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## Enantioselective synthesis of (*R*)- and (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamides

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### Abstract

Enantiomers of 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamides bearing different substituents in the aromatic ring are obtained by the cyclization of (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonates with the participation of the carboxy and methoxycarbonyl group, respectively. © 1998 Elsevier Science Ltd. All rights reserved.

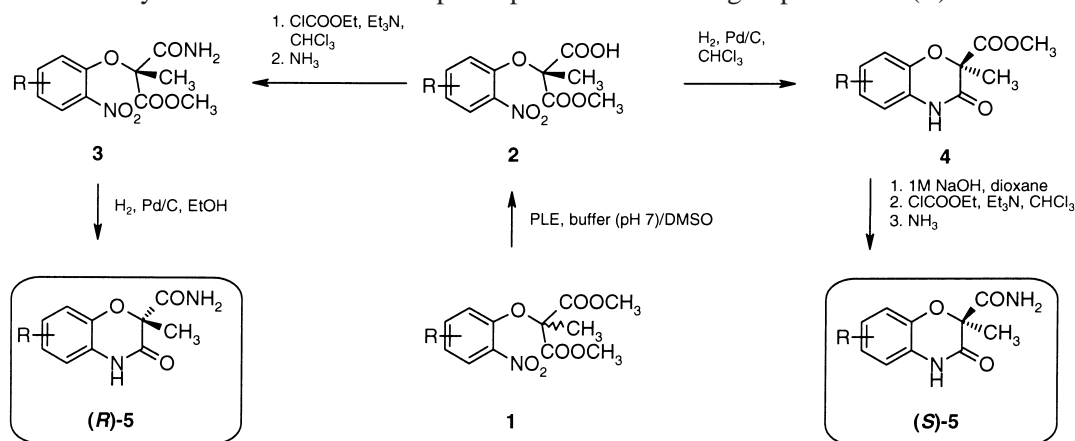
Both enantiomers of 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamides **5** with different substituents in the aromatic ring were required as key intermediates in the course of our ongoing research programme<sup>1,2</sup> directed towards the design and synthesis of peptidomimetics<sup>3</sup> in order to study the influence of chirality on biological activity within this class of compounds. Enantiomers of the parent compound **5** (R=H) became available via (*R*)- and (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acid which was obtained by resolution with (*R*)- and (*S*)-1-phenylethylamine. However, the resolution method proved to be unsuccessful with compounds bearing a substituent bound to the aromatic ring.<sup>4</sup> Therefore, we sought for an efficient stereoselective synthesis of enantiomers of **5**, possibly from a common readily available chiral precursor.

Now we wish to report that hitherto unknown enantiomers of 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamides **5** are readily accessible via reductive cyclization of common chiral precursors (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonates **2**, with the participation of a carboxy and methoxycarbonyl group, respectively. The preparation of malonates **2** by pig liver esterase catalyzed hydrolysis of prochiral dialkyl 2-methyl-2-(2-nitrophenoxy)malonates has been reported by us recently.<sup>5</sup> Interestingly, contrary to our expectations based on the generally known reactivity of carboxylic acid derivatives, *in situ* cyclization of the aromatic amines obtained by hydrogenation of **2** in chloroform afforded (*R*)-methyl 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylates **4** in 60–80% yield accompanied by small amounts of the corresponding (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids which could be easily separated simply by extraction. The preference of the carboxy or methoxycarbonyl group of **2** for cyclization after reduction of the nitro group was found

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to be solvent-dependent, and therefore this strategy can also be used for the synthesis of (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids on a preparative scale. The carboxylates **4** were efficiently transformed to amides (*S*)-**5**<sup>6</sup> using unexceptional chemistry by hydrolysis, subsequent activation of the resulting carboxylic acids by a mixed anhydride method, and reaction with ammonia. For the synthesis of (*R*)-**5**, the carboxy group of **2** was deactivated as a carboxamide. Compounds **3**, thus obtained from **2** by a mixed anhydride method,<sup>6</sup> after reduction of the nitro group in methanol, underwent a smooth *in situ* cyclization with exclusive participation of the ester group to afford (*R*)-**5**.<sup>6,7</sup>



**5**: R = H, 6-CH<sub>3</sub>, 7-CH<sub>3</sub>, 7-F, 6-OCH<sub>3</sub>

In conclusion, both enantiomers of 2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamides **5** with different substituents in the aromatic ring were efficiently prepared by selective reductive lactamization of common precursors, (*R*)-monomethyl 2-methyl-2-(2-nitrophenoxy)malonates **2**, employing a strategy of solvent- and derivatization-based reactivity manipulation of the carboxy group of **2**. Investigation of the full scope of this stereoselective synthesis is in progress and will be reported in due course.

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- (*R*)- and (*S*)-2,6-dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxamide: white crystals; (*R*)-isomer: mp 292–293°C (from MeOH),  $[\alpha]_D^{20}=+87.4$  ( $c=0.16$ , MeOH); (*S*)-isomer: mp 302–304°C (from MeOH),  $[\alpha]_D^{20}=-87.6$  ( $c=0.16$ , MeOH); IR (KBr):  $\nu$  3376, 3154, 1699, 1609, 1520, 1495, 1361, 1237, 1151, 814 cm<sup>-1</sup>; <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) 1.61 (s, 3H, 2-CH<sub>3</sub>), 2.20 (s, 3H, 6-CH<sub>3</sub>), 6.65 (d, 1H,  $J=1.8$  Hz, H-5), 6.72 (dd, 1H,  $J=8.1$  Hz,  $J=1.8$  Hz, H-7), 6.94 (d, 1H,  $J=8.1$  Hz, H-8), 7.32 and 7.51 (s br, 1H each, CONH<sub>2</sub>), 10.58 (s br, 1H, NH); MS (70 eV, EI):  $m/z=220$  (M<sup>+</sup>, 45%), 177 (100%). Anal. calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C 59.99, H 5.49, N 12.72. Found: C 59.72, H 5.48, N 12.59.
- The yields of (*R*)-**5** were 70–75% based on **2**.