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An expedient synthesis of the proposed biosynthetic precursor of the oxepine natural product, janoxepin

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ABSTRACT

An efficient synthetic route to the putative biosynthetic intermediate of the anti-plasmodial natural product janoxepin is described. This novel enamine-containing pyrazino[2,1-*b*]quinazoline-3,6-dione, and its synthetic precursors, should be of value in studies to elucidate the biosynthetic pathway leading to the oxepine family of natural products. The cornerstones of the synthesis are amide coupling, pyrazino[2,1-*b*]quinazoline-3,6-dione construction and aldol introduction of the enamine.

There is increasing fascination with the growing family of oxepine-containing natural products, particularly in terms of their structural determination, biological activity and biogenesis. We have become interested in this area from a synthetic viewpoint and recently reported the first total synthesis of the anti-plasmodial, oxepine-pyrimidinone-containing natural product janoxepin (**1**) (Fig. 1).[1]

In terms of the biosynthesis of oxepine-containing natural products such as janoxepin (**1**) and related compounds, oxepinamide D (**2**)[2] and brevianamide O (**3**),[3] a common proposal is that the oxepine ring is generated via enzymatic arene-epoxidation of a pyrazino[2,1-*b*]quinazoline-3,6-dione **4** followed by a rearrangement and ring-opening sequence (Scheme 1).[2–4]

The pyrazino[2,1-*b*]quinazoline-3,6-dione skeleton seen in **4** can be found in numerous natural products with considerable biological potential. Many of this family, including acetylardeemin,[5] fiscalin B[6] and serantrypinone[7] (amongst others[8]) have been the subject of elegant syntheses. However, these compounds do not bear the enamine moiety at C-4 present in **4** and the only natural product examples with this structural feature are aurantiomide C (**6**),[9] verrucine F (**7**)[10] and quinadoline A (**8**)[11] (Fig. 2), none of which have succumbed to total synthesis to date. We therefore decided to develop a synthetic route to prepare the putative janoxepin precursor **4**, both to aid biosynthetic studies in the oxepine natural product area, and to provide an entry into the pyrazino[2,1-*b*]quinazoline-3,6-dione natural products shown in Figure 2.

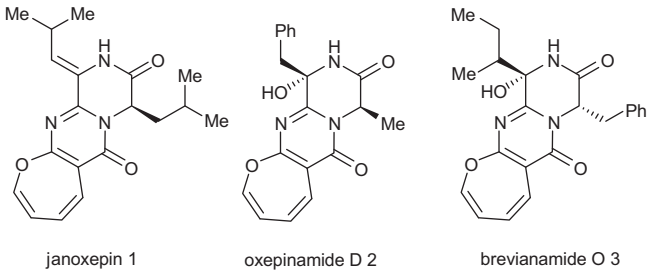

Figure 1. Representative oxepine natural products.

The retrosynthetic analysis of **4** (Scheme 2) relied upon introduction of the aliphatic enamine moiety via an aldol addition to an imidate-protected version of the known[12] pyrazino[2,1-*b*]quinazoline-3,6-dione **9**, followed by a selective elimination to furnish the *Z*-enamine. The tricyclic intermediate **9** would itself be constructed by a double cyclisation of the novel amine **10**, whilst an amide coupling sequence starting from the inexpensive and readily available isatoic anhydride (**11**), Fmoc-Gly-Cl **12** and D-leucine methyl ester (**13**) would ultimately be employed to synthesise this key intermediate.

The study therefore commenced with a modified coupling of the commercially-available isatoic anhydride (**11**) and D-leucine methyl ester (**13**) (Scheme 3) to furnish the known amide **14** in a much improved yield to that previously reported (87% vs 32%[13]). This was followed by a second coupling with the Fmoc-protected glycine chloride **12** to furnish the novel intermediate **15**. The Fmoc protecting group was then removed by treatment of **15** with piperidine to provide the key novel amine intermediate **10** in three

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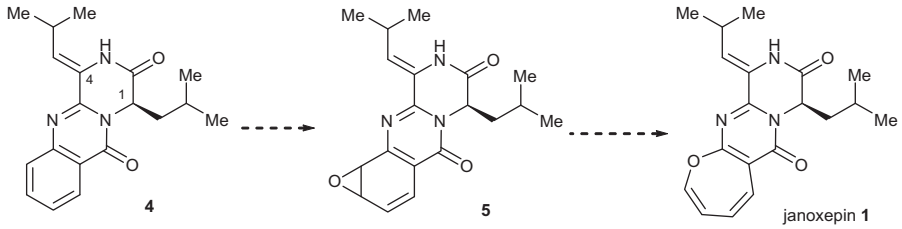


Scheme 1. Proposed biosynthesis of janoxepin (**1**).

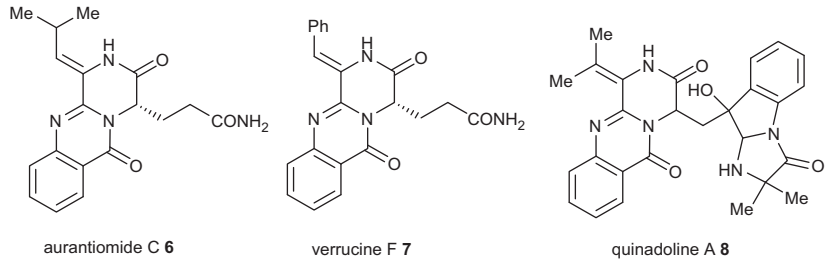
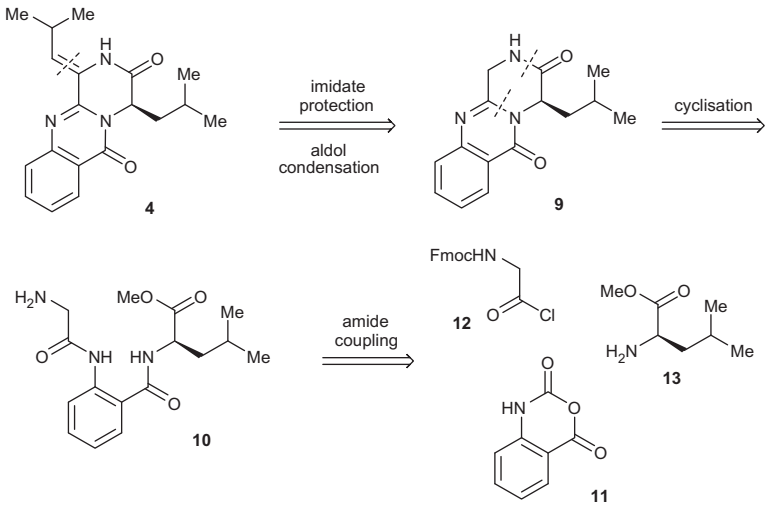
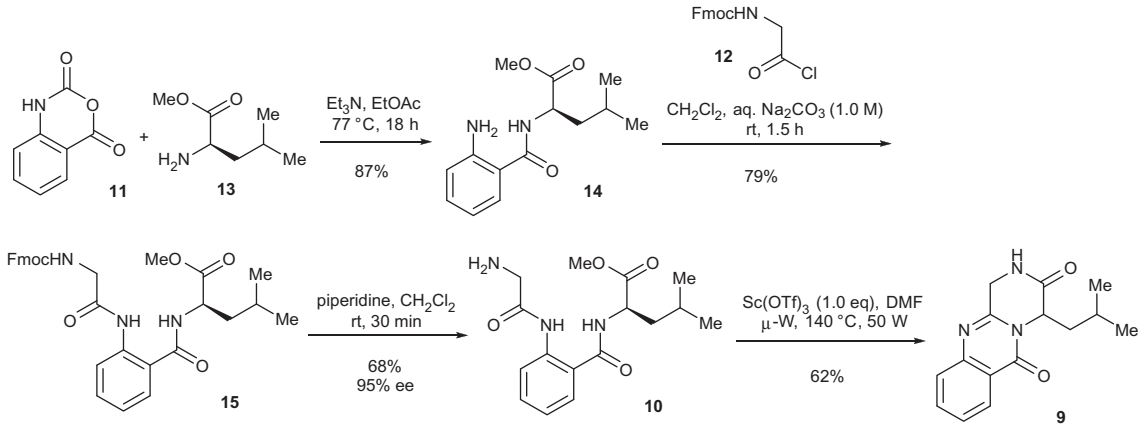


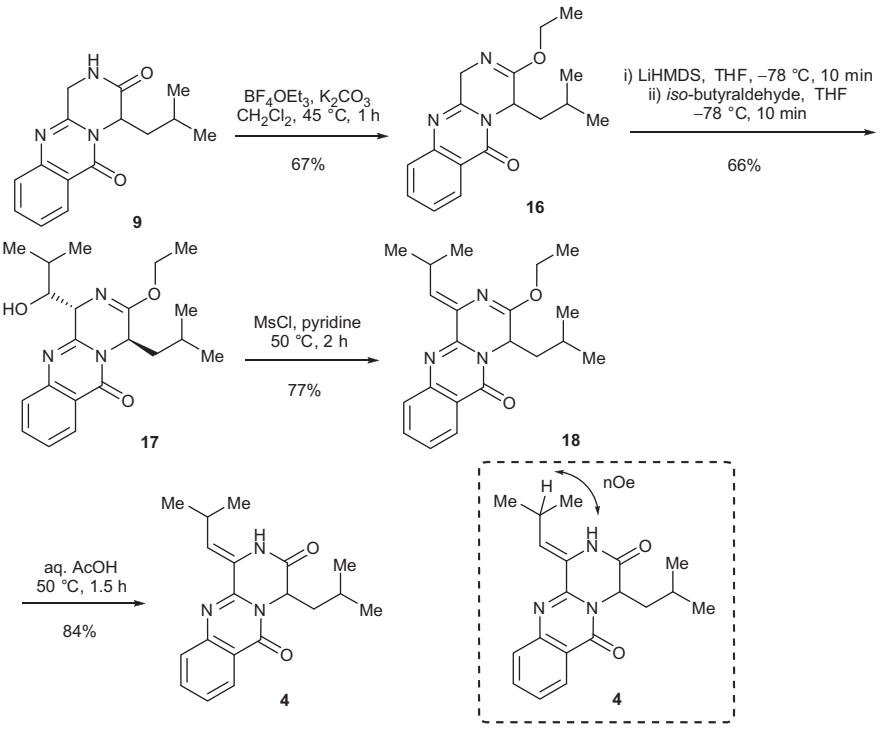
Figure 2. Structures of aurantiomide C (**6**), verrucine F (**7**) and quinadoline A (**8**).



Scheme 2. Retrosynthetic analysis.



Scheme 3. Synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione **9**.



Scheme 4. Synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione **4**.

steps, 47% overall yield and in 95% ee (as shown by chiral HPLC analysis).[14]

In order to effect the double cyclisation to convert amine **10** into pyrazino[2,1-*b*]quinazoline-3,6-dione **9** we utilised the Lewis acid mediated cyclisation procedure reported by Chu and co-workers.[15] Thus, a solution of amine **10** in DMF was treated with 1 equiv of scandium triflate and irradiated in a microwave reactor (CEM Discover) at 140 °C, 50 W for 2 min as reported,[15] but only a trace of the desired tricycle **9** was observed along with unreacted amine **10**. However, microwave irradiation at the same temperature for an extended period (10 min) gave pyrazino[2,1-*b*]quinazoline-3,6-dione **9** in 62% yield (Scheme 3). This result demonstrates that the Chu procedure[15] is compatible with a substituent at C-1 on the ketopiperazine ring. Disappointingly however, due either to the long reaction times, or simply the base-sensitivity of the compounds, complete racemisation was observed (**9**, 51:49 er) under the cyclisation conditions employed here.[16] Future work will investigate the effect of different side chains at the C-1 position and screen alternative Lewis acids in order to demonstrate the broader scope of this procedure. [Compound **9** has previously been prepared by a four-step solid phase 'discrete' synthesis in 53% overall yield from L-leucine-Wang resin, anthranilic acid and Fmoc-Gly-Cl; no isolated mass reported, optical purity unspecified.[12] The long reaction times and large excesses of anthranilic acid, Fmoc-Gly-Cl and iodine needed did not lend this procedure to the gram scale preparation of **9** required in this context].

The key step now remaining was to install the enamine moiety. Amide **9** was first converted into the novel imidate **16** using triethyloxonium tetrafluoroborate. This choice of amide protection has the virtue of facile subsequent removal under mild conditions, whilst being stable to the basic conditions required for ketopiperazine deprotonation and further manipulations. Aldol addition was effected by treatment of compound **16** with LiHMDS in THF at −78 °C followed by the addition of *iso*-butyraldehyde to afford alcohol **17** as a single diastereomer and in good yield. Treatment of **17** with methanesulfonyl chloride in pyridine, with heating to 50 °C, gave enamine **18** directly (as a single isomer) via a one-pot mesylation–elimination sequence. The preparation was completed by imidate hydrolysis using aqueous acetic acid with heating to 50 °C to furnish the target compound **4** in 43% overall yield over the three steps in racemic form (Scheme 4).

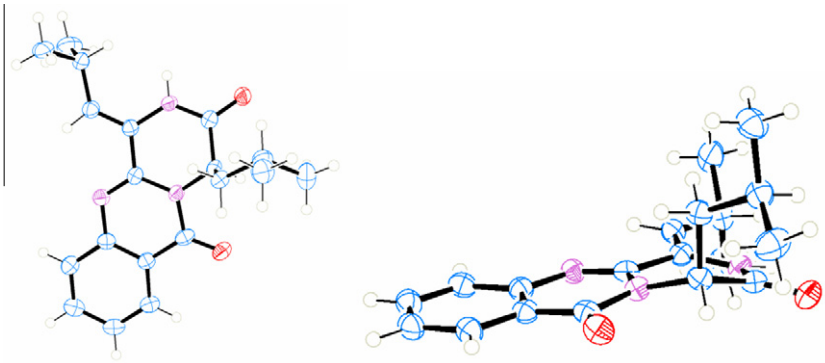
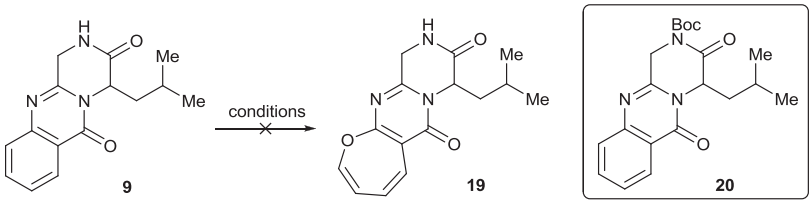


Figure 3. X-ray crystallography of (±)-**4**. ORTEP representations shown with ellipsoids at 50% probability. A single enantiomer (*R*) is shown for clarity. CCDC 862145.[18]

Table 1
Epoxidation conditions screened



Entry	Oxidant	Conditions
1	*m*-CPBA	CH_2Cl_2/aq $NaHCO_3$ (sat.), rt, 18 h
2	NaOCl	*n*-Bu_4NHSO_4, CH_2Cl_2, rt, 18 h
3	DMDO	Acetone, 0 °C–rt, 18 h

The structure of **4** was confirmed by ^1H and ^{13}C NMR spectroscopy in conjunction with COSY and HSQC experiments.[17] NOE correlations (Scheme 4) confirmed that the enamine was in the desired *Z*-configuration, and further proof of this was provided by X-ray crystallographic analysis (Fig. 3).[18]

Preliminary, if speculative, experiments were carried out to investigate whether chemical oxidation could be employed to effect the proposed biomimetic oxepine formation (Table 1). Pyrazino[2,1-*b*]quinazoline-3,6-dione **9** was chosen as the substrate for this study to preclude any problems with competing epoxidisation of an enamine double bond. Unfortunately, there was no sign of the hoped-for oxepine **19** (nor the intermediate epoxide) and only an inseparable mixture of *N*-oxide compounds, starting material and degradation products was observed (oxidation at the ketopiperazine C-4 position cannot be ruled out as this process has been reported previously[19]). In order to remove the possibility of *N*-oxide formation, the corresponding *N*-Boc derivative **20** was subjected to the same reagents with similarly disappointing results. We plan to investigate the chemical oxidation of the putative biosynthetic intermediate **4** and its imidate precursor **18** in due course; however these preliminary results suggest that arene oxidation will be difficult to achieve synthetically.

In summary, the putative biosynthetic precursor to janoxepin (**1**), pyrazino[2,1-*b*]quinazoline-3,6-dione **4**, has been prepared in an efficient eight-step synthesis starting from readily available and inexpensive starting materials. The methodology for installation of the enamine moiety, as well as that for pyrazino[2,1-*b*]quinazoline-3,6-dione construction, not only has application in the preparation of other oxepine biosynthetic precursors, but also in the synthesis of pyrazino[2,1-*b*]quinazoline-3,6-dione natural products **6–8** (Fig. 2). Strategies for the asymmetric synthesis of compounds of this type are currently being investigated. With a view to developing a biomimetic strategy for the synthesis of oxepine natural products, a preliminary investigation of chemical arene-epoxidation procedures was unsuccessful. However, an efficient route to these key biosynthetic precursors is now available to underpin future studies using enzymatic epoxidative biotransformations.

Acknowledgments

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14. HPLC: Chiralpak AD-H (80:20 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 7.25 min (94.91%), 9.09 min (5.09%).
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16. HPLC: Chiralpak OD (80:20 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 9.71 min (50.59%), 18.83 min (49.41%).
17. (±)-**4**: mp 229–231 °C (MeOH/*n*-hexane); R_f 0.55 (1:1 PE/EtOAc); Found: C, 69.89; H, 7.09; N, 12.81; $C_{19}H_{23}N_3O_2$ requires: C, 70.13; H, 7.12; N, 12.91%; υ_{max}/cm^{-1} 3187, 3078, 2960, 1686, 1582, 1562; δ_H (400 MHz, $CDCl_3$) 8.59 (1 H, br s), 8.27 (1 H, dd, *J* 8.0, 1.5), 7.76 (1 H, ddd, *J* 8.5, 7.0, 1.5), 7.69 (1 H, dd, *J* 8.5, 1.5), 7.47 (1 H, ddd, *J* 8.0, 7.0, 1.5), 6.45 (1 H, d, *J* 10.0), 5.58 (1 H, ddd, *J* 8.5, 5.5, 1.0), 2.75 (1 H, d sept, *J* 10.0, 6.5), 1.83–1.71 (2 H, m), 1.65 (1 H, ddd, *J* 13.5, 8.5, 5.5), 1.21 (3 H, d, *J* 6.5), 1.18 (3 H, d, *J* 6.5), 1.08 (3 H, d, *J* 6.5), 0.94 (3 H, d, *J* 6.5); δ_C (100 MHz, $CDCl_3$) 167.4, 160.4, 147.4, 145.1, 134.6, 127.8, 127.4, 126.8, 126.8, 124.9, 120.0, 53.7, 42.6, 26.1, 24.9, 23.1, 22.4, 22.3, 21.5; *m*/*z* (ESI) 326 $[MH]^+$. Calcd for $C_{19}H_{24}N_3O_2$: 326.1863. Found: $[M+H]^+$, 326.1859 (0.9 ppm error); HPLC: Chiralcel OD (95:5 *n*-hexane/*i*-PrOH, 1.0 mL min^{-1}) 9.74 min (50.10%), 20.02 min (49.90%).
18. X-Ray crystallography: CCDC 862145 contains the supplementary crystallographic data for this compound. Crystals were grown by slow diffusion (Et_2O/CH_2Cl_2).
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