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Biomimetic synthesis of the pyrrolobenzoxazine core of paeciloxazine

Dirk Schwaebisch, Kirill Tchabanenko, Robert M. Adlington, Andrew M. Cowley and Jack E. Baldwin*
Department of Chemistry, University of Oxford, Chemical Research Laboratory, Mansfield Road, Oxford, UK OX1 3TA. E-mail: jack.baldwin@chem.ox.ac.uk; Fax: +44-1865-275-632; Tel: +44-1865-275-671

Received (in Cambridge, UK) 10th August 2004, Accepted 14th September 2004
First published as an Advance Article on the web 25th October 2004

Starting from a protected L-tryptophan derivative the pyrrolobenzoxazine core unit of paeciloxazine can be synthesized in two oxidation steps.

Recently the novel antibiotic paeciloxazine (Fig. 1) was isolated from the *Paecilomyces* BAUA3058 strain. This compound shows activity against the nematode *Rhabditis pseudoelongata*.[1] Previously three similar compounds have been isolated, which differ from paeciloxazine in the nature of the sesquiterpene moiety or bear a chlorine substituent in the aromatic ring. All of these compounds show insecticidal and antibiotic properties.[2]

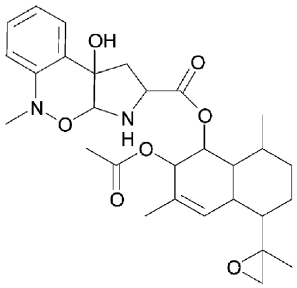


Fig. 1

We propose that the biosynthesis of the pyrrolobenzoxazine core unit starts from the *N*-methylated L-tryptophan and proceeds *via* a two oxidative step pathway yielding the target compound (Fig. 2).

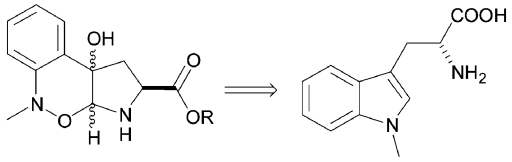
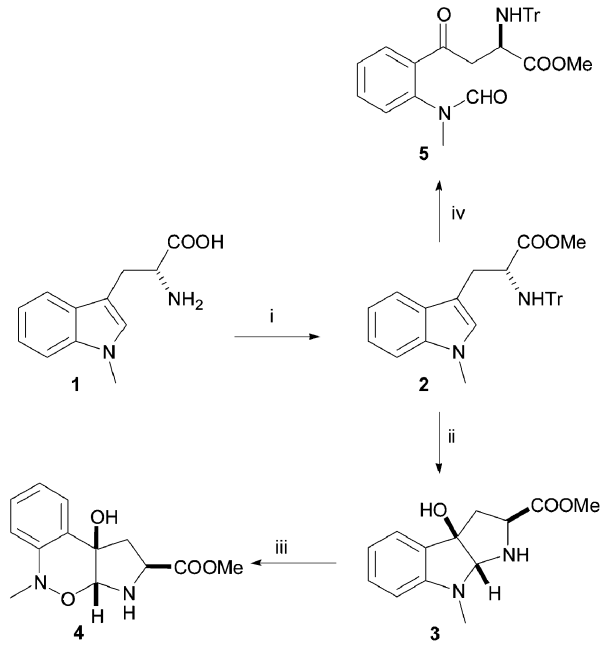


Fig. 2

To demonstrate this biomimetically, the known indole-*N*-methylated L-tryptophan **1**[3] was esterified and subsequently protected by tritylation of the NH_2-group resulting in the derivative **2** (Scheme 1). This compound was then subjected to DMDO-oxidation following a procedure described by Danishefsky *et al.*[4] for the monooxidation to a pyrroloindoline moiety (*e.g.* **2** → **3**). After optimisation we discovered that the use of 1.8 equivalents of DMDO[5] gave the best conversion of the starting tryptophan derivative and yield of the *N*-methyl-3-hydroxypyrroloindoline methyl ester **3**.[6] Subsequent cleavage of the trityl group under acidic conditions simplified purification of compound **3**. Unfortunately our attempts to achieve double oxidation directly to the desired pyrrolobenzoxazine fragment **4** met with failure; the use of two equivalents of the oxidizing agent resulted only in recovery of the single oxidation step product **3**, together with decomposition products. The use of other oxidants or higher reaction temperatures

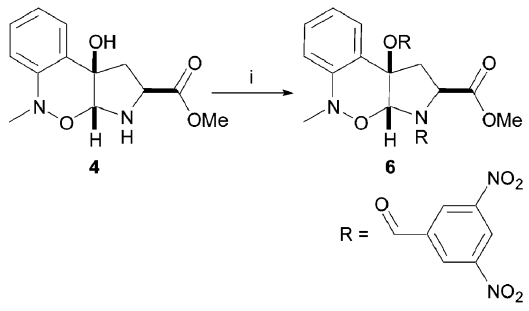


Scheme 1 *Reagents and conditions*: i: (a) AcCl, MeOH, reflux, 2 h, 99%, (b) TrCl, TEA, DCM, rt, 48 h, 69%; ii: (a) DMDO–sol., acetone, −78 °C, 2 h, (b) AcOH, MeOH, DCM, rt, 2 h, 40%; iii: MCPBA, DCM, 0 °C, 2 h, 49%; iv: *e.g.* ⩾2 equiv. MCPBA, rt.

led to the known oxidation of tryptophan to the formylated methyl kynurenine methyl ester **5**.[7]

Being unable to achieve a single step conversion of the protected tryptophan **2** into the benzoxazine **4**, we attempted oxidation of compound **3**. To our delight on treatment of **3** with *m*-chloro peroxybenzoic acid [which was added very slowly to a solution of **3** in dichloromethane at 0 °C] the target compound **4** was isolated as a single stereoisomer in a moderate yield after column chromatography.

Comparison of the NMR data[8] of the synthesized pyrrolobenzoxazine derivative **4** with the literature data for the natural products showed good correspondence. Furthermore, HMBC correlations showed only a weak interaction of the *N*-methyl



Scheme 2 *Reagents and conditions*: i: 3,5-Dinitrobenzoyl chloride (2 equiv.), pyridine, rt, 16 h, 51%.

DOI: 10.1039/b412300j

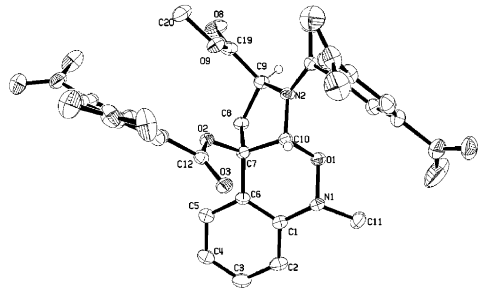
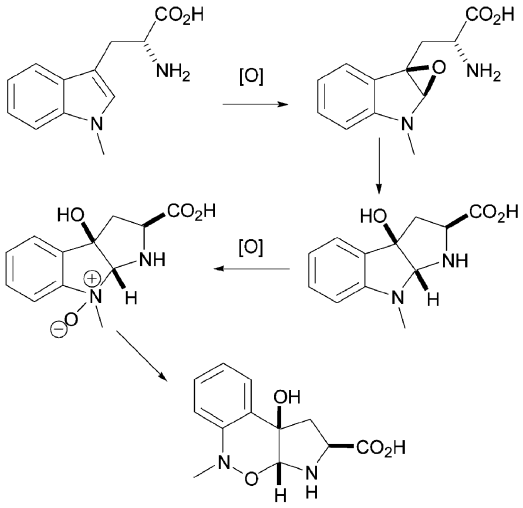


Fig. 3 X-Ray structure of compound **6**.



Scheme 3

carbon atom with the proton at the ring junction, whereas there was a much stronger correlation between the same atoms in the pyrroloindoline **3** consistent with oxygen insertion at the desired position. To establish whether the second oxidation proceeded with retention of the relative stereochemistry of the starting material, compound **4** was further derivatised by reacting with two equivalents of 3,5-dinitrobenzoyl chloride (Scheme 2). The resulting bis(dinitrobenzoic acid) derivative **6** showed that the relative stereochemistry of **3** was retained in the oxidised product **4** (see X-ray structure depicted in Fig. 3).[9] It is noteworthy that the absolute stereochemistry of the synthetic pyrrolobenzoxazine **4** corresponds to the one previously proposed for this component in the analogues of paeciloxazine.[2]

With the structure (**6**) proven to be that of the natural pyrrolobenzoxazine unit of paeciloxazine we can propose a biosynthetic pathway leading to the formation of this building block from the *N*-methyl tryptophan. In the first oxidation step the double bond of the indole ring is diastereoselectively epoxidized. The epoxide is opened by the amino group resulting in the pyrroloindoline moiety. In the second step the more basic tertiary anilinic nitrogen is oxidized resulting in an *N*-oxide. This then undergoes a diastereoselective Meisenheimer type rearrangement[10] to form the resulting pyrrolobenzoxazine derivative (Scheme 3).

In conclusion the pyrolobenzoxazine moiety of the natural product paeciloxazine can be synthesized in a short biomimetic pathway proceeding *via* two diastereoselective oxidation reactions starting from readily available protected L-tryptophan.

Notes and references

1 Y. Kanai, T. Fujimaki, S. Kochi, H. Konno, S. Kanazawa and S. Tokumasu, *J. Antibiot.*, 2004, **57**, 24.

2 (*a*) Y. Kojima, Y. Yamauchi, N. Kojima and B. Bishop, *PCT Int. Appl.*, WO 9519363, A1, 19950720, 1995; (*b*) D. A. Perry, H. Maeda and J. Tone, *Br. Pat. Appl.*, GB 2240100, A1, 19910724, 1991.

3 S. Yamada, T. Shiori, T. Itaya, T. Hara and R. Matsueda, *Chem. Pharm. Bull.*, 1965, **13**, 88.

4 T. Kamenecka and S. J. Danishefsky, *Chem.–Eur. J*, 2001, **7**, 41.

5 DMDO solutions were prepared according to: J. K. Randall, D. J. Batall, D. B. Sebesta and F. Li, *J. Org. Chem.*, 1991, **56**(3), 1153; Concentrations [0.045–0.08 M] were estimated by titrations with thioanisole and comparison of the integrals of the corresponding methyl protons in ^{1}H NMR spectrum.

6 Stereochemistry of **3** assumed by comparison to the analogous des-*N*-methyl, *tert*-butyl ester assigned in ref. 4.

7 (*a*) O. Hayaishi, in *Oxygenase*, ed. O. Hayaishi, Academic Press, New York, 1962; (*b*) O. Hayaishi, in *Molecular Mechanism of Oxygen Activation*, ed. O. Hayaishi, Academic Press, New York, 1974.

8 NMR data for compound **4**: δ_H (400 MHz, $CDCl_3$): 7.54 (m, 1H, Ar), 7.26 (m, 1H, Ar), 7.06 (m, 1H, Ar), 6.75 (m, 1H, Ar), 5.21 (s, 1H, OCH), 4.06 (dd, J = 1.5Hz, J = 9.0Hz, 1H, C*H*CO_2CH_3), 3.84 (s, 3H, OCH_3), 3.14 (s, 3H, NCH_3), 2.61 (dd, J = 1.0Hz, J = 13.5Hz, 1H, CH_2), 2.56 (dd, J = 1.5Hz, J = 13.5Hz, 1H, CH_2); δ_c (100.6 MHz, $CDCl_3$): 176.2 (*C*O_2CH_3), 149.6 (Ar_q), 129.3 (Ar_q), 128.1 (Ar), 127.3 (Ar), 122.0 (Ar), 112.0 (Ar), 94.3 (NO*C*(C)NH), 76.5 (COH), 57.8 (*C*HCO_2CH_3), 52.6 (CO_2CH_3), 42.0 (*C*H_2), 41.2 (NCH_3).

9 Crystal data for **6**: $C_{27}H_{20}N_6O_{14}$, M = 652.49, monoclinic, a = 12.4739(2), b = 8.0449(2), c = 14.3256(3) Å, U = 1401.02(5) Å^3, T = 150 K, space group $P2_1$, Z = 2, μ(Mo–K$_\alpha$) = 0.128 mm^{-1}, 12972 reflexions measured, 3398 unique (R_{int} = 0.0349) which were used in calculations. The final wR was 0.0350. CCDC 244254. See http://www.rsc.org/suppdata/cc/b4/b412300j/ for crystallographic data in .cif or other electronic format.

10 J. Meisenheimer, *Chem. Ber.*, 1919, **52**, 1667.