L- and D-homoserine and related C_4-chiral blocks

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ABSTRACT

L-Homoserine and its optical antipode, D-Homoserine serve as the convenient chiral starting materials for a series of cyclic and acyclic C_4-chiral synthons.

L-Homoserine (**1**) (Figure 1) is an important intermediate in the biosynthesis of the essential amino acids L-Methionine and L-Threonine (1) The small C_4 chiral unit, with three of the four carbons bearing amino, hydroxyl and carboxyl function, makes it a functionally rich intermediate capable of transformation into a variety of chiral compounds having applications in the fields of pharmaceutical, agricultural, cosmetic and fragrance industries. Figure 2 illustrates some of the potential chiral molecules that are derivable from L-Homoserine (**1**). The recent availability of L-Homoserine in industrial quantities has rendered access to these chiral structures possible in pilot and production level quantities (2).

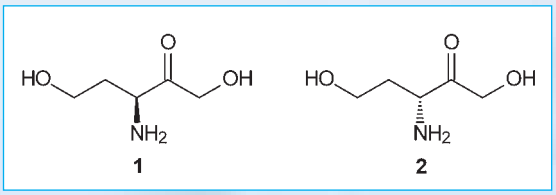

*Figure 1 – L-Homoserine (**1**) and D-Homoserine (**2**)*

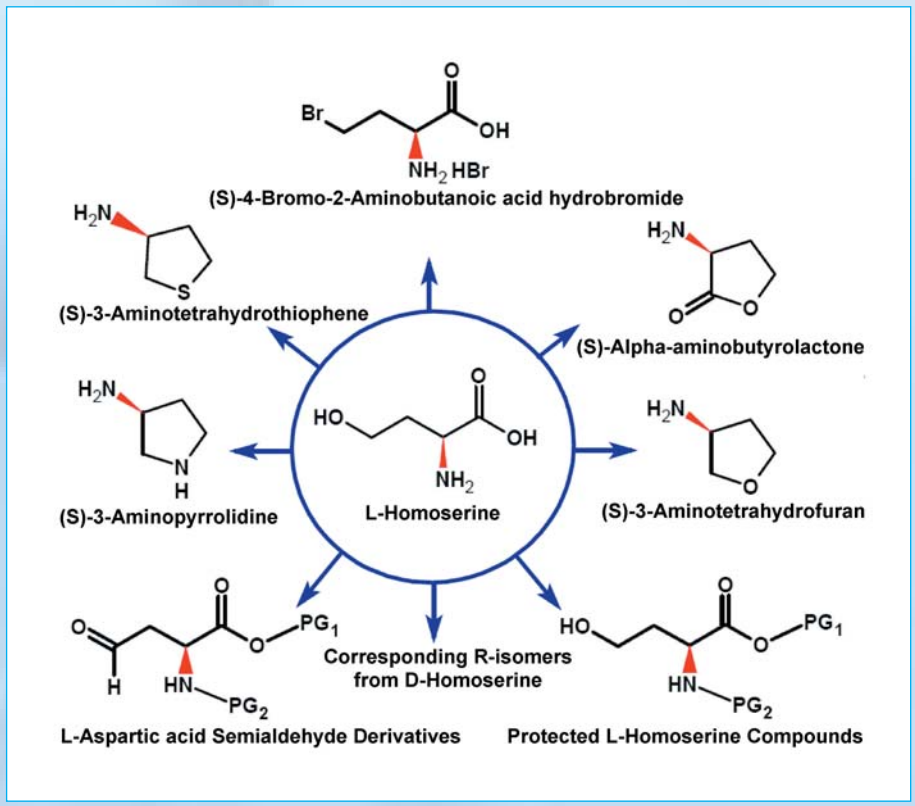

Figure 2 – L-Homoserine derived C_4-chiral compounds

BACTERIAL QUORUM-SENSING MOLECULES - (S)-ALPHA-AMINO-BUTYROLACTONE (3)

L-Homoserine cyclizes quite readily in acid medium giving rise to the cyclic 5-membered L-homoserine lactone salts ((S)-Alpha-aminobutyrolactone in Figure 2), serving as the core structure in antibacterial agents being developed to disrupt the intra-bacterial communication. Bacteria appear to communicate within their community by secretion of chemicals known as auto inducers (AI). When a certain concentration level of these auto inducers is reached signaling that a threshold level of bacterial population has been reached as a community, bacteria might initiate and indulge in any of their lethal activities as a coordinated community such as toxin production, formation of biofilms ensconcing them in a protective milieu, exchange of genetic material, invasion of host tissue, or even a physical phenomenon of bioluminescence etc.

Acylhomoserine lactones (AHLs) form the important chemical vocabulary of gram negative bacteria for conversation among them. By designing suitable AHLs, it is possible to confuse and disrupt this bacterial colloquium of interchange of information leading to the design of a new generation of antibacterials. Till now no such antibacterial is yet on the market but interesting developmental research is continuously reported. AHLs form an important structural feature of auto inducers (4) and L-Homoserine is an effective starting material for the synthesis of diverse AHLs.

Certain gram negative bacteria use these AHLs for not only conversation themselves but also use them to ward of competing gram positive bacteria (5).

(S)-3-AMINOTETRAHYDROFURAN

(S)-3-Aminotetrahydrofuran or its antipode form part of many investigational compounds being developed for various conditions as evidenced by several patents and publications (6). Earlier industrial access to chiral 3-aminotetrahydrofuran was possible through a lengthy route from L- or D-Malic acid. The present route from L- or D-Homoserine offers a shorter and more efficient strategy for such molecules (Figure 2).

(S)-3-AMINOPYRROLIDINE

Several drug candidates incorporate the chiral 3-aminopyrrolidine pharmacophore. As an example one can illustrate the Pfizer's compound PF-184298 (Figure 3) being developed for stress urinary incontinence (7). It was reported that there are no currently approved medication for SUI in the US and about 10 million people suffer from this condition. Also 3-aminopyrrolidine amides form the core pharmacophore for site-1 protease inhibitors, a class of compounds believed to combine the benefits of HMG-CoA reductase inhibitor with those of an acetyl-CoA inhibitor extending their applications beyond dislipidemia (8). Also this core structure is present in carbapenam and fluoroquinolone antibiotics (9).

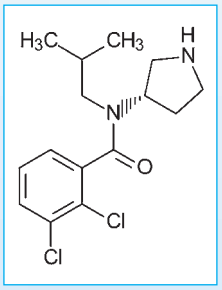

Figure 3 – PF-184298 incorporating (S)-3-aminopyrrolidine

(S)-4-BROMO-2-AMINOBUTANOIC ACID

Several papers have appeared on this versatile reagent that was used for the synthesis of non-natural amino acids (10). The isomer, (S)-4-Bromo-2-aminobutanoic acid, is readily available from L-Homoserine. Both the chiral isomers of 4-Bromo-2-aminobutanoic acid have found extensive use in synthesis. A general scheme is shown in Figure 4.

The nucleophile in Figure 4 ranged over a wide variety of amines, phenols and thiols. In addition, suitable organometallic coupling is also possible thus forming C-C bonds in stead of C-hetero atom bond formation (11).

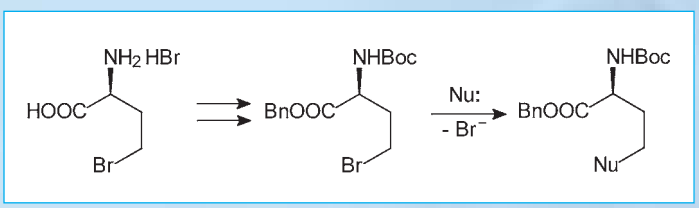

Figure 4 – Approach to non-natural amino acids

PROTECTED L-HOMOSERINE DERIVATIVES

Several compounds wherein the amino and/or carboxyl groups are protected are made easily from L-Homoserine for use in peptide synthesis. Especially interesting is the L-aspartic acid semialdehyde derivatives easily available from L-Homoserine (12).

CONCLUSION

The availability (2) of L-Homoserine and D-Homoserine has given a very ready access to several C_4 chiral synthons with diverse applications. A broad review of applications has been presented.

REFERENCES

1) Voet D, Voet JG, Pratt CW. ***Fundamentals of Biochemistry***, Third Edition; John Wiley & Sons, 2008, p.770
2) www.sabinsa.com; Several of the chiral intermediates are available now in pilot and production level quantities
3) Rice SA, McDougald D, Kumar N, Kjelleberg S. ***Curr. Opin. Investig. Drugs*** **2005**, *6*, 178
4) Geske GD, Wezeman RJ, Siegel AP, Blackwell HE. ***J. Am. Chem. Soc.*** **2005**, *127*, 12762; Geske GD, O'Neill JC, Miller DM, Mattmann ME, Blackwell HE. ***J. Am. Chem. Soc.*** **2007**, *129*, 13613
5) Kaufmann GF, Sartorio R, Lee SH, Rogers CJ, Meijler MM, Moss JA, Clapham B, Brogan AP, Dickerson TJ, Janda K. ***Proc. Natl. Acad. Sci. USA*** **2005**, *102*, 309
6) Marcello A, ***et al. J. Med. Chem.*** **2005**, *48*, 4312; see also WO 2000025780 A1
7) ***Chemical & Engineering News*** **2007**, *85* (19), 56
8) Hay BA, ***et al. Bioorg. Med. Chem. Lett.*** **2007**, *17*, 4411
9) See US Patent 6531594 B2
10) For a topical reference see, Ciapetti P, Falorini M, Mann A, Taddei M. ***Molecules Online*** **1998**, *2*, 86; see also Jiracek J, ***et al. J. Med. Chem.*** **2006**, *49*, 3982
11) Dunn MJ, Jackson RFW, Pietruszka J, Turner D. ***J. Org. Chem.*** **1995**, *60*, 2210
12) Meffre P. ***Amino Acids*** **1999**, *16*, 251