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Versatile Synthons for Optically Pure α-Amino Aldehydes and α-Amino Acids: (+)- and (−)-4,5-Dialkoxy-2-oxazolidinones

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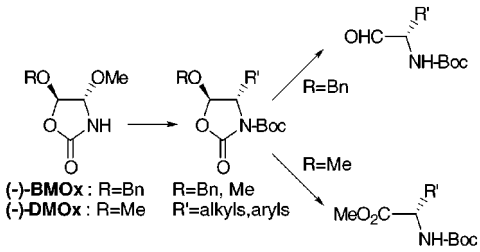
ABSTRACT



Both enantiomers of *trans*-5-benzyloxy-4-methoxy- (BMOx) and *trans*-4,5-dimethoxy-2-oxazolidinones (DMOx), which are readily accessible from simple 2-oxazolone heterocycles, represent good candidates for a new class of chiral synthons for use in the preparation of optically pure α-amino aldehydes and α-amino acids, respectively.

Optically active α-amino aldehydes,[1] as well as the corresponding α-amino acids,[2] have great potential as chiral building blocks for the synthesis of polyfunctional unusual amino acids, amino polyols, and peptide mimics, which include enzyme inhibitors, aminosugar antibiotics, and sympathomimetic amines. The diverse nature of the functional groups contained by the above compounds and the importance of accessing their absolute configuration require the development of an effective synthesis of α-amino aldehydes with the diverse side chains in optically pure form. The N-protected α-amino aldehydes can be generally prepared via the reduction of amino acids or derivatives thereof[1a,3] or by oxidation of the related 2-amino alcohols.[1a−c] In most cases, however, the isolation of α-amino aldehydes in optically pure form under either the basic or acidic conditions employed in the synthesis is not a simple task. There have appeared very few practically useful chiral synthons for a wide variety of α-amino aldehydes generated under mild, neutral conditions. This is in contrast to several types of chiral synthons for α-amino acids, the utility and versatility of which are well established.[2]

In this paper we wish to report on some promising chiral synthons, (+)- and (−)-*trans*-4-methoxy-5-benzyloxy- (BMOx) and *trans*-4,5-dimethoxy-2-oxazolidinones (DMOx), which function as electrophilic "chiral α-methoxyglycinal" derivatives (Figure 1).

The stereospecific substitution of the 4-methoxy groups

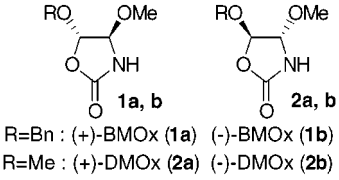


Figure 1. New chiral synthons for α-amino aldehydes and α-amino acids.

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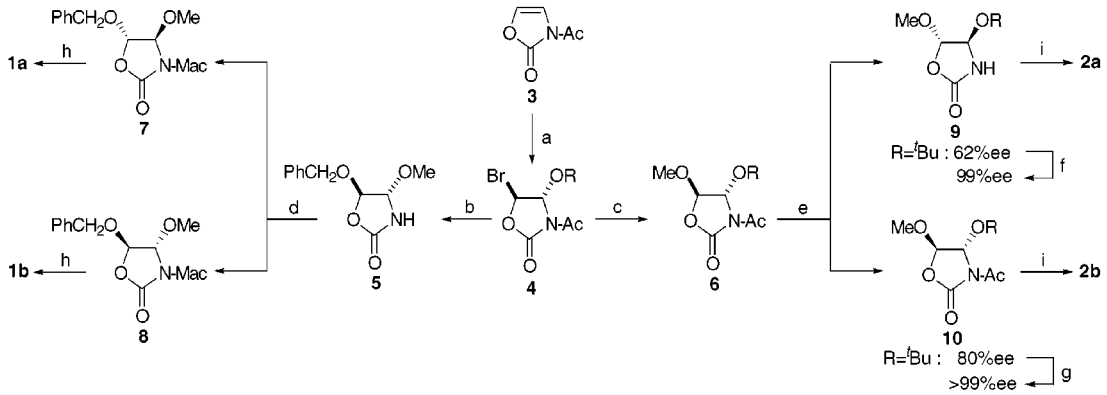
Scheme 1. Synthesis of Chiral Synthons **1a**,**b** and **2a**,**b**[a]



[a] (a) NBS, ROH, dioxane. (b) $^{i}Pr_2NEt$, BnOH. (c) $^{i}Pr_2NEt$, MeOH. (d) MacCl **11**, NaH, THF. (e) BH_3·THF, **12** (0. equiv), THF. (f) Step e was repeated. (g) Cs_2CO_3, MeOH, then recrystallization. (h) $LiBH_4$/MeOH (1:2), THF. (i) MeOH, BF_3·OEt_2.

of **1** and **2** for a variety of alkyl groups or aryl groups, followed by hydrogenolytic and oxidative ring cleavage, provides direct routes to optically pure α-amino aldehydes and α-amino acids, respectively.

Chiral Synthons, BMOx and DMOx (Scheme 1). The 4,5-dialkoxy-2-oxazolidinones are readily accessible from a simple 2-oxazolone heterocycle,[4] which has been shown to be sufficiently reactive to serve as a building block for the 2-amino alcohol skeletons found in a variety of bioactive compounds. The 3-acetyl-2-oxazolone (**3**) underwent regio- and stereoselective electrophilic addition with NBS in alcoholic media to give the *trans*-5-bromo-4-alkoxy adducts **4** exclusively, which were alcoholyzed with benzyl alcohol or methanol in the presence of tertiary amines. The optical resolution of the *trans*-5-benzyloxy-4-methoxy-2-oxazolidinones (BMOx) (**5**) thus formed was readily performed with the aid of 2*R*-methoxy-1*S*-apocamphanecarbonyl chloride (Mac-Cl) (**11**)[5] to give the diastereomeric *N*-Mac **7** and **8** derivatives, which were readily separable by chromatography on silica gel. The reductive removal of the chiral auxiliary from **7** and **8** gave (+)- and (−)-BMOx (**1a** and **b**), respectively, in 77% yield, each of which serves as new class of chiral synthons for a wide range of α-amino aldehydes.

An alternative procedure involving kinetic resolution through an amino alcohol-catalyzed enantioselective deacylation with borane[6] was explored with the *trans*-3-acetyl-4,5-dialkoxy derivatives **6**. This enantioselective deacetylation procedure proved to be, in practice, effective for the kinetic resolution of 4-*tert*-butoxy-5-methoxy-2-oxazolidinones (**6**, R = *t*-Bu), when the *cis*-fixed amino alcohols **12a**−**c** (Figure 2) were used as chiral ligands, as seen in

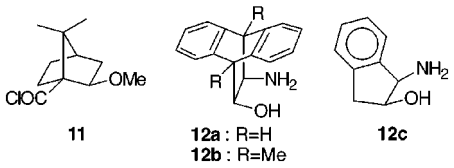


Figure 2. Chiral reagents used for optical resolution.

Table 1. The α,α-diphenyl-2-pyrrolidinemethanol and the derived *B*-methyl oxazaborolidines were much less effective as catalysts. The enantioselectivity was most affected by the size of the 4-alkoxy group. As a result, the bulky *tert*-butoxy was found to be the choice of substituents for achieving the highest selectivity. Using this method, the enantiomeric *trans*-

Table 1. Enantioselective Borane-Mediated Deacetylation of 3-Acetyl-4,5-dialkoxy-2-oxazolidinones **6** Catalyzed by Amino Alcohols **12**

entry	R	ligand	BH_3·THF (equiv)	temp (°C)	time (h)	yield (ee)[a] (%) **9**	**10**
1	Me	**12a**	2	20	1	24 (19)	76
2	^{i}Pr	**12a**	2	20	2	17 (51)	83
3	^{t}Bu	**12a**	2	20	2	41 (75)	59
4	^{t}Bu	**12a**	2	0	6	39 (80)	61 (62)
5	^{t}Bu	**12a**	2	20	3	26 (96)	74
6	^{t}Bu	**12b**	2	20	4	40 (75)	60
7	^{t}Bu	**12c**	2	0	4.5	35 (76)	63

[a] Determined by HPLC.

(1) For reviews, see: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30* 1531. (c) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121.

(2) For reviews, see: (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon press: Oxford, 1989. (b) Williams, R. M. *Aldrichimica Acta* **1992**, *25*, 11.

(3) For an example, see: Sawamura, M.; Nakayama, Y.; Kato, T.; Ito, Y. *J. Org. Chem.* **1995**, *60*, 1727.

(4) For reviews, see: (a) Kunieda, T.; Ishizuka, T. *Studies in Natural Products Chemistry, Stereoselective Synthesis* (*Part H*); Atta-ur-Rahman, Ed.; Elsevier Science Publishers: Amsterdam, 1993. (b) Kunieda, T.; Ishizuka, T. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 1018.

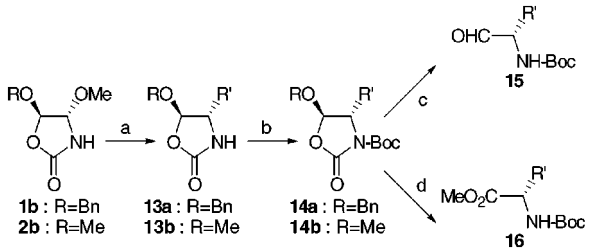
(5) Ishizuka, T.; Kimura, K.; Ishibuchi, S.; Kunieda, T. *Chem. Pharm. Bull.* **1990**, *38*, 1717.

(6) (a) Hashimoto, N.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1998**, *39*, 6317. (b) Yokoyama, K.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1999**, *40*, 6285.

4-*tert*-butoxy-5-methoxy compounds **9** and **10** were obtained in 38% (99% ee) and 33% (99% ee), although a repeated resolving procedure was required in the case of the partially differentiated former isomer. On successive treatment with MeOH/BF_3·OEt_2, both of the 4-*tert*-butoxy enantiomers **9** and **10** were converted to (+)- and (−)-DMOx (**2a** and **b**), respectively, in excellent yields.

Optically Pure α-Amino Aldehydes and α-Amino Acids (Scheme 2). The chiral *trans*-4,5-dialkoxy-2-oxazolidinones,

Scheme 2. Conversion to α-Amino Aldehydes **15** and α-Amino Acids **16**[a]



[a] (a) R′Li or R′MgX, CuCN, LiCl, BF_3·OEt_2, THF (R′ = allyl: allylTMS, $TiCl_4$, CH_2Cl_2). (b) $(Boc)_2O$, NEt_3, DMAP, CH_2Cl_2. (c) H_2, Pd−C, MeOH. (d) $KMnO_4$, KOH, ^{t}BuOH, H_2O then CH_2N_2 or PDC, MeOH, KOH, DMF.

BMOx and DMOx, which can be regarded as chiral α-methoxyglycinal equivalents, were treated with organo cuprates in the presence of BF_3·OEt_2, resulting in the regioselective replacement of the 4-methoxy group with *prim.* to *tert*-alkyl and aryl groups with full retention of configuration. It is assumed that this reaction proceeds via the acyliminium ion and the subsequent cuprate attack is effectively controlled by the vicinal OR groups. Thus, *trans*-4-substituted 5-alkoxy derivatives **13** were exclusively formed with no detectable contamination by *cis*-isomers. The facile conversion to the 4-substituted compounds **13** as well as into α-amino aldehydes and α-amino acids via *N*-Boc derivatives **14** is summarized in Table 2. It is also noteworthy that *N*-*tert*-butoxycarbonylation greatly facilitates the ring cleavage of 2-oxazolidinones.[7]

Hydrogenolysis of the *N*-Boc-4-substituted 5-benzyloxy-2-oxazolidnones **14a** with H_2/Pd−C proceeded at room temperature to give (*S*)-*N*-Boc-α-amino aldehydes **15** in optically pure form. An optical purity in excess of 99% ee was verified by HPLC analysis or by oxidation to the authentic α-amino acids, and no detectable racemization was detected during the ring opening, which proceeded under strictly neutral conditions.

Table 2. Conversion Yields to 4-Substituted 2-Oxazolidinones **13**, α-Amino Aldehydes **15**, and α-Amino Acids **16**

			yield (%)	
entry	synthon	R′	13	15
1	**1b**	Bu	76	87
2		^{i}Pr	76	80
3		^{t}Bu	74	97
4		Ph	80	81
5		Bn	90	93

			yield (%)	
entry	synthon	R′	13	16
6	**2b**	Bu	71	80
7		^{i}Pr	80	85
8		^{t}Bu	71	98
9		Ph	72	100
10		Bn	83	70
11		allyl	78	100

A variety of optically pure (*S*)-*N*-Boc-α-amino acids **16** were synthesized by the direct oxidation of *N*-Boc-4-substituted 5-methoxy-2-oxazolidinones **14b** with either $KMnO_4$ or PDC under basic conditions. An optical purity in excess of 99% ee was confirmed by HPLC analysis on chiral columns. The use of $NaBH_4$ in place of oxidizing agents such as $KMnO_4$ and PDC resulted in the direct formation of optically pure *N*-Boc-2-amino alcohols, which were also satisfactory precursors for 2-oxazolidinone auxiliaries, as previously shown.[8]

In conclusion, the (+)- and (−)-*trans*-4-methoxy-5-benzyloxy- (BMOx) and *trans*-4,5-dimethoxy-2-oxazolidinones (DMOx), which are readily accessible in stable, crystalline forms from simple heterocycle 2-oxazolones, represent good candidates for a new class of chiral synthons for use in the preparation of a wide variety of optically pure α-amino aldehydes and α-amino acids, as well as 2-amino alcohols.

Supporting Information Available: General experimental procedures and characterizations of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185.

(8) Matsunaga, H.; Ishizuka, T.; Kunieda, T. *Tetrahedron* **1997**, *53*, 1275.