Table 3). When using a more hindered diamine, exemplified by (±)-*trans*-1,2-diaminocyclohexane **5b** (entries ii–iv), the dihydropyrazines **6b**–**6d** were obtained in fair to excellent yields, reflecting their greater hydrolytic stability. It should be noted that when using cyclohexanediamine **5b**, the bis-amide by-products (corresponding to **9a**) were formed in relatively low yields (<15%), and the addition of HCl in Et_2O was not required.

Having shown that it was possible to produce dihydropyrazines **6a**–**d** *in situ* using TOP methodology, attention moved to the extended one-pot procedures. We recently reported the production of secondary and tertiary amines from activated alcohols using a MnO_2 mediated one-pot oxidation imine-formation reduction sequence.[8] We envisaged a similar sequence leading from α-hydroxyketones **1** to piperazines **9** (Table 4). Thus, the dihydropyrazine-forming reactions described above were repeated using MnO_2–$NaBH_4$. No piperazine formation was observed under these conditions, but

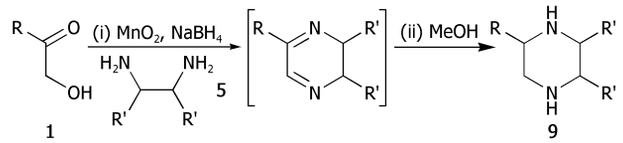
Table 3 MnO_2-mediated TOP dihydropyrazine formation[a,b]



Entry	R	R′	Dihydropyrazine	Yield (%) 6	7
i	Phenyl **1c**	H **5a**	**6a** 	53	26
ii	Phenyl **1c**	$(CH_2)_4$ **5b**	**6b** 	64	14
iii	2-Furyl **1d**	$(CH_2)_4$ **5b**	**6c** 	64	15
iv	Cyclohexyl **1b**	$(CH_2)_4$ **5b**	**6d** 	53	0

[a] Using MnO_2 (10 eq.), diamine (1.2 eq.) and powdered 4 Å mol. sieves in CH_2Cl_2 at reflux; when using diamine **5a**, 2.0 eq. of diamine were employed along with 2.0 M HCl in Et_2O (1 eq. with respect to diamine). Yield refers to isolated, chromatographically and spectroscopically pure product. [b] The products were purified immediately after work up (chromatography on deactivated neutral alumina) in order to prevent degradation.

Table 4 MnO_2–$NaBH_4$-mediated TOP piperazine formation[a]



Entry	R	R′	Piperazine	Yield (%)
i	Phenyl **1c**	H **5a**	**9a**	52
ii	Phenyl **1c**	$(CH_2)_4$ **5b**	**9b**	75
iii	2-Furyl **1d**	$(CH_2)_4$ **5b**	**9c**	60[b]
iv	Cyclohexyl **1b**	$(CH_2)_4$ **5b**	**9d**	84

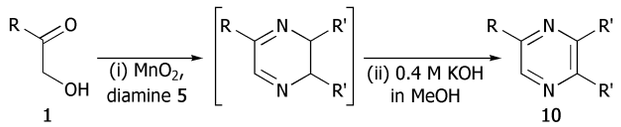
[a] Using MnO_2 (10 eq.), diamine (1.2 eq.), $NaBH_4$ (4.0 eq.) and powdered 4 Å mol. sieves in CH_2Cl_2 at reflux; when using diamine **5a**, 2.0 eq. of diamine were employed along with 2.0 M HCl in Et_2O (1 eq. with respect to diamine. Yield refers to isolated, spectroscopically pure product.

the addition of excess methanol to the reaction mixture after dihydropyrazine formation gave the corresponding piperazines **9a**–**d** in good yields (Table 4). As can be seen, the procedure gave good to excellent yields with aromatic (entries i–iii) and aliphatic α-hydroxyketones (entry iv). In the reactions using (±)-*trans*-1,2-diaminocyclohexane **5b** (entries ii–iv), only one diastereomeric product was isolated and we have tentatively assigned these as the all-equatorial adducts shown. There is literature precendence for this selectivity[16] and, furthermore, pertinent coupling constants in the ^{1}H NMR spectra were in the region expected for *trans*-diaxial protons, *e.g.* for H-2 to H-3_{axial} in compound **9b**, the *J* value is 10.4 Hz.

Finally, we investigated the TOP-dihydropyrazine formation-aromatisation sequence leading to pyrazines **10** (Table 5). To this end, the original dihydropyrazine formation was repeated in THF and toluene at reflux for extended periods of time in the presence of excess MnO_2 to effect the aromatisation. However, under these conditions, only trace amounts of pyrazines **8** were observed in the toluene reaction. The use of co-oxidants, such as DDQ and CAN, in these reactions resulted in complete degradation of the dihydropyrazines **6**. We eventually established that the addition of ~0.4 M KOH in methanol[3a,5b] to the refluxing reaction mixture after the formation of dihydropyrazines **6**, resulted in production of the corresponding pyrazines **10**. It should be noted that the addition of methanol alone did not achieve the desired transformation. The results are summarised in Table 5. As is apparent, the presence of an aromatic substituent facilitates aromatisation (*e.g.* entries i and iv *versus* vi and vii).

Finally, we examined the value of these methodologies with the complex, multifunctional substrate, hydrocortisone **11**. Exposure of **11** to the standard conditions for the formation

Table 5 MnO_2-mediated TOP-aromatisation pyrazine formation[a]



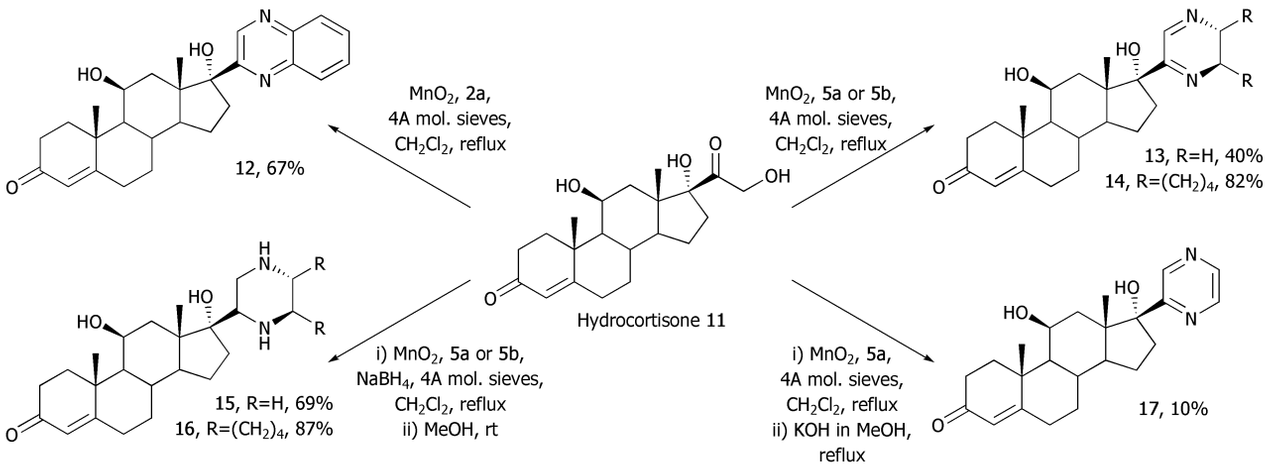
Entry	R	R′	Pyrazine	Yield (%)
i	Phenyl **1c**	H **5a**	**10a**[17a]	45
ii	4-BrC_6H_4 **1h**	H **5a**	**10b**	57
iii	2-Furyl **1d**	H **5a**	**10c**	60
iv	Phenyl **1c**	$(CH_2)_4$ **5b**	**10d**	66
v	2-Furyl **1d**	$(CH_2)_4$ **5b**	**10e**	64
vi	Cyclohexyl **1b**	H **5a**	**10f**[17b]	33
vii	Cyclohexyl **1b**	$(CH_2)_4$ **5b**	**10g**	0

[a] Using MnO_2 (10 eq.), diamine (1.2 eq.) and powdered 4 Å mol. sieves in CH_2Cl_2 at reflux; when using diamine **5a**, 2.0 eq. of diamine were employed along with 2.0 M HCl in Et_2O (1 eq. with respect to diamine). After consumption of the hydroxy ketone, KOH in MeOH was added to complete aromatisation. Yield refers to isolated, chromatographically and spectroscopically pure product.

of quinoxalines, dihydropyrazines, piperazines or pyrazines gave the novel derivatives **12**–**17** in moderate to excellent unoptimised yields (Scheme 5).

Conclusion

In conclusion, we have developed a novel methodology for the conversion of α-hydroxy ketones **1** into the corresponding quinoxalines **4** and dihydropyrazines **6** *via* MnO_2-mediated tandem oxidation processes with *in situ* trapping using 1,2-diamines. This methodology has been extended to allow the direct synthesis of piperazines **9** and pyrazines **10** in related TOP sequences from the corresponding α-hydroxy ketones **1** in fair to good yields. These MnO_2-TOPs offer the synthetic chemist significant time-cost benefits and, hence, we expect them to find applications in both academic and industrial environments. Further work is continuing to optimise and apply this new chemistry to more complex targets and compound-library synthesis.



Scheme 5 Hydrocortisone as a viable substrate for MnO_2-mediated TOP formation of heterocyclic and heteroaromatic functionality.

Experimental

General details: NMR spectra were recorded on Jeol EX-270 and EX-400 instruments using $CDCl_3$ as solvent unless otherwise stated. Tetramethylsilane was used as an internal standard in all cases. IR spectra were recorded on an ATI Mattson Genisis FT-IR or a ThermoNicolet IR100 spectrometer. Low resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionisation (CI) and high resolution mass spectra were recorded on a Micromass Autospec spectrometer. Flash column chromatography was carried out using Matrex silica gel 60 (70–200) or Brockmann grade 1 neutral alumina, deactivated by the addition of 6 wt% H_2O. The α-hydroxy ketones **1b**, **1d** and **1f** were synthesised from the corresponding methyl ketones using the method reported by Moriarty *et al.*[13] All other reagents were purchased from commercial sources and used without further purification. Activated MnO_2 was purchased from Aldrich chemical company, catalogue number 21,764–6. PE refers to petroleum ether (boiling point 40–60 °C).

Representative procedure for quinoxalines 4

2-Methylquinoxaline 4a. To a solution of α-hydroxyacetone **1a** (0.50 mmol, 0.037 g) in dry CH_2Cl_2 (25 mL) was added sequentially *o*-phenylenediamine **2a** (1.00 mmol, 0.108 g), powdered 4 Å molecular sieves (0.50 g) and activated MnO_2 (5.00 mmol, 0.435 g) and the mixture heated to reflux. After 45 min, TLC showed the reaction to be complete. The reaction mixture was cooled to RT, filtered through Celite® and the solid residues washed well with CH_2Cl_2. The solvent was removed *in vacuo* and the product purified by column chromatography (2 : 1 PE : EtOAc) to give the title compound **4a** (0.056 g, 79%) as an orange oil: R_f 0.23 (2 : 1 PE : EtOAc); ν_{max} (film) 1560, 1492, 1435, 1409, 1369 cm^{-1}; δ_H (270 MHz) 2.78 (3 H, s, CH_3), 7.65–7.75 (2 H, m, *H*-6,7), 7.98–8.03 (2 H, m, *H*-5,8), 8.72 (1 H, s, *H*-3); *m*/*z* (EI) 144 (M^+). Data consistent with literature values.[11a]

2-Cyclohexylquinoxaline 4b. Prepared by the procedure given for **4a** using 1-cyclohexyl-2-hydroxyethanone **1b**[13] (0.50 mmol, 0.106 g) and *o*-phenylenediamine **2a** (1.00 mmol, 0.108 g). Purified by column chromatography (2 : 1 PE : EtOAc) to give the title compound **4b** (0.083 g, 78%) as a brown solid: R_f 0.63 (2 : 1 PE : EtOAc); mp 46 °C (lit.[17] 48 °C); ν_{max} (film) 1559, 1490, 1445, 1364 cm^{-1}; δ_H (270 MHz) 1.32–1.94 (10 H, m, *H*-2′,3′,4′,5′,6′), 2.84 (1 H, tt, *J* 11.8 Hz, *J* 3.1 Hz, *H*-1′), 7.62 (2 H, m, *H*-6,7), 7.97 (2 H, m, *H*-5,8), 8.67 (1 H, s, *H*-3); *m*/*z* (CI) 213 (MH^+). Data consistent with literature values.[11b]

2-Phenylquinoxaline 4c. Prepared by the procedure given for **4a** using α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) and *o*-phenylenediamine **2a** (1.00 mmol, 0.108 g). Purified by column chromatography (3 : 1 PE : EtOAc) to give the title compound **4c** (0.081 g, 79%) as an orange solid: R_f 0.32 (3 : 1 PE : EtOAc); mp 81 °C (lit.[11c] 79–80 °C); ν_{max} (film) 1619, 1577, 1560, 1531, 1492, 1436, 1410, 1374 cm^{-1}; δ_H (270 MHz) 7.49–7.75 (3 H, m, *H*-3′,4′,5′), 7.77–7.81 (2 H, m, *H*-1′,6′), 8.10 (2 H, m, *H*-6,7), 8.19 (2 H, m, *H*-5,8), 9.45 (1 H, s, *H*-3); *m*/*z* (EI) 206 (M^+). Data consistent with literature values.[11c]

2-(2-Furanyl)quinoxaline 4d. Prepared by the procedure given for **4a** using 1-(2-furanyl)-2-hydroxyethanone **1d**[13] (0.50 mmol, 0.063 g) and *o*-phenylenediamine **2a** (1.00 mmol, 0.108 g). Purified by column chromatography (2 : 1 PE : EtOAc) to give the title compound **4d** (0.041 g, 89%) as an orange solid: R_f 0.55 (2 : 1 PE : EtOAc); mp 101 °C (lit.[18] 103 °C); ν_{max} (film) 1612, 1586, 1560, 1552, 1496, 1459 cm^{-1}; δ_H (270 MHz) 6.58 (1 H, dd, *J* 3.2 Hz, *J* 1.9 Hz, *H*-4′), 7.31 (1 H, d, *J* 3.2 Hz, *H*-3′), 7.64 (2 H, m, *H*-6,7), 7.68 (1 H, d, *J* 1.9 Hz, *H*-5′), 8.03 (2 H, m, *H*-5,8), 8.03 (1 H, s, *H*-3); *m*/*z* (EI) 196 (M^+). Data consistent with literature values.[11c]

2,3-Diphenylquinoxaline 4e. Prepared by the procedure given for **4a** using benzoin **1e** (0.50 mmol, 0.106 g) and *o*-phenylenediamine **2a** (1.00 mmol, 0.108 g). Purified by column chromatography (9 : 1 PE : EtOAc) to give the title compound **4e** (0.106 g, 75%) as a white solid: R_f 0.25 (9 : 1 PE : EtOAc); mp 128 °C (lit.[19] 125 °C); ν_{max} (film) 1558, 1477, 1441, 1395 cm^{-1}; δ_H (270 MHz) 7.33–7.39 (6 H, m, *H*-3′,4′,5′,3″,4″,5″), 7.50–7.54 (4 H, m, *H*-2′,6′,2″,6″), 7.72 (2 H, m, *H*-6,7), 8.08 (2 H, m, *H*-5,8); *m*/*z* (EI) 282 (M^+). Data consistent with literature values.[11d]

2-Phenyl-6,7-dimethylquinoxaline 4f. Prepared by the procedure given for **4a** using α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) and 4,5-dimethyl-1,2-phenylenediamine **2b** (1.00 mmol, 0.136 g). Purified by column chromatography (3 : 1 PE : EtOAc) to give the title compound **4f** (0.077 g, 66%) as an orange solid: R_f 0.48 (3 : 1 PE : EtOAc); mp 120 °C (lit.[2c] 124 °C); ν_{max} (film) 1538, 1485, 1449 cm^{-1}; δ_H (270 MHz) 2.51 (6 H, s, 2 × CH_3), 7.50–7.56 (3 H, m, *H*-3′,4′,5′), 7.88 (2 H, m, *H*-1′,6′), 8.16 (2 H, m, *H*-5,8), 9.22 (1 H, s, *H*-3); *m*/*z* (EI) 234 (M^+). Data consistent with literature values.[2c]

2-Cyclohexyl-6,7-dimethylquinoxaline 4g. Prepared by the procedure given for **4a** using 1-cyclohexyl-2-hydroxyethanone **1b**[13] (0.50 mmol, 0.106 g) and 4,5-dimethyl-1,2-phenylenediamine **2b** (1.00 mmol, 0.136 g). Purified by column chromatography (4 : 1 PE : EtOAc) to give the *title compound* **4g** (0.107 g, 89%) as an orange solid: R_f 0.40 (4 : 1 PE : EtOAc); mp 66 °C; ν_{max} (film) 1542, 1485, 1454, 1369 cm^{-1}; δ_H (270 MHz) 1.32–1.94 (10 H, m, *H*-2′,3′,4′,5′,6′), 2.90 (1 H, tt, *J* 11.9 Hz, *J* 3.3 Hz, *H*-1′), 2.40 (6 H, s), 7.72 (2 H, m, *H*-5,8), 8.59 (1 H, s, *H*-3);

δ_C (68 MHz) 20.2, 20.3, 25.8, 26.4, 32.3, 45.0, 128.1 (×2), 139.1, 140.2, 140.3, 141.0, 143.9, 160.1; *m/z* (CI) 241 (MH^+) [HRMS (CI) calcd. for $C_{16}H_{21}N_2$ 241.1705. Found 241.1703 (0.9 ppm error)].

2-Pentyl-6,7-dimethylquinoxaline 4h. Prepared by the procedure given for **4a** using 1- hydroxypentan-2-one **1f**[13] (0.50 mmol, 0.065 g) and 4,5-dimethyl-1,2-phenylenediamine **2b** (1.00 mmol, 0.136 g). Purified by column chromatography (2 : 1 PE : EtOAc) to give the *title compound* **4h** (0.071 g, 62%) as an orange oil: R_f 0.58 (2 : 1 PE : EtOAc); ν_{max} (film) 1628, 1552, 1488, 1464, 1362 cm^{-1}; δ_H (270 MHz) 0.82 (3 H, t, *J* 6.8 Hz, *H*-5′), 1.32–1.37 (6 H, m, *H*-2′,3′,4′), 2.40 (6 H, s, 2 × CH_3), 2.90 (2 H, m, *H*-1′), 7.72 (2 H, m, *H*-5,8), 8.57 (1 H, s, *H*-3); δ_C (68 MHz) 14.6, 20.9, 23.1, 30.0, 30.3, 32.2, 37.0, 128.5, 128.8, 139.9, 140.7, 141.0, 141.7, 145.5, 157.3; *m/z* (CI) 229 (MH^+) [HRMS (CI) calcd. for $C_{15}H_{21}N_2$ 229.1705. Found 229.1699 (2.6 ppm error)].

2-/3-Methylpyrido[2,3-*b*]pyrazine 4i. Prepared by the procedure given for **4a** using α-hydroxyacetone **1a** (0.50 mmol, 0.034 mL) and 2,3-diaminopyridine **2c** (1.00 mmol, 0.109 g). Purified by column chromatography (19 : 1 CH_2Cl_2 : MeOH) to give the title compound **4i** (0.048 g, 66%), a white solid, as a mixture of regioisomers (~7 : 1 3-methyl : 2-methyl as determined by ^1H NMR spectroscopy): R_f 0.27 (19 : 1 CH_2Cl_2 : MeOH); δ_H (270 MHz) *3-methylpyrido[2,3-*b*]pyrazine* 2.80 (3 H, s, CH_3), 7.61 (1 H, dd, *J* 8.2 Hz, *J* 3.4 Hz, *H*-7), 8.37 (1 H, dd, *J* 8.2 Hz, *J* 1.7 Hz, *H*-8), 8.77 (1 H, s, *H*-2), 9.07 (1 H, dd, *J* 3.4 Hz, *J* 1.7 Hz, *H*-6); *2-methylpyrido[2,3-*b*]pyrazine* 2.76 (3 H, s, CH_3), 7.64 (1 H, m, *H*-7), 8.31 (1 H, dd, *J* 8.5 Hz, *J* 1.7 Hz, *H*-8), 8.90 (1 H, s, *H*-3), 9.07 (1 H, m, *H*-6); δ_C (68 MHz) *3-methylpyrido[2,3-*b*]pyrazine* 22.9, 124.5, 136.0, 138.2, 147.2, 150.7, 154.0, 157.7; *m/z* (EI) 145 (M^+) [HRMS (EI) calcd. for $C_8H_7N_3$ 145.0640. Found 145.0639 (0.5 ppm error)]. The data for *2-methylpyrido[2,3-*b*]pyrazine* were consistent with those reported in the literature.[11e]

2-/3-Phenylpyrido[2,3-*b*]pyrazine 4j. Prepared by the procedure given for **4a** using α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) and 2,3-diaminopyridine **2c** (1.00 mmol, 0.109 g). Purified by column chromatography (EtOAc) to give the title compound **4j** (0.072 g, 69%), a yellow solid, as a mixture of regioisomers (~2 : 1 3-phenyl : 2-phenyl as determined by ^1H NMR spectroscopy): R_f 0.34 (EtOAc); δ_H (270 MHz) *3-phenylpyrido[2,3-*b*]pyrazine* 7.48–7.57 (3 H, m, *H*-3′,4′,5′), 7.65 (1 H, dd, *J* 8.3 Hz, *J* 4.1 Hz, *H*-7), 8.26–8.31 (2 H, m, *H*-1′,6′), 8.43 (1 H, dd, *J* 8.3 Hz, *J* 1.5 Hz, *H*-8), 9.14 (1 H, dd, *J* 4.1 Hz, *J* 1.5 Hz, *H*-6), 9.41 (1 H, s, *H*-2); *2-phenylpyrido[2,3-*b*]pyrazine* 7.48–7.57 (3 H, m, *H*-3′,4′,5′), 7.69 (1 H, dd, *J* 8.7 Hz, *J* 3.9 Hz, *H*-7), 8.15–8.19 (2 H, m, *H*-1′,6′), 8.46 (1 H, dd, *J* 8.7 Hz, *J* 1.5 Hz, *H*-8), 9.11 (1 H, dd, *J* 3.9 Hz, *J* 1.5 Hz, *H*-6), 9.50 (1 H, s, *H*-3); δ_C (68 MHz) *3-phenylpyrido[2,3-*b*]pyrazine* 124.8, 128.1, 129.3, 131.9, 135.7, 136.8, 138.2, 144.4, 150.8, 154.5, 154.7; *2-phenylpyrido[2,3-*b*]pyrazine* 125.7, 127.7, 129.3, 130.8, 135.9, 137.6, 138.6, 146.3, 150.4, 153.5, 158.7; *m/z* (EI) 207 (M^+) [HRMS (EI) calcd. for $C_{13}H_9N_3$ 207.0796. Found 207.0796 (0.2 ppm error)]. Data consistent with literature values.[2c,11f]

Quinoxalin-2-one 4k. Prepared by the procedure given for **4a** using methyl glycolate **1g** (1.20 mmol, 0.093 mL), 1,2-phenylenediamine **2a** (1.00 mmol, 0.108 g) and manganese dioxide (10.0 mmol, 1.043 g). Purified by column chromatography (EtOAc) to give the title compound **4k** (0.052 g, 36%) as a white solid: R_f 0.38 (EtOAc); mp 267–268 °C (lit.[20] 266–267 °C); δ_H (DMSO-d_6, 270 MHz) 7.25–7.34 (2 H, m), 7.54 (1 H, m), 7.77 (1 H, m), 8.16 (1 H, s, *H*-3); δ_C (DMSO-d_6, 68 MHz) 115.6, 123.1, 128.7, 130.6, 131.7, 132.0, 151.5, 154.8; *m/z* (CI) 147 (MH^+). Data consistent with literature values.[20]

Representative procedure for dihydropyrazines 6

2-Phenyl-5,6-dihydropyrazine 6a. To a solution of α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) in dry CH_2Cl_2 (25 mL) was added sequentially ethylenediamine **5a** (1.00 mmol, 0.07 mL), powdered 4 Å molecular sieves (0.50 g), 2.0 M HCl in Et_2O (1.00 mmol, 0.50 mL) and activated MnO_2 (5.00 mmol, 0.435 g) and the mixture heated to reflux. After 90 min, TLC showed the reaction to be complete. The reaction mixture was cooled to RT, filtered through Celite® and the solid residues washed well with CH_2Cl_2. The solvent was removed *in vacuo* and the product purified by column chromatography on neutral alumina deactivated with H_2O (6% w/w) (EtOAc to 19 : 1 EtOAc : MeOH) to give first the *title compound* **6a** (0.042 g, 53%) as a pale yellow oil: R_f 0.50 (EtOAc); ν_{max} (film) 3057, 2939, 2845, 1627, 1569, 1449, 929, 766, 694 cm^{-1}; δ_H (400 MHz) 3.55–3.62 (2 H, m), 3.65–3.71 (2 H, m), 7.42–7.49 (3 H, m, *H*-3′,4′,5′), 7.79–7.86 (2 H, m, *H*-1′,6′), 8.37 (1 H, t, *J* 1.4 Hz, *H*-3); δ_C (100 MHz) 44.8, 44.9, 126.6, 128.8, 130.7, 135.8, 152.4, 156.2; *m/z* (CI) 159 (MH^+) [HRMS (CI) calcd. for $C_{10}H_{11}N_2$ 159.0922. Found 159.0920 (1.3 ppm error)]. This was followed by *N-benzoyl-N′-formylethylenediamine* **7a** (0.026 g, 26%): R_f 0.12 (EtOAc); ν_{max} (film) 3064, 1651, 1539, 909, 733 cm^{-1}; δ_H (400 MHz) 3.46–3.52 (2 H, m), 3.53–3.60 (2 H, m), 7.31 (1 H, t, *J* 6.9 Hz, NH, exchanged in a D_2O shake), 7.34–7.42 (2 H, m, *H*-3′,5′), 7.44–7.51 (1 H, m, *H*-4′), 7.71 (1 H, t, *J* 4.4 Hz, NH, exchanged in a D_2O shake), 7.77–7.82 (2 H, m, *H*-1′,6′), 8.15 (1 H, s, NCHO); δ_C (100 MHz) 38.5, 40.5, 127.1, 128.6, 131.7, 133.9, 162.8, 168.7; *m/z* (CI) 193 (MH^+), 210 (MNH_4^+) [HRMS (CI) calcd. for $C_{10}H_{13}N_2O_2$ 193.0977. Found 193.0976 (0.5 ppm error)].

2-Phenyl-4a,5,6,7,8,8a-hexahydoquinoxaline 6b. Prepared by the procedure given for **6a** using α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) and *trans*-1,2-diaminocyclohexane **5b** (0.60 mmol, 0.07 mL). With *trans*-1,2-diaminocyclohexane **5b** no HCl is necessary as the amount of bis-amide formed is much lower than for ethylenediamine **5a**. The first eluting product was the *title compound* **6b** (0.068 g, 64%) as a pale yellow oil: R_f 0.50 (EtOAc); ν_{max} (film) 2931, 2856, 1681, 1565, 1447, 904, 762, 690 cm^{-1}; δ_H (400 MHz) 1.22–1.55 (4 H, m), 1.68–1.88 (2 H, m), 2.29–2.41 (2 H, m), 2.56–2.83 (2 H, m, *H*-4a,8a), 7.28–7.44 (3 H, m, *H*-3′,4′,5′), 7.70–7.81 (2 H, m, *H*-1′,6′), 8.23 (1 H, d, *J* 3.0 Hz, *H*-3); δ_C (100 MHz) 25.6, 33.4, 33.8, 59.0, 59.2, 126.8, 128.9, 130.7, 135.9, 151.9, 156.0; *m/z* (CI) 213 (MH^+) [HRMS (CI) calcd. for $C_{14}H_{17}N_2$ 213.1392. Found 213.1384 (3.4 ppm error)]. This was followed by *N-benzoyl-N′-formyl-trans-1,2-diaminocyclohexane* **7b** (0.017 g, 14%): R_f 0.24 (EtOAc); ν_{max} (film) 3304, 1665, 1636, 1554, 1536, 1291, 721, 667 cm^{-1}; δ_H (400 MHz) 1.08–1.39 (4 H, m), 1.72–1.81 (2 H, m), 1.91–2.14 (2 H, m), 3.81 (2 H, br s, *H*-1,2), 6.36 (1 H, d, *J* 3.2 Hz, NH, exchanged in a D_2O shake), 6.80 (1 H, d, *J* 3.8 Hz, NH, exchanged in a D_2O shake), 7.28–7.45 (3 H, m, *H*-3′,4′,5′), 7.66–7.75 (2 H, m, *H*-1′,6′), 8.05 (1 H, s, NCHO); δ_C (100 MHz) 24.7, 24.8, 32.3, 32.4, 52.4, 54.5, 127.2, 128.7, 131.7, 134.1, 162.1, 168.0; *m/z* (CI) 247 (MH^+) [HRMS (CI) calcd. for $C_{14}H_{19}N_2O_2$ 247.1447. Found 247.1446 (0.3 ppm error)].

2-(2-Furanyl)-4a,5,6,7,8,8a-hexahydoquinoxaline 6c. Prepared by the procedure given for **6a** using 1-(2-furanyl)-2-hydroxyethanone **1d**[13] (0.22 mmol, 0.028 g) and *trans*-1,2-diaminocyclohexane **5b** (0.30 mmol, 0.036 mL). With *trans*-1,2-diaminocyclohexane **5b** no HCl is necessary as the amount of bis-amide formed is much lower than for ethylenediamine **5a**. The first eluting product was the *title compound* **6c** (0.028 g, 64%) as a pale yellow solid: R_f 0.38 (EtOAc); mp 124–126 °C; ν_{max} (nujol) 1584, 1408, 1297 cm^{-1}; δ_H (400 MHz) 1.19–1.60 (4 H, m), 1.80–1.92 (2 H, m), 2.34–2.49 (2 H, m), 2.67–2.89 (2 H, m, *H*-4a,8a), 6.51 (1 H, m, *H*-4′), 6.99 (1 H, m, *H*-3′), 7.56 (1 H, s, *H*-5′), 8.19 (1 H, d, *J* 2.4 Hz, *H*-3); δ_C (100 MHz) 25.6,

25.7, 33.5, 33.8, 58.6, 59.3, 111.9, 113.1, 145.4, 147.5, 150.5; *m/z* (CI) 203 (MH^+) [HRMS (CI) calcd. for $C_{12}H_{15}N_2O$ 203.1184. Found 203.1183 (0.5 ppm error)]. This was followed by *N-furoyl-N′-formyl-trans-1,2-diaminocyclohexane* **7c** (0.009 g, 15%): R_f 0.18 (EtOAc); ν_{max} (film) 3246, 3048, 1650, 1640, 1575, 1538, 1332 cm^{-1}; δ_H (400 MHz) 1.18–1.45 (4 H, m), 1.70–1.88 (2 H, m), 2.01–2.18 (2 H, m), 3.75–3.94 (2 H, m, *H*-1,2), 6.30 (1 H, d, *J* 5.8 Hz, NH, exchanged in a D_2O shake), 6.48 (1 H, m, *H*-4′), 6.64 (1 H, d, *J* 6.7 Hz, NH, exchanged in a D_2O shake), 7.07 (1 H, m, *H*-3′), 7.45 (1 H, s, *H*-5′), 8.10 (1 H, s, NCHO); δ_C (100 MHz) 24.7, 24.9, 32.4, 32.5, 52.9, 53.2, 112.2, 114.6, 144.5, 147.6, 159.2, 161.7; *m/z* (CI) 237 (MH^+) [HRMS (CI) calcd. for $C_{12}H_{17}N_2O_3$ 237.1239. Found 237.1240 (0.5 ppm error)].

2-Cyclohexyl-4a,5,6,7,8,8a-hexahydoquinoxaline 6d. Prepared by the procedure given for **6a** using 1-cyclohexyl-2-hydroxyethanone **1b**[13] (0.25 mmol, 0.036 g) and *trans*-1,2-diaminocyclohexane **5b** (0.30 mmol, 0.036 mL). With *trans*-1,2-diaminocyclohexane **5b** no HCl is necessary as the amount of bis-amide formed is much lower than for ethylenediamine **5a**. The only product isolated was the *title compound* **6d** (0.029 g, 53%) as a pale yellow oil: R_f 0.43 (EtOAc); ν_{max} (film) 2930, 2856, 1587, 1449, 921, 733 cm^{-1}; δ_H (400 MHz) 1.09–1.51 (9 H, m), 1.51–1.68 (1 H, m), 1.70–1.81 (6 H, m), 2.22–2.36 (3 H, m), 2.45–2.64 (2 H, m, *H*-4a,8a), 7.75 (1 H, d, *J* 2.7 Hz, *H*-3); δ_C (100 MHz) 25.6, 25.7, 25.9, 25.9, 26.1, 29.3, 30.0, 33.4, 33.8, 44.7, 58.5, 59.3, 153.2, 163.9; *m/z* (CI) 219 (MH^+) [HRMS (CI) calcd. for $C_{14}H_{23}N_2$ 219.1861. Found 219.1854 (3.2 ppm error)].

Representative procedure for piperazines 9

2-Phenylpiperazine 9a. To a solution of α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) in dry CH_2Cl_2 (25 mL) was added sequentially ethylenediamine **5a** (1.00 mmol, 0.07 mL), powdered 4 Å molecular sieves (0.50 g), 2.0 M HCl in Et_2O (1.00 mmol, 0.50 mL), $NaBH_4$ (2.00 mmol, 0.076 g) and activated MnO_2 (5.00 mmol, 0.435 g) and the mixture heated to reflux. After 75 min, TLC showed complete conversion to the dihydropyrazine. The reaction mixture was cooled to RT and MeOH (6 mL) was added. After a further 20 h at RT, the mixture was filtered through Celite® and the solid residues washed well with CH_2Cl_2. The solvent was removed *in vacuo* and the product purified by acid/base extraction to give the *title compound* **6a** (0.042 g, 52%) as a colourless oil: ν_{max} (film) 3198, 2930, 2828, 1650, 1539, 1454, 1326, 1137, 877, 754, 699 cm^{-1}; δ_H (400 MHz) 1.95 (2 H, br s, 2 × NH), 2.55–3.16 (6 H, m, *H*-3,5,6), 3.67 (1 H, dd, *J* 15.7 Hz, *J* 4.0 Hz, *H*-2), 7.12–7.39 (5 H, m, *H*-2′,3′,4′,5′,6′); δ_C (100 MHz) 46.1, 47.8, 54.3, 62.0, 127.0, 127.5, 128.5, 142.7; *m/z* (CI) 163 (MH^+) [HRMS (CI) calcd. for $C_{10}H_{15}N_2$ 163.1235. Found 163.1234 (0.7 ppm error)].

2-Phenyl-1,2,3,4,4a,5,6,7,8,8a-decahydoquinoxaline 9b. Prepared by the procedure given for **9a** using α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) and *trans*-1,2-diaminocyclohexane **5b** (0.60 mmol, 0.07 mL). With *trans*-1,2-diaminocyclohexane **5b** no HCl was used. Acid/base extraction gave the *title compound* **9b** (0.081 g, 75%) as a colourless solid: mp 82–83 °C; ν_{max} (film) 3225, 3209, 2855, 2820, 1454, 1333, 1136, 755, 699, 652 cm^{-1}; δ_H (400 MHz) 1.15–1.40 (4 H, m), 1.55–1.85 (6 H, m), 2.26–2.48 (2 H, m, *H*-4a,8a), 2.78 (1 H, dd, *J* 11.8 Hz, *J* 10.4 Hz, $H\text{-}3_{axial}$), 3.06 (1 H, dd, *J* 11.8 Hz, *J* 2.9 Hz, $H\text{-}3_{equatorial}$), 3.85 (1 H, dd, *J* 10.4 Hz, *J* 2.9 Hz, $H\text{-}2_{axial}$), 7.17–7.40 (5 H, m, *H*-2′,3′,4′,5′,6′); δ_C (100 MHz) 25.0, 25.2, 32.0, 32.2, 54.5, 60.4, 62.4, 62.4, 127.0, 127.4, 128.5, 142.7; *m/z* (CI) 217 (MH^+) [HRMS (CI) calcd. for $C_{14}H_{21}N_2$ 217.1705. Found 217.1698 (3.2 ppm error)].

1,4-Diacetyl-2-(2-furanyl)-1,2,3,4,4a,5,6,7,8,8a-decahydoquinoxaline 9c. Prepared by the procedure given for **9a** using 1-(2-furanyl)-2-hydroxyethanone **1d**[13] (0.25 mmol, 0.032 g) and *trans*-1,2-diaminocyclohexane **5b** (0.30 mmol, 0.036 mL). With *trans*-1,2-diaminocyclohexane **5b** no HCl was used. After filtration, the solvents were removed *in vacuo* and the crude mixture taken up in CH_2Cl_2 (5 mL). To this was added Et_3N (1 mL) and acetyl chloride (1.00 mmol, 0.07 mL) and the mixture stirred at RT for 3 h. It was then poured into sat. $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (EtOAc) gave the *title compound* **9c** (0.044 g, 60%) as a colourless oil: R_f 0.14 (EtOAc); ν_{max} (nujol) 1662, 1629, 1411, 1324, 1307, 1183, 1144, 751 cm^{-1}; δ_H (270 MHz) 0.94–1.18 (1 H, m), 1.25–1.54 (3 H, m), 1.57–1.78 (2 H, m), 1.94 (3 H, s, CH_3), 2.07 (3 H, s, CH_3), 2.44–2.83 (1 H, m), 2.85 (1 H, br d, J 11.9 Hz), 3.43 (1 H, dt, *J* 2.2 Hz, *J* 10.8 Hz), 3.72 (1 H, dt, *J* 2.6 Hz, *J* 10.8 Hz), 3.99 (1 H, m), 5.15 (1 H, br s, *H*-2), 6.28 (1 H, m, *H*-3′), 6.33 (1 H, m, *H*-4′), 7.35 (1 H, s, *H*-5′); δ_C (68 MHz, toluene-d_8, 80 °C) 22.1, 22.3, 25.6, 25.8, 32.2, 32.6, 47.7, 52.5, 58.0, 58.9, 108.1, 111.0, 142.2, 154.7, 170.5, 171.7; *m/z* (CI) 291 (MH^+) [HRMS (CI) calcd. for $C_{16}H_{23}N_2O_3$ 291.1710. Found 291.1713 (1.5 ppm error)].

2-Cyclohexyl-1,2,3,4,4a,5,6,7,8,8a-decahydoquinoxaline 9d. Prepared by the procedure given for **9a** using 1-cyclohexyl-2-hydroxyethanone **1b**[13] (0.25 mmol, 0.036 g) and *trans*-1,2-diaminocyclohexane **5b** (0.30 mmol, 0.036 mL). With *trans*-1,2-diaminocyclohexane **5b** no HCl was used. Acid/base extraction gave the *title compound* **9d** (0.047 g, 84%) as a colourless solid: mp 78–80 °C; ν_{max} (film) 3362, 3290, 3226, 1341, 833 cm^{-1}; δ_H (400 MHz) 0.85–1.00 (2 H, m), 1.02–1.36 (8 H, m), 1.54–1.82 (9 H, m), 2.09–2.41 (4 H, m), 2.41–2.51 (2 H, m), 2.99–3.11 (1 H, m); δ_C (100 MHz) 24.9, 25.1, 26.2, 26.3, 26.5, 29.2, 29.4, 31.7, 32.2, 41.3, 50.1, 60.8, 61.4, 61.6; *m/z* (CI) 223 (MH^+) [HRMS (CI) calcd. for $C_{14}H_{27}N_2$ 223.2174. Found 223.2167 (3.2 ppm error)].

Representative procedure for pyrazines 10

2-Phenylpyrazine 10a. To a solution of α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) in dry CH_2Cl_2 (25 mL) was added sequentially ethylenediamine **5a** (1.00 mmol, 0.07 mL), powdered 4 Å molecular sieves (0.50 g), 2.0 M HCl in Et_2O (1.00 mmol, 0.50 mL) and activated MnO_2 (5.00 mmol, 0.435 g) and the mixture heated to reflux. After 2.5 h, TLC showed complete conversion to the dihydropyrazine. The reaction mixture was cooled to RT and ~0.4 M KOH in MeOH (5 mL) was added. The mixture was returned to reflux for a further 20 h, then was filtered through Celite® and the solid residues washed well with CH_2Cl_2. The solvent was removed *in vacuo* and the product purified by column chromatography on neutral alumina deactivated with H_2O (6% w/w) (3 : 1 PE : EtOAc) to give the title compound **10a** (0.035 g, 45%) as a colourless solid: mp 74 °C (lit.[16a] 72 °C); ν_{max} (film) 2904, 2854, 1728, 1464, 1379, 1271 cm^{-1}; δ_H (270 MHz) 7.49–7.52 (3 H, m, *H*-3′,4′,5′), 7.98–8.04 (2 H, m, *H*-2′,6′), 8.50 (1 H, d, *J* 2.4 Hz, *H*-6), 8.63 (1 H, dd, *J* 2.4 Hz, ^4J 1.5 Hz, *H*-5), 9.03 (1 H, d, ^4J 1.5 Hz, *H*-3); δ_C (100 MHz) 127.0, 129.2, 130.0, 136.4, 142.3, 143.0, 144.3, 152.9; *m/z* (CI) 157 (MH^+). Data consistent with literature values.[17a]

2-(4-Bromophenyl)pyrazine 10b. Prepared by the procedure given for **6a** using 1-(4-bromophenyl)-2-hydroxyethanone **1h** (0.50 mmol, 0.108 g) and ethylenediamine **5a** (1.00 mmol, 0.07 mL). Column chromatography (3 : 1 PE : EtOAc) gave the *title compound* **10b** (0.067 g, 57%) as a yellow oil: R_f 0.29 (3 : 1 PE : EtOAc); ν_{max} (film) 1555, 1470, 1412, 1385 cm^{-1}; δ_H (400 MHz) 7.64 (2 H, d, *J* 8.9 Hz, *H*-3′,5′), 7.90 (2 H, d, *J* 8.9 Hz, *H*-2′,6′), 8.53 (1 H, s, *H*-6), 8.63 (1 H, s, *H*-5), 9.04 (1 H, s, *H*-3); δ_C (100 MHz) 125.2, 129.2, 132.9, 135.8, 142.5, 143.7, 144.8, 152.3; *m/z* (CI) 232/234 (MH^+) [HRMS (CI) calcd. for $C_{10}H_7N_2{}^{81}Br$ 233.9792. Found 233.9795 (1.1 ppm error)].

2-(2-Furanyl)pyrazine 10c. Prepared by the procedure given for **6a** using 1-(2-furanyl)-2-hydroxyethanone **1d**[12] (0.50 mmol, 0.064 g) and ethylenediamine **5a** (1.00 mmol, 0.07 mL). Column chromatography (2 : 1 PE : EtOAc) gave the *title compound* **10c** (0.044 g, 60%) as a yellow oil: R_f 0.67 (2 : 1 PE : EtOAc); ν_{max} (film) 1590, 1470, 1411, 1384 cm^{-1}; δ_H (270 MHz) 6.57 (1 H, m, *H*-4′), 7.15 (1 H, m, *H*-3′), 7.60 (1 H, m, *H*-5′), 8.42 (1 H, d, *J* 2.7 Hz, *H*-6), 8.53 (1 H, d, *J* 2.7 Hz, *H*-5), 8.97 (1 H, s, *H*-3); δ_C (100 MHz) 111.3, 112.9, 138.3, 141.2, 143.1, 144.7, 145.0, 147.9; *m*/*z* (CI) 147 (MH^+) [HRMS (CI) calcd. for $C_8H_7N_2O$ 147.0558. Found 147.0558 (0.0 ppm error)].

2-Phenyl-5,6,7,8-tetrahydoquinoxaline 10d. Prepared by the procedure given for **6a** using α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) and *trans*-1,2-diaminocyclohexane **5b** (0.60 mmol, 0.07 mL). With *trans*-1,2-diaminocyclohexane **5b** no HCl was used. Column chromatography (3 : 1 PE : EtOAc) gave the *title compound* **10d** (0.069 g, 66%) as a colourless oil: R_f 0.31 (2 : 1 PE : EtOAc); ν_{max} (film) 2937, 2861, 1457, 1444, 1380, 1142, 775, 694 cm^{-1}; δ_H (270 MHz) 1.78–1.94 (4 H, m, *H*-6,7), 2.83–2.98 (4 H, m, *H*-5,8), 7.29–7.43 (3 H, m, *H*-3′,4′,5′), 7.82–7.91 (2 H, m, *H*-1′,6′), 8.64 (1 H, s, *H*-3); δ_C (68 MHz) 22.7, 22.7, 31.8, 32.8, 126.8, 129.0, 129.3, 137.0, 138.9, 149.8, 151.3, 152.4; *m*/*z* (CI) 211 (MH^+) [HRMS (CI) calcd. for $C_{14}H_{15}N_2$ 211.1235. Found 211.1234 (0.7 ppm error)].

2-(2-Furanyl)-5,6,7,8-tetrahydoquinoxaline 10e. Prepared by the procedure given for **6a** using α-hydroxyacetophenone **1c** (0.50 mmol, 0.068 g) and *trans*-1,2-diaminocyclohexane **5b** (0.60 mmol, 0.07 mL). With *trans*-1,2-diaminocyclohexane **5b** no HCl was used. Column chromatography (3 : 1 PE : EtOAc) gave the *title compound* **10e** (0.069 g, 66%) as a colourless oil: R_f 0.31 (2 : 1 PE : EtOAc); ν_{max} (film) 2937, 2861, 1457, 1444, 1380, 1142, 775, 694 cm^{-1}; δ_H (270 MHz) 1.78–1.94 (4 H, m, *H*-6,7), 2.83–2.98 (4 H, m, *H*-5,8), 7.29–7.43 (3 H, m, *H*-3′,4′,5′), 7.82–7.91 (2 H, m, *H*-1′,6′), 8.64 (1 H, s, *H*-3); δ_C (68 MHz) 22.7, 22.7, 31.8, 32.8, 126.8, 129.0, 129.3, 137.0, 138.9, 149.8, 151.3, 152.4; *m*/*z* (CI) 211 (MH^+) [HRMS (CI) calcd. for $C_{14}H_{15}N_2$ 211.1235. Found 211.1234 (0.7 ppm error)].

2-Cyclohexylpyrazine 10f. Prepared by the procedure given for **6a** using 1-cyclohexyl-2-hydroxyethanone **1b**[13] (0.50 mmol, 0.106 g) and ethylenediamine **5a** (1.00 mmol, 0.07 mL). Column chromatography (3 : 1 PE : EtOAc) gave the *title compound* **10f** (0.027 g, 33%) as a yellow oil: R_f 0.38 (3 : 1 PE : EtOAc); ν_{max} (film) 1558, 1441, 1381 cm^{-1}; δ_H (400 MHz) 1.32–1.94 (10 H, m, *H*-2′,3′,4′,5′,6′), 2.75 (1 H, dd, *J* 11.9 Hz, *J* 2.4 Hz, *H*-1′), 8.37 (1 H, s, *H*-3), 8.39 (2 H, m, *H*-5,6); δ_C (100 MHz) 25.8, 26.3, 32.4, 44.0, 142.2, 143.6, 143.9, 161.0; *m*/*z* (EI) 162 (M^+) [HRMS (EI) calcd. for $C_{10}H_{14}N_2$ 162.1157. Found 162.1156 (0.8 ppm error)].

11,17-Dihydroxy-10,13-dimethyl-17-quinoxalin-2-yl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydocyclopenta-[*a*]phenanthren-3-one 12

Prepared by the procedure given for **4a** using hydrocortisone **1i** (0.20 mmol, 0.072 g) and *o*-phenylenediamine **2a** (0.40 mmol, 0.043 g). Purified by column chromatography (EtOAc) to give the *title compound* **12** (0.058 g, 67%) as an orange solid: R_f 0.50 (EtOAc); mp 266–268 °C; ν_{max} (nujol) 3392, 1638, 1276, 1231, 1227, 1112, 942, 865, 775 cm^{-1}; δ_H (400 MHz) 0.86 (3 H, s, CH_3), 1.01 (1 H, dd, *J* 10.7 Hz, *J* 3.1 Hz), 1.08–1.18 (1 H, m), 1.31 (1 H, dd, *J* 14.0 Hz, *J* 2.1 Hz), 1.37 (3 H, s, CH_3), 1.50–1.64 (1 H, m), 1.77 (1 H, dt, *J* 4.6 Hz, *J* 13.4 Hz), 1.86–2.51 (12 H, m), 3.04 (1 H, dd, *J* 12.5 Hz, *J* 11.9 Hz), 4.41 (1 H, s, OH), 4.61 (1 H, s, OH), 5.61 (1 H, s, C=CH), 7.67–7.76 (2 H, m, *H*-6,7), 7.96–8.07 (2 H, m, *H*-5,8), 9.01 (1 H, s, *H*-3); δ_C (100 MHz) 18.5, 21.0, 24.3, 31.9, 32.2, 32.8, 33.8, 34.9, 35.0, 39.3, 39.4, 49.1, 51.9, 56.1, 68.4, 84.8, 122.3, 129.0, 129.1, 129.8, 130.3, 140.5, 141.2, 143.9, 157.0, 172.7, 199.8; *m*/*z* (CI) 433 (MH^+), 415 ($MH^+ - H_2O$) [HRMS (CI) calcd. for $C_{27}H_{33}N_2O_3$ 433.2491. Found 433.2497 (1.3 ppm error)].

17-(5,6-Dihydropyrazin-2-yl)-11,17-dihydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrocyclopenta-[*a*]phenanthren-3-one 13

Prepared by the procedure given for **6a** using hydrocortisone **1i** (0.20 mmol, 0.072 g) and ethylenediamine **5a** (0.40 mmol, 0.027 mL). Purified by column chromatography (25 : 1 to 15 : 1 CH_2Cl_2 : MeOH) to give the *title compound* **13** (0.030 g, 40%) as the only isolated product, a pale yellow solid: R_f 0.24 (9 : 1 CH_2Cl_2 : MeOH); mp 130–132 °C; ν_{max} (nujol) 3404, 1659, 1615, 1590, 1276, 1233, 1189, 1119, 950, 926, 868 cm^{-1}; δ_H (400 MHz) 0.96 (3 H, s, CH_3), 1.01–1.04 (1 H, m), 1.06–1.21 (1 H, m), 1.42 (3 H, s, CH_3), 1.34–1.52 (3 H, m), 1.54–1.65 (1 H, m), 1.71–1.95 (3 H, m), 1.96–2.09 (3 H, m), 2.12–2.28 (2 H, m), 2.33 (1 H, m), 2.39–2.53 (2 H, m), 2.73 (1 H, m), 3.34–3.55 (4 H, m, DHP), 3.87 (1 H, br s, OH), 4.43 (1 H, br s, OH), 5.66 (1 H, s, C=CH), 8.11 (1 H, d, *J* 1.5 Hz, imine); δ_C (100 MHz) 18.5, 21.1, 24.2, 31.5, 32.2, 32.8, 33.5, 33.9, 35.1, 39.3, 39.9, 43.9, 44.5, 48.5, 51.7, 56.1, 68.5, 84.7, 122.4, 152.6, 162.2, 172.4, 199.7; *m*/*z* (CI) 385 (MH^+) [HRMS (CI) calcd. for $C_{23}H_{33}N_2O_3$ 385.2491. Found 385.2489 (0.5 ppm error)].

17-(4a,5,6,7,8,8a-Hexahydroquinoxalin-2-yl)-11,17-dihydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradeca-hydrocyclopenta[*a*]phenanthren-3-one 14

Prepared by the procedure given for **6a** using hydrocortisone **1i** (0.20 mmol, 0.072 g) and *trans*-1,2-diaminocyclohexane **5b** (0.24 mmol, 0.028 mL). Purified by column chromatography (EtOAc to 19 : 1 EtOAc : MeOH) to give the *title compound* **14** (0.072 g, 82%) as an inseparable mixture of diastereomers (~1 : 1 A : B), a colourless solid: R_f 0.19 (EtOAc); mp 123–125 °C; ν_{max} (nujol) 3393, 1658, 1615, 1584, 1233, 1118, 915, 730 cm^{-1}; δ_H (400 MHz) 0.88 (3 H, s, CH_3A), 0.93 (3 H, s, CH_3B), 0.94–1.00 (1 H, m, A + B), 1.02–1.18 (1 H, m, A + B), 1.24–1.57 (6 H, m, A + B), 1.39 (3 H, s, CH_3A + B), 1.60–2.06 (11 H, m, A + B), 2.08–2.82 (10 H, m, A + B), 3.68 (1 H, br s, OH, A), 4.39 (1 H, br s, OH, A + B), 4.52 (1 H, br s, OH, B), 5.62 (1 H, s, C=CH A + B), 7.98 (1 H, d, *J* 2.8 Hz, imine A), 8.04 (1 H, d, *J* 2.7 Hz, imine B); δ_C (100 MHz) 18.4/18.5 (CH_3), 21.0/21.1 (CH_3), 24.0/24.3 (CH_2), 25.4/25.5 (CH_2), 25.5/25.5 (CH_2), 31.4/31.5 (CH), 32.2 (CH_2), 32.7/32.8 (CH_2), 32.9/33.7 (CH_2), 33.0/33.1 (CH_2), 33.5/33.5 (CH_2), 33.8 (CH_2), 34.9 (CH_2), 39.2/39.3 (C), 39.5/40.0 (CH_2), 48.0/48.9 (C), 51.5/51.6 (CH), 56.1/56.1 (CH), 58.1/58.3 (CH), 58.8/59.1 (CH), 68.2/68.3 (CH), 84.1/84.5 (C), 122.2/122.3 (CH), 151.5/152.4 (CH), 161.7/161.8 (C), 172.6/172.7 (C), 199.7/199.7 (C) [The pairs of signals were tentatively assigned due to their similar chemical shift and type; however, this is by no means a definitive assignation]; *m*/*z* (CI) 439 (MH^+) [HRMS (CI) calcd. for $C_{27}H_{39}N_2O_3$ 439.2961. Found 439.2967 (1.4 ppm error)].

11,17-Dihydroxy-10,13-dimethyl-17-piperazin-2-yl-1,2,6,7,8,9,-10,11,12,13,14,15,16,17-tetradecahydocyclopenta[*a*]phenan-thren-3-one 15

Prepared by the procedure given for **9a** using hydrocortisone **1g** (0.20 mmol, 0.072 g) and ethylenediamine **5a** (0.40 mmol, 0.027 mL). Acid/base extraction gave the *title compound* **15** (0.054 g, 69%) as a colourless solid: mp 104–106 °C; ν_{max} (CH_2Cl_2) 3445, 3053, 2934, 1661, 1451, 1266, 1133, 909, 738, 704 cm^{-1}; δ_H (400 MHz) 0.73–3.16 (28 H, m), 1.02 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 4.33 (1 H, br s, OH), 5.63 (1 H, s, C=CH); δ_C (100 MHz) 16.9, 21.1, 23.4, 31.3, 32.3, 32.7, 33.9, 35.0, 37.3, 39.3, 41.5, 45.5, 45.8, 46.6, 46.9, 52.1, 56.0, 61.5, 68.2, 83.6, 122.2, 173.0, 199.9; *m*/*z* (CI) 389 (MH^+) [HRMS (CI) calcd. for $C_{23}H_{37}N_2O_3$ 389.2804. Found 389.2807 (0.8 ppm error)].

17-(Decahydroquinoxalin-2-yl)-11,17-dihydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrocyclopenta-[*a*]phenanthren-3-one 16

Prepared by the procedure given for **9a** using hydrocortisone **1g** (0.20 mmol, 0.072 g) and *trans*-1,2-diaminocyclohexane **5b** (0.24 mmol, 0.028 mL). With *trans*-1,2-diaminocyclohexane **5b** no HCl was used. Acid/base extraction gave the title compound **16** (0.077 g, 89%) as a mixture of several diastereomers (as shown by ^{1}H and ^{13}C NMR spectroscopy), a colourless solid: mp 112–113 °C; ν_{max} (nujol) 3429, 2870, 2727, 1657, 1461, 1377, 749 cm^{-1}; *m/z* (CI) 443 (MH^+) [HRMS (CI) calcd. for $C_{27}H_{43}N_2O_3$ 443.3274. Found 443.3275 (0.4 ppm error)].

11,17-Dihydroxy-10,13-dimethyl-17-pyrazin-2-yl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydocyclo-penta[*a*]phenanthren-3-one 17

Prepared by the procedure given for **10a** using hydrocortisone **1g** (0.20 mmol, 0.072 g) and ethylenediamine **5a** (0.40 mmol, 0.027 mL). Column chromatography (EtOAc to 4 : 1 EtOAc : MeOH) gave the *title compound* **17** (0.008 g, 10%) as a colourless solid: R_f 0.34 (9 : 1 CH_2Cl_2 : EtOAc); mp 185–190 °C (decomp.); ν_{max} (nujol) 3455, 2953, 1642, 1614, 1234, 1157, 1116, 1915, 859 cm^{-1}; δ_H (400 MHz) 0.84 (3 H, s, CH_3), 1.08 (1 H, m), 1.13–1.34 (3 H, m), 1.43 (3 H, s, CH_3), 1.50–1.64 (2 H, m), 1.81–2.12 (6 H, m), 2.12–2.21 (1 H, m), 2.23–2.30 (1 H, m), 2.32–2.40 (1 H, m), 2.42–2.57 (2 H, m), 2.82 (1 H, m), 4.18 (1 H, br s, OH), 4.49 (1 H, br d, *J* 2.8 Hz, OH), 5.70 (1 H, s, C=CH), 8.53 (2 H, br s, *H*-pyraz.), 8.82 (1 H, s, *H*-pyraz.); δ_C (100 MHz) 18.6, 21.2, 24.3, 32.2, 32.4, 33.0, 34.1, 35.0, 35.2, 39.5, 39.6, 48.7, 51.8, 56.3, 68.8, 84.4, 122.6, 142.6, 143.1, 143.3, 157.2, 172.4, 199.8; *m/z* (CI) 383 (MH^+) [HRMS (CI) calcd. for $C_{23}H_{31}N_2O_3$ 383.2321. Found 383.2331 (2.6 ppm error)].

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