Tetrahedron 69 (2013) 969–1011

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 995

Advances in serinals for asymmetric synthesis

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ARTICLE INFO

Article history:
Received 5 November 2012
Available online 23 November 2012

Keywords:
Serinals
Chiral pool synthesis
Unnatural amino acids
Ceramides
Natural products
Building blocks

Contents

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0040-4020/$ – see front matter
http://dx.doi.org/10.1016/j.tet.2012.11.054

1. Introduction

The presence of asymmetry in every part of Nature has an immense impact in chemistry mainly in synthetic organic chemistry and/or chemical biology. In particular, asymmetry is an essential dimension in the pharmaceuticals area[1] where both of the enantiomers interact differently with chiral environments; one of the enantiomers is of interest and the other could either be inactive or possess undesired properties. In fact, the topic of asymmetry is very important to extend the chiral versions of existing drugs and/or new bioactive entities to be introduced, having an enormous demand worldwide in the present day. In search of important chiral compounds, organic chemists predominantly concentrated either on chiral synthons or chiral auxiliaries.[2] Gratifyingly, among them serinals have been accepted as a valuable chiral pool in synthetic organic chemistry in recent years.

The synthetically versatile serinals have found a large number of applications in the synthesis of important natural products, pharmaceuticals, modified amino acids and proteins. The last few decades have witnessed a steeply growing interest in the exploitation of these chiral aldehydes for the synthesis of a large number of natural products and diverse bioactive molecules, as well as potent chiral building blocks and so on. Hence, their applications occupy an important position in the currently reported literature. In this connection, a great deal of research efforts have been directed to developing several types of cyclic and acyclic serinals including the popular so-called Garner's aldehyde[3] (**1**), and Reetz's (**2**),[4] Rapoport's (**3**)[5] and Lajoie's serinal (**4**)[6] (Fig. 1). However, in spite of the vast interest in and wide applications of these serinals in the field of chemistry, only a limited literature has been systematically documented.[7] Nonetheless, the exponential growth of the reported literature on this topic and the inadequate nature of meaningful and coherent documentation motivated us to write a review article on different architecturally intriguing serine aldehydes for the first time. It covers the scientific literature published since September, 2000. Thus, this review would be envisaged as being a beneficial document in the domain of chemical sciences to produce chiral molecules.

The application of the aforementioned orthogonally protected small chiral auxiliaries will be emphasized for the synthesis of unnatural amino acids, amino acids with constrained rings particularly glycines, the important molecule glutamic acid and its analogues, spiro-proline and 3-hydroxy-4-methylproline as the crucial moiety of macrocyclic peptidic anticancer, antifungal, antibiotic and antiviral natural products like echinocandins, sporiofungin A and so on. This discussion also includes the synthesis of 2-carboxy-3,4-methanopyrrolidine as a potent inhibitor for proline metabolism, including other unnatural serine, arginine and tyrosine analogues. Since the 1950s, fluorine-containing drugs such as 5-fluorouracil (anticancer), 9′-fluorohydrocortisone (inflammatory), atorvastatin and fluticasone propionate (asthma) have occupied an important position in pharmacy. The profound successes of fluorine-containing drugs continue to enrich research in medicinal chemistry for novel drug discovery. Aimed at the pooling of chiral fluorinating compounds, serinals play an important role; fluoroamino acids like homopentafluorophenylalanine, fluoro-iminoethyl-L-lysine (fluoro-L-NIL), as nitric oxide synthase (*i*NOS) inhibitors, 4,4-difluoroglutamine and so on are considered as potential drug candidates.

Interestingly, the stereochemistry and structure of serine aldehyde are highly appropriate for the synthesis of bioactive sphingosine, ceramides, sphingomyelin, cerebrosides, sphingolipid metabolites such as sphingosine-1-phosphate, boron-dipyrromethene (BODIPY)-labelled sphingosine, aminophosphonates, D-*ribo*-phytosphingosine derivatives, polyyne-containing sphingoids and fluorinated sphingosine analogues.

It is also well-known that synthetic and natural polyhydroxylated *N*-heterocyclic compounds (pyrrolidines, piperidines, piperazines, indolizines and their homologues), commonly referred to as azasugars and iminosugars, are becoming important leads for drug development in a variety of therapeutic areas, which include treatment of cancer, glycosphingolipid storage disorders, type-II diabetes and viral diseases such as HIV and hepatitis B and C. Amazingly, serinals play a key involvement in the synthesis of *trans*-(3*S*)-amino-4-alkyl- and 4-aryl-piperidines, 2,6-disubstituted piperidine alkaloids, (−)-andrachcinidine, (+)-adenophorine, (+)-5-deoxyadenophorine, fagomine, deoxynojirimycin and their congeners like *galacto*, deoxy-*galacto*, *manno*, *allo*, *altro*, *gulo* and *ido* deoxynojirimycins.

Natural product synthesis, both total and partial (semisynthesis), has placed a significant role within the research community due to the scarcity in Nature, the biologically intriguing and structurally interesting properties and the requirement of larger quantities of these compounds for further extensive biological investigations and/or medicinal applications. Gratifyingly, the aforesaid small, but important, chiral pools have allowed the synthesis of bioactive natural products such as (−)-kaitocephalin, sintokamide C, hydroxyenduracididine, mannopeptimycin antibiotics, anticancer pachastrissamine, asperazine, balanol, antibacterial carbacepham, antifungal and anticancer ulapualide A, scyphostatin, a potent inhibitor of neutral sphingomyelinase, an antitumour antibiotic AT2433-A1, glycosidase inhibitors hyacinthacines A2 and A3 and 5-*epi*-hyacinthacines A3 and so forth.

In this review, we will also describe the important contribution of the above aldehydes to produce chiral building blocks and molecular scaffolds in constructing combinatorial libraries with the development of new and effective methodologies that have led to the synthesis of natural products and pharmaceuticals and a practical understanding of their organic synthesis.

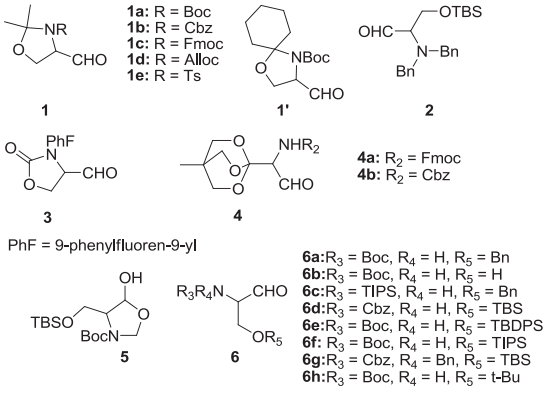

Fig. 1. General structures of various serinals: Garner's aldehyde (**1**), Reetz's (**2**), Rapoport's (**3**) and Lajoie's (**4**) and other serinals (**5** and **6**).