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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.

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[1,2] directed towards the design and synthesis of peptidomimetics[3] 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.[4] 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.[5] 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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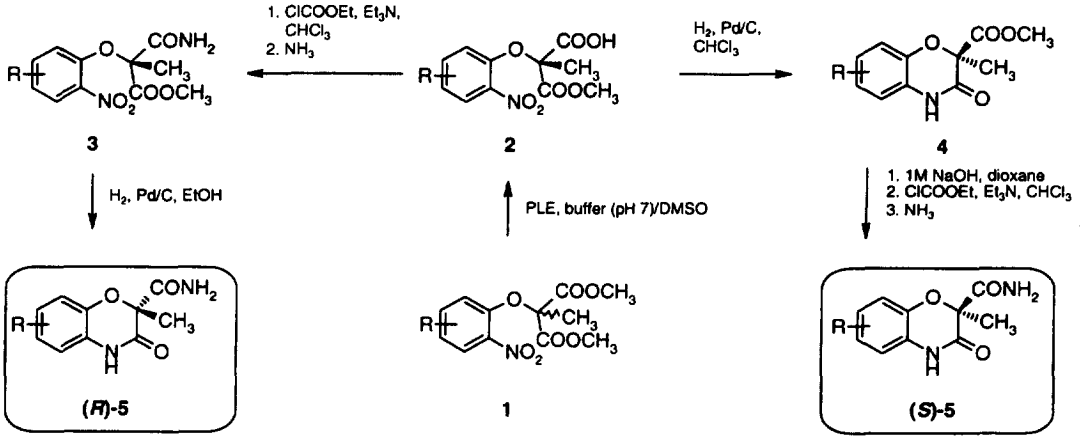
to be solvent-dependent, and therefore this strategy can also be used for the synthesis of (*S*)-2-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylic acids on a preparative scale. The carboxylates **4** were efficiently transformed to amides (*S*)-**5**[6] using unexceptional chemistry by hydrolysis, 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,[6] 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**.[6,7]



5: R = H, 6-CH_3, 7-CH_3, 7-F, 6-OCH_3

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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6. (*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): ν 3376, 3154, 1699, 1609, 1520, 1495, 1361, 1237, 1151, 814 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) 1.61 (s, 3H, 2-CH_3), 2.20 (s, 3H, 6-CH_3), 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, $CONH_2$), 10.58 (s br, 1H, NH); MS (70 eV, EI): *m/z*=220 (M^+, 45%), 177 (100%). Anal. calcd for $C_{11}H_{12}N_2O_3$: C 59.99, H 5.49, N 12.72. Found: C 59.72, H 5.48, N 12.59.
7. The yields of (*R*)-**5** were 70–75% based on **2**.