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TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of (2*S*,2′*R*)-*erythro*-methylphenidate

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Abstract

A new approach towards the enantioselective synthesis of (2*S*,2′*R*)-*erythro*-methylphenidate (**1**) is described. The key step in the synthesis utilizes Evans' 4-substituted-2-oxazolidinone chiral auxiliary to control the diastereofacial selectivity in the hydrogenation of enamine intermediate **6**, yielding the hydrogenated product **7** with excellent diastereoselectivity. Methanolysis of **7** afforded **1** with excellent enantiopurity. © 1999 Elsevier Science Ltd. All rights reserved.

(±)-*threo*-Methylphenidate hydrochloride (Ritalin® hydrochloride) is a mild nervous system stimulant marketed for the treatment of children with attention deficit hyperactivity disorder (ADHD). (2*R*,2′*R*)-*threo*-(+)-Methylphenidate hydrochloride has been reported to be five times[1] to thirty-eight times[2] more active than the corresponding (2*S*,2′*S*)-*threo*-(−)-methylphenidate hydrochloride. Original synthesis of (2*R*,2′*R*)-*threo*-(+)-methylphenidate hydrochloride utilized the resolution of (±)-*erythro*-α-phenyl-α-(2-piperidyl)acetamide to obtain enantiomerically pure l-*erythro*-α-phenyl-α-(2-piperidyl)acetamide, which was subjected to epimerization, hydrolysis, and esterification.[1,3] Resolution of (±)-*threo*-methylphenidate hydrochloride by enzymatic hydrolysis as well as classical resolution methods have recently been reported.[4–11] A synthesis of (2*R*,2′*R*)-*threo*-(+)-methylphenidate hydrochloride using D-pipecolic acid as the starting material was also reported, however, D-pipecolic acid had to be prepared by resolution.[12] We recently reported the first enantioselective synthesis of (2*R*,2′*R*)-*threo*-(+)-methylphenidate hydrochloride,[13] which is now followed by other reports.[14–16] We were also interested in an enantioselective synthesis of (2*S*,2′*R*)-*erythro*-(−)-methylphenidate because it could be epimerized to (2*R*,2′*R*)-*threo*-(+)-methylphenidate, as the epimerization of l-*erythro*-α-phenyl-α-(2-piperidyl)acetamide to the corresponding *threo*-isomer was known.[1] In this communication, we wish to report our results on the enantioselective synthesis of (2*S*,2′*R*)-*erythro*-methylphenidate (**1**).

Our strategy towards (2*S*,2′*R*)-*erythro*-methylphenidate (**1**), as depicted in Scheme 1, utilizes Evans' (*S*)-4-substituted-2-oxazolidinone chiral auxiliary to control the diastereofacial selectivity in the hydrogenation of enamine intermediate **I**. We envisioned that in enamine intermediate **I**, the possible

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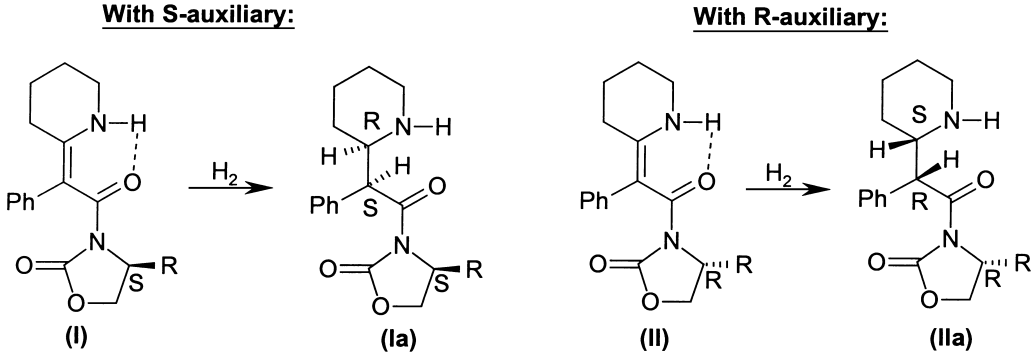
hydrogen bonding between the carbonyl oxygen and N-H hydrogen would probably lock the geometry of the double bond as *Z*, and the dipole–dipole interaction between the two carbonyl groups would further regulate the geometry of **I** as shown in Scheme 1. Accordingly, hydrogenation of **I** would occur in the face opposite to that of the 4-substituent in the chiral auxiliary, providing hydrogenation product **Ia** with the (2*S*,2′*R*) configuration. Further manipulations of **Ia** would afford (2*S*,2′*R*)-*erythro*-methylphenidate. Similarly, (*R*)-4-substituted-2-oxazolidinone chiral auxiliary would yield the (2*R*,2′*S*)-*erythro*-methylphenidate.

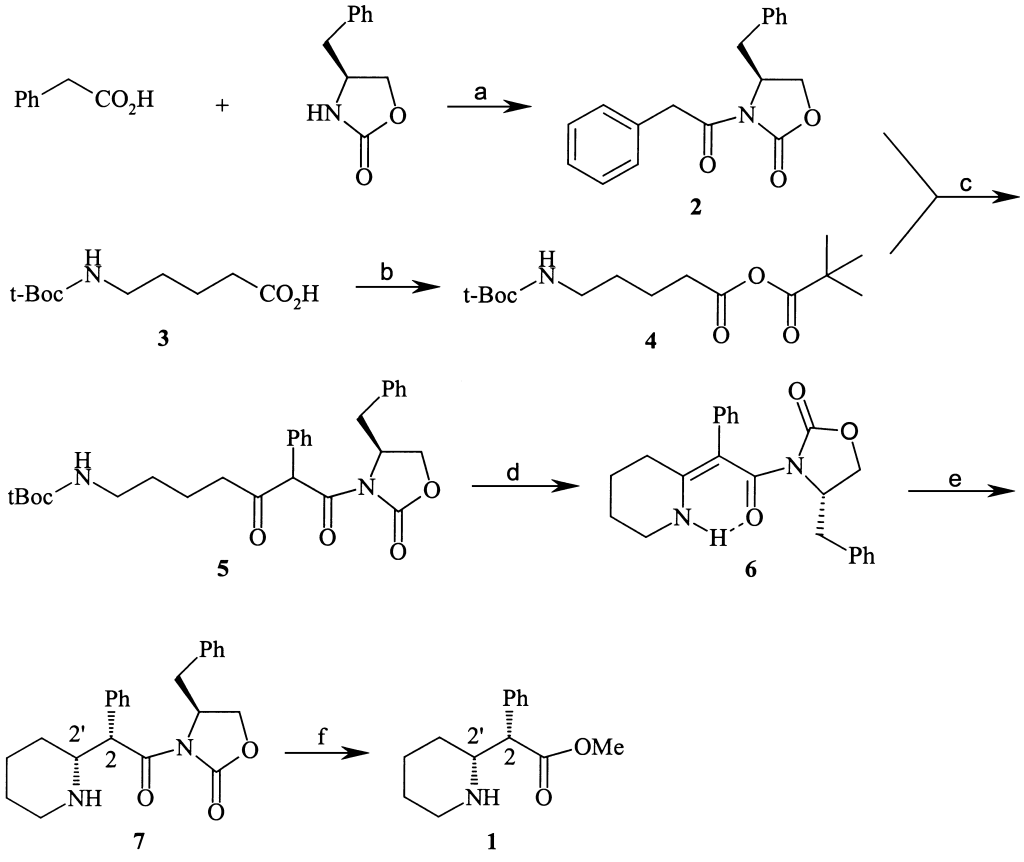


Scheme 1.

Synthesis of the key enamine intermediate **6** is depicted in Scheme 2. It is based on the acylation of (*S*)-4-benzyl-*N*-phenylacetyl-2-oxazolidinone (**2**) with the mixed anhydride **4**, followed by the deprotection of the *t*-butyloxycarbonyl group with simultaneous cyclization to give enamine intermediate **6**. Compound **2** was obtained in 85% yield by acylation of (*S*)-4-benzyl-2-oxazolidinone with phenylacetic acid using the procedure developed in our laboratories.[17] Mixed anhydride **4** was synthesized quantitatively by acylation of carboxylic acid **3** with pivolyl chloride and triethylamine. The acylation of **2** with **4** in the presence of LiHMDS in THF afforded the desired *C*-acylated product **5** along with the *O*-acylated products. Such an *O*-acylation problem has been observed before.[18] Compound **5** could not be completely purified from other by-products and was used directly in the next step. Cleavage of the *t*-butyloxycarbonyl group in **5** with trifluoroacetic acid, and neutralization of the reaction mixture with aq. $NaHCO_3$ furnished the desired enamine intermediate **6** in 30% combined yield over two steps (Scheme 2) after a silica gel chromatography. ^{1}H NMR confirmed the structure of **6** and that it was a single isomer.[19] Chemical shift of the NH proton indicated an intramolecular H-bonding with the carbonyl group of the chiral auxiliary. Hydrogenation of **6** in ethyl acetate yielded **7** in 95% yield with an excellent diastereoselectivity (97:3).[19] The amount of Pd–C (10%) varied from 2% to 20% depending on the purity of **6**, but it had no impact on the diastereoselectivity of the reaction. We found that **6** had to be rigorously purified by silica gel chromatography before hydrogenation. Treatment of **7** with methanol[20] in the presence of LnI_3 afforded (2*S*,2′*R*)-*erythro*-methylphenidate (**1**)[12] in 85% yield after a silica gel chromatography. The enantiopurity of **1** was excellent (2*S*,2′*R*:2*R*,2′*S* 97:3).[21]

Interestingly, use of (*S*)-4-phenyl-2-oxazolidinone chiral auxiliary furnished the enamine intermediate which was a mixture of H-bonded and non-H-bonded conformers, as suggested by ^{1}H NMR. As expected, hydrogenation of this enamine over Pd–C yielded a mixture of diastereoisomers.

In summary, a novel approach towards an enantioselective synthesis of (2*S*,2′*R*)-*erythro*-methylphenidate (**1**) is described. The key step in the synthesis utilizes Evans' 4-substituted-2-oxazolidinone chiral auxiliary to control the diastereofacial selectivity in the hydrogenation of enamine intermediate **6**, yielding the hydrogenated product **7** with excellent diastereoselectivity. Methanolysis of **7**



Scheme 2. (a) *t*-BuCOCl, Et_3N, $PhCH_3$, 80°C, 12 h (85%); (b) *t*-BuCOCl, Et_3N, $PhCH_3$, rt, 4 h (100%); (c) LiHMDS, THF, 0°C, 1 h; (d) (i) CF_3CO_2H, CH_2Cl_2, 0°C to rt, 4 h, (ii) $NaHCO_3$ (30% in two steps); (e) 10% Pd–C, EtOAc, rt, 24 h (95%); (f) MeOH, LnI_3, THF, rt, 16 h (85%)

afforded **1** with excellent enantiopurity. This approach could also be used to synthesize the corresponding (2*R*,2′*S*)-*erythro*-methylphenidate by using (*R*)-4-benzyl-2-oxazolidinone chiral auxiliary.

Acknowledgements

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