ORGANIC LETTERS

2012
Vol. 14, No. 4
1122–1125

Total Synthesis of an Oxepine Natural Product, (±)-Janoxepin

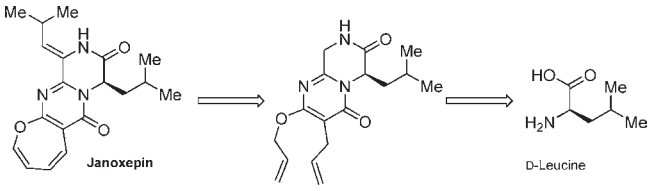
Richard G. Doveston, René Steendam, Stuart Jones, and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.

richard.taylor@york.ac.uk

Received January 9, 2012

ABSTRACT



The total synthesis of (±)-janoxepin, a novel antiplasmodial D-leucine derived oxepine-pyrimidinone-ketopiperazine isolated from the fungus *Aspergillus janus*, is described. The cornerstones of the synthetic route are pyrimidinone preparation, ring-closing metathesis, aldol introduction of the enamide, and dihydro-oxepine elaboration. This synthetic route proved very efficient for the formation of a number of janoxepin analogues, including dihydro-janoxepin and tetrahydro-janoxepin.

Janoxepin (**1**) was isolated from the fungus *Aspergillus janus* in 2005 by Sprogøe and co-workers and shown to display antiplasmodial activity against the malaria parasite *Plasmodium falciparum* 3D7 (IC_{50} 28 mg/mL).[1] Structurally, janoxepin is fascinating, being based on an oxepine-pyrimidinone-ketopiperazine tricyclic core derived from D-leucine. The overall structure of janoxepin was determined by a combination of MS and NMR spectroscopy, with the *Z*-configuration of the exocyclic enamide moiety being confirmed by ^{1}H NMR NOE correlations (Figure 1).

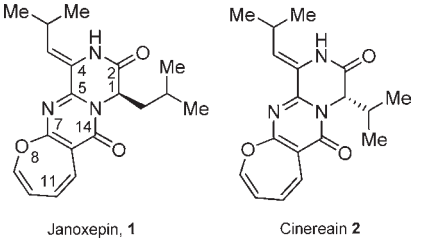


Figure 1. Structure of janoxepin (**1**).

Examples of reduced oxepine-based natural products such as the brevetoxin-like polyether marine metabolites[2] and dihydro-oxepine epidithiodiketopiperazines[3] are well-known and have been the subject of synthetic studies. However, examples containing a higher degree of unsaturation are rare.[4] That said, janoxepin belongs to a small family of pyrimidinone-annelated oxepine natural products including one very close relative in cinereain (**2**)[5] and a number of other related compounds (oxepinamides A–D,[6,7] brevianamides O–P,[8] protuboxepins A–B,[9] circumdatin A (asperloxin A),[10] and circumdatin B).[11]

(1) Sprogøe, K.; Manniche, S.; Larsen, T. O.; Christopherson, C. *Tetrahedron* **2005**, *61*, 8718.

(2) For reviews see: Yamaguchi, S. *Heterocycles* **2009**, *79*, 243. Snyder, N. L.; Haines, H. M.; Peczuh, M. W. *Tetrahedron* **2006**, *62*, 9301. Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301.

(3) Codelli, J. A.; Puchlopek, A. L. A.; Reisman, S. E. *J. Am. Chem. Soc.*, DOI: 10.1021/ja209354e, Publication Date (Web): 24 Oct 2011.

(4) For naturally occurring dibenzo-oxepines and their synthesis, see: Olivera, R.; San Martin, R.; Churruca, F.; Domınguez, E. *Org. Prep. Proced. Int.* **2004**, *36*, 297.

(5) Cutler, H. G.; Springer, J. P.; Arrendale, R. F.; Arison, B. H.; Cole, P. D.; Roberts, R. G. *Agric. Biol. Chem.* **1988**, *52*, 1725.

(6) Belofsky, G. N.; Anguera, M.; Jenson, P. R.; Fenical, W.; Köck, M. *Chem.—Eur. J.* **2000**, *6*, 1355.

(7) Lu, X.-H.; Shi, Q.-W.; Zheng, Z.-H.; Ke, A.-B.; Zhang, H.; Huo, Y.; Ma, C.-H.; Ren, X.; Li, Y.-Y.; Lin, J.; Jiang, Q.; Gu, Y.-C.; Kiyota, H. *Eur. J. Org. Chem.* **2011**, *4*, 802.

(8) Li, G.-Y.; Li, L.-M.; Yang, T.; Chen, X.-Z.; Fang, D.-M.; Zhang, G.-L. *Helv. Chim. Acta* **2010**, *93*, 2075.

(9) Lee, S. U.; Asami, Y.; Lee, D.; Jang, J.-H.; Ahn, J. S.; Oh, H. *J. Nat. Prod* **2011**, *74*, 1284.

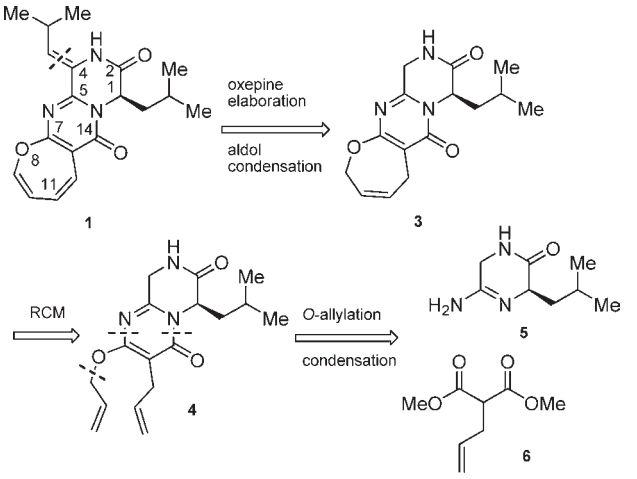
(10) Ookura, R.; Kito, K.; Ooi, T.; Namikoshi, M.; Kusumi, T. *J. Org. Chem.* **2008**, *73*, 4245. See also (erroneous structural assignment): Rahbæck, L.; Breinholt, J.; Frisvad, J. C.; Christopherson, C. *J. Org. Chem.* **1999**, *64*, 1689.

(11) Bode, H. B.; Bethe, B.; Höfs, R.; Zeeck, A. *ChemBioChem* **2002**, *3*, 619.

10.1021/ol300039x
Published on Web 01/30/2012

The oxepine natural products are not only of interest in terms of their biological properties but are also intriguing from a biosynthetic viewpoint: benzene epoxidation/rearrangement has been proposed as a biogenetic route to such oxepine ring systems.[1,7,11] Our interest, however, was to develop a practical synthetic route to the oxepine-based natural products, particularly to janoxepin and synthetic analogues, and the benzene epoxidation route did not seem well-suited to this objective. To the best of our knowledge, there have been no syntheses, or synthetic approaches, reported for janoxepin (**1**). Indeed, as far as we are aware, no syntheses of any oxepine-based natural products lacking benzannelation have yet been reported (which is remarkable as cinereain (**2**) was described as long ago as 1988).

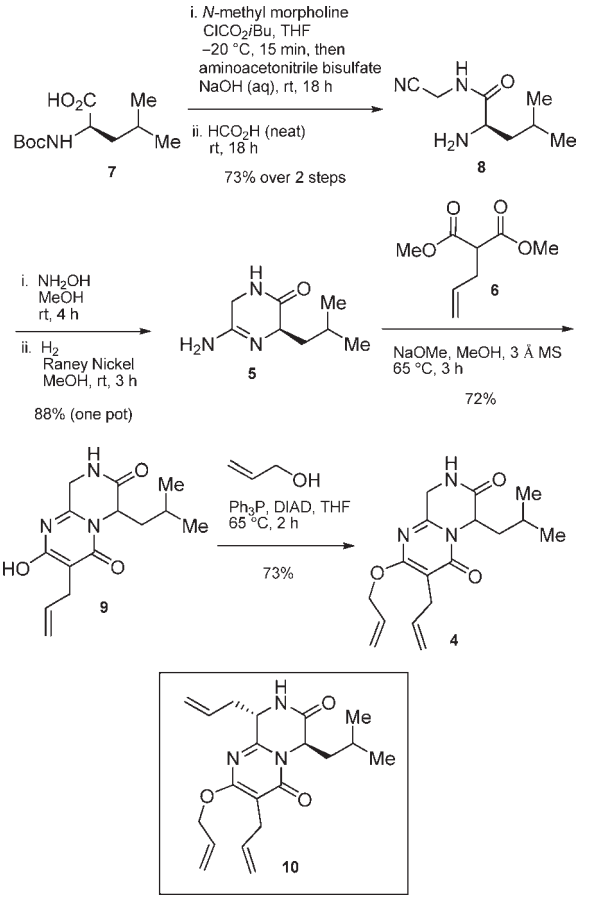
Scheme 1. Retrosynthetic Analysis



The proposed retrosynthetic analysis (Scheme 1) was based upon late-stage dihydro-oxepine elaboration preceded by introduction of the enamide using an aldol condensation between dihydro-oxepine **3** and *iso*-butyraldehyde; dihydro-oxepine **3** would then be prepared from the diallyl pyrimidinone precursor **4** using ring-closing metathesis (RCM) with D-leucine being employed as the ultimate starting material. This approach has the virtue of brevity, and utility for analogue synthesis, but its speculative nature needs emphasis; we could not find a single literature example of oxepine synthesis proceeding by elaboration of the corresponding dihydro-oxepine (see later discussion).

The synthetic study therefore commenced with the preparation of the diallylated pyrimidinone **4** from commercially available *N*-Boc-D-leucine **7** as shown in Scheme 2. Mixed anhydride formation followed by coupling with aminoacetonitrile and Boc deprotection gave the known amine **8** in excellent yield.[12] Amine **8** was next subjected to an efficient, telescoped one-pot oximation–hydrogenation cyclization sequence (based on a published procedure)[13] to

Scheme 2. Synthesis of Diallyl Pyrimidinone **14**



furnish the desired novel amidine **5** {$[\alpha]_D^{22}$ −47 (*c* 1.00, MeOH)} in just 4 steps and 64% overall yield from D-leucine.

Condensation of cyclic amidine **5** with the commercially available allylmalonate **6** using NaOMe as base and strictly anhydrous conditions furnished the required pyrimidinone **9** in excellent yield (72%) on an 8 g scale, although we were disappointed to observe that racemization of the stereogenic center had occurred.[14] The *O*-allylation of compound **9** was investigated next, and the use of allyl alcohol under Mitsunobu conditions (DIAD, PPh_3) was found to be optimal giving the required diallylated pyrimidinone **4** in 73% yield.[14] Interestingly, the use of more conventional alkylating conditions (e.g., allyl bromide, Bu_4NI, K_2CO_3) gave much lower yields of product **4** with substantial quantities of the *bis*-alkylated product **10** being isolated (as a single diastereomer).

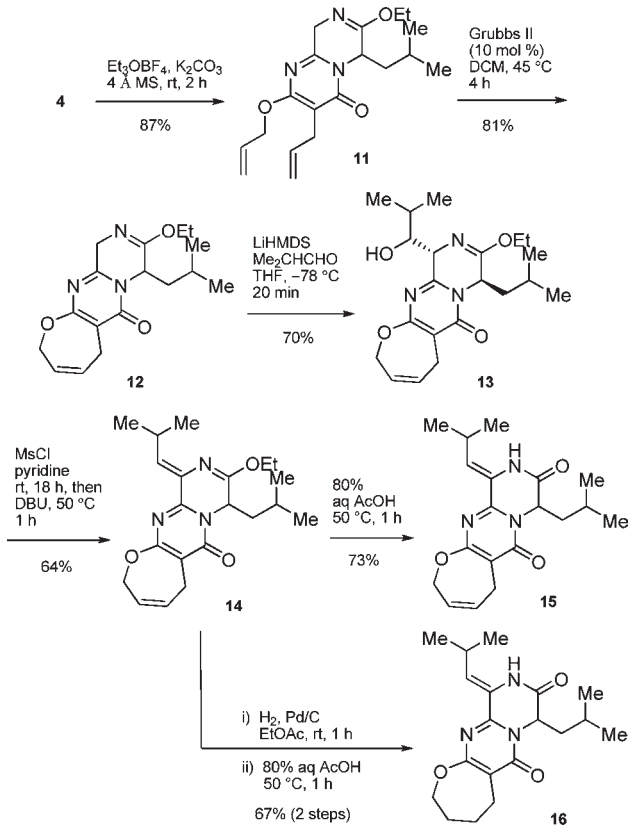
Having previously established that imidate-protected amides were optimal substrates for aldol addition to the ketopiperazine ring, it was found most efficient to protect diallyl pyrimidinone **4** as imidate **11** prior to the key RCM step. (when RCM was carried out first, the basic conditions needed for imidate formation also gave dihydro-oxepine

(12) Frizler, M.; Lohr, F.; Furtmann, N.; Kläs, J.; Gütschow, M. *J. Med. Chem.* **2011**, *54*, 396.

(13) Kuse, M.; Kondo, N.; Ohyabu, Y.; Isobe, M. *Tetrahedron* **2004**, *60*, 835.

(14) {$[\alpha]_D^{22}$ + 0.8 (*c* 1.01, MeOH)}; confirmed by HPLC analysis of compound **14** [Chiralpak AD-H, *n*-hexane/*i*-PrOH (9:1), 1 mL min^{-1}; 14.15 min, 47.3%; 15.10 min, 52.7% (ca. 5% ee)]; see Supporting Information.

Scheme 3. Dihydro-janoxepin **15** and Tetrahydro-janoxepin **16** Preparation



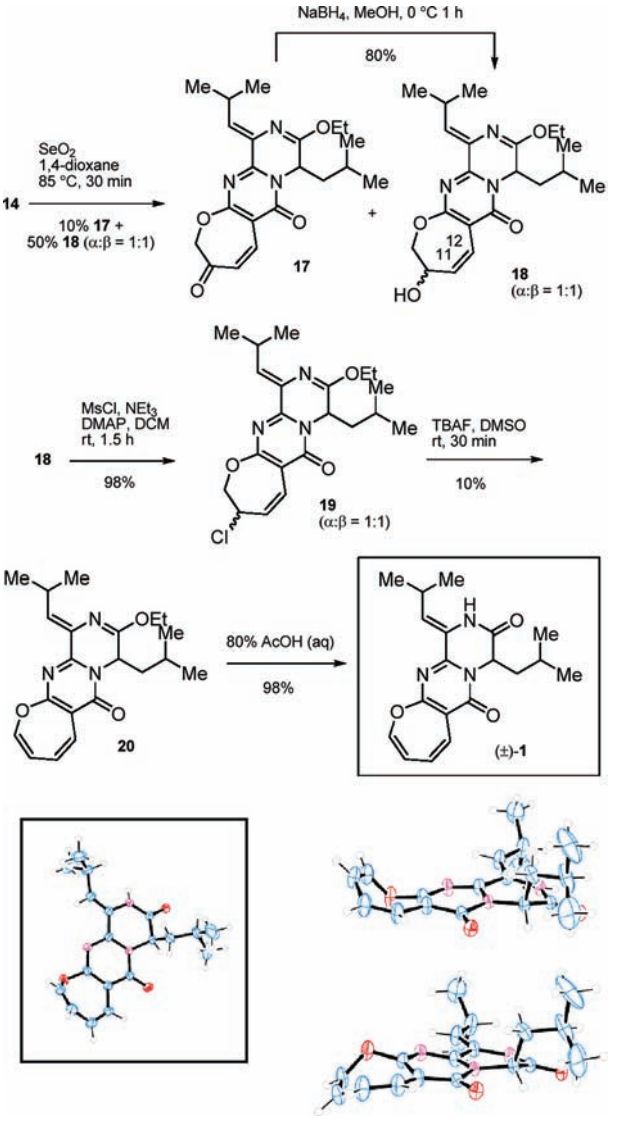
rearrangement products).[15] Subsequent treatment of compound **11** with the Grubbs second generation catalyst (benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium) then provided dihydro-oxepine **12** in excellent yield as shown in Scheme 3.

We were now in a position to effect the aldol elaboration. This was achieved by deprotonation of imidate **12** with LiHMDS and addition of *iso*-butyraldehyde, which provided aldol adduct **13** as a single diastereomer in excellent yield (70%). A mesylation–elimination sequence was then employed to give enamine **14** as a single isomer. Next, imidate hydrolysis gave dihydro-janoxepin **15** in 73% yield, again as a single enamine isomer, which was confirmed to be in the *Z*-configuration *via* ^{1}H NMR NOE experiments. In pursuit of other novel analogues, hydrogenation of dihydro-oxepine intermediate **14** followed by imidate hydrolysis also provided tetrahydro-janoxepin **16** as the *Z*-alkene.

The key step that remained in order to complete the synthesis of janoxepin (**1**) was to convert one of the dihydro-oxepine intermediates into the corresponding oxepine. This proved to be extremely difficult, however. Initial attempts centered around the formation of 1,2-dibromides, or 1,2-diol-derived sulfonates, and then double elimination to give the required diene. Unfortunately,

(15) Ramachary, D. B.; Ramakumar, K.; Bharanishashank, A.; Narayana, V. V. *J. Comb. Chem.* **2010**, *12*, 855 and references therein.

Scheme 4. Synthesis of Janoxepin (**1**)[a]



[a] X-ray structure of janoxepin (**1**) depicted using ORTEP-3 (CCDC 848130).

the elimination sequences all failed, possibly due to the inherent strain of the oxepine (and the base-sensitivity of dihydro-oxepines).[15] After considerable experimentation, an alternative sequence, illustrated in Scheme 4, was devised in which the two alkenes are introduced in a stepwise manner.

Treatment of dihydro-oxepine **14** with selenium dioxide gave allylic oxidation producing a mixture of allylic alcohol **18** (50%, α:β = 1:1) along with a small amount of the corresponding ketone **17** (10%), which could be converted back into alcohol **18** (α:β = 1:1) using sodium borohydride. The 11,12-location of the double bond was established from ^{1}H NMR multiplicities (for a single diastereomer, H-11 and H-12 were observed as a doublet of doublets and doublet, respectively) and was further confirmed by COSY, ^{13}C and HSQC NMR experiments.

Following a screen of numerous methods for the dehydration of allylic alcohol **18** to generate oxepine **20** (including sulfurane reagents, acid catalysis, Chugaev elimination, Shapiro/Bamford–Stevens chemistry, selenide oxidation, Tsuji–Trost elimination), it was found necessary to proceed by way of the corresponding chloride **19** (α:β = 1:1) which was formed directly, and in near-quantitative yield, using methanesulfonyl chloride in dichloromethane. Chloride **19** underwent TBAF-mediated dehydrohalogenation[16] to produce oxepine **20** in low (10%), but entirely reproducible, yield which could not be improved upon following an optimization study of base, solvent, and temperature. Although all starting material was consumed in the reaction, no other products could be identified from a complex mixture of polar byproducts. In order to ascertain whether one diastereomer of chloride **19** was undergoing elimination preferentially, the diastereomers of allylic alcohol **18** were separated and the two compounds were subjected separately to the chlorination conditions. However, in both cases an inseparable diastereomeric mixture of chlorides **19** (α:β = 1:1) was obtained preventing further experimentation. The reasons for the disappointing elimination yield leading to oxepine **20** are not yet fully understood, although the base-sensitivity of dihydro-oxepines[15] and the acid and light sensitivity of oxepines[17] are well recognized. However, it must be emphasized that, to our knowledge, this is the first reported preparation of an oxepine from the corresponding dihydro-oxepine (although benzannelated oxepines[18] and dihydro-analogues[3] have been prepared by an eliminative approach). Finally, imidate hydrolysis furnished janoxepin (**1**) in near-quantitative yield. The ^{1}H and ^{13}C NMR data for the synthetic material were in excellent agreement with those published in the isolation paper (*e.g.*, δ_C (reported):[1] C-9 – C-14, 142.9, 117.1, 127.6, 125.5, 110.3, 160.4). δ_C (found): C-9 – C-14, 143.0, 117.2, 127.8, 125.6, 110.5, 160.4). [See Supporting Information for a detailed comparison.]

However, the melting point of synthetic janoxepin (179–180 °C) did not match the reported value (88–89 °C).[1,19] This could be due to polymorphism or to the fact that our material was racemic, but to provide unambiguous structural proof we subjected synthetic janoxepin to X-ray crystallographic analysis. The first X-ray crystal structure of janoxepin (**1**), shown in Scheme 4, confirmed our structural assignment and indicated that it exists in two oxepine conformers in the solid state.[20]

In principle, double deprotonation of racemic janoxepin followed by enantioselective protonation[21] of the resulting enolate should provide a route to the enantioenriched natural product. Unfortunately, using bases such as *sec*-BuLi and a chiral proton source such as (−)-ephedrine resulted in complete decomposition of the substrate, and decomposition was also observed starting from imidate **20** (again demonstrating the base-sensitivity of these oxepines).

In summary, we have completed the first total synthesis of an oxepine-based natural product, and the first of any oxepine-pyrimidinone natural product, the antiplasmodial janoxepin (**1**), confirming the published[1] structural assignment by X-ray crystallography.

The synthesis of janoxepin (**1**) was accomplished in 13 steps from readily available Boc-D-leucine **7** using ring-closing metathesis, aldol introduction of the enamide, and oxepine elaboration as the key steps. The same synthetic approach has been employed to prepare janoxepin analogues including dihydro-janoxepin **15** and tetrahydro-janoxepin **16**. We are currently optimizing the route, in particular the method of oxepine construction, as well as investigating other enantioselective strategies. Ultimately, this methodology will be employed to prepare other members of the oxepine natural product family.

Acknowledgment. We would like to thank the EPSRC (R.G.D.) and the University of York (S.J.) for PhD funding, the Erasmus scheme and the University of Nijmegen for exchange support (R.S.), and Professor C. Christopherson, Department of Chemistry, University of Copenhagen for helpful correspondence. We are also grateful to Dr. A. C. Whitwood for X-ray crystallography studies and to Dr. K. Heaton for invaluable assistance with mass spectrometry.

Supporting Information Available. Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all novel compounds. Crystallographic data for janoxepin (**1**) (CCDC 848130). This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Dura, R. D.; Paquette, L. A. *Synthesis* **2006**, 2837.

(17) Boyd, D. R.; O'Kane, G. A. *Tetrahedron Lett.* **1987**, *38*, 6395. Agarwal, R.; Boyd, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2869.

(18) Hoffmann, H.; Djafara, H. *Z. Naturforsch.* **1989**, *44b*, 220.

(19) E-mail correspondence with Prof. Carsten Christophersen, Department of Chemistry, University of Copenhagen (22 June, 2011) established that the original notebooks, samples, and NMR spectra were no longer available.

(20) CCDC 848130 (**1**) contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

(21) Martin, J.; Plaquevent, J. C.; Maddaluno, J.; Rouden, J.; Lasne, M. C. *Eur. J. Org. Chem.* **2009**, 5414 and references therein.

The authors declare no competing financial interest.