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Syntheses of optically active 2-amino-4-oxobutyric acid and N,O-protected derivatives*

Review Article

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Summary. Strategies for the synthesis of optically active aspartaldehyde derivatives are reviewed. Most of them are using the chiral pool: allylglycine or naturally occurring homoserine, aspartic acid or methionine and side chain modifications. This will be developed in the first part. Some other original routes are also displayed in the second part. Different aspects of each strategy are discussed: the nature and number of steps, the problem of protecting groups, the price and availability of starting materials. Some synthetic applications of such interesting chiral synthons are shown in the last part.

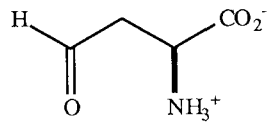
Keywords: Amino acids – Unusual amino acids – Aspartic acid β-semialdehyde – Aspartaldehyde – 2-Amino-4-oxobutyric acid – Enantioselective synthesis

Abbreviations: Ac, acetyl; An, Anisyl or 4-methoxy benzyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BOP·PF_6, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, Cbz, benzyloxycarbonyl; DCC, dicyclohexylcarbodiimide; DIBAL, diisobutyl aluminum hydride; DIPEA, diisopropyl ethyl amine; DMF, dimethyl formamide; DMSO, dimethylsulfoxide; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride; HP, 4-hydroxy phenyl; MP, 4-methoxy phenyl; NCS, N-chlorosuccinimide; NMR, nuclear magnetic resonance; PCC, pyridinium chlorochromate; Pht, phthaloyl; Ser, serine; *t*Bu, *tert*-butyl; TEMPO, 2,2,6,6-tetramethyl piperidine-1-oxyl; TFA, trifluoro acetic acid; Trityl, triphenyl methyl; Val, valine

Introduction

(*S*)-2-amino-4-oxobutyric acid **1a** (also called L-aspartic acid β-semialdehyde or 3-formyl-L-alanine and here will be named as "aspartaldehyde") is

*This paper is dedicated to RV.



1a

a biosynthetic intermediate for several important proteinogenic amino acids such as L-lysine, L-methionine (*via* L-homoserine, L-cystathionine and L-homocysteine) and L-isoleucine (*via* L-homoserine and L-threonine) (Fig. 1). It is derived from L-aspartic acid whose side chain carboxylic group is selectively reduced to the aldehyde by an enzyme-catalyzed reduction of L-aspartic acid β-phosphate. A second enzyme-catalyzed reduction may then lead to L-homoserine (Metzler, 1977). L-lysine is an essential amino acid biosynthesized in bacteria and higher plants by the so-called diaminopimelate pathway. Diaminopimelic acids are also essential constituents of peptidoglycan, a component of bacterial cell walls. Inhibition of the enzymes involved in the biosynthetic pathways of these amino acids, including enzymes with aspartic acid β-semialdehyde **1a** as substrate, represents an important target for herbicide and bactericide research and enzymological studies on this compound have been performed in that respect (Tudor et al., 1993; Coulter et al., 1996; Cox et al., 1996; Blickling et al., 1997). It is noteworthy that aspartaldehyde containing peptides are commercially available as enzyme inhibitors (see for example BACHEM catalog).

Apart from being an α-amino acid with inherent chirality, aspartic acid β-semialdehyde **1a** is also a chiral β-amino (or-carboxy) aldehyde (Toujas et al., 1997) and as a polyfunctional chiral compound, it represents an interesting chiral building block for the preparation of biologically active molecules of interest.

The need to produce enantiomerically pure compounds is now almost a necessity, not only for use as pharmaceuticals but also as aroma and flavour chemicals, pesticides and herbicides, dyes and pigments, liquid crystals or non-linear optical materials. While new structures increase in complexity, usually the number of steps for their preparation increases too. These structures must therefore be synthesized in enantiopure form but also efficiently, economically and using safe starting materials for man and environment (Richards and McCague, 1997; Davies and Reider, 1996; Cannarsa, 1996). Therefore, different approaches to the preparation of optically active aspartic acid β-semialdehyde **1a** and N,O-protected derivatives have been described in the literature. Chirality is introduced into a synthesis using four options that may overlap (Crosby, 1992, 1997):

- The chiral pool where the requisite configuration is provided for in the starting material used and is maintained throughout the remainder of the synthesis. Inherent chirality of Nature is used and starting materials are natural amino acids, hydroxy acids, terpenes, carbohydrate or alkaloids. Also included in this section is the use of non natural but

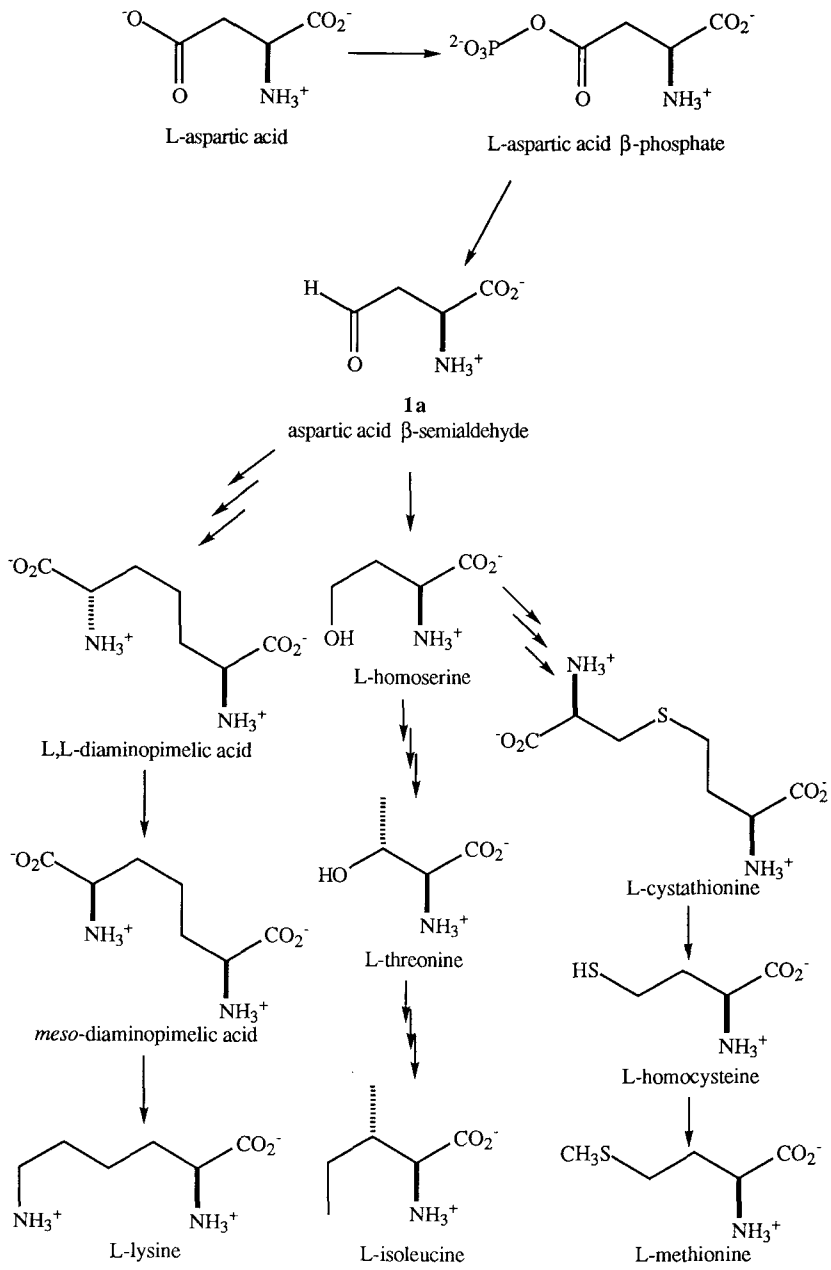


Fig. 1. Some biosynthetic reactions of aspartic acid

readily available enantiopure commercial products as chiral building blocks.

- Resolution methods where the precursor is provided as a racemic mixture and enantiomers have to be separated by crystallization or chromatography for instance.
- Fermentation and enzymatic transformation where the action of an enzyme on an optically inactive substrate (chiral racemic or non-chiral) is used.

– Asymmetric synthesis where the single isomer product is obtained by introducing the asymmetry into a non-chiral material.

All these strategies have been used in the synthesis of optically active α-amino acids (Barrett, 1985; Coppola, 1987; Williams, 1989; Duthaler 1994). A natural approach to the preparation of optically active aspartic acid β-semialdehyde **1a** or N,O-protected derivatives (including amides), as products or as key intermediates in sufficient quantity, is to use the chiral pool and especially commercially available α-amino acids by side chain modifications. This strategy has been widely employed and will be developed in the first part of this review. For some other specific applications, different strategies have led to optically active aspartic acid β-semialdehyde **1a** or N,O-protected derivatives and these will be considered in the second part. In the last part, a non exhaustive series of targets having optically active aspartaldehyde derivatives as synthetic intermediates are given.

1 Synthesis of optically active aspartic acid β-semialdehyde and derivatives by side chain modifications of α-amino acids

1.1 From allylglycine

The aldehydes **1** are obtained by oxidative cleavage of the double bond of allylglycine derivatives **2** (Fig. 2 and Table 1).

This strategy was used in the very first syntheses of free aspartic acid β-semialdehyde **1a** to elucidate the biosynthetic pathway (Black and Wright, 1955abc; Neuberger and Tait, 1962). Unprotected **1a** was revealed to be rather unstable (dry state or in solution) except perhaps in cold acidic solution. At that time optically active allylglycine was not commercially available and was synthesized using the classical acetamidomalonate route (Albertson, 1946; Barrett, 1985) followed by an acylase catalyzed deprotection in a later step to obtain L-allylglycine. Now, both enantiomers of allylglycine are commercially available (for recent use of L- or D-allylglycine see Girard et al., 1998; Williams and Liu, 1998; Gao et al., 1998) although they are rather expensive and consequently the enantioselective synthesis of allylglycine derivatives continues to be a challenge (see for example: Hanessian and Yang, 1996; Katagiri et al., 1996; Kazmaier, 1996; Cox et al., 1996; Myers et al., 1997).

Ozonolysis was originally performed directly on free L-allylglycine (Black and Wright, 1955b) but the product could only be identified by enzymatic

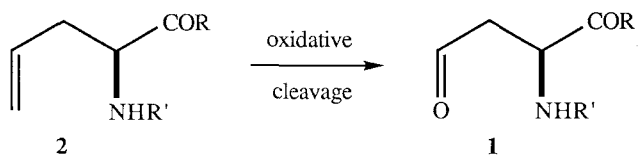


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Fig. 2. Synthesis of aspartaldehyde from allylglycine

assay (95% yield). Much later, this method was employed to produce **1a** in 88% yield (enzymatic analysis) but with low purity (Coulter et al., 1996). Nevertheless, it is still commonly used (see for example Schindler and Viola, 1994; Giorgianni et al., 1995). More efficient syntheses of unprotected **1a** are clearly needed. Other protected derivatives **2** were afterwards subjected to ozonolysis (Geze et al., 1983) (>76% yield); (Balwin et al., 1988a) (yield unknown); (Jungheim et al., 1991) (96% yield); (Tudor et al., 1993; Blickling et al., 1997) (75% yield). In the latter case, a free stable convenient solid form of optically active aspartic acid β-semialdehyde is obtained after deprotection as a hydrate of the trifluoro acetate salt.

After amino protection, oxidative cleavage was also performed using performic acid and sodium metaperiodate through a lactone alcohol interme-

Table 1. Oxidative cleavage of L-allylglycine derivatives according to Fig. 2

Exp. conditions	R,R′	Yield	Reference
i:O_3, HCl, H_2O ii:Dowex H+	R = OH, R′ = H	95% (c)	(Black and Wright, 1955b) (a), (Chang and Walsh, 1981) (e), (Schindler and Viola, 1994), (Giorgianni et al., 1995)
i:O_3 ii:Me_2S	R = OMe, R′ = Boc	>76% (b) 96%	(Geze et al., 1983) (Jungheim et al., 1991)
	R = D-Val, R′ = (*S*)-$CO(CH_2)_3$ -$CH(CO_2H)NH_2$	–	(Baldwin et al., 1988a)
	R-R′ = (*R*)-OCH_2CHPh	>75% (b)	(Agami et al., 1992, 1993) (a) (f)
i:O_3 ii:NEt_3	R = OAn, R′ = Boc	75%	(Tudor et al., 1993) (a) (Blickling et al., 1997)
i:HCO_2H, H_2O_2 ii:NaOH iii:$NaIO_4$	R = OH, R′ = Cbz	low (i:35%)	(Neuberger and Tait, 1962) (a), (Weinkam and Jorgensen, 1971) (d),
	(R = OMe, R′ = Cbz)		(Cavrini et al., 1976) (a)
i:OsO_4 ii:$NaIO_4$	R = OMe, OEt, O*t*Bu; R′ = Cbz	>70% (b)	(Fushiya et al., 1981a,b) (d)
cat. OsO_4, $NaIO_4$	R = D-Ser(OBn)OMe, R′ = $COCH_2OPh$	>67% (b)	(Baldwin et al., 1989a)
	R-R′:cyclic peptide	76%	(Itokawa et al., 1993) (a)
	R = N-pyrrolidine ring R′ = Cbz	>63% (b)	(Szeto et al., 1995) (Stockman et al., 1996)

(a) Synthesis of the aldehyde **1** is described in the experimental section. (b) Yield for a sequence with limited number of steps and including oxidative cleavage. (c) By enzymatic analysis. (d) Chemical or physical characterizations of aldehyde **1** included in the reference. (e) L-[4-^{2}H]-aspartaldehyde **1** is synthesized. (f) (*R,R*)-stereoisomer **1** is concerned.

diate, apparently in low yield (Neuberger and Tait, 1962; Weinkam and Jorgensen, 1971; Cavrini et al., 1976).

Oxidative cleavage by treatment with osmium tetroxide and sodium metaperiodate also led to the aldehyde (Fushiya et al., 1981ab) (stoichiometric OsO_4, >70% yield); (Baldwin et al., 1989a) (cat. OsO_4, >67% yield); (Itokawa et al., 1993) (cat. OsO_4, 76% yield); (Szeto et al., 1995; Stockman et al., 1996) (cat. OsO_4, >63% yield).

It is worth noting that the precursor L-allylglycine derivative **2** is also obtained from a L-glutamyl residue of a peptide (Itokawa et al., 1993). L-[4-^{2}H]- aspartaldehyde has also been synthesized *via* 4,5-dideuterio-L-allylglycine, obtained from L-propargylglycine (D_2, Lindlar catalyst, D_2O then O_3, DCl, D_2O) (Chang and Walsh, 1981). An aspartaldehyde derivative has also been used as an intermediate in a chemical correlation to (R)-homoserine lactone. The key step in the synthesis of the optically active allylglycine derivative is an aza-Cope rearrangement with stereospecific Cα-Cβ bond formation coupled with iminium ion hydrolysis (Agami et al., 1992, 1993). In the other cases, enzymatically obtained or commercial L-allylglycine (or derivatives) seems to have been used.

1.2 From or via *homoserine*

The aldehydes **1** are obtained by oxidation of the primary alcohol of a N,O-protected derivative of optically active homoserine **3** obtained from homoserine or from its γ-lactone after ring opening (Ohfune et al., 1981; Oida et al., 1989; Matsuura et al., 1994a; Weitz et al., 1997) (Fig. 3 and Tables 2-1, 2-2).

Although both enantiomers of homoserine are commercially available, they are rather expensive. Therefore, derivatives **3** have been synthesized from less expensive optically active natural α-amino acids, by side chain modifications: mainly aspartic acid (Uzar, 1991) but also methionine. Treatment of methionine with methyl bromide or iodide in aqueous solution is an easy access to homoserine (Cooper et al., 1978; Baldwin et al., 1988b; Koch and Buchardt, 1993) although lactonization is likely to occur. $NaBH_4$ reduction of a mixed anhydride derivative of the acid side chain of aspartic acid has also led to homoserine derivatives **3**. This strategy needs to have partially protected aspartic acid derivatives available. Moreover, unlike methyl, ethyl and benzyl esters of N-Cbz-homoserine, *tert*-butyl ester does not lactonize (Valerio et al., 1988; Tong et al., 1990, 1992).

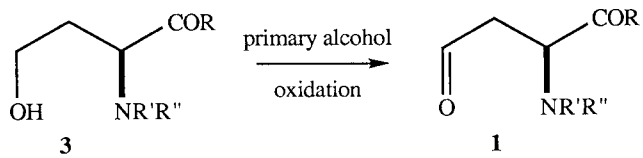


Fig. 3. Synthesis of aspartaldehyde from homoserine

Oxidation of the alcohol **3** was performed using Cr^{VI} based reagents: CrO_3, pyridine or PCC (Table 2-1); Swern ($COCl_2$, DMSO then NEt_3 or DIPEA); Pfitzner-Moffatt (DCC, DMSO) or TEMPO catalyzed NaOCl oxidation (Table 2-2). Interesting comparison elements on these oxidation methods have been reported by Mock and Moffat (Mock and Moffat, 1982); Tong and Perish (Tong et al., 1990, 1992; Perish, 1994). TEMPO or DMSO based oxidations seem to give aldehydes **1** in good yield and with higher chemical and optical purity (Table 2-2). Aldehyde **1** with R = OBn, R′ = Cbz, R″ = H is also optically stable in pyridine at room temperature for 3 hours (Baldwin et al., 1989b).

In one case, the acid functionality of the protected L-homoserine derivative is obtained by a ruthenium catalyzed oxidation of the p-methoxyphenyl group, the optically active aromatic precursor being obtained from (*R*)-p-hydroxyphenylglycine in a multi step procedure (Matsuura et al., 1994b) (Fig. 4). The protocols are given.

1.3 Directly from aspartic acid

The aldehydes **1** are obtained by a selective reduction of the side chain of a reactive aspartic acid derivative **5** obtained from a selectively α-carboxyl protected aspartic acid derivative **4** (Fig. 5).

Table 2-1. Oxidation of L-homoserine derivatives according to Fig. 3: Cr^{VI} based reagents

Exp. conditions	R, R′, R″ (c)	Yield	Reference
CrO_3, pyridine	R = OBn, R′ = Cbz	69%	(Keith et al., 1975) (a) (Baldwin et al., 1989b) (d)
	R = O*t*Bu, R′ = Boc (f)	74%	(Ramsamy et al., 1982) (a)
	R = O*t*Bu, R′ = Boc (f) ([4-^{2}H]-**1**)	70%	(Ramalingam and Woodard, 1988) (a)
	R = O*t*Bu, R′ = Cbz (f)	81%	(Faust et al., 1984) (a)
	R = O*t*Bu, R′ = Cbz (f)	60%	(Valerio et al., 1988) (a)
PCC	R = OBn, R′ = Boc, R″ = alkyl	75%	(Ohfune et al., 1981) (d) (Ohfune and Nomoto, 1981), (Oida et al., 1989)(e)
	R = OBn, R′ = Cbz	70%	(Fushiya et al., 1988a) (a)
	R = NMe_2, R′ = Boc	>54% (b)	(Weitz et al., 1997) (a)
	R = O*t*Bu, R′ = Cbz (f)	>67% (b)	(Weitz et al., 1997) (a)
	R = OAn, R′ = Boc (from L-methionine)	>40% (b)	(Baldwin and Flinn, 1987) (d)

(a) Synthesis of the aldehyde **1** is described in the experimental section. (b) Yield for a sequence with limited number of steps and including oxidative cleavage. (c) Unless otherwise noted: R″ = H and (*S*)-homoserine or its lactone are used as starting material (d) Chemical or physical characterizations of aldehyde **1** included in the reference. (e) (*R*)-enantiomer **1** is concerned. (f) (*S*)-aspartic acid is used as starting material.

Table 2-2. Oxidation of L-homoserine derivatives according to Fig. 3: DMSO and TEMPO based reagents

Exp. conditions	R, R′, R″ (c)	Yield	Reference
DMSO, DCC, $CH_3PO_3H_2$	R = OBn, R′ = Cbz	72%	(Mock and Moffat, 1982) (a)
DMSO, DCC, Pyridine, TFA	R = O*t*Bu, R′ = $COCH_2Cl$ or $COCH_2PO(OEt)_2$ (d)	61%	(Ben-Bari et al., 1995) (a)
DMSO, $(COCl)_2$ then NEt_3	R = OBn, R′ = Boc	>82% (b)	(Matsuura et al., 1994a) (a),
	R = O*t*Bu, R′ = Boc, R″ = alkyl (see Fig. 4)	94%	(Matsuura et al., 1994b) (a)
	R = OBn, R′ = Boc, Cbz	–	(De la Figuera et al., 1994, 1995)
	R = O*t*Bu, R′,R″ = dibenzyltriazone (d)	92%	(Knapp et al., 1992) (a)
	R = O*t*Bu, R′ = Boc ([4-^{2}H]-**1**) (d)	–	(Townsend et al., 1988)
	R = O*t*Bu, R′ = Boc	93%	(Werner et al., 1997) (a)
	R = O*t*Bu, R′ = Boc (d)	>87% (b)	(Shioiri et al., 1997) (a)
NaOCl, TEMPO	R = O*t*Bu, R′ = Boc (d)	79%	(Tong et al., 1990) (Tong et al., 1992) (a)
		82%	(Perish, 1992) (Perish, 1994) (a)

(a) Synthesis of the aldehyde **1** is described in the experimental section. (b) Yield for a sequence with limited number of steps and including oxidative cleavage. (c) Unless otherwise noted: R″ = H and (*S*)-homoserine or its lactone are used as starting material (d) (*S*)-aspartic acid is used as starting material.

Compounds **4** are either commercially available or synthesized from optically active aspartic acid in a multistep procedure. Selective protection and reduction on such derivatives is often problematic. For example, DIBAL reduction of N-trityl dibenzyl L-aspartate does not lead to the γ-semialdehyde and N-trityl-L-homoserine lactone was the only isolable product, the nature of the amino protecting group being critical (Baldwin et al., 1987). This reduction proved to be unreliable for some authors: $LiHAl(OtBu)_3$ acid chloride reduction failed (Baldwin and Lee, 1986); use of Bu_3SnH worked with low yield (Bold et al., 1990). Nevertheless, most of the procedures involve a Rosenmund reduction or Bu_3SnH reduction of the acyl chloride. Also described are reductions of Weinreb amide with DIBAL and thioester reductions with Et_3SiH (Table 3).

It is interesting to add in this section that an L-aspartic residue of a cyclopeptide was reduced to an aspartaldehyde derivative using the Vilsmeier-Haack reagent {DMF, $(COCl)_2$} followed by uncompleted $NaBH_4$ reduction (41% Yield) (Emmer et al., 1994) (the protocol is included).

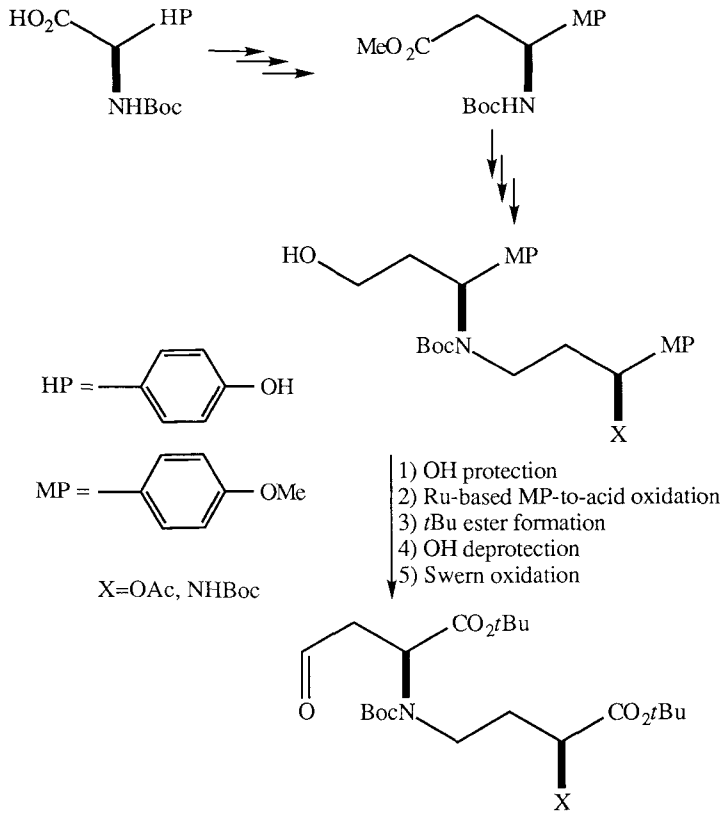


Fig. 4. Synthesis of aspartaldehyde from p-hydroxyphenylglycine *via* homoserine

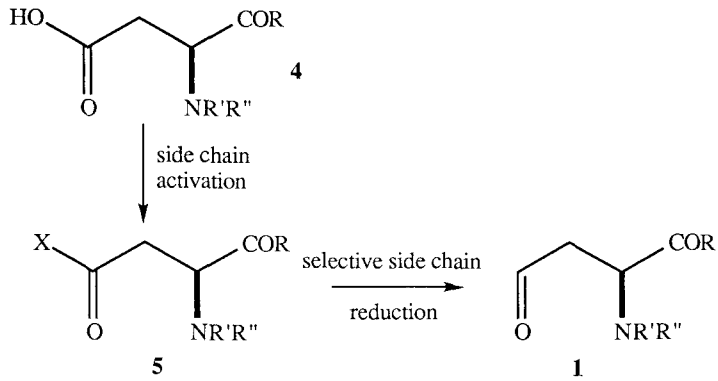


Fig. 5. Direct synthesis of aspartaldehyde from aspartic acid

Moreover, homologous N,N-diprotected L-glutamic acid semialdehyde has been synthesized recently from L-glutamic acid using this strategy. In this case too, the nature of amino protection seems to be critical (Kokotos et al., 1998).

Table 3. Reduction of L-aspartic acid derivatives **4** into aspartic acid β-semialdehyde derivatives **1** according to Fig. 5

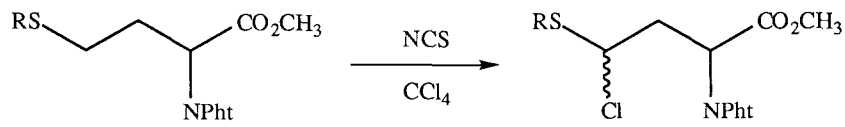
Exp. conditions	X, R, R′, R″ (c)	Yield	Reference
$SOCl_2$ then H_2, Pt	X = Cl, R = OEt, R′ = $COCF_3$	84%	(Weygand and Fritz, 1965) (a)
		–	(Faust et al., 1983) (a) (d)
$SOCl_2$ then H_2, Pd/C	X = Cl, R = OMe, R′ = $COCF_3$ (e)	73%	(Svete et al., 1994) (a)
$SOCl_2$ then H_2, $Pd/BaSO_4$	X = Cl, R = OMe, R′ = $COCF_3$	90%	(David and Veyrières, 1970) (a)
	X = Cl, R-R″ = OCH_2, R′ = Cbz	69%	(Bold et al., 1990) (a)
	X = Cl, R-R″ = OCH_2, R′ = CO_2Me	77%	(Hoffmann and Zeiss, 1992)
	X = Cl, R-R′ = $OC(CF_3)_2$	55%	(Winkler and Burger, 1996) (a) (Burger et al., 1995)
$SOCl_2$ then Bu_3SnH	X = Cl, R-R″ = OCH_2, R′ = Cbz	(b)	(Baldwin and Lee, 1986) (a)
$SOCl_2$ then Bu_3SnH, cat. $Pd(PPh_3)_4$	X = Cl, R = OMe, R′ = Cbz	>77%	(Ornstein et al., 1994)
Et_3N, $CH_3ONHCH_3 \cdot HCl$, $BOP \cdot PF_6$ then DIBAL	X = NMe(OMe), R = O*t*Bu, R′ = Boc	69%	(Wernic et al., 1989) (a)
DCC, EtSH then Et_3SiH, Pd/C	X = SEt, R = O*t*Bu, R′ = Boc	77%	(Bergmeier, 1993) (a)
EDCI, EtSH, DMAP then Et_3SiH, Pd/C	X = SEt, R = N(indoline or tetrahydroquinoline), R′-R″ = Pht	61%	(Robl et al., 1995)

(a) Synthesis of the aldehyde **1** is described in the experimental section. (b) Yield unknown, aldehyde **1** is unstable and is used as crude in the next step. (c) Unless otherwise noted, R″ = H and (*S*)-aspartic acid is used as starting material (d) Chemical or physical characterizations of aldehyde **1** are included in the reference. (e) Both enantiomers of **1** are described.

1.4 Directly from methionine

We reported in 1991 that the side chain of suitable S-substituted homocysteine derivatives **6ab** could be oxidized in a regioselective way using a Pummerer like reaction (Meffre et al., 1991) (Fig. 6).

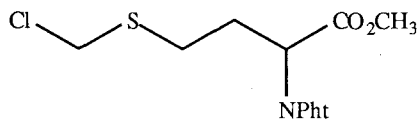
The phthaloyl amino protecting group is chosen to avoid any internal amine participation. Introduction of a phthaloyl protection has found great utility in synthesis (Easton and Hutton, 1998). Amine diprotection is necessary since the same reaction conducted on the N-benzyloxycarbonyl (NHCbz) and on the N-*tert*-butyloxycarbonyl (NHBoc) analogues did not lead to clean



6a R=C_6H_5 **7a** R=C_6H_5
6b R=CH_3 **7b** R=CH_3

Fig. 6. Side chain chlorination of S-substituted homocysteine derivatives

α-chlorination but to unidentified products. The key step is a Pummerer like reaction using easily handled N-chlorosuccinimide (NCS) in carbon tetrachloride. α-Chlorination is chosen because of its regioselectivity towards α-methylene compared with an α-methyl. In the case of **6b**, NMR analysis of the crude mixture of chlorinated intermediates (mixture of isomers) indicates that chlorination occurs mainly at the methylene (formation of major **7b** and of minor isomer **8**) although some vinylsulfide products are also present at this stage of the reaction (Meffre et al., 1991; Meffre, 1998). Succinimide formed in the reaction is not soluble in CCl_4, floats on the surface (unlike NCS), indicating completion of the reaction, and is easily separated by filtration.



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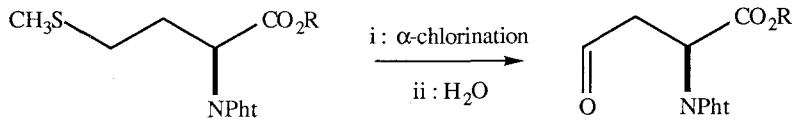
This result opens a general and simple route to the synthesis of a wide range of aspartic acid β-semialdehyde derivatives especially because recent results in our laboratory indicate that other N-diprotections work as well. Indeed, transient chlorinated intermediates (mixture of isomers) are not isolated and different kinds of products are formed depending on the subsequent reaction conditions (Meffre et al., 1991, 1995; Meffre, 1998; Dehmlow and Westerheide, 1993). In particular, chlorination of the optically active esters of N-phthaloyl methionine **6b,c** followed by hydrolysis leads to the aldehydes **1b,c** (Fig. 7 and Table 4).

The same strategy was used in 1993 in the synthesis of the ethyl (S)-2-phthalimido-4-oxobutanoate **1c** from L-methionine using corrosive sulfuryl chloride as chlorinating agent and a "time consuming" hydrolysis (Dehmlow and Westerheide, 1993) (Table 4). However, partially racemized compounds seem to be obtained probably due to the harsh experimental conditions (Meffre et al., 1995). We observed that hydrolysis using $HgCl_2$, $CdCO_3$, H_2O; NCS, $AgNO_3$, acetonitrile or $CuCl_2{\cdot}2H_2O$, CuO, H_2O, acetone leads to fair yields but is not environmentally safe. Best results were obtained when hydrolysis of the transient chlorinated intermediates is immediately performed using water and nitrogen bubbling to help remove methanethiol from the reaction mixture (CH_3SH and HCl are formed during hydrolysis). Under



6b, R=Me

6c, R=Et

1b, R=Me

1c, R=Et

Fig. 7. Direct synthesis of aspartaldehyde from methionine

Table 4. Formation of optically active N-phthaloyl aspartic acid β-semialdehyde derivatives **1b,c** by α-chlorosulfide hydrolysis according to Fig. 7

Exp. conditions	R	Yield	Reference
SO_2Cl_2, CCl_4; NEt_3 then H_2O, 5 days	R = OEt	64% (b)	(Dehmlow and Westerheide, 1993) (a)
NCS, CCl_4, then H_2O, 20 h, N_2 bubbling	R = OMe, OEt	67% (c) (e)	(Meffre et al., 1995, 1999) (a)
NCS, CCl_4, then $NaHCO_3$, H_2O	R = OMe	35% (d)	(Meffre et al., 1995) (a)

(a) Synthesis of the aldehyde **1** is described in the experimental section. (b) Enantiomeric excess of **1c** is unknown. (c) Enantiomeric excess of **1b** is greater than 90% (^1H, ^{19}F NMR spectroscopy of diastereomeric fluorinated imidazolidine derivatives of aldehyde **1b**) (Cuvinot et al., 1989). (d) Dimethyl dithioacetal is also isolated in 26% yield. (e) Racemic **1b** has recently been obtained from aspartic acid according to a strategy described in Fig. 5 (X = Cl) (Bratusek et al., 1996).

these conditions, aldehydes **1b,c** are formed in good yield and optical purity (Meffre et al., 1995, 1999) (Table 4).

2 Miscellaneous syntheses

Some other less obvious routes have led to optically active aspartaldehyde derivatives for special purposes. Regioselective formylation of the L-aspartic acid derivative **9** led to compound **10** (mixture of enol and aldehyde) and hydrogenation followed by decarboxylation furnished the aldehyde in good yield (Garvey et al., 1990) (Fig. 8). The preparation of aldehyde **11** is included in the experimental part.

Dihydropyrrole **12** (derived from L-proline: Shono et al., 1982) was treated with ozone and reductive work up conditions (Me_2S) allowed the formation of the optically active aspartaldehyde derivative **13** (Fig. 9). This approach provides a general and original access to a wide variety of β-amino aldehydes (Bubert et al., 1994).

Free aspartaldehyde was recently prepared using a strategy previously developed for the synthesis of α-amino acid β,γ-enol ethers possessing bio-

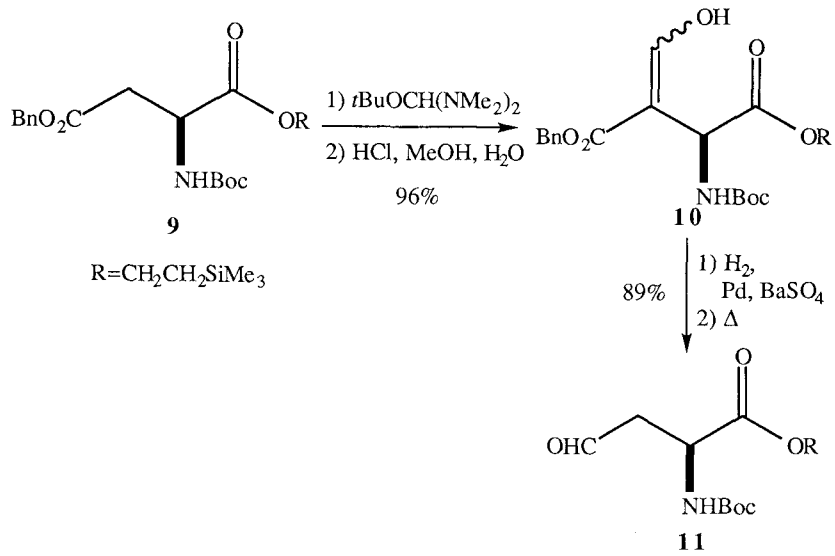


Fig. 8. Synthesis of aspartaldehyde from aspartic acid by formylation and decarboxylation

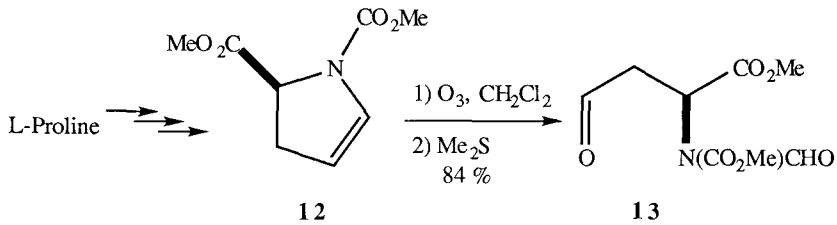


Fig. 9. Synthesis of aspartaldehyde from proline

logical activity (Keith et al., 1978) as pyridoxal phosphate dependent enzyme inhibitors (Walsh, 1982). Coulter and collaborators have used the classic acetamidomalonate route followed by an acylase in the resolution step (Barrett, 1985). Hydrolysis of (*S*)-2-amino-4-methoxybut-3-enoic acid **16** furnished free aspartaldehyde **1a** good enough for biological studies (Coulter et al., 1996) (Fig. 10). The protocols for the synthesis of intermediates and product are given (Keith et al., 1978; Coulter et al., 1996).

3 Some synthetic applications

Concluding remarks

There are few routes to free optically active aspartaldehyde, mainly used in biochemical assays: three from allylglycine (Black and Wright, 1955b; Tudor et al., 1993; Neuberger and Tait, 1962) (Fig. 2 and Table 1) and one from achiral diethyl acetamidomalonate and enzymatic resolution (Coulter et al., 1996) (Fig. 10).

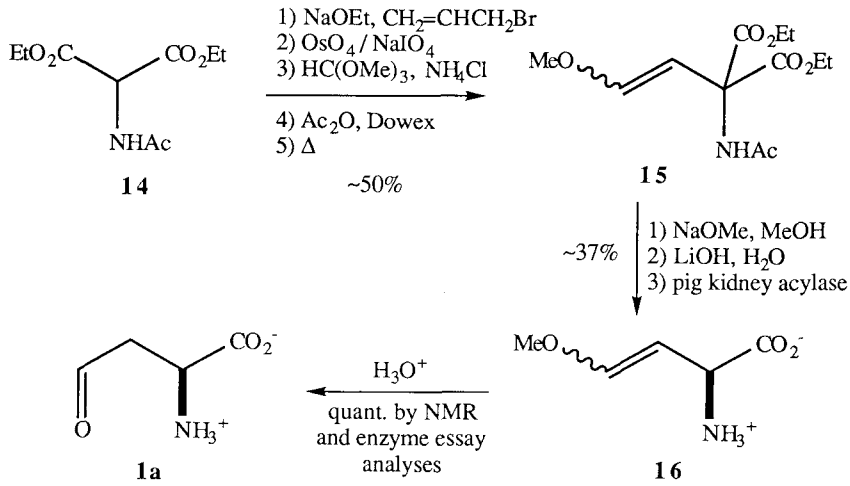


Fig. 10. Synthesis of aspartaldehyde from diethyl acetamidomalonate

The other previously mentioned optically active aspartaldehyde derivatives have been used in the synthesis of a wide range of biologically active molecules. Nicotianamine and analogues have been prepared from aspartaldehyde (see for example Shioiri et al., 1997; Matsuura et al., 1994; Fushiya et al., 1988b; Ripperger, 1988; Faust and Schreiber, 1989). These substances act as iron chelating agents and promote the uptake and transport of iron required for the chlorophyll biosynthesis in higher plants (Fig. 11). The key step is a reductive amination on the aldehyde.

Aspartaldehyde is also the key intermediate in the synthesis of many unusual amino acids. Among others are found homoquisqualic acid (Venkatraman et al., 1994; quisqualic acid is a glutamic acid analogue that affects the central nervous system); 4-oxo-L-norvaline by diazomethane homologation (Werner et al., 1997); 4-phosphono-2-aminobutanoic acid derivative for incorporation into peptides to obtain stable *O*-phosphoserine containing peptide mimics (Perish, 1994, 1992); L-phosphinothricin, a herbicide (Hoffmann and Zeiss, 1992); L-armentomycin and its fluoro analogue, antibiotic agents (Winkler and Burger, 1996); L-N6-hydroxylysine, component of siderophore mycobactin T (Genêt et al., 1993) (Fig. 12).

Peptidomimetics have also been prepared using aspartaldehyde: a 1,2,5-trisubstituted 1,4-diazepine-3-one with intramolecular peptide synthesis (Weitz et al., 1997; Pellegrini et al., 1997); a 2-amino-3-oxo-hexahydroindolizino[8,7-b]indole-5-carboxylate using a Pictet-Spengler reaction (de la Figuera et al., 1994); azepinone nuclei formed by intramolecular addition of an oxonium ion (derived from aspartaldehyde) to a proximal aromatic ring (Robl et al., 1995); a bicyclic thiazolidine lactam via condensation with D-cysteine (Subasinghe et al., 1993) (Fig. 13).

Recently, a formal total synthesis of the indolizidine alkaloid (−)-slaframine has been described using aspartaldehyde as an intermediate

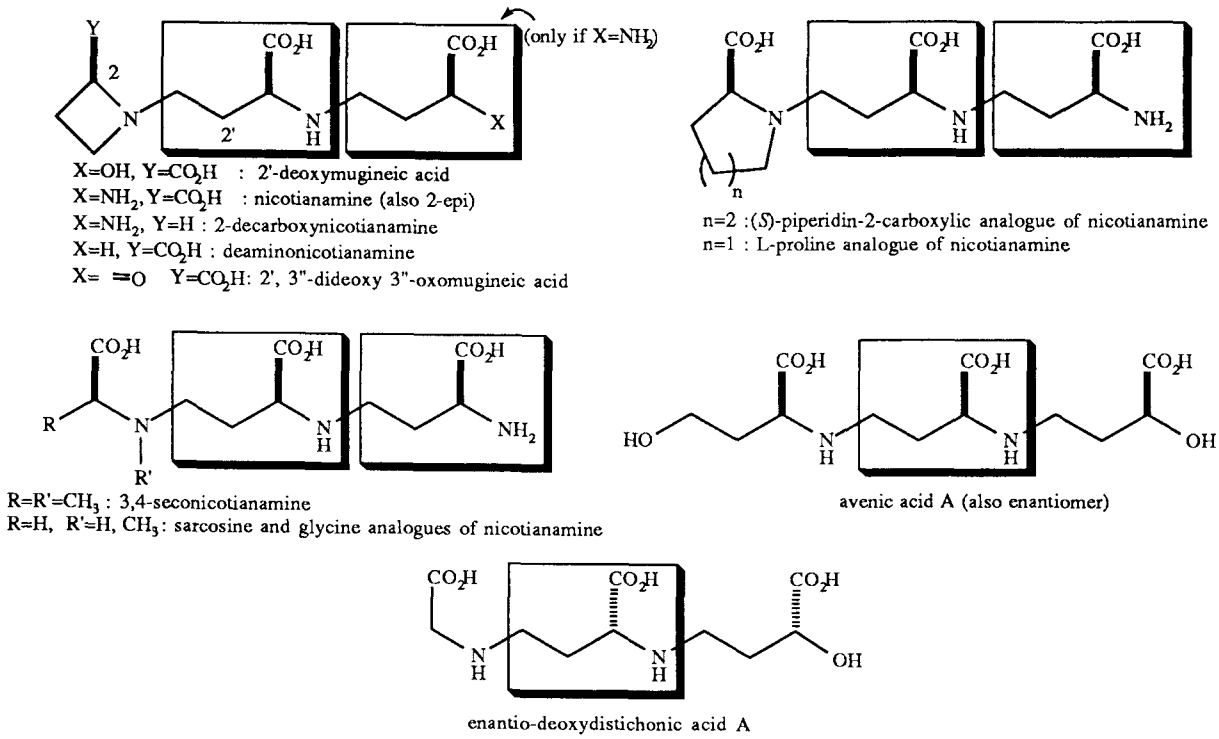


Fig. 11. Nicotianamine and analogues: the substructure derived from aspartaldehyde is framed

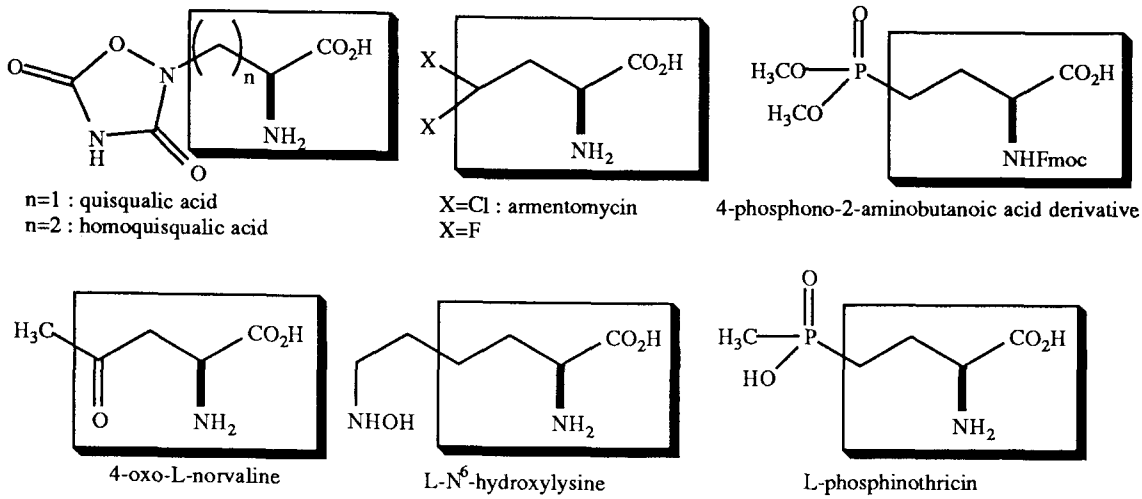


Fig. 12. Unusual amino acids: the substructure derived from aspartaldehyde is framed

with the key step being an intramolecular aldol reaction (Szeto et al., 1995). Optically active hydroxymethyl substituted cyclopentylamine precursors of carbocyclic nucleosides (isosteres of nucleosides with antiviral and antineoplastic activities) have also been prepared *via* aspartaldehyde

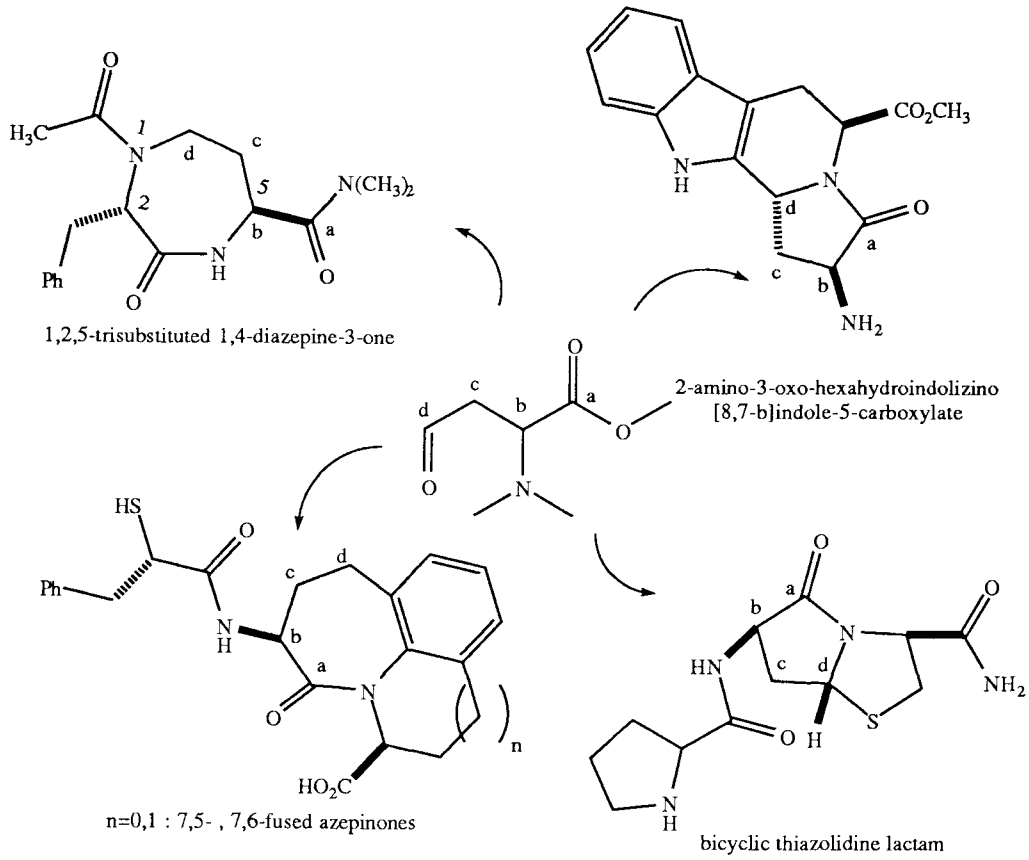


Fig. 13. Dipeptide mimetics: skeleton derived from aspartaldehyde is indicated

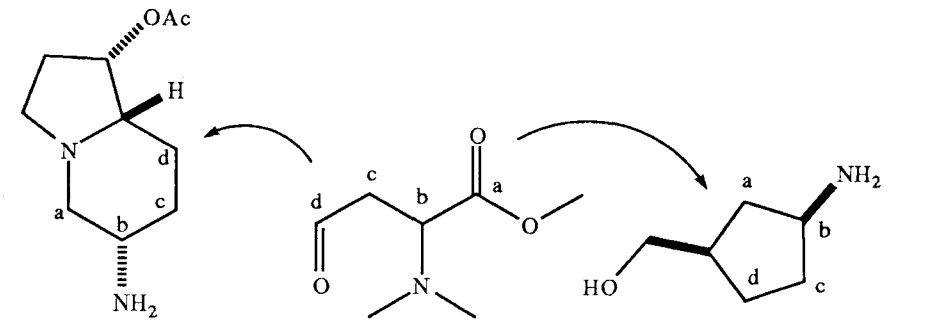


Fig. 14. Other chiral compounds obtained from aspartaldehyde

and regioselective Dieckmann cyclisation (Bergmeier et al., 1993) (Fig. 14).

The examples given above do not constitute an exhaustive list but clearly demonstrate that differently protected optically active aspartaldehyde deriva-

tives are interesting chiral synthons. Organic chemists need to produce enantiomerically pure aspartaldehyde derivatives using cheap starting material and efficient protocols not only for synthetic reasons but also for biochemical and biological applications and new strategies for increasing their ease of access and chemical diversity are welcome. A promising field of research would be asymmetric synthesis using this chiral synthon.

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