Chem. Rev. **2005,** *105,* 3167–3196

α,β-Diamino Acids: Biological Significance and Synthetic Approaches

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Received March 14, 2005

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1. Introduction

The discovery of nonproteinogenic amino acids among natural products, either in native state or as fragments of complex molecules, has increased the level of interest in this family of molecules from different scientific standpoints. Compounds with valuable biological properties can be found among these atypical amino acids. In addition, they have served as building blocks for the synthesis of new molecules or as surrogates of native amino acids in known peptidic entities to modulate their biological behavior.

In this context, α,β-diamino acids and their derivatives esters and amides, have attracted a great deal of attention among organic chemists and biochemists through the years. This interest has been due to the ubiquitous nature of α,β-diamino acids as key structural fragments of biologically active compounds. This review will deal with the biological significance, the therapeutic uses, and other interesting applications of α,β-diamino acids and their derivatives found in the existing literature.

Additionally, aside from the above considerations, the structural complexity of these molecules, having two vicinal chiral centers has also represented a challenge for synthetic organic chemists, especially the synthesis of enantiopure materials. Therefore, the aim of this article will also be to provide a deep and general view of the existing methodology for the synthesis of aliphatic α,β- or 2,3-diamino acids and their simple derivatives, esters or amides. Among the compounds considered in this review, either of the amino groups can be acylated or contained within a heterocyclic structure. Cyclic analogues such as imidazolidines and piperazines will be included in the article; however, aziridines and 3-amino-β-lactams will be out of the scope of this review and will be only considered as intermediates in the synthesis of acyclic derivatives since extensive revisions of their chemistry already exist in the literature.[1]

2. Relevance of Molecules Containing α,β-Diamino Acids

2.1. Natural Products

Free α,β-diamino acids have been detected as part of living organisms (Chart 1). Indeed, the presence of the simplest member of the family, α,β-diaminopropionic acid (Dpr or A_2pr, frequently referred to in the literature as Dap), has been confirmed in protein-free extracts from Bombyx insects (D-Dpr)[2] and it is a common constituent of the amino acid pool of seeds from various species of *Mimosa* and *Acacia*.[3] Among other examples, the two diastereomers of α,β-diaminobutanoic acid (α,β-Dab) have been identified in the root nodules of *Lotus tenuis* inoculated with *Rhizobium* strain NZP2213.[4] Recently, both Dpr and α,β-Dab have been detected in a sample of the Murchison meteorite, and this supports the formation of polypeptide structures under primitive Earth conditions and suggests polycondensation reactions of diamino acids into early peptide−nucleic acid material as one conceivable pathway for prebiotic evolution of DNA and RNA genomes.[5]

Within the large number of nonproteinogenic amino acids isolated from plants as secondary metabolites, the group of heterocyclic β-substituted alanines is of special interest to biochemistry, ecology, and neurochemistry (Chart 1).[3,6] L-Quisqualic acid, an amino acid first isolated from the seeds of *Quisqualis indica L.* that has been used in Chinese medicine as a vermicide, is able to function as an agonist at multiple EAA (excitatory amino acid) receptor sub-

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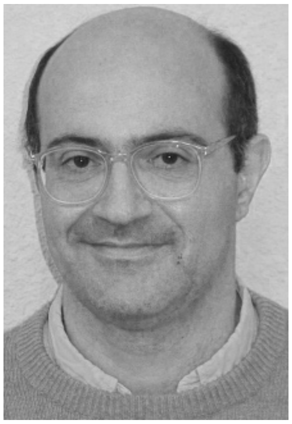
10.1021/cr0406561 CCC: $53.50

Alma Viso was born in Madrid (Spain) in 1964. She obtained a B.S. degree in Chemistry in 1987 and a Ph.D. in 1992 from Universidad Complutense de Madrid (UCM). In 1992, she moved to Massachusetts Institute of Technology (MIT) as a Fulbright fellow to work with Stephen L. Buchwald for 18 months. She joined the faculty at UCM (Madrid) in 1993 as an Assistant Professor and was promoted to Associate Professor in May 2002. In December 2002, she joined Instituto de Química Orgánica General, CSIC, as a Staff Researcher (Científico Titular). Her current research interests are focused in two main areas, the development of new methodologies in asymmetric synthesis using sulfoxides and sulfinamides and the application of these novel methods to efficient syntheses of therapeutically valuable products.



Roberto Fernández de la Pradilla was born in Logroño (Spain) in 1958. He received his B.S. degree in Chemistry from Universidad Complutense de Madrid (UCM) in 1980 and a Ph.D. degree from The University of Michigan in 1985 under the supervision of Joseph P. Marino. After postdoctoral work at UCM (Madrid), he became Assistant Professor there in 1987. In 1988, he joined Instituto de Química Orgánica General, CSIC, as a Staff Researcher (Científico Titular) and was promoted to Senior Staff Researcher (Investigador Científico) in 2000. In 1992–93, Dr. Fernández de la Pradilla was a Visiting Scientist with Rick L. Danheiser at Massachusetts Institute of Technology (MIT) for 18 months. His current scientific interests involve the development of novel synthetic strategies that rely on chiral sulfoxides with particular emphasis on strategies that allow for multiple asymmetric transformations, as well as pursuing straightforward applications of these methods to the synthesis of bioactive products.

Ana B. García was born in Valladolid (Spain) in 1975. She obtained her B.S. degree in Chemistry from Universidad Autónoma de Madrid (UAM) in 1998. She then joined the group of Dr. A. Viso and Dr. R. Fernández de la Pradilla at Instituto de Química Orgánica General, CSIC, to carry out graduate work on the synthesis of vicinal dinitrogenated compounds from enantiopure sulfinimines. After receiving her Ph.D. in 2003, she spent one year at Universidad de Alcalá de Henares (UAH) working on cationic heteroaromatic systems with DNA intercalating properties under the guidance of Prof. Juan J. Vaquero. She now holds a postdoctoral position with Prof. Herbert Waldmann at Max Planck Institute for Molecular Physiology in Germany, working on the synthesis of natural product derived libraries. Her research interests include asymmetric synthesis and synthesis of natural products on solid support.

Aida Flores was born in Murcia (Spain) in 1979. She obtained her B.S. degree in Chemistry from Universidad Autónoma de Madrid (UAM) in 2001. She then joined the group of Dr. A. Viso and Dr. R. Fernández de la Pradilla at Instituto de Química Orgánica General, CSIC, to carry out graduate work, and she is expected to obtain her Ph.D. degree in 2006. In 2004, she spent three months in the laboratories of Gary Molander at the University of Pennsylvania.

types in the central nervous system. It has high affinity for the kainate, AMPA, and the metabotropic receptors. It also inhibits the Ca^{2+}/Cl^{-}-dependent glutamic acid uptake system in brain synaptic plasma membrane preparations and an *N*-acetyl α-linked acidic dipeptidase that hydrolyzes the brain dipeptide Ac−Asp−Glu−OH.[7] Mimosine, another nonproteinogenic plant α,β-diamino acid derived from seeds of *Leucaena leucicephala* or *Mimosa pudica*, has attracted a great deal of attention due to its capacity to act as a specific blocker of the cell cycle. Mimosine may block cell proliferation by multiple mechanisms, and some mimosine derivatives have been considered as iron (III) chelators with potential activity against β-thalassaemia.[8] Willardine and isowillardine belong also to this family of heterocyclic β-substituted alanines, and in particular, willardine has been characterized as an agonist of AMPA and kainate receptors.[9] Among others, lupinic acid, isolated from *Lupinus angustifolius*,[10] β-(5-oxoisoxazol-2(5*H*)-yl) alanine (BIA, β-isoxazolinone alanine), found in *Lathyrus sativus*, and pyrazol-1-yl alanine, characterized as a hypoglycemic agent and isolated from pressed juice of *Citrullus vulgaris*,[11] have been classified within this family and have been the object of different synthetic and biosynthetic studies.[12]

Two of the simplest α,β-diamino acid derivatives occurring in plants are neurotoxic to animals: L-β-

Chart 1. Free α,β-Diamino Acids in Nature

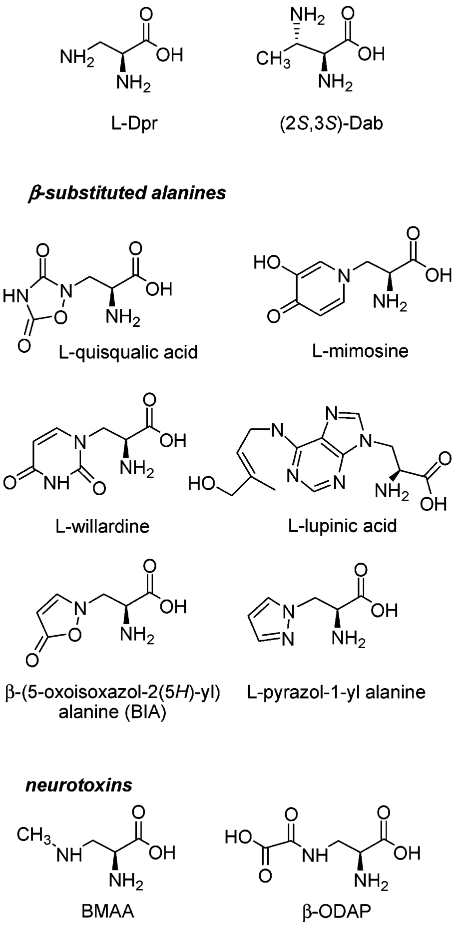
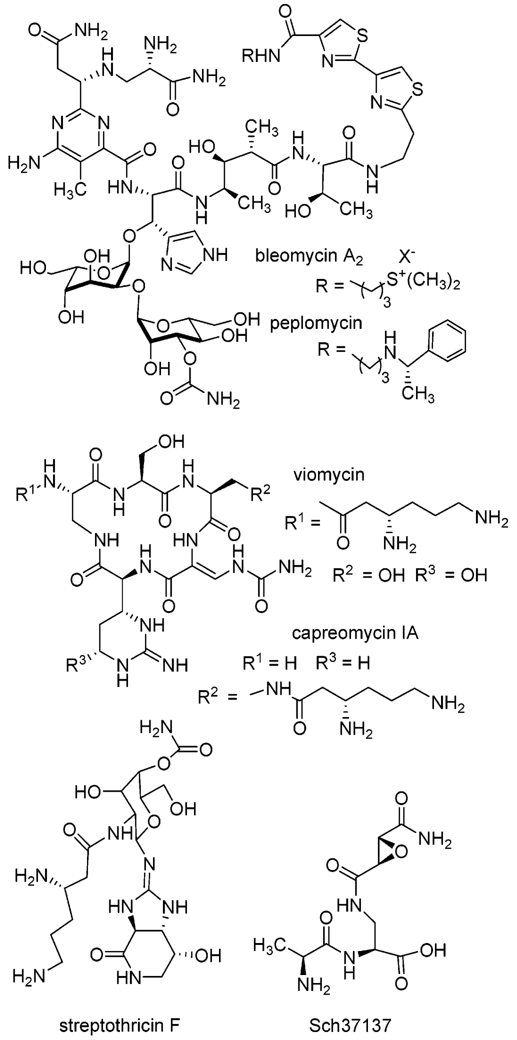


Chart 2. Natural Peptidic Antibiotics I



methylaminoalanine (BMAA) and 3-(N-oxalyl)-L-2,3-diaminopropionic acid (β-ODAP). BMAA is an agonist of the ionotropic glutamate receptors that occurs in the cycad *Cycas micronesia* Hill in Guam.[13] BMAA may have originally played a role as an antiherbivore compound in the plant but is now of great interest because of its link to a neurodegenerative disease with clinical and histological aspects similar to amyotrophic lateral sclerosis, Alzheimer's disease, and parkinsonism dementia (ALS-PDC). Biomagnification of BMAA in the Guam ecosystem has been proposed. Initially produced by cyano bacteria, BMAA is concentrated in cycad seeds that feed flying foxes, a prized food item of the indigenous people. Those who died of ALS-PDC have high amounts of BMAA in their brain tissues, which would explain the incidence of ALS-PDC among this group, 50−100 times higher than elsewhere.[14] On the other hand, although certain *Lathyrus* species have been found to be suitable as multipurpose legume crops, their use is limited by the presence, mainly in seeds, of β-ODAP an ionotropic glutamate receptor agonist,[15] which causes latyrism, a paralysis of the lower limbs, which occurs in humans and to a lesser extent in animals. The presence of β-ODAP is both a public health problem and a barrier to the utility of a very beneficial staple crop, grass-pea. For these reasons, many efforts have been devoted to find food processing methods to eliminate the neurotoxin by solid fermentation[16] or mild acidic treatment that causes rearrangement of β-ODAP to the nontoxic isomer α-ODAP.[17] A selected *L. cicera* cultivar containing low levels of β-ODAP has also been reported.[18] Furthermore, in vivo studies have demonstrated that BIA is the biosynthetic precursor of β-ODAP in *L. Sativus*.[12a,19]

Bacterial cultures are frequently the source of simple α,β-diamino acids such as (+)-2,3-diaminosuccinic acid,[20] antineoplastic agents such as 539A, containing the α,β-diamino acid streptolutin,[20b] and peptidic antibiotics that include α,β-diamino acid residues in their structures (Chart 2). The bleomycins (blenoxane), isolated from *Streptomyces verticillus*[21] are a group of antitumor antibiotics clinically used for the treatment of Hodgkin's lymphoma, tumors of testis, and carcinomas of skin, head, and neck. The potent activity of bleomycins is attributed to the oxygen activation and DNA cleavage by the formation of a unique iron-chelate of the β-aminoalanine-pyrimidine-β-hydroxyhistidine moiety of this unusual glycopeptide.[22] A few years later, peplomycin, a derivative of bleomycin, less toxic and with a wide antitumor spectrum, was introduced.[23] Tuberactomycins isolated from several strains of *Streptomyces* are essential components in the drug arsenal against *Mycobacterium tuberculosis* infections.[24] Units of Dpr and tuberactidine are contained in their structure.[25] The proposed mode of action of viomycin (tuberacto-

Chart 3. Natural Peptidic Antibiotics II

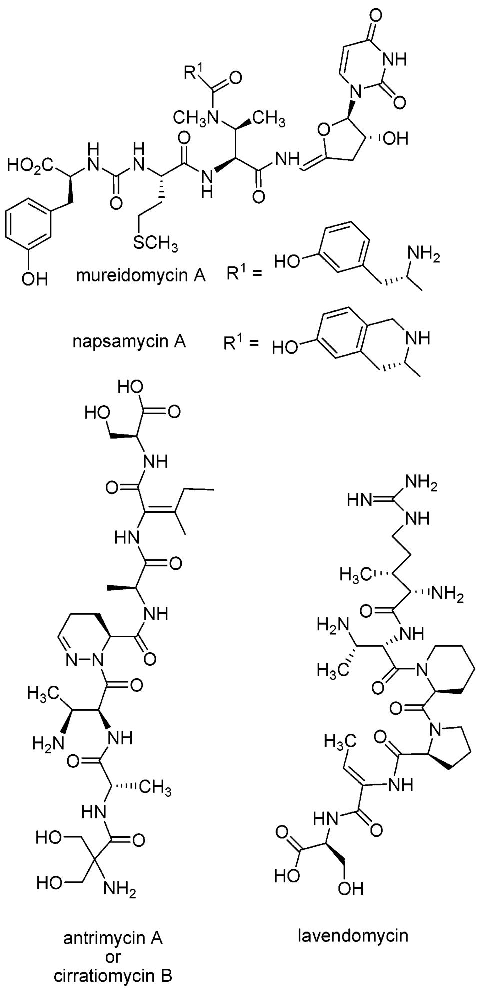
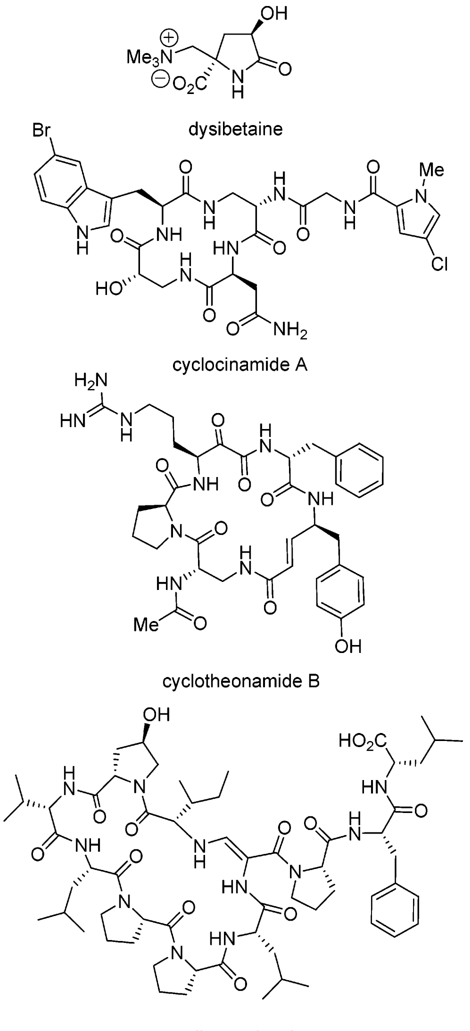


Chart 4. α,β-Diamino Acid Derivatives from Marine Organisms



mycin B) is inhibition of protein synthesis at the stage of amino acid transfer from charged tRNA to active ribosome complexes.[26] Viomycin recognizes specific RNA sites, and different studies have led to understanding of the molecular basis of RNA–viomycin binding and recognition.[27] Capreomycins (capastat), isolated from *streptomyces capreolus*, are a family of amino glycoside antibiotics also used to treat tuberculosis. They contain two residues of Dpr, one of which is important for biological activity, and capreomycidine[28] and are thought to have the same mode of action as the structurally related viomycin.[29] Streptothricin F is a broad-spectrum peptidic nucleoside antibiotic first isolated from *Streptomyces lavendulae* that contains a unit of the unusual diamino acid derivative streptolidine. This cyclic peptide is one example of the streptothricin class of antibiotics, which only differ in the number of β-lysine residues.[30] Among other interesting compounds found in the literature, antifungals Sch37137 and A19009, isolated from *Micromonospora sp.* and *Streptomyces sp.*, respectively, are derivatives of Dpr that selectively inhibit glucosamine-6-phosphate synthase from *Candida albicans*.[31]

Screening soil microorganisms for the production of antibiotics specifically active against *Pseudomonas* aeruginosa led to structurally related peptidylnucleoside antibiotics mureidomycins,[32] napsamycins,[33] and pacidamycins[34] that contain a fragment of α,β-Dab within their structures (Chart 3). These compounds are potent and specific blockers of bacterial peptidoglycan synthesis through inhibition of translocase, showing a low level of toxicity against mammalian cells. α,β-Dab is also contained in a variety of other peptidic antibiotics such as amphomycin,[35] aspartocin,[36] glumamycin,[37] and lavendomycin.[38] Furthermore, structurally equivalent antrimycins[39] and cirratiomycins[40] are a family of dehydroheptapeptides containing α,β-Dab isolated from different microorganisms. Among them, antrimycin A was characterized as an antitubercular agent. Additionally an α,β-Dab residue is present in FR900490, an immunomodulating peptide isolated from fungus *Discosia sp.*[41]

On the other hand, in the past decades, the ocean has become a great source of unique chemical structures, and biologically interesting molecules containing α,β-diamino acid residues within their structure have also been isolated from marine organisms (Chart 4). For example dysibetaine was recently isolated from the aqueous extract of the marine sponge *Dysidea herbacea* collected from Yap, Micronesia.[42] Furthermore, routine screening focused on detecting agents active against solid tumors led to the discovery of cyclocinamide A, an unusual halogenated hexapeptide from marine sponge *Psammocinia sps*. that contains a 5-bromoindole, as well as a 4-chloro-*N*-methylpyrrole, within the structure.[43] In addition, cyclotheonamides A and B, cyclic pentapeptides isolated from marine sponge *Theonella swinhoei* with high activity as inhibitors of serine proteases such as thrombin, have motivated a number of studies focused in their characterization and biological properties, as well as the development of different synthetic approaches.[44] Finally, recently isolated callynormine A contains an α,β-unsaturated α,β-diamino acid residue as part of this unusual marine peptide structure. It has been proposed that the double bond imposes conformational restrictions to peptides as an alternative to disulfide bridges.[45]

2.2. Synthetic Peptides and Related Compounds

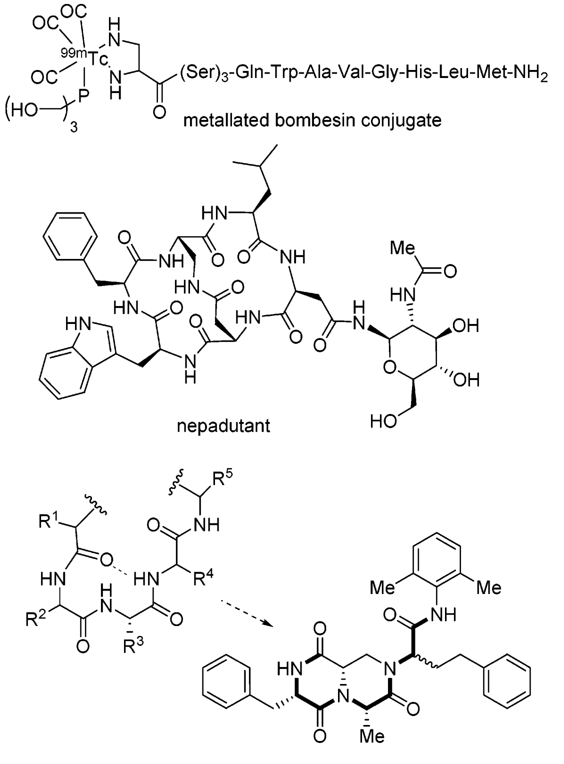
In some instances, α,β-diamino acids have played a central role in replacing natural amino acids in peptidic structures in the search for modifications of the biological activities and stabilities to peptidases. Within the context of peptide design, Dpr and its derivatives, mono-, di-, and trimethylated at the β-nitrogen atom, have been used as surrogates of Asn residues in a protein matrix. These residues, especially the *N*-alkylated derivatives, would be able to introduce simultaneously specific polar interactions and a nonpolar surface area compatible with hydrophobic environments. In fact, incorporation of the monomethyl amino acid at position 16 of a 33-residue peptide (GCN4-p1) promotes heterodimerization with other helixes containing an Asp at the same position by means of formation of a buried salt bridge at the helix/helix interface of the dimer.[46] Dpr has also been used to build peptide models to study the interaction of a polyleucine-based α-helical transmembrane peptide with phosphatidylcholine bilayers. The presence of terminal Dpr instead of Lys attenuates the hydrophobic mismatched effects of the peptide on the thermotropic phase behavior of the host phosphatidylcholine bilayer, in contrast to the predictions of the snorkel model.[47] On the other hand, specific substitution of Lys by Dpr and other diamino acids in a 17-residue alanine−lysine peptide has been examined to assess the influence in α-helix propensity using circular dicroism measurements. The results confirmed that helix propensity decreases with the length of the side-chain (Dpr).[48] Additionally, by means of ^{1}H NMR spectroscopy, the helicity in water has been determined for a series of template-nucleated alanine−lysine peptides, in which Lys residues have been replaced by Dpr among other diamino acids to assess the role of Lys in stabilizing the helix.[49] Within a similar context, an α-methyl-α-amino-β-methylamino acid residue was incorporated into a linear heptapeptide with the β-nitrogen as part of the backbone, and conformational studies by NMR spectroscopy and CD measurements did not show indication of helical structures.[50]

On the other hand, designing artificial ion-selective channel proteins is an active area of research that could shed light on the understanding of the function of natural ion channels and the transport of ions through the cellular membranes. In this context and focused on the search of anion selective channels, Dpr, among other residues, has been introduced at position 18 of alamethicine channels as a surrogates of Gln. While Lys18 produced high anion selectivity, the presence of Dpr results in a reversal of ion selectivity, probably due to chloride ions compensating for the local charge of the amino side chain in a wide region of the pore.[51] In another recent article, the use of L-Dpr as part of a cyclic peptide capable of forming artificial transmembrane ion channels by self-assembly of planar peptide rings has been reported. The pH dependence of ionic conductance indicated that the amino group of Dpr may play a role in the conductance of the peptide channels.[52]

Interestingly, in a different context, imidazolyl alanine has been used in a study focused on developing a peptide catalyst capable of mimicking enzyme activities. Indeed, incorporation of imidazolyl alanine into a peptidic β-turn backbone promotes kinetic resolution of racemic *trans*-*N*-(2-hydroxycyclohexyl)-acetamide through *O*-acylation reactions. In the presence of Ac_2O, generation of an enantio-discriminating acylimidazolium intermediate as acylating species has been proposed to explain the different reactivity of each enantiomer.[53]

Aside from the above studies, radiolabeled peptides are becoming a potential tool for quantitative in vivo receptor imaging of receptor-expressing tissues. Among the existing methodologies, condensation of a radiolabeled aldehyde (or capable of being labeled) and a hydroxylamino derivative provides a chemoselective method to label peptidic compounds. In this context, Dpr has been used as part of a starting initiator unit containing the aminooxy linker for oxime ligation in the solid-phase peptide synthesis of radiolabeled compounds.[54] In a parallel context, bombesin (BBN), a peptide that binds to gastrin-releasing peptide receptors (GRPrs), overexpressed on a variety of human cancer cells, has been modified by introduction of a Dpr residue at the *N*-terminus. The BBN conjugate forms complexes with^{99m} Tc(I) and Re(I) through the Dpr residue, that specifically target GRPrs in vitro and in vivo in human tumor cells (Chart 5). These results open new promising perspectives in the use of radiopharmaceuticals in nuclear medicine.[55] In addition to the above examples, a number of peptidic molecules containing Dpr residues within their sequence have been studied due to their biological activity and their potential therapeutic value. There are recent examples of this class of compounds such as GR231118, a neuropeptide Y_1 receptor antagonist,[56] nepadutant, a tachykinin NK_2 receptor antagonist,[57] and a series of cyclic peptide analogues of Agouti-related protein (AGRP) with activity as agonists of the melanocortin-4 receptor.[58] Especially relevant is the role of Dpr in the design of a cyclic CCK8 analogue selective for the cholecystokinin CCK_A receptor, based on structural information provided by ^{1}H NMR spectroscopy of the complex CCK8-CCK_A. The presence of an intramolecular amide bond between the amino side-chain of Dpr and the carboxyl terminus secures a conformation for the new peptide that mimics the bioactive conformation of CCK8 in the complex.[59]

Chart 5. Synthetic Peptides



metallated bombesin conjugate

nepadutant

β-turn peptide mimetic

Finally, some of the simplest α,β-diamino acids also offer unique opportunities in combinatorial chemistry.[60] As a consequence now, a number of orthogonally protected building blocks based on α,β-diaminopropionic acid are commercially available. In fact, amino acids containing an extra amino group result in usefulness as linkers in solid-phase synthesis, allowing for the creation of diversity in chemical libraries.[61] Consequently, focused on β-turn mimetic design, bicyclic diketopiperazine libraries have been synthesized using orthogonally protected piperazine-2-carboxylic acid or α,β-diaminopropionic acid as linkers of hydroxymethyl polystyrene resin.[62] Similarly, α,β-diaminopropionic acid derivatives have been linked to *p*-methylbenzhydrylamine resin for the solid-phase synthesis of cyclic guanidines and hydantoins.[63]

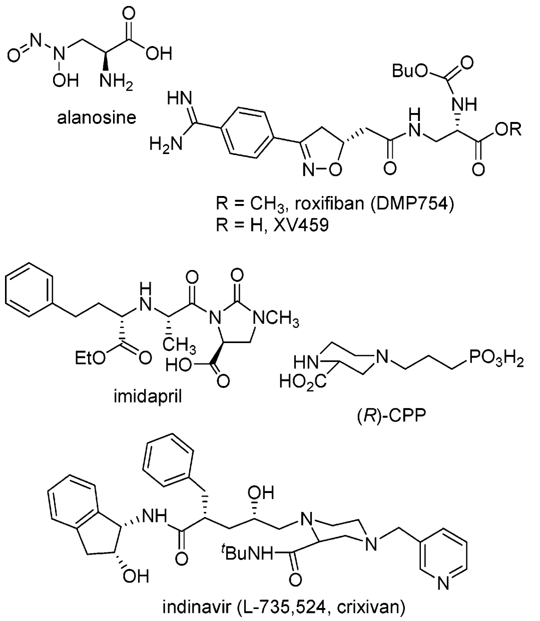
2.3. Therapeutically Useful Compounds

In the context of drug discovery and focused on the assessment of structure–activity relationships (SAR), α,β-diamino acids have been used as building blocks for the synthesis of analogues of nonpeptidic molecules or small peptidomimetics. Certainly, the introduction of α,β-diamino acid residues has not always resulted in compounds with improved biological profiles; however, these observations probably indicate that modifications in crucial points of the molecules have been made, especially when complete loss of bioactivity is observed.[64] Nevertheless, several other studies have reported molecules with attractive biological profiles, comparable to the lead compounds, such as analogues of antitumor PT523[65] and analogues of angiotensin-converting enzyme (ACE) inhibitor, enalapril.[66] Interestingly, the synthesis of a nonpeptidic library of potential VLA-4 antagonists has resulted in the identification of a potent lead compound containing an α,β-diamino acid residue, capable of inhibiting the binding of VLA-4 and fibronectine. This compound provides a good starting point for further optimization.[67] In addition, the parallel synthesis of a library of side-chain-modified diamino acid hydroxamates has led to the identification of a family of D-diaminopropionic acid hydroxamates as potent inhibitors of procollagen C-terminal proteinase with potential application against fibrotic diseases.[68]

Similarly to vicinal diamines, α,β-diamino acid derivatives have a great capacity to form chelates with different metals and have been used as ligands, either directly implicated in complexation to the metal or as tethers between different moieties of the ligands.[69] Consequently, different research groups have taken advantage of this behavior in the search of new anticancer drugs. Complexes of Pd(II) and diamino succinates have been evaluated for antitumor activity in MDA-MB468 and HL-60 cell lines and DNA binding capacities (pUC8 plasmid).[70] Similarly, *cis*-dichloro(D,L-diaminopropionate ethyl ester)palladium(II) and *cis*-dichloro(D,L-diaminopropionate ethyl ester)platinum(II) have been synthesized and their cytotoxic activities in several tumor cell lines have been evaluated. In addition, the interaction of these complexes with DNA, in vitro and in vivo, has been examined.[71] More recently, a group of α,β-diaminopropionamide platinum complexes, bearing groups capable of interacting with DNA at the amide ligands have been prepared. Unfortunately, the values of cytotoxicity in a number of tumor cell lines were higher than expected ($IC_{50} > 50\ \mu M$). Furthermore, α,β-diaminopropionamide platinum complexes conjugated to neomycin B and guanidinoneomycin B have been found to generate RNA selectivity upon the cis platinum moiety.[72]

Aside from the above studies, there are several α,β-diamino acid derivatives that have been recognized for their therapeutic value and extensive research has been devoted to their development as useful drugs (Chart 6). Among them, alanosine is an antineoplastic agent, produced by fermentation of *Streptomyces alanosinicus*, with a high antitumor activity in L1210 and P388 murine leukemias.[73] Structurally, alanosine is bioisosteric to L-aspartic acid and contains an *N*-nitroso-*N*-oxyalkylamine moiety and therefore is a potential redox-sensitive NO-releasing compound.[74] Indeed, the use of alanosine for treatment of T-cell acute lymphoblastic leukemia (T-ALL) has been proposed on the basis of its capacity to act as inhibitor of de novo synthesis of AMP and its toxicity for methylthioadenosine phosphorylase (MTAP)-deficient tumor cell lines.[75] Roxifiban, also referred to as DMP754, is the ester prodrug of XV459, an α,β-diamino acid-derived compound that behaves as a selective oral antagonist of the platelet glycoprotein IIb/IIIa receptor. Potential benefits in cardiovascular disorders such as intravascular thrombosis and unstable angina pectoris have been proposed for this compound.[76] Another interesting compound is imidapril, also known as tanatril, in which the α,β-

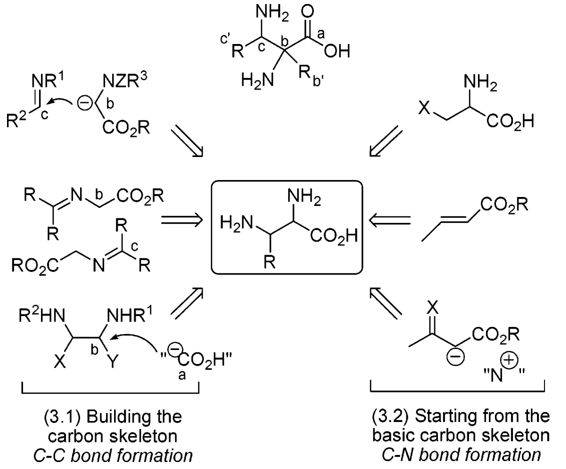
Chart 6. Therapeutically Useful α,β-Diamino Acids



diamino acid residue is part of an imidazolidinone ring. Imidapril stops the synthesis of angiotensin II by inhibition of ACE and has been used clinically in the treatment of hypertension, chronic congestive heart failure, acute myocardial infarction, and diabetic nephropathy.[77]

On the other hand, 2-carboxypiperazine analogues constitute a special group within the pharmaceutically interesting α,β-diamino acid derivatives in which the two nitrogen atoms are embedded in an aliphatic six-membered ring, and several studies have included carboxypiperazines as a basic scaffold of SAR studies.[78] For example, a new family of cyclic matrix metalloproteinase (MMP) inhibitors derived from (±)-piperazine-2-carboxylic acid has been described. One of them has shown a high affinity for MMPs 1, 3, 9, and 13 and cocrystallization with MMP-3 has provided X-ray data of one complex.[79] In another report, the 2-carboxypiperazine skeleton has been employed for the synthesis of a constrained analogue of enkephalin.[80] In addition, the *R* enantiomer of 4-(3-phosphopropyl)-2-piperazine carboxylic acid (CPP) has been identified as a potent and selective antagonist of the *N*-methyl-D-aspartate (NMDA) subtype glutamate receptors with potential therapeutic utility in the treatment of epilepsy and the amelioration of neuronal damage from cerebral ischemia.[81] Draflazine and mioflazine belong to a family of carboxamide piperazines that have been studied extensively for their capacity to enhance extracellular adenosine concentrations by specific binding to adenosine transporter in cardiac tissue and thereby protect heart tissue against ischemia-induced damage.[82] However, the 2-carboxypiperazine that has caused a major impact in drug discovery is undoubtedly indinavir (also referred to as L-735,524 and crixivan), an orally bioavailable HIV protease inhibitor and one of the most important therapeutic agents to date to treat HIV infection. Nevertheless, the fast emergence of drug-resistant mutants of the HIV virus increases the need for more potent and bioavailable protease inhibitors to achieve sustained viral suppression in vivo, and a number of studies dealing with modifications of the original indinavir structure are emerging.[83]

Chart 7. Representative Routes toward α,β-Diamino Acids



3. Synthetic Approaches to α,β-Diamino Acids

The structural complexity of these diamino acids, with two vicinal nitrogen-bearing chiral centers, has also represented a challenge for synthetic organic chemists, especially the synthesis of enantiopure materials. Within this context, in the past years, a number of synthetic routes of variable length, yield, and complexity have been reported. Chart 7 gathers some representative synthetic routes toward α,β-diamino acid derivatives. The methods found in the literature can be classified essentially in two main categories: (section 3.1) methods that require construction of the carbon backbone and (section 3.2) methods that start from the basic carbon skeleton and modify the nature of the functional groups.

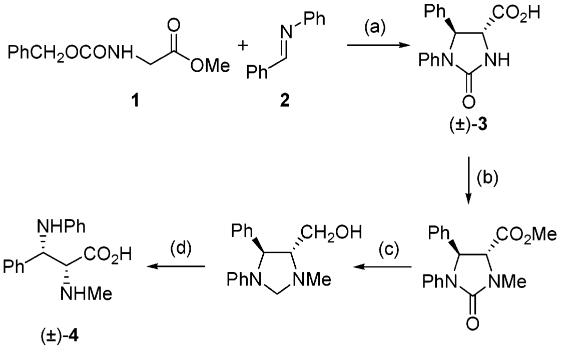
3.1. Construction of the Carbon Backbone

The development of new methodologies to form carbon−carbon bonds is essential for the progress of organic synthesis. In this context, the search of adequate methodologies for the approach to α,β-diamino acids represents a synthetic challenge. Within this category, different groups can be established with respect to the carbon−carbon bond that is formed in the key step, and therefore, the following section has been organized according to methods in which the b−c, a−b, b−b′, or c−c′ bonds are formed (Chart 7).

3.1.1. Methods in Which the b–c Bond Is Formed

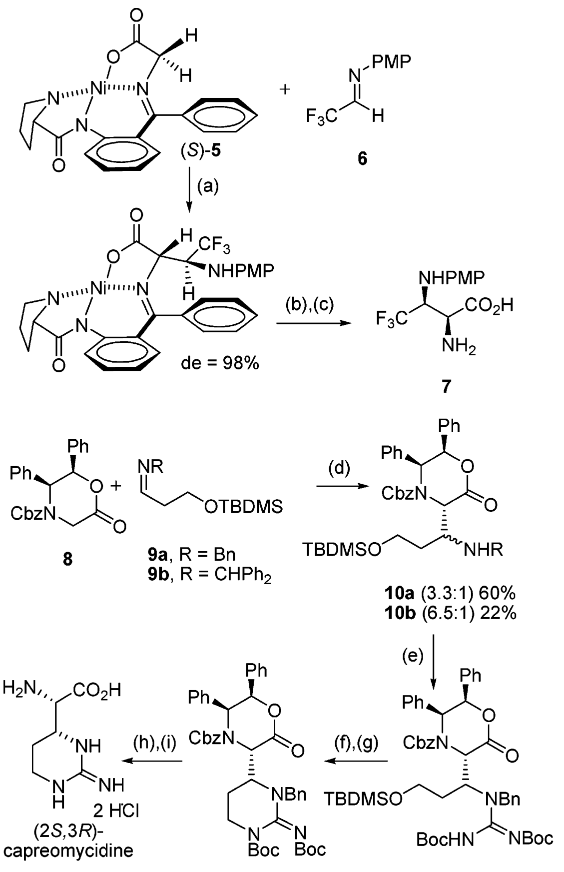
3.1.1.1. Imines and Related Compounds as Electrophiles. The nucleophilic addition of glycinates to imines and related compounds plays a pivotal role within this category. This strategy has been applied in the past to the synthesis of 3-amino-β-lactams through the nucleophilic addition of an α-amino enolate to the imine producing an α,β-diamino ester intermediate that cyclizes to yield the azetidin-2-one ring. However, the use of suitably functionalized precursors can circumvent cyclization

Scheme 1



Reagents and conditions: (a) $NaNH_2$, HMPT. (b) MeI, Ag_2O, DMF. (c) $LiAlH_4$, Et_2O. (d) CrO_3, aqueous HOAc.

Scheme 2



Reagents and conditions: (a) Et_3N, LiCl, DMF, 91%, 1 h. (b) HCl, MeOH. (c) Dowex-H, NH_4OH. (d) i. LiHMDS; ii. Me_2AlCl; iii. **9a** or **9b** THF, −78 °C, 1 h. (e) BocN=C(SMe)NHBoc, Et_3N, AgOTf, DMF, rt, 3 h. (f) 1.7% HF, MeCN, 2 h, rt, 81-91%. (g) DIAD, PPh_3, THF, 0 °C 15 min, rt 1 h. (h) H_2, $PdCl_2$, 115 psi, 4 d. (i) 0.5 M HCl, reflux, 1.5 h, 95%.

to the β-lactam.[84] An example of this approach is the stereoselective one-pot synthesis of (±)-2-oxo-1,5-diphenyl-4-carboxylic acid, **3**, by addition of the enolate derived from *N*-benzyloxycarbonyl glycinate **1** to imine **2**. Carboxyimidazolidinone **3** is transformed into (±)-2,3-diamino-3-phenylpropanoic acid, **4**, by reduction of the urea to an aminal followed by oxidation under acidic conditions that allows for the simultaneous removal of the aminal and recovery of the carboxylic moiety (Scheme 1).[85]

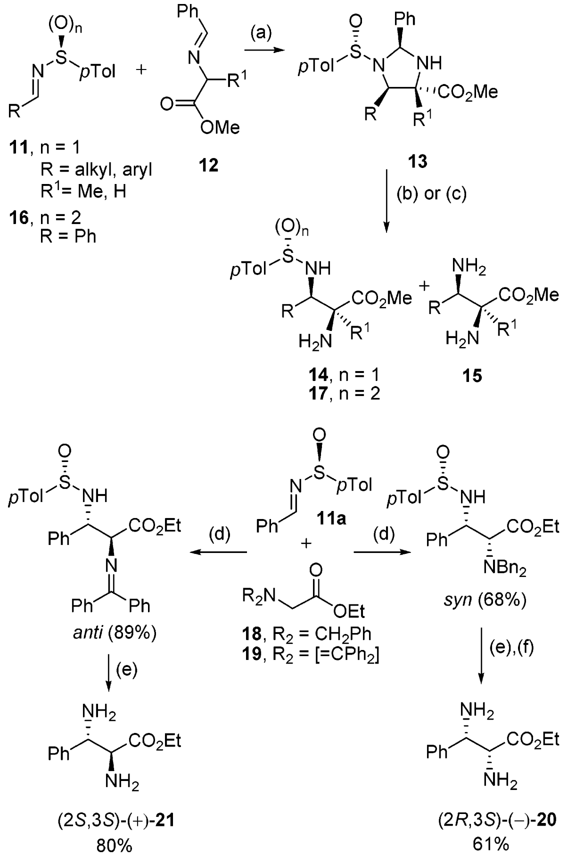
Asymmetric versions of this route involving chiral glycinates can also be found in recent literature. Thus, the addition of an enantiopure Ni(II) complex of α-imino glycinate **5** to trifluoromethylimine **6**, takes place with a high degree of diastereocontrol giving rise to fluorinated *syn*-3-trifluoromethyl-2,3-diamino acid, **7**, with 98% diastereomeric excess (Scheme 2).[86] A parallel approach has been used for the asymmetric synthesis of (2*S*,3*R*)-capreomycidine within the context of the total synthesis of capreomycin IB. Indeed, the aluminum enolate of a chiral oxazinone derived from glycine **8** reacts with benzylimine **9a** to produce an inseparable 3.3:1 mixture of Mannich products **10a** in 60% yield. A significant improvement in selectivity was achieved using benzhydryl imine **9b** (6.5:1) but with a lower yield (**10b**, 22%). Other attempts to improve the selectivity were unsuccessful. Subsequently, five additional steps, including complete epimerization to the desired (2*S*,3*R*) diastereoisomer, were necessary to transform the diasteromeric mixture of **10a** into capreomycidine (Scheme 2).[87]

Chiral sulfinimines **11** can act as chiral inductors in the highly stereoselective stepwise addition of lithiated α-imino esters **12** in the presence of $BF_3 \cdot Et_2O$ to afford enantiopure 2-carbomethoxy-*N*-sulfinylimidazolidines **13** (Scheme 3). In some cases, this methodology allows for the synthesis of imidazolidines with quaternary centers (R^1 = Me). From **13**, enantiopure *syn*-*N*-sulfinyl-α,β-diamino esters (**14**) or α,β-diamino esters (**15**) can be selectively produced through fairly general aminal cleavage procedures. Acidic conditions for aminal cleavage of **13** can be modulated by choosing a nonnucleophilic solvent (THF/H_2O vs MeOH) to preserve the sulfinamide moiety and thus achieve different degrees of functionalization at the amino groups. Interestingly, the reaction of achiral *N*-sulfonyl imine **16** (R = Ph) and lithiated α-imino glycinate **12** (R^1 = H) provided racemic *N*-sulfonyl α,β-diamino esters **17** with low diastereoselectivity.[88] A parallel strategy has been addressed by the group of Davis in the synthesis of syn and anti α,β-diamino esters (**20**, **21**) recently used in the total synthesis of (−)-agelastatin A. It has been demonstrated that the diastereoselectivity (syn or anti) in the addition of glycinates derived from **18** and **19** to the sulfinimine **11a** can be completely controlled by proper selection of the nitrogen protecting group in the glycinate. The different stereochemical outcome of these reactions, for *N*,*N*-dibenzylglycinate **18** or *N*-benzhydrylglycinate **19** was attributed to different geometries (*E* vs. *Z*, respectively) adopted by the enolates in either transition state (Scheme 3).[89]

Within the same general approach, an example of double diastereoselection has also been used for the asymmetric synthesis of β-carboline containing α,β-diamino esters (Scheme 4). Indeed, chiral cyclic iminium ion **22** prepared from triptamine was submitted to addition of (−) and (+)-8-phenylmenthol-derived α-imino glycinates **23a** and **23b**. In both reactions an enantiomerically pure single adduct was obtained with *syn*-**24** or *anti*-**25** stereochemistry, respectively. Further structural evidence was achieved by NMR analysis of diketopiperazines **26** and **27**.[90]

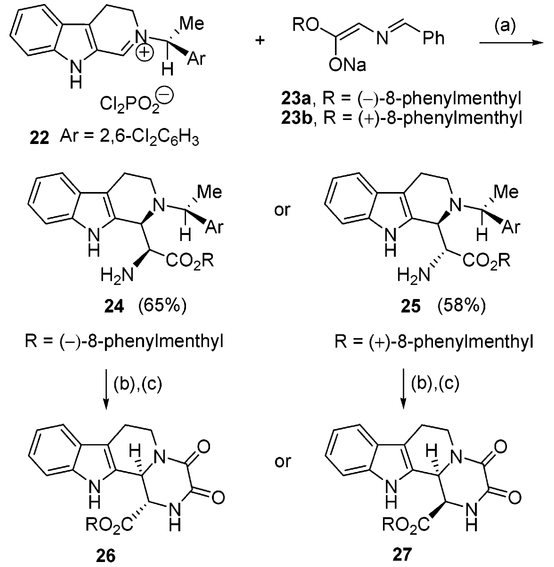
Asymmetric catalysis also constitutes a useful tool in the synthesis of α,β-diamino esters. In this context, the chiral Lewis acid-stabilized imino glycinate eno-

Scheme 3



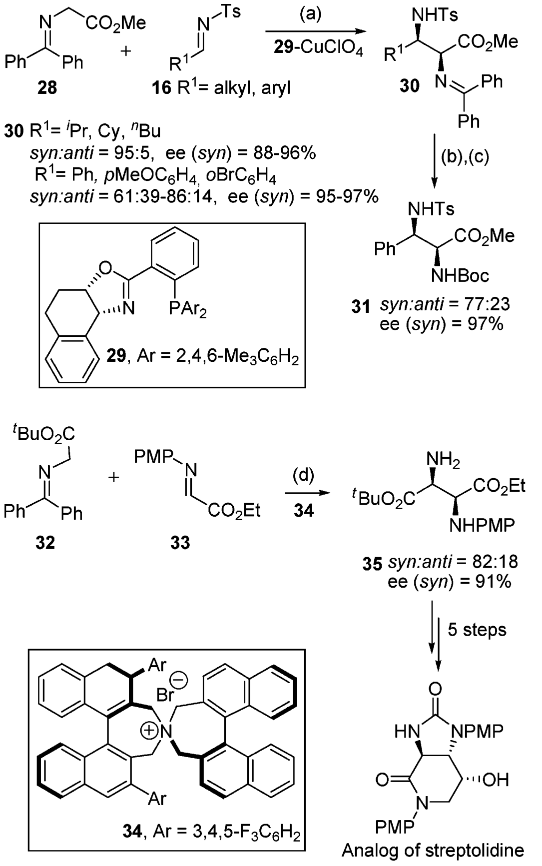
Reagents and conditions: (a) **12**+ LDA + **11** (or **16**), then BF$_3$·Et$_2$O, −78 °C to rt. (b) H$_3$PO$_4$, THF-H$_2$O, rt, 68-84% fo **14**. (c) H$_3$PO$_4$, MeOH-H$_2$O, rt, 59-65% for **15**. (d) LDA, −78 °C, THF then **11a**. (e) TFA, EtOH. (f) Pd(OH)$_2$, H$_2$, EtOH.

Scheme 4



Reagents and conditions: (a) THF, −78 °C. (b) DMAP, ClCOCO$_2$Et. (c) Pd-C (10% mol), (NH$_4$)HCO$_2$.

Scheme 5

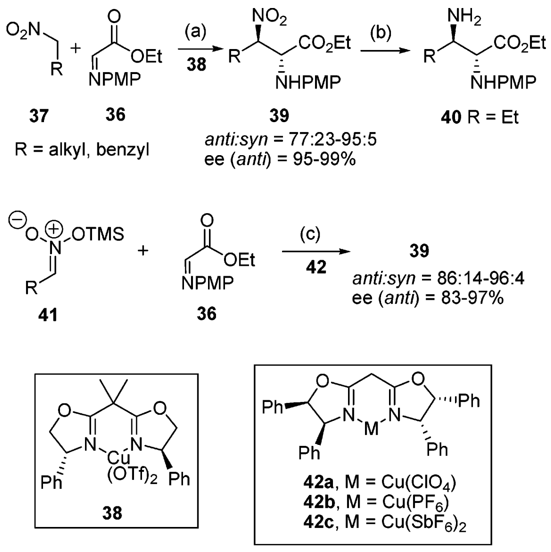


Reagents and conditions: (a) Et$_3$N, THF, 4 Å MS, 61-99%. (b) 2 N HCl, Et$_2$O. (c) (Boc)$_2$O, Na$_2$CO$_3$. (d) 17% aqueous NaOH, mesitylene, **34** (2% mol) then 1 N HCl, THF.

late, generated from **28** and Et$_3$N in the presence of 10% of CuClO$_4$ and chiral oxazoline **29**, reacts with a group of *N*-sulfonyl imines, **16**, to afford as major products *syn*-α,β-diamino esters **30** with good enantiomeric excesses (88−97%). Interestingly, the aliphatic nature of *N*-sulfonyl imines **16** is crucial to reach a good syn/anti diastereoselectivity (95:5). Acidic hydrolysis of the benzhydryl group and introduction of a *t*-butoxycarbonyl group finally yielded **31**.[91] Similarly, enantiomerically enriched syn diamino succinate **35** [de, 64%; ee (syn), 91%], a derivative of 3-amino aspartate, has been prepared through phase-transfer-catalyzed Mannich reaction of **32** with imine **33** in the presence of 2% of *N*-spiro C$_2$-symmetric chiral quaternary ammonium salt **34**. The synthesis of a precursor of streptolidine, constituent of the streptothricin antibiotics was also reported in five linear steps from **35** (Scheme 5).[92]

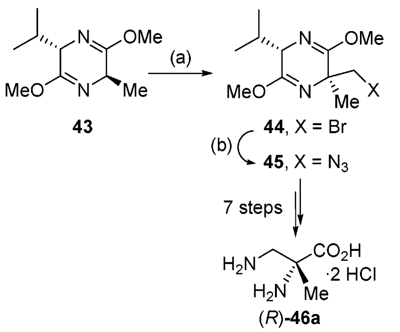
Imines are also susceptible to nucleophilic addition of nitroalkanes. Recently, the group of Jørgensen has developed one of the most efficient protocols for the synthesis of α,β-diamino esters, the catalytic enantioselective aza-Henry reaction between imino ester **36** and nitro compounds **37** (R = alkyl, benzyl). The reaction proceeds at room temperature with high anti/syn diastereoselectivity (from 77:23 to 95:5) and ee values above 95% for major *anti*-β-nitro-α-amino esters, **39**, in the presence of base (Et$_3$N) and a Cu(II) complex based on a chiral bisoxazoline ligand **38**.[93] Furthermore, the use of base can be avoided using silyl nitronates **41** (R = alkyl) instead of nitro compounds. The reaction gives good conversions either with *N*-*p*-tosyl imino ester or with the more electron rich *N*-*p*-methoxyphenyl or *N*-phenyl imino esters. In this process, the use of chiral copper−bisoxazoline complexes, **42**, secures excellent anti/syn

Scheme 6



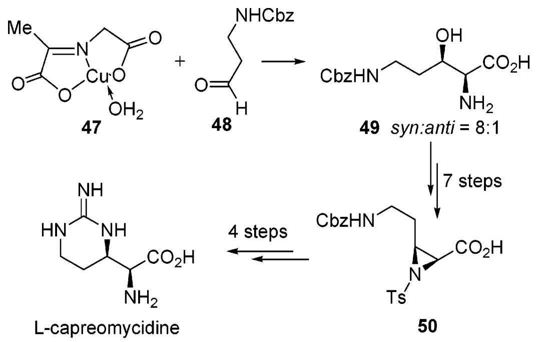
Reagents and conditions: (a) Et_3N, **38** (20% mol), rt or 0 °C. (b) Raney Ni, H_2, 80%. (c) THF, **42** (20% mol), −100 °C.

Scheme 7

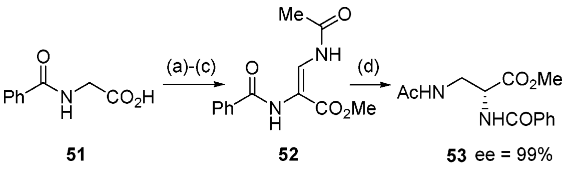


Reagents and conditions: (a) BuLi, THF, −78 °C, 15 min., then CH_2Br_2, THF, −70 °C, 30 h, 69%. (b) NaN_3, DMSO, 80 °C, 48 h.

Scheme 8



Scheme 9



Reagents and conditions: (a) $Me_2NCH(OMe)_2$, toluene, reflux. (b) NH_4OAc, MeOH, rt. (c) MeCOCl, base, CH_2Cl_2-Et_2O. (d) (*R,R*)-EtDuPhos-Rh (I), H_2, 60-90 psi, 15-60 h.

selectivities and high ee values for the final products. In any case, the resulting α-amino-β-nitro ester **39** (R = Et) can be readily converted into *anti*-α,β-diamino ester **40** by hydrogenation with Raney Ni in high yield (Scheme 6).[94]

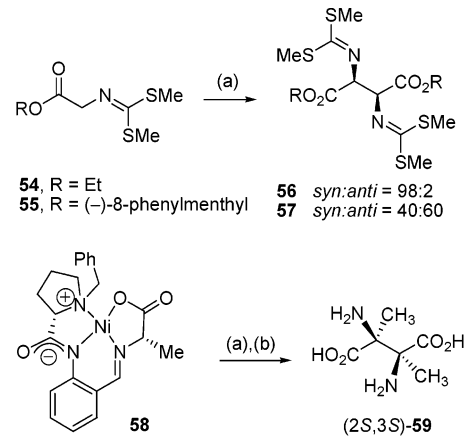
3.1.1.2. Other Electrophiles. Reactions of glycinates and related compounds with electrophiles different from imines have also been employed to build the b−c carbon−carbon bond of α,β-diamino acids and derivatives. In 1991, the group of Mittendorf reported the enantioselective synthesis of α,β-diamino acid **46** by diastereoselective alkylation of bislactim ether **43** with dibromomethane followed by nucleophilic substitution of the bromomethyl bislactim ether **44** with sodium azide. After reduction of azide **45**, a six-step sequence leads to the production of enantiopure α-methyl-α,β-diamino acid **46a** as a hydrochloride salt (Scheme 7).[95]

Following this general strategy, other electrophiles were employed, such as *N*-bromomethylphthalimide, in the context of the synthesis of α,α-disubstituted α,β-diamino acids as fragments of cyclic amidine-containing peptidomimetics[96] and ethyl formate in the condensation with ethyl hippurate to give (±)-quisqualic acid, further submitted to enzymatic resolution.[97] In addition, the synthesis of L-capreomycidine has also been addressed by construction of the b−c carbon−carbon bond. In this route, the key synthetic intermediate is β-hydroxy-L-ornitine derivative **49**, which was readily prepared by condensation of *N*-piruvylideneglycinate copper (II) complex **47** and β-(benzyloxycarbonylamino) propionaldehyde, **48**, as electrophile as an 8:1 mixture of syn/anti isomers. After separation, the syn (threo) isomer was acylated and resolved by means of an acylase. β-hydroxy-L-ornitine was finally transformed in L-capreomycidine through a synthetic sequence that includes formation and then cleavage of a cis aziridine ring in **50** (Scheme 8).[98]

Amide acetals also have resulted in useful electrophiles in the synthesis of α,β-diamino acids as in the synthesis of piperidino and pyrrolidino diamino acids analogues to streptolutin.[99] Furthermore, the highly enantioselective synthesis of α,β-diaminopropionic acid derivatives **53** has been achieved following this strategy (Scheme 9). Condensation of hippuric acid, **51**, with dimethylformamide dimethyl acetal, followed by treatment with NH_4OAc in MeOH and then acylation of the resulting enamide produced α,β-dehydro-α,β-diamino ester **52**. The key step for the enantioselective synthesis of **53** is the remarkable asymmetric hydrogenation of **52** using the (*R*,*R*)-EtDuPhos−Rh(I) complex that provides α,β-diamino esters in yields above 99% and ee's of 99%.[100]

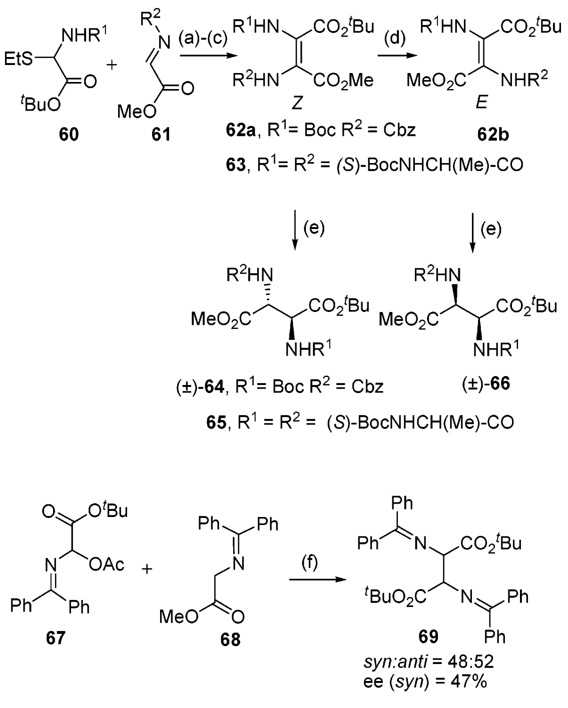
3.1.1.3. Dimerization of Glycinates. In some instances, dimerizations of glycinates and related compounds[101] have been used for the synthesis of diamino succinates (3-amino aspartates). Early attempts within this approach explored the photodimerization of methyl *N*-acylglycinate and related *N*-acylamino esters to give an equimolecular mixture of diastereomers.[101b] Besides, free 2,3-diaminosuccinic acids have been obtained as an equimolecular mixture of racemic and meso diastereoisomers by reaction between ethyl *N*-acetyl malonate and 2-acetoxy glycinate in the presence of sodium hydride followed

Scheme 10



Reagents and conditions: (a) BuLi, THF, –78 °C; then I_2, –78 °C to rt, 20 h, 80% for **54**, **55** and MnO_2, 1 h, 20 °C, 52% for **58**. (b) 2 N HCl, MeOH then Dowex-50, 54%.

Scheme 11



Reagents and conditions: (a) **60**, SO_2Cl_2, CH_2Cl_2, 0 °C. (b) PPh_3. (c) **61**, Et_3N, THF, –78 °C, 61%. (d) Et_2NH, MeOH, 70 °C, 52%. (e) $[Rh(COD)Cl]_2$dppf, 90 bar, H_2, toluene, 80 °C. (f) $Pd(OAc)_2$, MeCN, (*R*)-BINAP, 24 h, NaH, 77%.

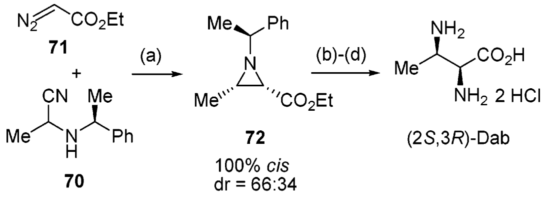
by removal of protecting groups and hydrolysis.[102] More recently, a highly diastereoselective oxidative dimerization of glycinates **54** has been reported by enolization with ^{t}Buli, LDA, or ^{s}BuLi followed by treatment with iodine to afford racemic syn (threo) diamino succinates **56** (syn/anti > 98:2) in high yield. Unfortunately, this dimerization is highly substrate-dependent and efforts to effect the enantioselective oxidative dimerization of (−)-8-phenylmenthyl glycinate **55** produced a 40:60 mixture of syn and anti diamino succinates **57**. The syn and anti isomers were separated and submitted to nonepimerizing hydrolysis to give the enantiopure free (2*S*,3*S*)-3-aminoaspartic acid and the meso isomer.[103] On the other hand, oxidative dimerization of a chiral Ni(II) complex, **58**, derived from α-imino alaninate occurs by treatment with *n*-BuLi followed by addition of pentyl iodide or MnO_2 to afford after acidic hydrolysis (−)-(2*S*,3*S*)-2,3-dimethyl-2,3-diaminosuccinic acid, **59**. Interestingly, similar Ni(II) complexes, derived from glycine or valine, do not undergo the above oxidative dimerization (Scheme 10).[104]

Very recently, another diastereoselective route toward diaminosuccinic acid derivatives that relies on the dimerization of two fragments obtained by glycinate transformations has been reported. The coupling of α-ethylthioglycinate **60** and α-acyliminoglycinate **61** mediated by PPh_3 afforded a good yield of *Z*-dehydrodiamino succinate, **62a**, that can be readily converted to the *E* isomer, **62b**, under basic conditions. Cis-selective catalytic hydrogenation of both *Z* and *E* dehydrodiamino acids allowed for the efficient and diastereoselective synthesis of anti and syn orthogonally protected diamino succinates **64** and **66**. Furthermore, the presence of chiral centers in the starting dehydrosuccinate **63** provided enantiopure anti diamino succinate **65** through diastereoselective hydrogenation.[105] Finally, enantioselective catalysis has also been used in the synthesis of diamino succinates **69**. Indeed, 2-acetoxyimino glycinate **67** was submitted to a palladium-mediated π-azaallylic substitution using α-iminoglycinate **68** derived sodium enolate as nucleophile and a several chiral phosphine ligands. Unfortunately, although the yields are fairly good, diasteromeric ratios (D,L/meso) are moderate and ee values for the D,L pair are low (Scheme 11).[106]

3.1.1.4. Through Cyclic Intermediates. Cycloaddition reactions, one of the most useful tools for the construction of carbon−carbon bonds, have also been used in the synthesis of α,β-diamino acids. In this context, imines and related compounds containing C=N bonds can undergo stereocontrolled cycloaddition with a number of species that render cyclic precursors of α,β-diamino acids. One of these cyclic precursors are 2-alkoxycarbonyl aziridines, readily available by Lewis acid-mediated [2 + 1] cycloaddition of imines and alkyl diazoacetates. Studies on this process comprise the use of Lewis acids,[107] metal complexes based on Cu(I) and chiral oxazolines,[108] Rh(II) and sulfur ylides,[109] boron-based catalyst VAPOL-B,[110] prepared from vaulted biphenanthrol, [(*S*)-VAPOL], and cinchona-derived quaternary ammonium salts as chiral phase-transfer catalysts.[111]

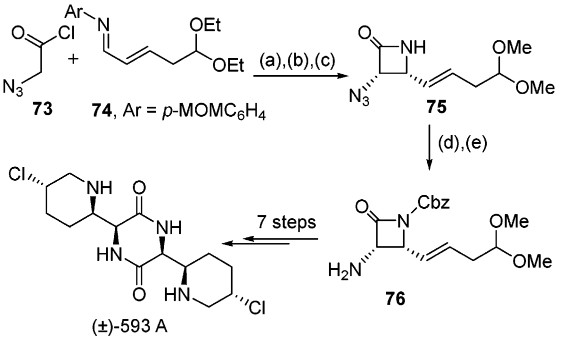
Alternatively, 1,3,5-triazines, *N*-methoxymethylanilines, and 2-amino nitriles can be used as the source of imines in the presence of the Lewis acid.[108b,112] In particular, $SnCl_4$ and 2-amino nitriles derived from 1-(*R* or *S*)-phenylethylamine **70**, provide in situ formation of the iminium ion in the reaction with diazoacetate **71**. In this example, aziridine **72** is obtained with complete cis selectivity and with moderate diastereoselectivity relative to the chiral auxiliary. Further transformation of 2-ethoxycarbonyl aziridine **72** into the corresponding enantiopure free α,β-diamino acid [*syn*-(2*R*,3*S*)-Dab] was reported in three steps (Scheme 12).[113] Other methods are available for the synthesis of 2-carboxyaziridines such as aza-Darzens reaction of imines and α-haloenolates[114] and reaction with α-carboxamide sulfo-

Scheme 12



Reagents and conditions: (a) SnCl$_4$, CH$_2$Cl$_2$, rt. (b) TMSN$_3$, BF$_3$·OEt$_2$. (c) H$_2$, Pd-C, (Boc)$_2$O. (d) 6 N HCl.

Scheme 13



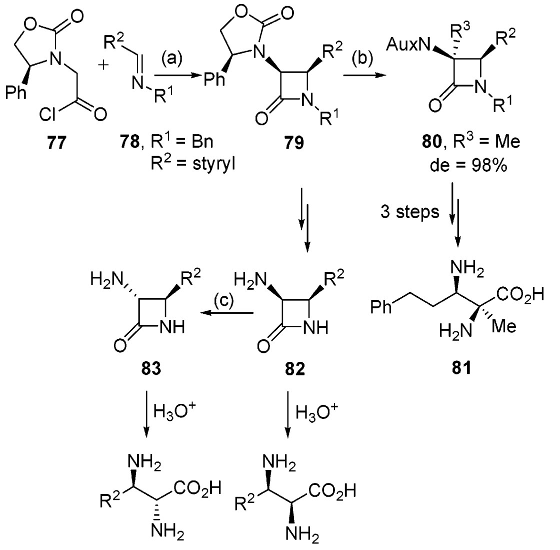
Reagents and conditions: (a) Et$_3$N. (b) HCl, CH(OMe)$_3$, MeOH, reflux. (c) CAN, THF, H$_2$O, 0 °C. (d) CbzCl, Et$_3$N, CH$_2$Cl$_2$, −30 °C. (e) Zn, HOAc, Et$_2$O, CH$_2$Cl$_2$, rt.

nium ylides;[115] however, their coverage is out of the scope of this review.

3-Amino-β-lactams are valuable precursors to α,β-diamino acid derivatives. These intermediates are available by the [2 + 2] ketene−imine cycloaddition, also referred to as Staudinger reaction, using a suitable amino ketene equivalent or another ketene equivalent such as 2-acetoxyacetyl chloride that allows for straightforward introduction of an amino group at C-3 after β-lactam formation.[116] The preparation of amino taxol side-chain precursors has been addressed using this strategy.[117] Alternatively, 3-azido β-lactams are available by cycloaddition of imines **74** and azido ketenes **73**, and an example of this approach was employed in the total synthesis of antibiotic (±)-593A. In fact, after [2 + 2] cycloaddition, 3-azido β-lactam **75** was transformed into 3-amino β-lactam **76** that spontaneously dimerized to a diketopiperazine then leading to the target antibiotic (Scheme 13).[118]

A more straightforward route to enantiopure α,β-diamino acids has been reported using the Evans−Sjögren acid chloride **77** with imine **78**. The resulting *cis*-3-amido-4-styryl-β-lactam, **79**, can be then alkylated diastereoselectively at C-3 (**80**), furnishing after complete removal of protecting groups and β-lactam cleavage (three steps), free α-methyl-α,β-diamino acid, **81** (Scheme 14).[119] The group of Ojima has shown that *cis*-(*S*,*R*)-3-amino-β-lactams **82**, readily obtained from **79**, can be converted to enantiopure (*S*,*R*)-α,β-diamino acids by acidic hydrolysis in quantitative yield. In addition, cis lactam **82** can undergo epimerization to trans isomer **83** by aldimine formation followed by treatment with base. Further acidic hydrolysis afforded (*R*,*R*)-α,β-diamino acids in good yield (Scheme 14).[116b,120]

Scheme 14



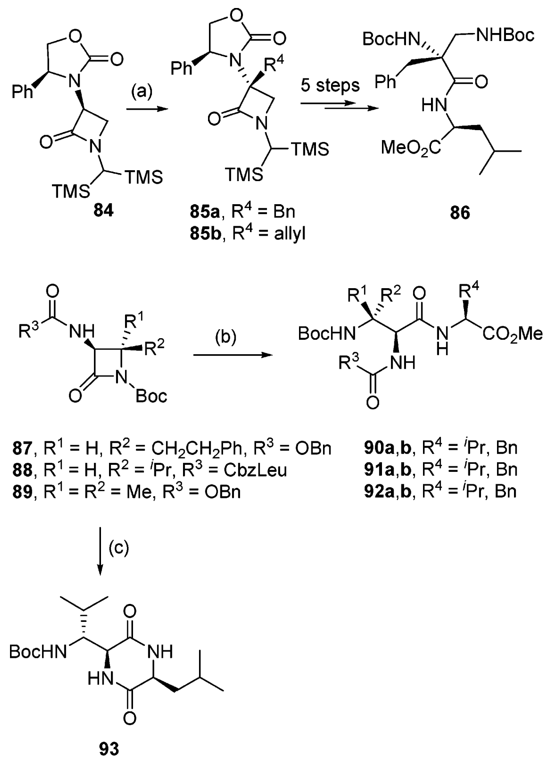
Reagents and conditions: (a) Et$_3$N, CH$_2$Cl$_2$, −78 °C to rt. (b) LHMDS, MeI. (c) PhCHO, LHMDS.

More recently, the diastereoselective C-3 alkylations of 4-unsubstituted 3-amido-β-lactam **84** with benzylic and allylic bromides to give **85a**,**b** have served to demonstrate that the oxazolidinone auxiliary alone can exert a high degree of stereocontrol, leading to the opposite relative configuration in the alkylation step (see Scheme 14). Finally, β-lactam **85a** was transformed into α,β-diamino acid derivative **86** in five linear steps. The highly efficient transformation of enantiopure Boc-protected 3-amino-β-lactams into α-alkyl-α,β-diamino acid residues incorporated as part of a peptide backbone has been also developed by the group of Palomo.[116c,121] Indeed, upon treatment with (*S*)-phenylalanine or (*S*)-valine methyl esters and sodium azide, β-lactams **87** and **88** afforded dipeptides **90a**,**b** and **91a**,**b**. However, sodium azide failed in promoting peptidic coupling with 4,4-disubstituted β-lactam **89**, and the presence of potassium cyanide was necessary to reach a good yield of the highly substituted dipeptides **92a**,**b**. Another useful transformation reported by this group is the catalytic hydrogenation of 3-amido β-lactam **88** that promotes β-lactam cleavage followed by ring closure to diketopiperazine **93** (Scheme 15).[122]

2-Carboxyimidazolines and imidazolidines are cyclic analogues of α,β-diamino acids, easily accessible via [3 + 2] cycloaddition of imines and azomethine ylides. Thermolysis of β-lactam-fused oxazolidinone **94** is an efficient method for the in situ generation of azomethine ylides. The dipole thus generated **95** and reacted with aromatic *N*-sulfonyl imines **16** giving racemic *N*-sulfonyl aryloxycarbonyl imidazolidines **96** with low diastereoselectivity (exo/endo = 3:1, Scheme 16). Interestingly, 2*H*-azirines can also act as 1,3-dipolarophiles, trapping the above azomethine ylide (**95**) to give intermediates that can be easily transformed into 1-azacepham analogues.[123]

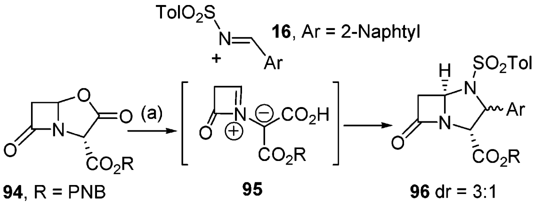
Asymmetric [3 + 2] dipolar cycloaddition of azomethine ylides and imines has been addressed using chiral sulfinimines **11** and enolates **97** derived from α-alkyl-α-imino esters (from Phe, Ala, Leu) and LDA. In the absence of any Lewis acid additive, **97** behaves as a dipole, giving enantiopure *N*-sulfinyl methoxycarbonyl imidazolidines **98** with a remarkably high

Scheme 15



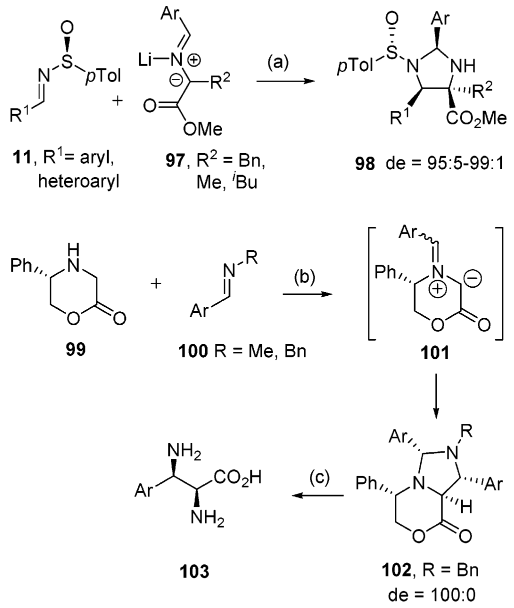
Reagents and conditions: (a) LDA, R^4X, THF, –78 °C to rt, 16 h, 70-90%. (b) (*S*)-$H_2NCH(R^4)CO_2Me$, DMF, NaN_3 (for **87**, **88**) or KCN (for **89**), DMF, rt, 10-14 h, 70-89%. (c) H_2, Pd-C, EtOH, rt, 14 h, 90%.

Scheme 16



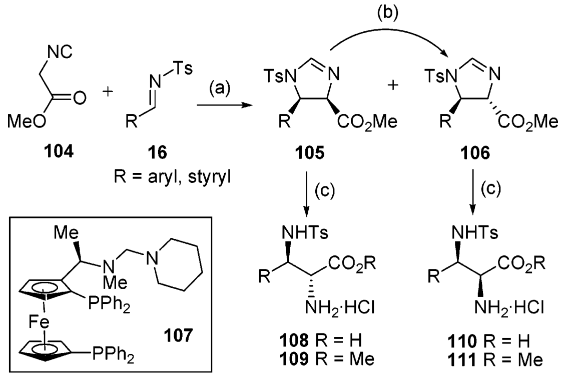
Reagents and conditions: (a) MeCN, sealed tube 80 °C, 20 h, 49%.

Scheme 17



Reagents and conditions: (a) THF, LDA, –70 °C to 4 °C, 37-80%. (b) PPTS, toluene, reflux. (c) TFA, MeOH-H_2O (10:1), $Pd(OH)_2$, H_2, 5 bar.

Scheme 18

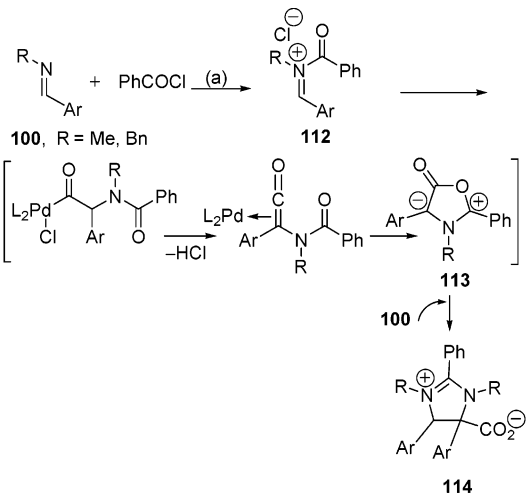


Reagents and conditions:
(a) AuCl (*c*-hexNC); **105**:**106**, 89:11-95:5
$RuH_2(PPh_3)_4$; **105**:**106**, 13:87-5:95
$AuCl·SMe_2$, **107**; (4*R*,5*S*)-**105**, ee = 96%-99%.
(b) Et_3N, CH_2Cl_2, reflux. (c) 6 N HCl for **108** and **110**; HCl, MeOH for **109** and **111**.

degree of endo stereocontrol and an excellent diastereofacial discrimination of the starting sulfimine.[124] Within this context, the group of Harwood reported that chiral azomethine ylides **101** generated in situ from (5*S*)-phenylmorpholin-2-one, **99**, in the presence of aromatic aldimines **100** and pyridinium *p*-toluenesulfonate can undergo cycloaddition with excess imine to give imidazolidines **102** as single products. Finally, hydrogenolysis of the adducts under acidic conditions released the corresponding enantiopure *syn*-α,β-diamino acids **103** in excellent yields (Scheme 17).[125]

A remarkable example within this context is the reaction between lithiated isocyanoacetates and Schiff bases to give racemic 2-unsubstituted imidazolines that undergo acidic hydrolysis to produce racemic α,β-diamino acids.[126] Furthermore, the reaction of methyl isocyanoacetate **104** with *N*-sulfonyl imines **16** (R = aryl, (*E*)-styryl) is catalyzed by transition metal complexes such as AuCl(NC*c*-hex) to give racemic cis imidazolines **105** with high diastereoselectivity. The reaction was very slow for other imines (*N*-aryl, *N*-phosphinyl), and other metal complexes [Ag(I), Rh(I), Ru(II)] gave lower cis selectivity. Imidazolines **105** were readily converted into *anti*-α,β-diamino acids **108** or their methyl esters **109** by 6 N HCl or HCl–MeOH, respectively. Alternatively, racemic cis imidazoline **105** (R = Ph) can be isomerized into the thermodynamically more stable trans isomer, **106**, by treatment with Et_3N, and then acidic hydrolysis or methanolysis gives the corresponding *syn*-α,β-diamino acids **110** or esters **111** (Scheme 18).[127] Interestingly, the group of Lin has observed that $RuH_2(PPh_3)_4$ as catalyst and CH_2Cl_2–MeOH 1:3 as solvent provides opposite diastereoselectivity for the cycloaddition to *N*-sulfonyl imines **16** (R = aryl, (*E*)-styryl, *t*Butyl). Racemic trans imidazolines **106** were thus obtained as major products (trans/cis = 95:5–87:13) in good yields.[128] Furthermore, an enantioselective cycloaddition can be carried out in the presence of a catalytic amount of Au(I) complex bearing a chiral ferrocenylphosphine ligand, **107**. As above,

Scheme 19



Reagents and conditions: (a) $Pd_2(dba)_3$ (5% mol), bipy (10% mol), MeCN, 55 °C, CO, 62-92%.

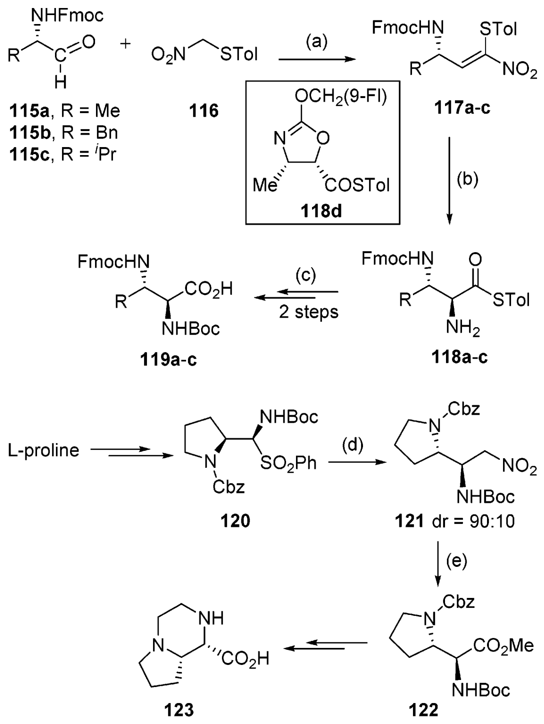
Au(I) catalysis produces cis imidazolines (4*R*,5*R*)-**105** (R = aryl) as optically pure materials (ee: 96–99%) that were converted to anti diamino esters (2*R*,3*R*)-**109** using a parallel procedure.[129]

Finally, the synthesis of α-amino acid-derived imidazolines **114** reported by Arndtsen can also be held in this category (Scheme 19). Palladium-mediated formation of a transient cyclic 1,3-dipole, **113**, has been invoked in this work by insertion of carbon monoxide in an *N*-acyliminium species, **112**, formed in situ followed by dipolar cycloaddition of **113** with a second molecule of imine **100** to afford zwitterionic carboxyimidazoline **114** in good yield.[130]

3.1.2. Methods in Which the a–b Bond Is Formed

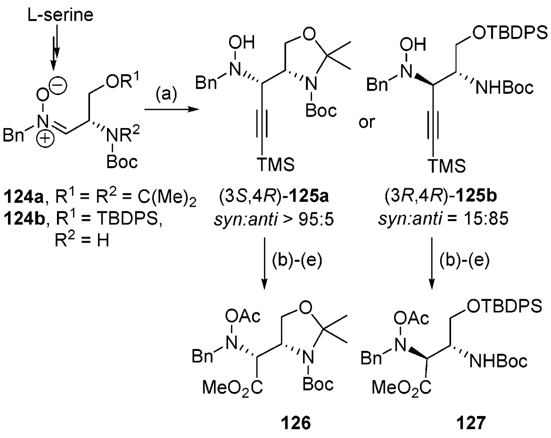
3.1.2.1. Nucleophilic Synthetic Equivalents of CO_2R. Construction of the a–b carbon–carbon bond is another key approach in the synthesis of α,β-diamino acids. In fact, the carboxylic group is introduced in the molecule by means of a synthetic equivalent as a nucleophile or electrophile and then additional manipulation to give the carboxylic group is usually needed. Within this context, nitro compounds have been employed as nucleophiles to form the a–b carbon–carbon bond (Scheme 20). The group of Jackson has developed a new route to enantiopure *anti*-α,β-diamino acids based on the stepwise condensation of (*p*-tolylthio)nitromethane, **116**, and α-amino aldehydes **115a–c**. The resulting nitroalkenes, **117a–c**, were submitted to nucleophilic epoxidation using lithium *tert*-butyl hydroperoxide and diastereoselective epoxide cleavage using NH_3 to render α,β-diamino thioesters **118a–c**. Only for **118a**, small amounts of oxazoline **118d** (10%) were isolated as a result of a secondary carbamate cyclization process. Finally, **118a–c** were transformed in two steps into differentially protected *anti*-α,β-diamino acids **119a–c**.[131] On the other hand, diamino sulfone **120**, readily prepared from L-proline in a few steps, can act as an *N*-acyliminium synthetic equivalent in the addition of nitromethane anion giving nitro diamine **121** in a 90:10 diastereomeric ratio. The major anti isomer was submitted to Nef reaction followed by esterification to give a 72% yield of α,β-diamino ester **122** that can be transformed into bicyclic piperazine **123** by a reported procedure.[132]

Scheme 20



Reagents and conditions: (a) i. ^tBuOK, ^tBuOH-THF; ii. $MeSO_2Cl$, $^iPr_2EtN$,CH_2Cl_2, 69-80%. (b) i. $LiOO^tBu$, toluene; ii. NH_3, 35-57%. (c) i. Boc_2O, THF, 97-99%; ii. H_2O_2, NaOH, 63-91%. (d) $MeNO_2$, THF, NaH, rt, 78%. (e) i. $KMnO_4$, KOH-K_2HPO_4, ^tBuOH, rt. ii. K_2CO_3, MeI, DMF, rt (72% for 2 steps).

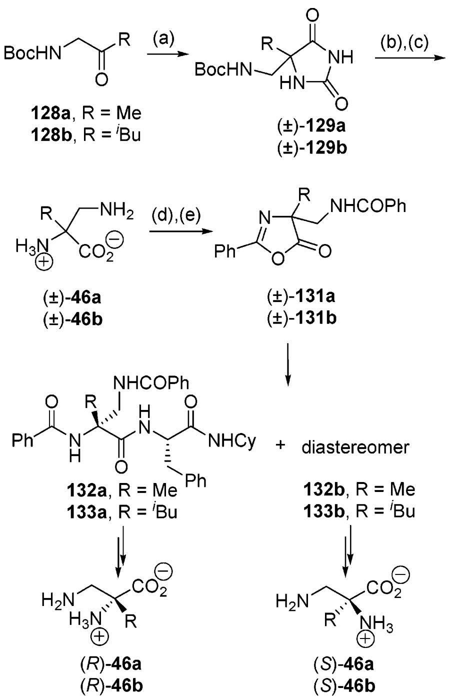
Scheme 21



Reagents and conditions: (a) LiC≡CTMS, THF, –80 °C, 68-97%. (b) Bu_4NF, THF, rt, 70-80 %. (c) Ac_2O, pyr, 1 h, rt. (d) $RuCl_3$-$NaIO_4$, MeCN, rt. (e) CH_2N_2, Et_2O, 72-76% (3 steps).

The use of terminal alkynes as synthetic equivalents of the carboxylic acid moiety is well documented in organic synthesis and has been applied to the synthesis of α,β-diamino acids (Scheme 21). The group of Merino has demonstrated that addition of lithium trimethylsilylacetylide to nitrone **124a**, readily available from L-serine, takes place with a high degree of diastereocontrol (>95:5) to give propargylhydroxylamine (3*S*,4*R*)-**125a**. In contrast, changing protecting groups in the starting nitrone (**124b**) allows for an inversion of the diastereoselectivity giving (3*R*,4*R*)-**125b** as a major isomer (85:15).

Scheme 22



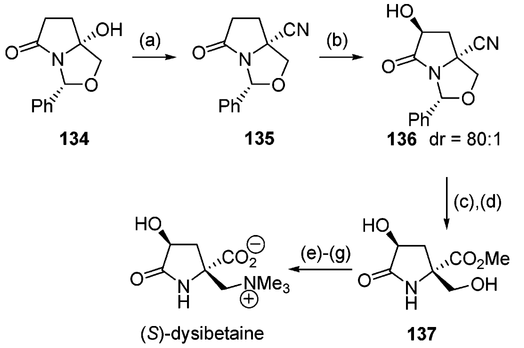
Reagents and conditions: (a) $(NH_4)_2CO_3$, KCN, EtOH-H_2O. (b) TFA, CH_2Cl_2. (c) $Ba(OH)_2$-H_2O, Δ. (d) TMSCl, ^{i}Pr$_2$EtN, CH_2Cl_2, PhCOCl. (e) DCC, CH_2Cl_2. (f) (S)-NH_2(Bn)CHCONHCy, NMP, 80 °C.

Subsequently, (3*S*,4*R*)-**125a** and (3*R*,4*R*)-**125b** were transformed into *syn*-**126** and *anti*-**127** α,β-diamino esters, respectively, by removal of the trimethylsilyl group, *O*-acylation, alkyne oxidation with $RuCl_3$–$NaIO_4$, and esterification. These authors also reported that a parallel strategy can be carried out using 2-lithiofuran instead of lithium trimethylsilylacetylide in the addition to the nitrone.[133]

The group of Obrecht has examined the Bücherer–Bergs reaction of α-amido ketones **128a**,**b** and potassium cyanide in the presence of ammonium carbonate to produce racemic hydantoins **129a**,**b** in good yields that, after cleavage of the protecting carbamate and saponification, rendered α-alkyl α,β-diamino acids **46a** and **46b** as racemic materials. Further *N*-benzoylation and cyclization to oxazolones **131a** and **131b** followed by condensation with L-phenylalanine cyclohexylamide furnished diasteromeric peptides **132a**,**b** and **133a**,**b** that were readily separated and submitted to X-ray analysis. Finally, peptide cleavage and removal of benzamide protecting groups rendered independently both enantiomers of 2-aminomethyl alanine **46a** and 2-aminomethyl leucine **46b** (Scheme 22).[134]

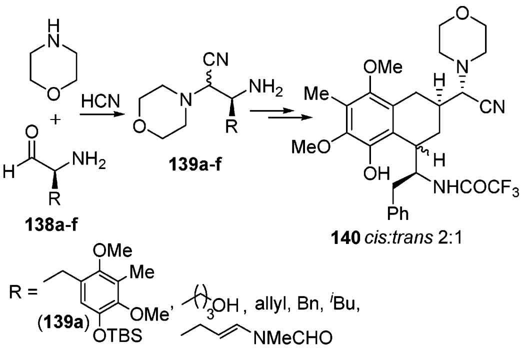
On the other hand, the Strecker reaction, involving addition of cyanide to α-amino imines provides an efficient access to α,β-diamino nitriles that in some cases have been transformed into different α,β-diamino acid derivatives. This strategy was employed to synthesize peptidic enalapril analogues containing an α,β-diamino acid residue, as inhibitors of the angiotensin-converting enzyme,[66] as well as for the synthesis of octapeptide angiotensin II analogues containing an α,β-diamino acid unit.[64b] Very recently, the Strecker methodology has been used in the total synthesis of enantiopure dysibetaine and related compounds (Scheme 23).[135] In fact, enantiopure bicyclic δ-lactam **134** was used as precursor of an *N*-acyliminium ion for the diastereoselective addition of trimethylsilyl cyanide to render **135**. After a highly diastereoselective hydroxylation at C-4 to give **136** (dr = 80:1), hydrogenolysis followed by acidic hydrolysis and esterification rendered hydroxymethyl lactam **137**. Substitution of the side-chain hydroxyl group was effected by means of azide displacement onto a mesylate derivative, and then suitable manipulation of the functional groups afforded natural (2*S*,4*S*)-dysibetaine. In the same paper, the synthesis of a racemic analogue is described through direct C-4 alkylation of methyl pyroglutamate using Eschenmoser's salt.

Scheme 23



Reagents and conditions: (a) TMSCN, $SnCl_4$, 65%. (b) KHMDS, MoOPH, toluene, THF, 81%. (c) 6 N HCl. (d) CH_2N_2 Et_2O, 59% over 2 steps. (e) i. MsCl-Pyr; ii. NaN_3, DMF, 28% over 2 steps. (f) H_2, Pd-C, MeOH. (g) i. MeI, ^{i}Pr$_2$EtN, THF; ii. Dowex 550A, 61%.

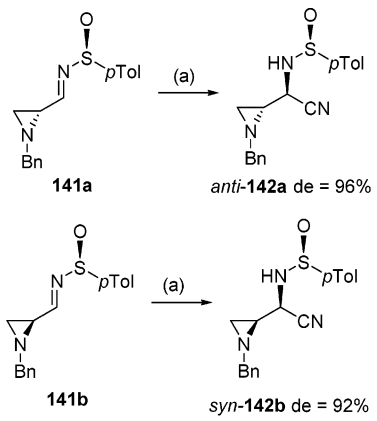
Scheme 24



The Strecker protocol has been applied to the preparation of α,β-diamino nitriles useful as C-protected α-amino aldehydes (Scheme 24). The group of Myers has reported the transformation of optically pure α-amino aldehydes **138a**–**f** into α,β-diamino nitriles **139a**–**f** as a mixture of diastereomers at C-1 but with complete retention of the configuration at C-2. The lability of the amino nitrile can be modulated depending of the nature of the amine, with morpholino derivatives being more stable. The stability of diamino nitrile **139a** toward epimerization under different reaction conditions has also been proven carrying out the synthesis of tetrahydroisoquinoline **140** related to saframycins.[136]

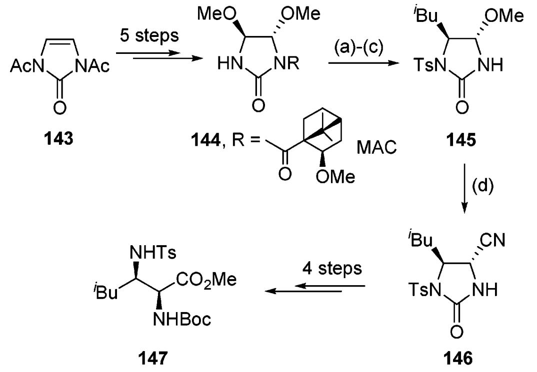
Asymmetric Strecker reactions have been carried out using chiral imines generated from enantiopure (*R*)-α-phenylethylamine with moderate diastereose-

Scheme 25



Reagents and conditions: (a) TMSCN, CsF, THF, –50 °C, 98%.

Scheme 26

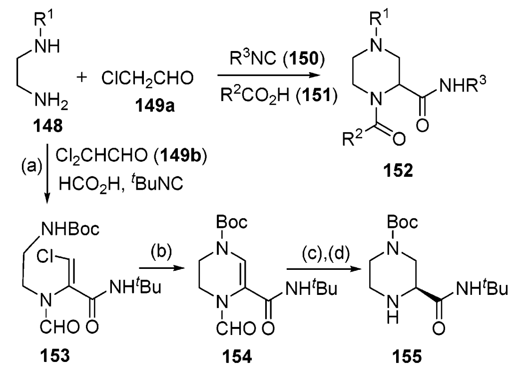


Reagents and conditions: (a) ^{i}BuCuCNMgBr, LiCl, $BF_3 \cdot Et_2O$, THF. (b) TsCl, BuLi, THF. (c) BnSH, BuLi, THF. (d) TMSCN, $BF_3 \cdot Et_2O$, CH_2Cl_2.

lectivity.[137] In contrast, enantiopure 2-aziridinesulfinimines **141a** and **141b** have been treated with trimethylsilylcyanide with high diastereocontrol by the sulfinyl moiety to give, after crystallization, enantiopure aziridine amino nitriles **142a** and **142b** (Scheme 25).[138]

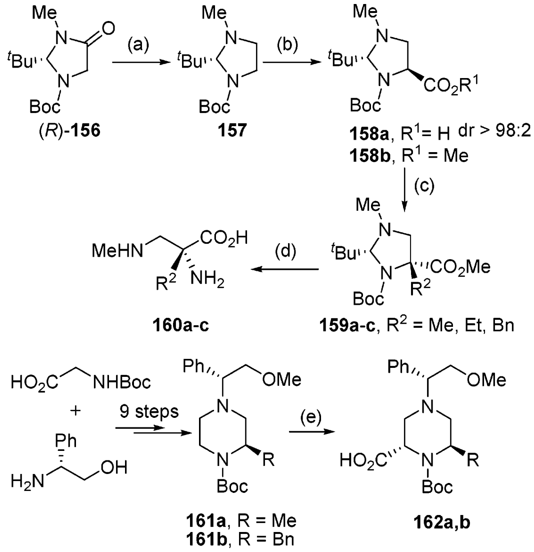
Recently, the modular synthesis of *syn*-α,β-diamino ester **147** has been reported via sequential addition of cyanocuprate and cyanide to a dimethoxyimidazolidinone. The key intermediate enantiopure dimethoxyimidazolidinone, **144**, generated in five steps from **143**, underwent nucleophilic addition of *iso*-butylcyanocuprate to an in-situ-generated acyliminium ion followed by introduction of a tosyl group and removal of the chiral auxiliary (MAC) to afford *N*-tosyl methoxyimidazolidinone **145** that was submitted to diastereoselective Lewis acid-mediated addition of TMSCN to give **146**. Finally, four steps comprising acidic hydrolysis of the cyanide group and imidazolidinone cleavage rendered enantiopure *syn*-α,β-diamino ester **147** in good yield (Scheme 26).[139]

Scheme 27



Reagents and conditions: (a) **149**, toluene, 50 °C, then **150**, **151**, MeOH, 2 days, rt, then Et_3N, 3 h, rt, (~100%). (b) KO^{t}Bu, THF, 3 h, 60%. (c) MeOH, [(*R*)-BINAP(COD)Rh]OTf, H_2, 100 atm. (d) aqueous NH_2NH_2, 100 °C, 91%.

Scheme 28

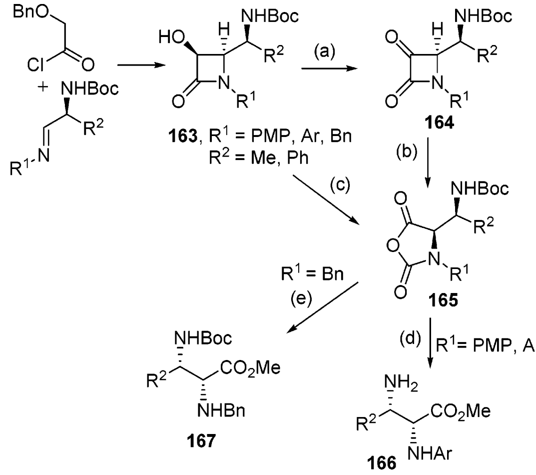


Reagents and conditions: (a) $LiBH_4$ cat., $LiBHEt_3$, THF, reflux, 90 min, 90%. (b) TMEDA, ^{t}BuLi, Et_2O, –70 °C, 30 min then CO_2, 3 h, (84% for **158a**) or CO_2, 3 h then CH_2N_2 (84% for **158b**). (c) ^{i}Pr$_2$NH, THF, ^{n}BuLi, –60 °C to rt, 20 min , R^2X, 12 h, 60-86%. (d) i. TFA, CH_2Cl_2, 14 h; ii. 2 N NaOH, rt, 1 h; iii. Dowex 50x8, 60-75%. (e) ^{s}BuLi, TMEDA, CO_2, THF, 50% for **162a** and 71% for **162b**.

Finally, the multicomponent Ugi condensation has been used as the key step for the assembly of piperazine-2-carboxamides (Scheme 27). This one-pot procedure consists of reaction between a mono-*N*-alkylethylenediamine, **148**, α-chloroacetaldehyde, **149a**, an isocyanide, **150**, and a carboxylic acid, **151**, to give racemic piperazine carboxamides **152** in a very efficient manner. Furthermore, access to enantiopure piperazines is also possible using α,α-dichloroacetaldehyde, **149b**, through a stepwise sequence. Indeed, isolation of open-chain intermediate, **153**, followed by sequential treatment with Et_3N and KO^{t}Bu led to tetrahydropyrazine **154**. Asymmetric hydrogenation of **154** in the presence of Rh–BINAP catalyst allowed for the synthesis of enantiopure piperazine **155** a fragment of HIV-protease inhibitor indinavir.[140]

3.1.2.2. Electrophilic Synthetic Equivalents of CO_2R and Other Approaches. In contrast to the approaches above, the introduction of the carboxylic group as an electrophile has been scarcely explored. An example developed by the group of Seebach starts from glycine-derived imidazolidinone (*R*)-**156** (Boc-BMI) (Scheme 28). Deoxygenation of **156** using lithium triethylborohydride in combination with lithium borohydride rendered acylimidazolidine **157**,

Scheme 29

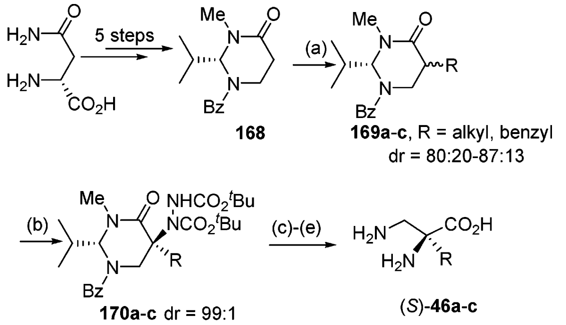


Reagents and conditions: (a) DMSO, P_2O_5, 16 h, rt, 78-83%. (b) *m*CPBA, CH_2Cl_2, –40 °C, 1 h, 90-98%. (c) NaOCl, TEMPO cat., $NaHCO_3$, KH_2PO_4-K_2HPO_4, KBr, CH_2Cl_2, 0 °C, 92%. (d) MeOH, TMSCl, rt, 24 h, 80%, (e) MeOH, reflux, 72-90%.

which upon directed-metalation by treatment with ^{t}BuLi followed by trapping with CO_2 diastereoselectively afforded carboxyimidazolidines **158a**,**b** (dr > 98:2). Subsequent diastereocontrolled alkylation of **158b** using alkyl halides and then acidic hydrolysis allowed for the isolation of a number of enantiopure free α,β-diamino acids **160a**–**c**. In addition, since (*S*)-**156** is equally accessible, the enantiomeric α,β-diamino acids are also available. A parallel approach has been used in the synthesis of 2-carboxypiperazines by the group of Quirion. In fact, piperazines **161a**,**b**, available in nine steps from (*R*)-(−)-phenylglycinol and *N*-Boc-glycine, were transformed into 2-carboxypiperazine **162a**,**b** by diastereoselective metalation of C-6 and quenching with CO_2 furnishing the 2,6-trans isomers as single products.[141]

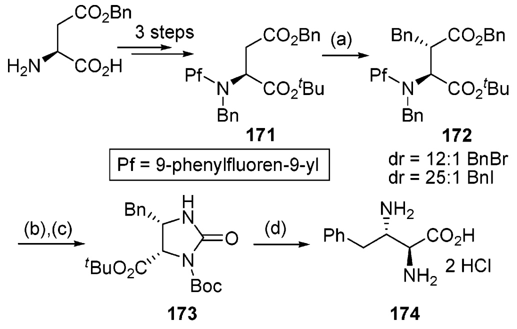
On the other hand, [2 + 2] ketene–imine cycloadditions have been applied to form the a–b carbon–carbon bond of α,β-diamino acids with the oxidative treatment of β-lactams as key step of this strategy (Scheme 29). Indeed, in 1994, the group of Palomo reported that enantiopure 3-hydroxy-4-(aminoalkyl) β-lactams **163**, readily available from the corresponding acid chloride and optically pure α-amino imines, were efficiently oxidized to α-keto β-lactams **164** under Collin's conditions (DMSO, P_2O_5) and then to *N*-carboxy anhydrides (NCAs) **165** under Baeyer–Villiger conditions (*m*-CPBA). In addition, a couple of years later, the authors found an improved one-step oxidative cycloexpansion protocol using TEMPO that allows for direct transformation of 4-hydroxy β-lactams **163** into NCAs **165**. No epimerization was detected in any of the above oxidative processes. Ensuing esterification of NCAs **165** upon reaction with MeOH and trimethylsilyl chloride rendered enantiopure, differentially protected *syn*-α,β-diamino esters **166** and **167**.[142]

Scheme 30



Reagents and conditions: (a) LDA, RX, THF, 80-85%, (b) LDA, DBAD, 45-73%. (c) TFA, CH_2Cl_2, rt. (d) Raney Ni, MeOH, 69 bar, rt. (e) 6 N HCl, 90 °C, 27-89% (3 steps).

Scheme 31



Reagents and conditions: (a) KHDMS, BnX, 75%. (b) H_2, Pd-C, $(Boc)_2O$, 60 psi, 86%. (c) DPPA, Et_3N, MeCN, 91%. (d) 2 N HCl.

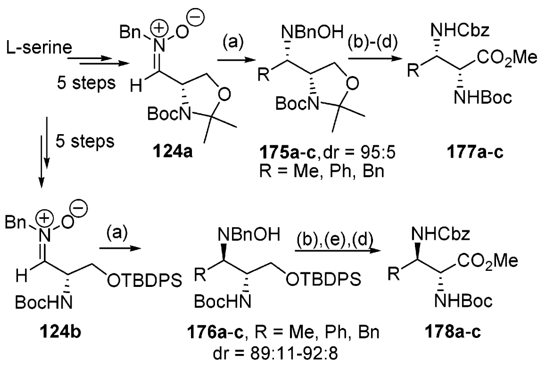
3.1.3. Methods in Which the b–b′ or c–c′ Bonds Are Formed

The number of routes to introduce carbon substituents on the diamino acid skeleton is considerably smaller than the number of approaches found for the above disconnections. One of these methods, developed by the group of Juaristi, relies on optically pure pyrimidinone **168** available in five steps from (*R*)-asparagine (Scheme 30). This cyclic intermediate, **168**, is submitted to enolate alkylation using LDA and alkyl halides with low diastereoselectivity to produce **169a**–**c**, which undergo a highly diastereoselective electrophilic amination of the enolate with di-(*tert*-butyl) azodicarboxylate (DBAD) affording **170a**–**c**. After three more steps to remove the cyclic aminal and protecting groups, free α-alkyl-α,β-diamino acids (*S*)-**46** (R = alkyl, benzyl) are obtained. A parallel route from (*S*)-asparagine provided the enantiomeric diamino acids.[143]

Another remarkable example reported by Rapoport in 1990, relied on an *N*-protected aspartic acid derivative as starting material **171**, in which the two carboxyl groups are differentially protected (Scheme 31). Selective alkylation at carbon 3 with KHMDS and benzyl halides took place affording **172** with a high degree of diastereocontrol essentially exerted by the specific substitution at nitrogen and influenced by the nature of the benzyl halide (I vs Br). After selective reduction of the benzyl ester and exchange of protecting group at nitrogen, Curtius reaction with diphenyl phosphorazidate (DPPA) gave Boc-imidazolidinone **173**, which upon acidic hydrolysis finally rendered enantiopure *syn*-α,β-diamino acid **174**.[144]

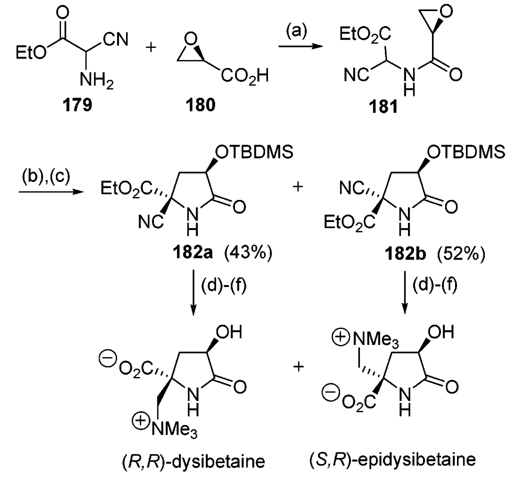
Within this family of methods, the group of Merino has reported an effective route for the diastereoselective synthesis of *syn*- or *anti*-α,β-diamino esters.

Scheme 32



Reagents and conditions: (a) RMgX (3 equiv), THF, –50 °C. (b) H_2, $Pd(OH)_2$-C, 70 psi, rt then CbzCl, aqueous $NaHCO_3$, THF, rt. (c) *p*TsOH, MeOH, reflux. (d) $RuCl_3$, $NaIO_4$, CCl_4, H_2O, rt then CH_2N_2, Et_2O, 0 °C. (e) Bu_4NF, THF, rt.

Scheme 33



Reagents and conditions: (a) DCC, EtOAc, 85%. (b) NaOEt, THF. (c) TBSOTf, 2,6-lutidine, CH_2Cl_2. (d) PtO_2, H_2, EtOH, HCl, 100%. (e) i. H_2CO, Pd-C, H_2; ii. $NaHCO_3$, MeI, THF, 100%. (f) Dowex 550A, MeOH, 55 °C, 97%.

Indeed, nucleophilic additions of Grignard reagents to nitrones **124a** and **124b**, both prepared from L-serine in five linear steps, take place with opposite diastereoselectivity by attack to the *Si* and *Re* faces, respectively (Scheme 32). The different behavior found for **124a** and **124b** is attributed to the influence that the protecting groups exert on the reactive conformation of the nitrones. The resulting *N*-benzylhydroxylamines **175a**–**c** and **176a**–**c** were submitted to hydrogenation, exchange of the protecting groups, and finally oxidation of the hydroxymethyl moiety, and esterification rendered optically pure α,β-diamino esters **177a**–**c** (syn) and **178a**–**c** (anti).[145]

Finally, in a recent report from the group of Snider, the total synthesis of (−)- and (+)-dysibetaine has been addressed using as a key step the intramolecular cleavage of an oxirane ring to construct the pyrrolidinone ring (Scheme 33). Initial *N*-acylation of ethyl amino(cyano)acetate **179** with (*R*)-glycidic acid **180** gave glycinamide **181** that underwent intramolecular alkylation upon treatment with NaOEt to give a 45:55 mixture of diastereomeric hydroxy pyrrolidinones that was readily separated after silylation to **182a**,**b**. Subsequent hydrogenation of the cyano group followed by permethylation and saponification of **182a** and **182b** rendered (*R,R*)-dysibetaine and (*S,R*)-epidysibetaine, respectively.[146]

3.2. Introduction of the Nitrogen Atoms in the Carbon Backbone

3.2.1. From Readily Available α-Amino Acids

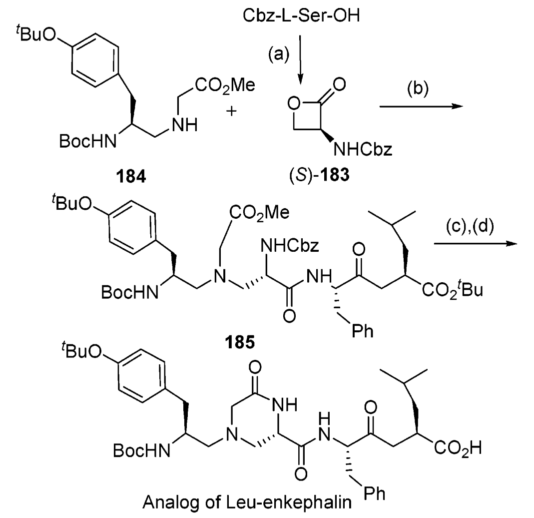
Among the compounds available from nature, α-amino acids bearing suitable functional groups attached to the side chain represent one of the key starting materials for the synthesis of α,β-diamino acids. Indeed, a plethora of synthetic approaches can be found through the literature consisting of the manipulation of functional groups that already exist in commercially available α-amino acids with the additional advantage of using enantiopure starting materials.

3.2.1.1. From Serine and Related Amino Acids. Within this context, α-amino acids containing a β-hydroxy group, such as serine, threonine, and allothreonine, have been frequently employed for the synthesis of α,β-diamino acids through conversion of the alcohol into an amine,[147] and by far, the most studied approach is the Mitsunobu reaction. This protocol has been successfully applied in a number of examples;[148] however, a suitable combination of protecting groups at the acid, the α-nitrogen, and the newly introduced β-nitrogen should be chosen to prevent undesired side reactions such as β-elimination, aziridine formation, etc. and to ensure a reasonable yield of α,β-diamino acid derivative.[149,38b] On the other hand, the group of Vederas has found that, when Mitsunobu conditions are applied to *N*-protected L-serine in the absence of an external nucleophile, (*S*)-3-[(*tert*-butoxycarbonyl)amino]oxetan-2-one **183** is readily formed without epimerization.[150] This enantiopure intermediate has been useful in the synthesis of natural β-amino alanines such as β-pyrazol-1-yl-L-alanine[151] and analogues of willardine,[9b] and in the synthesis of enantiopure 2-carboxypiperazine derivatives,[152] such as a constrained Leu–enkephalin analogue.[80] A key step in this synthesis was the one-pot opening of β-lactone **183** with secondary amine **184** followed by coupling of the resulting free acid with a dipeptide. The linear tripeptide, **185**, generated underwent cyclization upon hydrogenolysis of the Cbz group to form the piperazinone ring. Deprotection using 1:1 TFA/CH_2Cl_2 yielded the target compound, an analogue of Leu–enkephalin (Scheme 34).

In contrast, the direct nucleophilic substitution on suitable protected β-tosyl serine and threonine derivatives or even on β-chloroalanine is scarcely documented.[153,73a] One of the strategies to circumvent secondary reactions is the temporary reduction of the carboxylic group of L-serine or L-threonine to a protected hydroxymethyl derivative which then, after azide nucleophilic substitution at β-carbon, is reoxidized to the α,β-diamino acid.[154,39b]

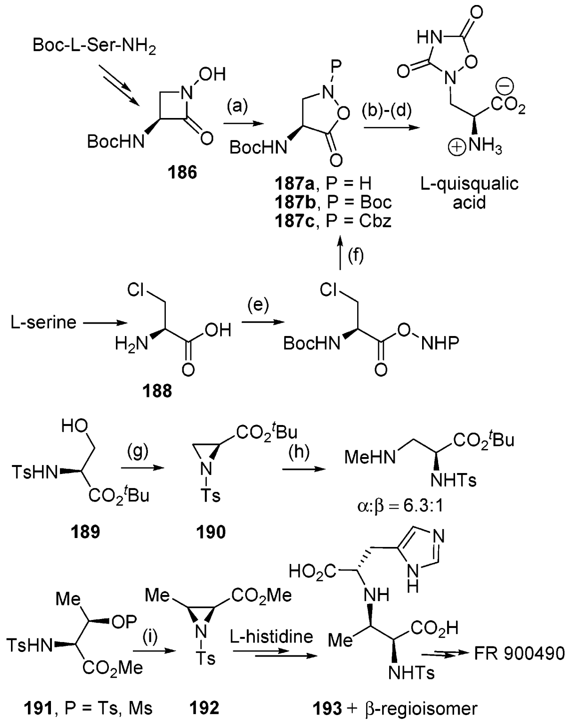
The group of Baldwin has used *N*-Boc-L-serine carboxamide for internal delivery of the amide nitrogen onto the β-carbon atom of serine to provide *N*-hydroxy β-lactam **186**[155] that was cleanly isomerized to isoxazolidin-4-one **187** in the presence of 3%

Scheme 34



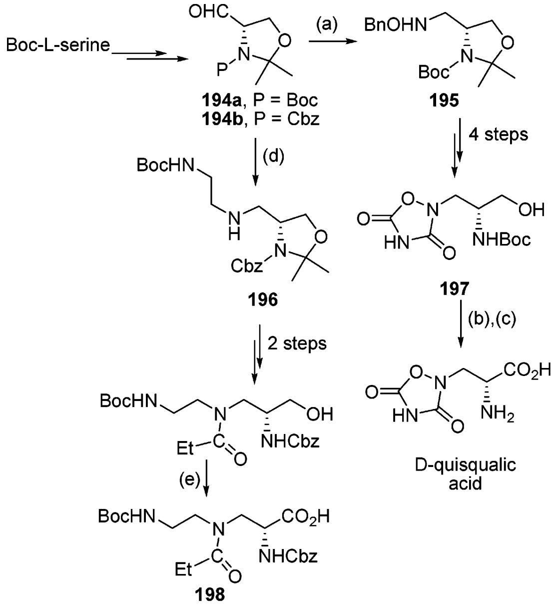
Reagents and conditions: (a) PPh_3, DMAD, THF, −78 °C to rt, 72%. (b) MeCN, 65 °C, then H-Phe-Leu-O^{t}Bu, EDC, NHS, DMF, 23 °C, 24 h, 55%. (c) H_2, 1 atm, Pd-C (10% mol), EtOH, 23 °C. (d) 1:1 TFA-CH_2Cl_2, 23 °C, 6 h, quantitative.

Scheme 35



Reagents and conditions: (a) LiSEt (3% mol), THF, rt. (b) EtOCONCO, THF, rt. (c) NaOH, THF, rt. (d) TFA, 20 °C then Doxew 50W-X8. (e) PNH-OH, EDCI, CH_2Cl_2. (f) NaH, DMF, 0 °C to rt. (g) PPh_3, DEAD, THF. (h) $MeNH_2$, CH_2Cl_2, rt, 90 °C. (i) Et_3N, THF.

Scheme 36

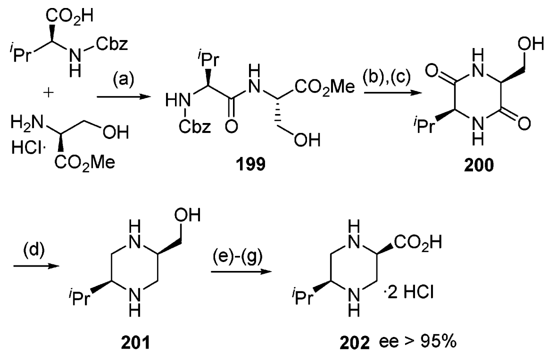


Reagents and conditions: (a) i. $BnONH_2\cdot HCl$, py, 95%; ii. $NaBH_3CN$, HOAc, 76%. (b) $RuCl_3\cdot NaIO_4$, MeCN, H_2O, CCl_4, 95%. (c) TFA, Dowex50 WX8, 54%. (d) BocNH-$(CH_2)_2$-NH_2, $NaBH_3CN$, MeOH-HOAc, 35%. (e) CrO_3, H_2SO_4, H_2O, acetone, 64%.

LiSEt in THF. From this cyclic intermediate, suitable manipulation of the nitrogen (*N*-2) followed by hydrogenolysis of the N−O bond furnished enantiopure β-amino alanine derivatives such as L-quisqualic acid (Scheme 35).[156] A more efficient route to isoxazolidin-4-ones **187** was reported by the same group; in this route isoxazolidin-4-ones **187b**,**c** were obtained in good yields from β-chloroalanine **188** by esterification with *N*-Boc or *N*-Cbz-hydroxylamine followed by cyclization with sodium hydride in DMF at high dilution.[157] An alternative intramolecular nitrogen delivery in L-serine and L-threonine derivatives can take place by formation of an aziridine ring and subsequent opening with nitrogen nucleophiles.[158] Thus, β-hydroxy α-tosylamino ester **189** can undergo an intramolecular Mitsunobu reaction rendering an optically pure *N*-tosyl aziridine, **190**, which subsequently suffered regioselective nucleophilic attack of a primary amine at the β-carbon to yield α,β-diamino esters.[159] On the other hand, there are several reports in the literature where a β-hydroxy α-amino acid, **191**, derived from threonine, is transformed into a cis aziridine, **192**, by intramolecular nucleophilic substitution of the α-nitrogen onto a β-tosyloxy or β-mesyloxy moiety.[160] As gathered in Scheme 35, further treatment of *N*-tosylaziridine **192** with L-histidine results in a mixture of dipeptides **193** with low regioselectivity in the cleavage of the aziridine (C-α/C-β). These dipeptides were separated and transformed into immunomodulator peptide FR 900490.[41a]

Finally, there are a few reports in which the hydroxymethyl group of L-serine is converted into the new carboxylic group in the target α,β-diamino acid (Scheme 36). This approach has been used in the synthesis of D-quisqualic acid from Garner's aldehyde, **194a**, obtained from L-serine.[161] Subsequent oxime formation, followed by reduction using sodium cyanoborohydride led to acetonide **195**, which, after synthetic manipulation of the newly introduced nitrogen atom to build the heterocycle and acetonide cleavage, afforded *N*-Boc amino alcohol **197** in four steps. After oxidation with $RuCl_3$/$NaIO_4$ and *N*-Boc cleavage with CF_3CO_2H, D-quisqualic acid was obtained in 17% overall yield.[162] A parallel approach was followed for the synthesis of homochiral 4-azalysine derivatives **198** employed in solid-phase synthesis. In this case, reductive amination of Garner's

Scheme 37



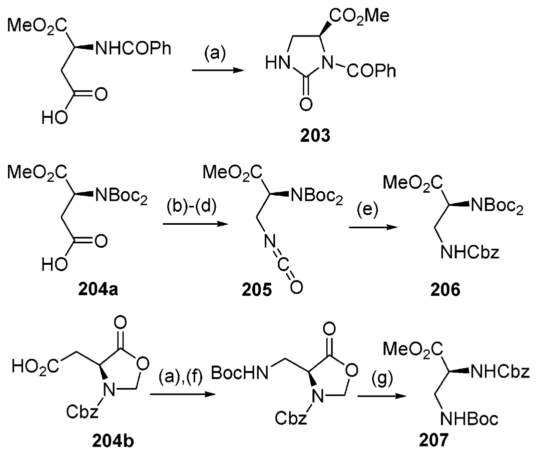
Reagents and conditions: (a) EtOCOCl, EtOAc, 4-methylmorpholine, −10 °C to 25 °C, 16 h, 66%. (b) Pd-C (10% mol), cyclohexane-MeOH, 70 °C, 5 h. (c) MeOH, 70 °C, 110 h, 86%. (d) LAH, THF, 65 %. (e) $(Boc)_2O$, MeCN, rt, 20 °C, 87 %. (f) $NaIO_4$, acetone-H_2O, $RuO_2{\cdot}H_2O$, 25 °C, 3 h, 85%. (g) 3 M HCl, EtOAc, rt, 30 min, 63%.

aldehyde, **194b**, is performed using an ethylenediamine derivative to afford **196**, which after acetonide cleavage and oxidation yielded 4-azalysine derivative **198**.[163]

This approach was also applied to the synthesis of enantiopure 2-carboxypiperazines (Scheme 37). Falorni and co-workers developed a general and versatile approach to the synthesis of optically active 5-alkylpiperazine-2-carboxylic acids based on cyclization of L- or D-serine with α-amino acids.[164] Thus, (*S*)-*N*-benzyloxycarbonylvaline (from L-valine, 99% ee) was condensed with L-serine methyl ester to give the *N*-protected dipeptide **199** in 66% yield. After removal of the Cbz group, cyclization and reduction of dioxopiperazine **200** with an excess of lithium aluminum hydride gave 2-hydroxymethylpiperazine, **201**. Subsequent Boc protection, ruthenium-catalyzed oxidation with sodium periodate, and complete deprotection under acidic conditions afforded enantiopure 5-*iso*-propyl-2-carboxypiperazine as hydrochloride **202** (ee > 95%). The same group reported an efficient stereocontrolled synthesis of (*R*)-2-carboxy-4-(3-phosphonopropyl)piperazine [(*R*)-CPP] derivatives, a selective antagonist of the NMDA receptor, by this strategy. The enantiomerically pure 2-substituted ring was prepared through cyclo-Gly−Ser from commercial products.[165,81]

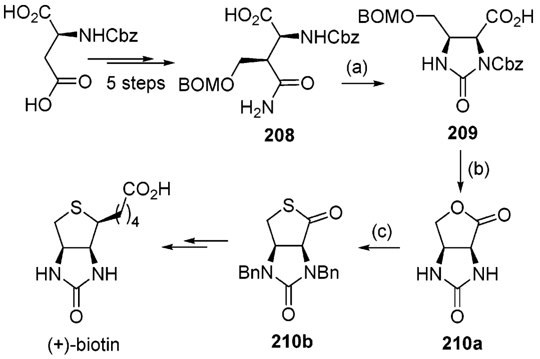
3.2.1.2. From Aspartic Acid and Related Amino Acids. Aside from using *β*-hydroxy amino acids, a common approach to L-Dpr involves either a Curtius rearrangement of free L-aspartic acid[166] or a Hofmann reaction of an L-asparagine derivative.[148c] The main side process in these reactions is formation of imidazolidinones through intramolecular trapping of the isocyanate intermediate by the vicinal nitrogen atom. In fact, an *N*-acetamido L-asparagine derivative in the presence of Br_2 and NaOH or *N*-benzamido L-aspartic acid with diphenylphosphoryl azide (DPPA) provide exclusively imidazolidinone **203** (Scheme 38).[167] However, a suitable combination of *N*-protecting groups and reagents efficiently converts asparagine and aspartic acid derivatives into α,*β*-diamino acid derivatives.[163b,168] Furthermore, it has been illustrated by different groups that a clever use of the reagents can provide orthogonally protected L-Dpr derivatives **206** and **207** by reacting isocyanate intermediates such as **205**, from the Curtius rearrangement of **204a**,**b**, with benzyl alcohol or *tert*-butyl alcohol, respectively (Scheme 38).[169]

Scheme 38



Reagents and conditions: (a) DPPA, Et_3N, 80 °C. (b) EtOCOCl, Et_3N. (c) aqueous NaN_3. (d) toluene, reflux, 87% over 3 steps. (e) BnOH, CuCl, 95%. (f) ^tBuOH, $SnCl_4$, 70 °C. (g) i. 1 N NaOH, acetone, 0 °C; ii. 6 N HCl.

Scheme 39



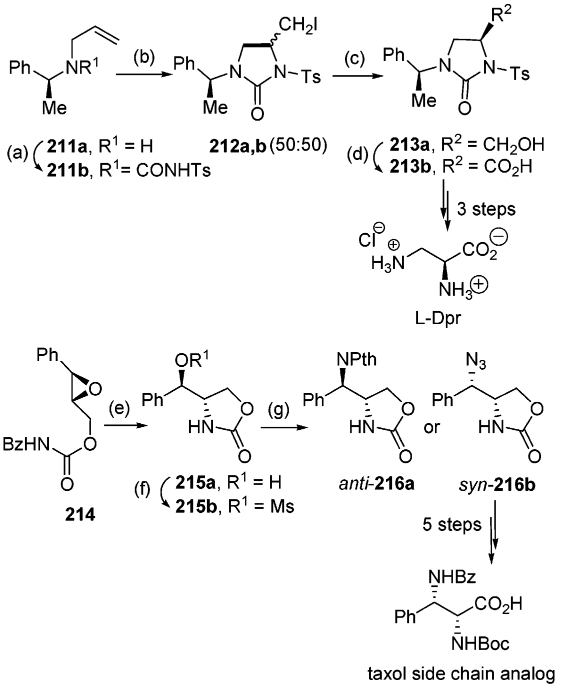
Reagents and conditions: (a) NaOCl, NaOH, H_2O, 70%. (b) H_2, $Pd(OH)_2$-C, MeOH, 80%. (c) i. BnBr, NaH, DMF, 84%; ii. KSAc, DMF, 92%.

Within the same context, L-aspartic acid has been used as starting material for the synthesis of **211**, a key intermediate for the synthesis of (+)-biotin.[170] Indeed, enantiopure *β*-hydroxymethyl asparagine derivative **208**, prepared from *N*-Cbz L-aspartic acid in five steps, was submitted to Hofmann rearrangement to afford cyclic urea **209** with no epimerization. Removal of the protecting group (BOM) by hydrogenation led to bicyclic *γ*-lactone **210a** that was converted into **210b** by *N*-benzylation and thiolactone formation (Scheme 39).

3.2.2. From Allylic Alcohols and Amines

Optically pure allylic alcohols and amines are valuable precursors to α,*β*-diamino acids. The key step in these approaches is an internal delivery of a nitrogen atom from the group attached to the hydroxy or amino group to the unsaturated carbon−carbon bond. Consequently, the degree of diastereoselectivity in the intramolecular transfer is crucial for efficient access to the target molecules. A few examples of

Scheme 40

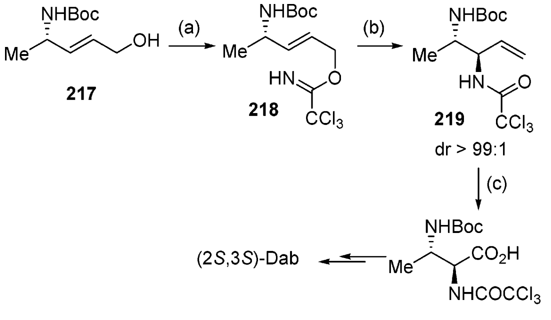


Reagents and conditions: (a) TsN=C=O, rt, >99%. (b) I$_2$, THF, NaHCO$_3$, 92%. (c) i. chromatography SiO$_2$; ii. AgOAc, HOAc, reflux; iii. K$_2$CO$_3$, EtOH, 80%. (d) CrO$_3$, H$_2$SO$_4$, H$_2$O, acetone, 60%. (e) i. NaH, THF, reflux, 88%; ii. LiOH, H$_2$O, THF, rt, 85%. (f) MsCl, NEt$_3$, 89%. (g) KPhtalimide, DMF, 79% for **216a** and NaN$_3$, TMSCl, DMF, 64% for **216b**.

these approaches are gathered below. In the first, developed by the group of Cardillo (Scheme 40), enantiopure allylic amine **211a**, prepared from (*S*)-α-phenylethylamine, was readily converted into *N*-tosyl urea **211b**. Iodine-mediated cyclization was nonselective affording a 50:50 mixture of iodo imidazolidinones **212a**,**b**. Subsequent chromatographic separation of **212a** followed by transformation into hydroxymethyl imidazolidinone **213a** and oxidation rendered acid **213b**, which after three steps gave L-Dpr.[171] In a related route reported by the group of Rossi in an approach to a taxol side-chain analogue, enantiopure epoxy carbamate **214**, prepared from cinnamyl alcohol via Sharpless asymmetric epoxidation, was treated with sodium hydride to produce oxazolidinone **215a** with complete inversion of stereochemistry at the epoxide carbon. Activation of the hydroxyl group as a methanesulfonate ester, **215b**, and further displacement using potassium phthalimide with undesired retention of configuration, gave *anti*-**216a**, which after treatment with hydrazine was submitted to an X-ray analysis. In contrast, when mesylate **215b** was treated with sodium azide and TMSCl, *syn*-**216b** was produced exclusively. Intermediate **216b** was transformed into the target α,β-diamino acid derivative by suitable manipulation of the protecting groups and oxidation in five steps (Scheme 40).[172]

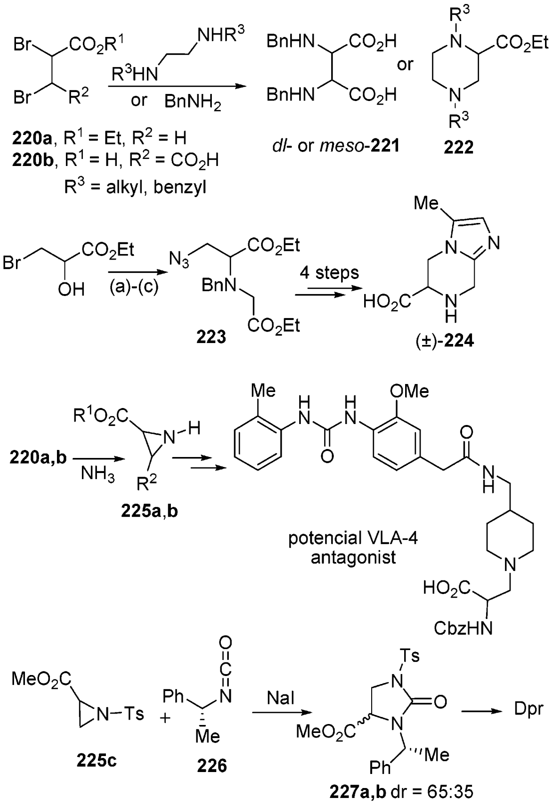
In a different example, reported by the group of Ernst and Bellus (Scheme 41), allylic alcohol **217** was transformed into trichloroacetimidate **218** and further palladium-catalyzed aza-Claisen rearrangement led exclusively to anti vicinal diamine **219** (dr > 99:1). Oxidative cleavage of the double bond and removal of the protecting groups gave (2*S*,3*S*)-diaminobutanoic acid.[173]

Scheme 41



Reagents and conditions: (a) Cl$_3$CCN, NaH, Et$_2$O, rt, 1 h, 96%. (b) PdCl$_2$(MeCN)$_2$ (6% mol), rt, 3 h, 48%. (c) RuCl$_3$·H$_2$O (cat.), NaIO$_4$, H$_2$O-MeCN-CCl$_4$, rt, 81%.

Scheme 42

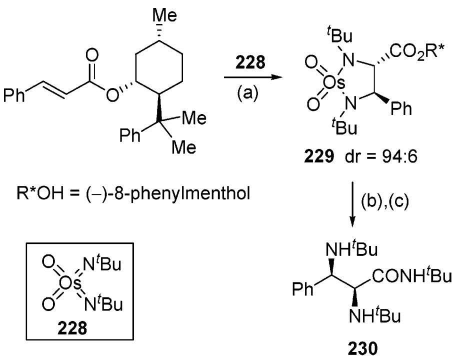


Reagents and conditions: (a) NaN$_3$, EtOH-H$_2$O, 75 °C, 17 h. (b) (F$_3$CSO$_2$)$_2$O, lutidine, CH$_2$Cl$_2$, 0 °C, 15 min. (c) BnNHCH$_2$CO$_2$Et, CH$_2$Cl$_2$, 0 °C to rt, 90 min.

3.2.3. From α,β-Unsaturated Alkenoates and Functionalized Alkanoates

3.2.3.1. From Haloalkanoates. One of the most efficient routes found among the earlier endeavors to synthesize these compounds consists of treating α,β-dibromo propionates **220a** or succinates **220b**, either commercially available or prepared by addition of bromine to α,β-unsaturated precursors, with nitrogen nucleophiles (Scheme 42). Following this approach, *meso*- and DL-2,3-diaminosuccinic acid derivatives **221** have been independently synthesized upon reaction with 2 equiv of benzylamine,[174] and 2-carboxypiperazines **222** can be readily obtained

Scheme 43

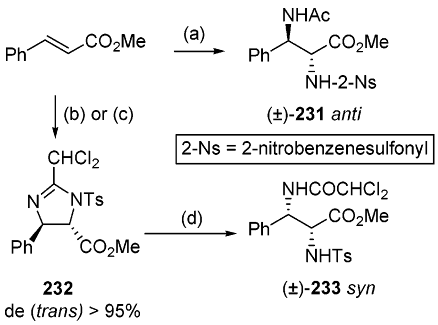


Reagents and conditions: (a) THF, –15 °C. (b) ^{t}BuNH$_2$, ZnCl$_2$. (c) NaBH$_4$, EtOH, rt, 95%.

when 1,2-ethylenediamine derivatives are used.[175] Furthermore, sequential introduction of the nitrogen nucleophiles has also been reported in the context of the synthesis of piperazines fused to azole rings using ethyl-β-bromo-α-hydroxy propanoate as starting material. Bromide displacement with sodium azide followed by triflate formation and substitution with ethyl-*N*-benzyl glycinate gave azido amino ester **223**, which was finally manipulated furnishing piperazine carboxylic acids **224** (Scheme 42).[176] However, when ammonia is used as the nucleophile, racemic methoxycarbonyl aziridines **225**, readily resolved by enzymatic means, were obtained.[177] This protocol has been recently used for the synthesis of enantiopure Dpr[178] and of VLA-4 antagonists containing an α,β-diamino acid residue by submitting the aziridine intermediates to nucleophilic ring opening with ammonia or sodium azide.[67] Alternatively, in a recent report from the group of Nadir, a facile route for the synthesis of α,β-diamino acids is disclosed by reaction of 2-methoxycarbonyl aziridine, **225c**, generated from an α,β-unsaturated ester, with chiral isocyanate **226** in the presence of sodium iodide to produce a mixture of imidazolidinones **227a**,**b** with low diastereoselectivity (65:35) by means of initial iodide-mediated aziridine opening. After separation and acidic cleavage, both enantiomers of Dpr are available. Similarly, an additional alkyl substituent can be placed α to the ester moiety of the starting aziridine allowing for the synthesis of α-alkyl-α,β-diamino acids.[179]

3.2.3.2. From Alkenoates. Aside from the above examples, it could be easily envisioned that enantioselective diamination of α,β-unsaturated acids is the shorter route to α,β-diamino acids; however, the direct asymmetric diamination of olefins is a reaction comparatively less studied than the related dihydroxylation process. In fact, the stoichiometric osmium-mediated diamination of fumarates and cinnamates with bis(*tert*-butylimido) complex **228** is a stepwise process and in the presence of (DHQD)$_2$-PHAL or (DQD)$_2$PHAL leads essentially to racemic products. However, incorporation of a (−)-8-phenylmenthyloxy auxiliary to the cinnamate provides complex **229** in excellent diastereomeric ratio (94:6). Further reaction with *tert*-butylamine and ZnCl$_2$ provides an amide that was submitted to osmium removal with sodium borohydride furnishing α,β-diamino amide **230** in good yield (Scheme 43).[180]

Scheme 44

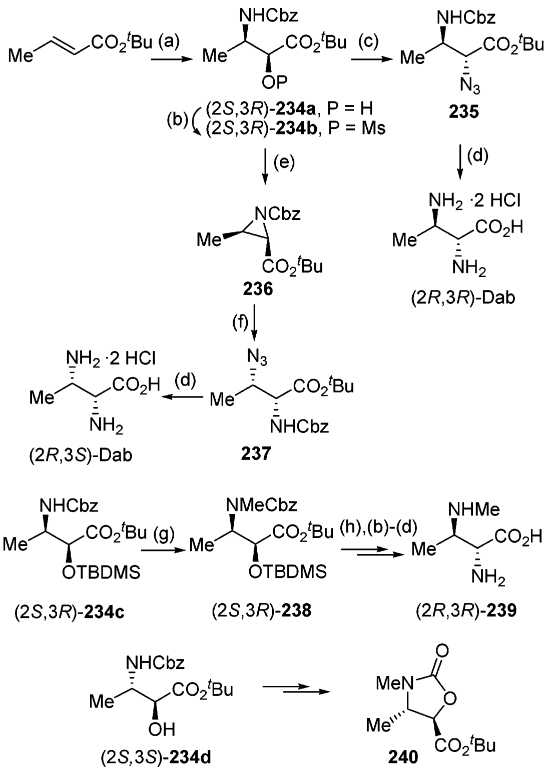


Reagents and conditions: (a) i. 2-NsNCl$_2$, MeCN; ii. aqueous Na$_2$SO$_3$, 74%. (b) TsNCl$_2$, MeCN, [(C$_3$F$_7$CO$_2$)$_2$Rh]$_2$·PPh$_3$ (cat.), 4 Å MS, 51%. (c) TsNCl$_2$, MeCN, FeCl$_3$·PPh$_3$ (cat.), 63%. (d) 6 N HCl, 70 °C, 92%.

The group of Li has reported the first direct electrophilic diamination of α,β-unsaturated esters using *N*,*N*-dichloro-2-nitrobenzenosulfonamide (2-NsNCl$_2$) in acetonitrile (Scheme 44).[181] The process takes place with complete anti diastereoselectivity, and the use of acetonitrile is crucial since a molecule of solvent is apparently responsible for delivering the second nitrogen atom to the final racemic anti α,β-diamino ester (±)-**231**. Further studies by this group have revealed that the use of *N*,*N*-dichloro-*p*-toluenesulfonamide in the presence of Rh(II)- or Fe(III)-containing metal catalysts using acetonitrile again provides efficient access to racemic trans imidazolines **232** that can be readily transformed into *syn*-α,β-diamino esters (±)-**233** upon acidic hydrolysis.[182]

Different groups have envisioned that α,β-diamino acid derivatives could be prepared efficiently by Sharpless asymmetric aminohydroxylation of α,β-unsaturated esters followed by adequate manipulations of the resulting amino alcohols. The group of Janda (Scheme 45),[183] has described that the regio- and enantioselective aminohydroxylation of *tert*-butyl crotonate using (DHQD)$_2$PHAL gave (2*S*,3*R*)-**234a**, and then mesylation of the alcohol afforded *syn*-amino mesylate **234b**. Nucleophilic substitution of the mesylate with sodium azide to give **235** followed by hydrogenation and deprotection under acidic conditions rendered enantiopure *anti*-α,β-diamino acid (2*R*,3*R*)-Dab. In contrast, treatment of mesylate **234b** with KO^{t}Bu rendered *cis*-aziridine **236**, which was cleaved with trimethylsilyl azide to give **237**. Subsequent hydrogenation and deprotection produced enantiopure syn diamino acid (2*R*,3*S*)-Dab. Williams followed a parallel approach (Scheme 45) to independently synthesize both enantiomers of *anti*-2-amino-3-methylaminobutanoic acid **239**.[184] In fact, silyl ether **234c**, prepared from (2*S*,3*R*)-**234a**, was *N*-methylated with sodium hydride and dimethyl sulfate to render **238**, which after five steps, comprising mesylate formation and displacement with azide, was transformed into (2*R*,3*R*)-**239**. The above approach allowed for the synthesis of (2*S*,3*S*)-**239** by simply using (DHQ)$_2$PHAL as a ligand in the aminohydroxylation step; however, the synthesis of the syn isomers was unsuccessful, since all attempts to process (2*S*,3*S*)-**234d**, prepared by Mitsunobu reaction of (2*R*,3*S*) β-amino alcohol, following the same

Scheme 45



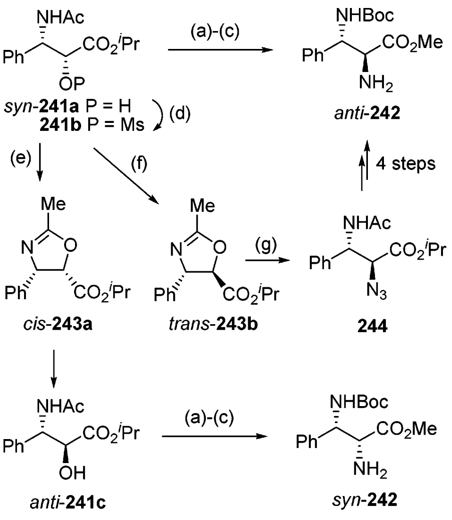
Reagents and conditions: (a) $(DHQD)_2PHAL$ (5%), $K_2OsO_2(OH)_4$ (4%), CbzNHCl, $MeCN$-H_2O, 0 °C. (b) MsCl, Et_3N, CH_2Cl_2. (c) NaN_3, DMF. (d) i. H_2, Pd-C, MeOH; ii. TFA, CH_2Cl_2 then 1 N HCl. (e) KO^tBu, THF. (f) $TMSN_3$, MeOH. (g) NaH, Me_2SO_4, THF. (h) 5% HF, MeCN.

series of transformations yielded oxazolidinone **240** as major product.

In a very similar sequence recently reported by the group of Lee, *syn*-**241a**, prepared by Sharpless aminohydroxylation of isopropyl cinnamate, was used for the synthesis of the corresponding enantiopure α,β-diamino ester *anti*-**242** using a Mitsunobu reaction with hydrazoic acid to invert the hydroxyl group attached at the α-carbon (Scheme 46). In addition, *syn*-**241a** was converted to *anti*-**241c** through mesylation and in-situ formation of an oxazoline intermediate, **243a**, promoted by the presence of the acetamido group at the β-carbon. Finally, *anti*-**241c** was transformed into enantiopure α,β-diamino ester *syn*-**242** following the same synthetic sequence. Furthermore, treatment of mesylate **241b** with DBU results in a clean epimerization and cyclization to trans oxazoline **243b**. Attempts of nucleophilic ring cleavage in both epimers, **243a** and **243b**, revealed huge differences in reactivity that can be predicted by ab initio molecular calculations. In particular, trans oxazoline **243b** reacted with trimethylsilyl azide affording anti azide **244** while cis **243a** was cleanly recovered under identical reaction conditions. After hydrogenation, azide **244** was finally transformed into enantiopure *anti*-α,β-diamino ester **242**.[185]

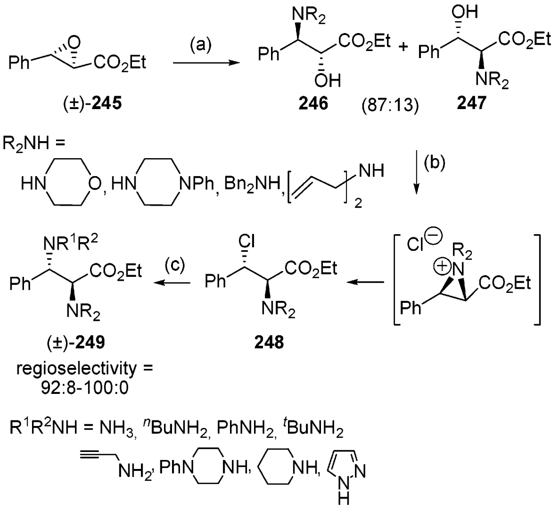
Within the same context, the group of Sharpless has outlined a short and highly versatile route to a series of α,β-diamino esters from the mixture of regioisomeric anti aminohydroxy propanoates, **246** and **247**, prepared from trans glycidic ester **245** and a secondary amine (Scheme 47). Subsequent mesylation of the mixture provided exclusively β-chloroamino ester **248** in quantitative yield via in-situ chloride attack to an aziridinium ion. Regeneration of the aziridinium ion from isolated **248**, followed by in-situ reaction with a wide range of nitrogen nucleophiles took place with excellent yields and regioselectivities furnishing racemic *anti*-α,β-diamino esters **249** as major products. Furthermore, the mixture of **246** and **247** underwent a one-pot procedure, mesylation and nucleophilic attack of the amine, to give **249** through the aziridinium ion in an extremely efficient manner.[186]

Scheme 46



Reagents and conditions: (a) i. HCl, MeOH, reflux; ii. Boc_2O, Et_3N, 0 °C to rt, 87%. (b) PPh_3, HN_3, DEAD, 90%. (c) H_2, Pd-C, EtOAc, 99%. (d) MsCl, Et_3N, CH_2Cl_2, 93%. (e) $KHCO_3$, acetone, H_2O, 70 °C, 62%. (f) DBU, $CHCl_3$, reflux, 76%. (g) $TMSN_3$, MeOH, 70 °C, 90%.

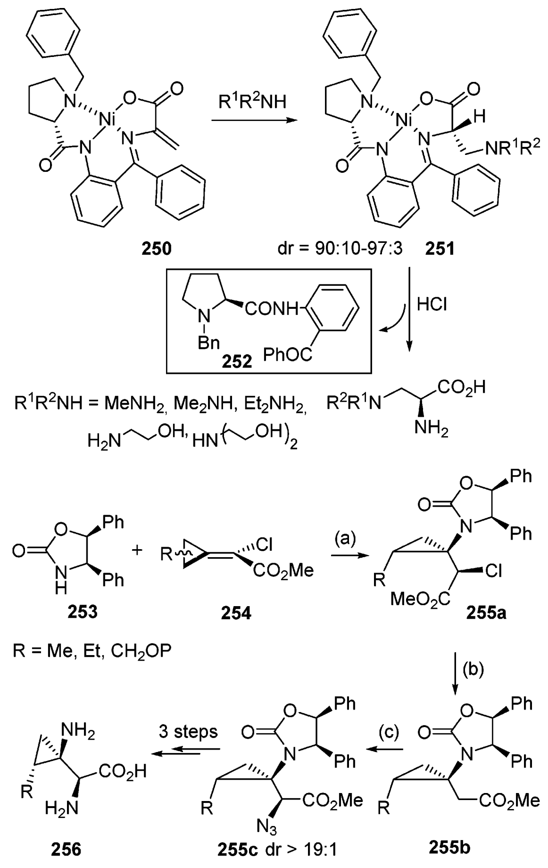
Scheme 47



Reagents and conditions: (a) R_2NH, EtOH, reflux, 94-99%. (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 94-99%. (c) R^1R^2NH, K_2CO_3, MeCN, 72-99%.

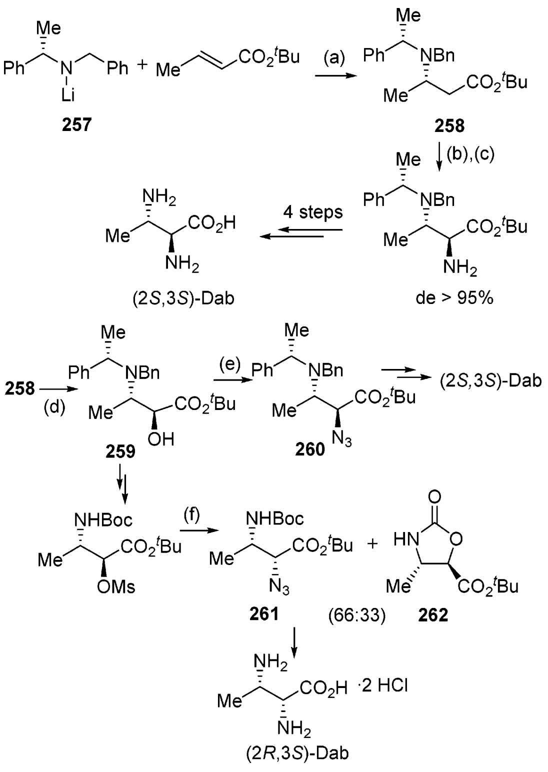
A different approach takes advantage of the Michael-acceptor character of α,β-unsaturated acid derivatives to nitrogen nucleophiles. Within this context, α,β-dehydroalanine derivatives have been extremely useful starting materials containing the α-nitrogen for the Michael addition of amines.[11a,187]

Scheme 48



Reagents and conditions: (a) DB-18-cr-6, THF, KH and separation, 48-79%. (b) Zn-Cu, THF-H₂O, 61-92%. (c) i. LiHMDS, trisylazide, –78 °C; ii. HOAc, rt, 65-85%.

Scheme 49

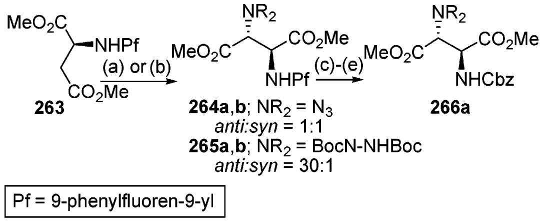


Reagents and conditons: (a) THF, –78 °C. (b) i. LDA, THF, –78 °C; ii. trisylazide, THF, –78 °C; iii. HOAc, THF, –78 °C to rt, 32%. (c) PPh₃, THF, H₂O, rt, 91%. (d) i. LDA, THF, –78 °C; ii. (–)-(camphorsulfonyl)oxaziridine. (e) PPh₃, DEAD, HN₃ or (PhO)₂PON₃ or phtalimide. (f) NaN₃, DMF, 55%.

In an interesting example of the above methodology (Scheme 48) from the group of Belokon, the asymmetric synthesis of α,β-diamino acids is performed via a chiral complex of Ni(II) with a dehydroalanine derivative, **250**. The presence of chiral ligand **252** in the complex provides a high facial discrimination for the attack of an amine affording the *Re* adduct **251** in diastereomeric ratios ranging from 90:10 to 97:3 depending on the nature of the reacting amine. After crystallization of the mixtures, treatment under acidic conditions allowed for the synthesis of the enantiopure (*S*)-α,β-diamino acids and the recovery of the chiral ligand **252**.[188] In another asymmetric example, optically active oxazolidinone **253** was used as Michael donor in the addition to 2-chloro-2-cyclopropylideneacetates **254** affording Michael adducts **255a** with excellent trans selectivity (Scheme 48). After separation and reductive dehalogenation, two diastereomeric cyclopropyl acetic acid derivatives **255b** were obtained. Either diastereomer can be used as precursor to new cyclopropyl α,β-diamino acids, introducing the amino group by electrophilic azide transfer. In fact, once the lithium enolate is formed, quenching with trisyl azide led to azide **255c** with high diastereoselectivity, which after deprotections afforded conformationally restrained enantiopure *anti*-α,β-diamino acids **256**.[189] More recently, a related strategy starting with 2-chloro-2-cyclopropylideneacetate **254** (R = H) has been employed for the synthesis of cyclopropylmethoxycarbonyl piperazine derivatives.[190] On the other hand, the regioselectivity of the Michael addition can be reversed by the presence of a nitro group attached to the β-carbon of the α,β-unsaturated ester. However, this approach, employed in a study for the synthesis and evaluation of angiotensin II analogues, provided a nondiastereoselective mixture of *syn*- and *anti*-α,β-diamino acids as racemic materials.[64b]

In this context, when the starting α,β-unsaturated ester does not have a pre-existing nitrogen atom in the molecule, the synthesis of the α,β-diamino acid requires two steps, Michael addition of an amine to introduce the β-nitrogen and subsequent amination of an enolate to introduce the α-nitrogen. The groups of Seebach and Davies have independently examined the above methodology (Scheme 49).[191,192] In particular, Davies showed that addition of chiral secondary lithium amide **257** was crucial to obtain β-amino ester **258** with complete diastereocontrol. Further diastereoselective trapping of the enolate with trisyl azide (anti, de > 95%) followed by Staudinger reaction and hydrolysis of the iminophosphorane intermediate led, after four more steps, to enantiopure *anti*-α,β-diamino acid, (2*S*,3*S*)-Dab. Furthermore, after anti α-hydroxylation of the enolate using chiral (−)-(camphorsulfonyl)oxaziridine, these authors envisioned that amino alcohol **259** could undergo a double inversion of the α-hydroxyl group by submission to Mitsunobu conditions through the in-situ formation of an aziridinium ion. In fact, the efficiency of the double-inversion process was proven using either diphenylphosphoryl azide, hydrazoic acid, or

Scheme 50



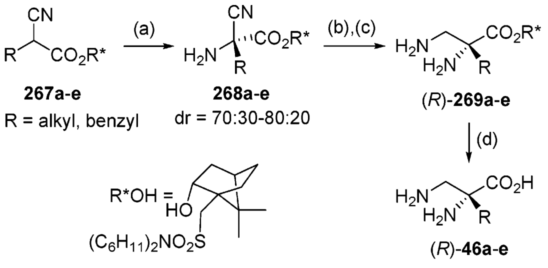
Reagents and conditions: (a) KHMDS, trisylazide, THF, –78 °C. (b) LiHMDS, HMPA-THF, DBAD, 80%. (c) separation. (d) H_2, Pd-C, MeOH, rt. (e) CbzCl, CH_2Cl_2, rt, 87% over 3 steps.

phthalimide, affording **260** with retention of the configuration. After suitable manipulation, **260** was transformed into *anti*-α,β-diamino acid (2*S*,3*S*)-Dab. In contrast, displacement of the mesylate derived from **259** with sodium azide gave a 66:33 mixture of syn azide **261** and oxazolidinone **262**. After separation, hydrogenation, and acidic deprotection, enantiopure *syn*-α,β-diamino acid (2*R*,3*S*)-Dab was also available.

3.2.3.3. Electrophilic Amination of Enolates. The diastereoselective electrophilic amination of β-amino enolates provides an efficient access to α,β-diamino acid derivatives of diverse structure. This reaction has been used for the introduction of a nitrogen atom at C-3 of β-lactams within the synthesis of an analogue of rhodopeptin B5 containing an α,β-diamino acid residue[193] and also for the amination at α-carbon of piperidinyl acetic acid derivatives in a study focused on the synthesis of analogues of streptolutin as enantiopure materials.[194] Furthermore, this approach has been successfully employed by the group of Sardina in the diastereocontrolled synthesis of 2,3-diamino succinates also referred to in the literature as 3-amino aspartates (Scheme 50). These authors have observed that regioselective (C-3) lithium or potassium enolate formation in dimethylaspartate **263** followed by quenching with trisyl azide provided an equimolecular mixture of both azide epimers, *syn*- and *anti*-**264a**,**b** that were further transformed into different 3-amino aspartate derivatives. However, upon quenching with di-*tert*-butylazodicarboxylate (DBAD) in the presence of HMPA as cosolvent, a highly diastereoselective 30:1 mixture of *anti*- and *syn*-α,β-diamino aspartates **265a**,**b** was obtained, which after separation and functional group manipulation led independently to enantiopure anti and syn dimethyl 3-amino aspartate derivatives **266a** and **266b** (not shown in the scheme).[195] A parallel approach has been employed recently for the synthesis of 3-azido aspartates that were used as orthogonally protected units for their incorporation into peptide structures analogues of somatostatin.[196] A similar strategy was also employed in the total synthesis of Antrimycin D_v.[39d]

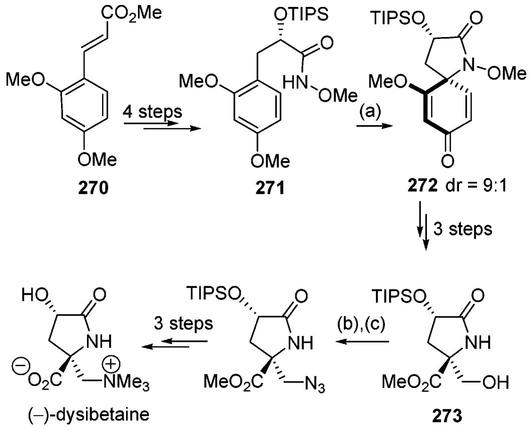
The electrophilic amination of enolates has also been applied to 2-cyano propanoates for the synthesis of α,β-diamino acids. The group of Cativiela found that 2-alkyl- and 2-benzyl-2-cyano propanoates **267** containing a (1*S*,2*R*,4*R*)-10-(dicyclohexylsulfamoyl)-isobornyloxy group as chiral auxiliary (R*) can be converted into 2-amino-2-cyano propanoates **268** with moderate to good diastereoselectivites upon treatment with LHMDS and *O*-(diphenylphosphinyl)-hydroxylamine (Scheme 51). By separation and hydrogenation with rhodium on alumina, diastereomerically pure (2*R*)-**268** were readily transformed into α,β-diamino esters **269**, which finally rendered enantiopure α-substituted α,β-diamino acids (*R*)-**46a**−**e** by reaction with KOH/methanol.[197]

Scheme 51



Reagents and conditions: (a) LiHMDS, $Ph_2P(O)ONH_2$, THF, –78 °C to rt, 60-70%. (b) separation. (c) H_2, Rh-Al_2O_3, MeOH-NH_3, 83%-quantitative. (d) KOH, MeOH, 90-95%.

Scheme 52

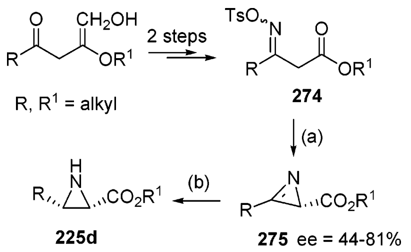


Reagents and conditions: (a) PIFA, CH_2Cl_2, MeOH, –78 °C to –30 °C, 99%. (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 87%. (c) NaN_3, DMF, 80 °C, 63%.

Within the context of introducing the nitrogen as an electrophile, a recent and interesting example was brought to light by the group of Wardrop in the total synthesis of (−)-dysibetaine (Scheme 52). The synthetic route commenced from α,β-unsaturated ester **270**, which was readily converted into enantiopure α-silyloxy methoxylamide **271** in four steps using Sharpless asymmetric dihydroxylation and regioselective reduction of the β-hydroxyl group as the key steps. Subsequent generation of an *N*-acylnitrenium ion using phenyliodine(III) bis(trifluoroacetate) (PIFA) promoted spirocyclization to afford spirodienone **272** as an inseparable 9:1 mixture of C-5 epimers. After ozonolysis, formyl group reduction, and N−O reductive cleavage, **272** was converted into **273**. Azide displacement onto a mesylate generated from **273** followed by removal of the silyl group, hydrogenation of the azide, permethylation, and ester hydrolysis finally furnished (−)-dysibetaine.[198]

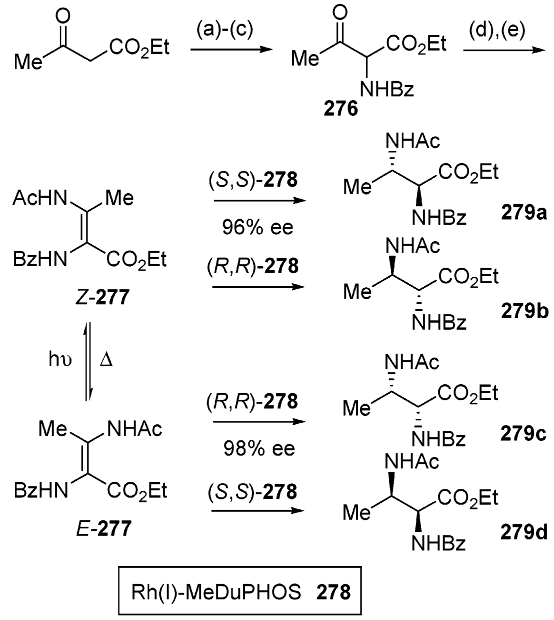
3.2.3.4. From β-Keto Esters and Related Compounds. The use of β-keto esters as precursors to α,β-diamino acid derivatives is also documented in the literature. For instance, enantioenriched alkoxycarbonyl aziridines **225d** were prepared by an asym-

Scheme 53



Reagents and conditions: (a) quinidine (10% mol or stoichiometric), K_2CO_3, toluene. (b) $NaBH_4$.

Scheme 54

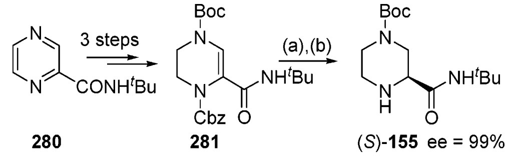


Reagents and conditions: (a) $NaNO_2$, aqueous HOAc, 0 °C, 81%. (b) Al(Hg), THF. (c) BzCl, 63% (3 steps). (d) NH_4OAc, MeOH, 81%. (e) AcCl, pyr, CH_2Cl_2-Et_2O.

metric Neber reaction (Scheme 53), consisting of treatment of sulfonic esters of ketoximes **274** with a catalytic amount (10%) of quinidine and 10 equiv of K_2CO_3. Disubstituted azirines **275** thus generated in moderate ee's (80%) suffered subsequent reduction with sodium borohydride to give exclusively *cis*-alkoxycarbonyl aziridines **225d** in good yields.[199]

In another recent report by the group of Robinson, ethyl acetoacetate was used as a starting material for an α-nitrosation followed by reduction and benzoylation to furnish α-amino-β-ketoester **276** (Scheme 54). Subsequent treatment of **276** with ammonium acetate and acetylation led to α,β-unsaturated α,β-diamino esters **277** as a separable 4:1 mixture of *E*/*Z* isomers that can be interconverted by thermal or photochemical isomerization. Nevertheless, the key process in this report is the highly enantioselective hydrogenation of α,β-unsaturated α,β-diamino esters *E*-**277** or *Z*-**277** using (*R*,*R*)- or (*S*,*S*)-MeDuPHOS–Rh(I) triflate **278** as chiral catalyst that provides all four isomers of α,β-diaminobutanoic acid derivatives **279a**–**d** in ee > 95%.[200] Similarly, a bisferrocenyl phosphine has been used as chiral ligand in the asymmetric hydrogenation of α,β-dehydro-α,β-diamino esters catalyzed by a rhodium(I) complex.[201] Furthermore, the recent availability of routes to α,β-unsaturated α,β-diamino ester derivatives[202] could increase the versatility of this approach.

Scheme 55



Reagents and conditions: (a) H_2, [(*R*)-BINAP(COD)Rh]OTf, MeOH, 70 bar, 96%. (b) Pd-C, H_2 MeOH

Within this context, asymmetric hydrogenation of pyrazine derivatives is one of the more efficient routes to enantiopure 2-carboxypiperazine derivatives. Classically, routes to enantiomerically pure piperazine-2-carboxylic acid were based on fractional crystallization of diastereomeric ammonium salts from chiral acids [i.e., (*S*)-CSA][83c,203] or diasteromeric menthyl esters[204] and enzymatic kinetic resolution.[205] Indeed very recently, a novel amidase acting on (±)-piperazine-2-*tert*-butylcarboxamide has been identified from *Pseudomonas sp*. MCI3434. The enzyme acts on the *R*-isomer to yield (*R*)-piperazine-2-carboxylic acid.[206] However, recent reports of asymmetric hydrogenation have provided a convenient route to these cyclic α,β-diamino acid derivatives (Scheme 55).[207,208] In fact, pyrazine **280** was submitted to partial hydrogenation and then to sequential introduction of *N*-protecting groups to afford tetrahydropyrazine. The catalytic enantioselective hydrogenation of tetrahydropyrazine **281** using [(*R*)-BINAP-(COD)Rh]TfO afforded the orthogonally protected piperazine in 96% yield and 99% ee; subsequent hydrogenolytic removal of the Cbz group gave enantiopure (*S*)-**155**, a valuable intermediate in the synthesis of indinavir.

4. Conclusions

The remarkable ubiquity of these nonproteinogenic amino acids along with the widespread presence of this structural motif in a number of molecules with diverse therapeutic applications have been brought to light in this overview of the chemistry of α,β-diamino acids. Furthermore, this article shows that α,β-diamino acids are becoming useful tools for the study of the nature of peptidic entities seeking to control and to modify the behavior of peptidic molecules with a relevant role in living organisms.Therefore, the development of short, general, and efficient synthetic routes to α,β-diamino acids is important. Despite the number of approaches to these diamino acids, there are still many challenges in the area, in particular, focused in structurally diverse and enantiopure materials, with the catalytic enantioselective carbon–carbon bond formation and the enantioselective hydrogenation of α,β-unsaturated α,β-diamino acids being among the more promising approaches to fulfill the above requirements.

This article clearly demonstrates that the rich chemistry of α,β-diamino acids has suffered a great advance in the past decades; new applications and synthetic routes for these products have been developed; however, future endeavors in this area will provide new routes and applications of these fascinating molecules.

5. Acknowledgment

This work was supported by DGICYT (BQU2003-02921) and CAM (GR/SAL/0823/2004). We thank JANSSEN-CILAG for generous additional support and CAM for a doctoral fellowship to A.F.

6. References

(1) (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (c) Lee, W. K.; Ha, H.-J. *Aldrichim. Acta* **2003**, *36*, 57. (d) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Curr. Med. Chem.* **2004**, *11*, 1873.

(2) Corrigan, J. J.; Srinivasan, N. G. *Biochemistry* **1966**, *5*, 1185.

(3) Evans, C. S.; Qureshi, M. Y.; Bell, E. A. *Phytochemistry* **1977**, *16*, 565.

(4) Shaw, G. J.; Ellingham, P. J.; Bingham, A.; Wright, G. J. *Phytochemistry* **1982**, *21*, 1635.

(5) Meierhenrich, U. J.; Muñoz Caro, G. M.; Bredehöft, J. H.; Jessberger, E. K.; Thiemann, W. H.-P. *Proc. Natl. Acad. Sci.* **2004**, *101*, 9182.

(6) Ikegami, F.; Murakoshi, I. *Phytochemistry* **1994**, *35*, 1089.

(7) (a) Subasinghe, N.; Schulte, M.; Roon, R. J.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1992**, *35*, 4602. (b) Hermit, M. B.; Greenwood, J. R.; Bräuner-Osborne, H. *J. Biol. Chem.* **2004**, *279*, 34811.

(8) (a) Chang, H.-C.; Lee, T.-H.; Chuang, L.-Y.; Yen, M.-H.; Hung, W.-C. *Cancer Lett.* **1999**, *145*, 1. (b) Dobbin, P. S.; Hider, R. C.; Hall, A. D.; Taylor, P. D.; Sarpong, P.; Porter, J. B.; Xiao, G.; van der Helm, D. *J. Med. Chem.* **1993**, *36*, 2448.

(9) (a) Martínez, A. P.; Lee, W. W. *J. Org. Chem.* **1965**, *30*, 317. (b) Jane, D. E.; Hoo, K.; Kamboj, R.; Deverill, M.; Bleakman, D.; Mandelzys, A. *J. Med. Chem.* **1997**, *40*, 3645. (c) Nollet, A. J. H.; Pandit, U. K. *Tetrahedron* **1969**, *25*, 5983.

(10) (a) MacLeod, J. K.; Summons, R. E.; Parker, C. W.; Lethan, D. S. *J. Chem. Soc., Chem. Commun.* **1975**, *19*, 809. (b) Duke, C. C.; MacLeod, J. K.; Summons, R. E.; Lethan, D. S.; Parker, C. W. *Aust. J. Chem.* **1978**, *31*, 1291.

(11) (a) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **1999**, *40*, 4099. (b) Saito, K.; Kanda, R.; Kurosawa, M.; Murakoshi, I. *Can. J. Chem.* **1994**, *72*, 188.

(12) (a) Ikegami, F.; Ongena, G.; Sakai, R.; Itagaki, S.; Kobori, M.; Ishikawa, T.; Kuo, Y.-H.; Lambein, F.; Murakoshi, I. *Phytochemistry* **1993**, *33*, 93. (b) Ikegami, F.; Mizuno, M.; Kihara, M.; Murakoshi, I. *Phytochemistry* **1990**, *29*, 3461.

(13) (a) Copani, A.; Canonico, P. L.; Catania, M. V.; Aronica, E.; Bruno, V.; Ratti, E.; van Amsterdan, F. T. M.; Gaviraghi, G.; Nicoletti, F. *Brain Res.* **1991**, *558*, 79. (b) Vega, A.; Bell, E. A. *Phytochemistry* **1967**, *6*, 759. (c) Davis, A. J.; Hawkes, G. E.; O'Brien, P.; Wang, G.; Nunn, P. B. *J. Chem. Res. (S)* **1991**, 84.

(14) (a) Murch, S. J.; Cox, P. A.; Banack, S. A.; Steele, J. C.; Sacks, O. W. *Acta Neurol. Scand.* **2004**, *110*, 267. (b) Cox, P. A.; Banack, S. A.; Murch, S. J. *Proc. Natl. Acad. Sci.* **2003**, *100*, 13380. (c) Banack, S. A.; Cox, P. A. *Botan. J. Linn. Soc.* **2003**, *143*, 165.

(15) (a) Ross, S. M.; Roy, D. N.; Spencer, P. S. *J. Neurochem.* **1989**, *53*, 710. (b) Sabri, M. I.; Lystrup, B.; Roy, D. N.; Spencer, P. S. *J. Neurochem.* **1995**, *65*, 1842.

(16) Yigzaw, Y.; Gorton, L.; Solomon, T.; Akalu, G. *J. Agric. Food Chem.* **2004**, *52*, 1163.

(17) (a) Bruyn, A.; Becu, C.; Lambein, F.; Kebede, N.; Abegaz, B.; Nunn, P. B. *Phytochemistry* **1994**, *36*, 85. (b) Zhao, L.; Li, Z.; Li, G.; Chen, X.; Hu, Z. *Phys. Chem. Chem. Phys.* **1999**, *1*, 3771. (c) Abegaz, B. M.; Nunn, P. B.; De Bruyn, A.; Lambein, F. *Phytochemistry* **1993**, *33*, 1121.

(18) (a) White, C. L.; Hanbury, C. D.; Young, P.; Phillips, N.; Wiese, S. C.; Milton, J. B.; Davidson, R. H.; Siddique, K. H. M.; Harris, D. *Anim. Feed Sci. Technol.* **2002**, *99*, 45. (b) Hanbury, C. D.; White, C. L.; Mullan, B. P.; Siddique, K. H. M. *Anim. Feed Sci. Technol.* **2000**, *87*, 1.

(19) Lambein, F.; Ongena, G.; Kuo, Y.-H. *Phytochemistry* **1990**, *29*, 3793.

(20) (a) Hochstein, F. A. *J. Org. Chem.* **1959**, *24*, 679. (b) Pettit, G. R.; Von Dreele, R. B.; Herald, D. L.; Edgard, M. T.; Wood, H. B. *J. Am. Chem. Soc.* **1976**, *98*, 6742.

(21) (a) Umezawa, H.; Maeda, K.; Takeuchi, T.; Okami, Y. *J. Antibiotics, Ser. A* **1966**, *19*, 200. (b) Umezawa, H.; Muraoka, Y.; Fujii, A.; Naganawa, H.; Takita, T. *J. Antibiotics* **1980**, *33*, 1079. (c) Galm, U.; Hager, M. H.; Van Lanen, S. G. V.; Ju, J.; Thorson, J. S.; Shen, B. *Chem. Rev.* **2005**, *105*, 739.

(22) (a) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107. (b) Boger, D. L.; Ramsey, T. M.; Cai, H.; Hoehn, S. T.; Stubbe, J. *J. Am. Chem. Soc.* **1998**, *120*, 9139. (c) Hashimoto, S.; Wang, B.; Hecht, S. M. *J. Am. Chem. Soc.* **2001**, *123*, 7437. (d) Katano, K.; An, H.; Aoyagi, Y.; Overhand, M.; Sucheck, S. J.; Stevens, W. C., Jr.; Hess, C. D.; Zhou, X.; Hecht, S. M. *J. Am. Chem. Soc.* **1998**, *120*, 11285.

(23) (a) Yamamoto, T.; Yoneda, K.; Ueta, E.; Osaki, T. *Jpn. J. Pharmacol.* **2001**, *87*, 41. (b) Asano, Y.; Ihn, H.; Shikada, J.; Kadono, T.; Kikuchi, K.; Tamaki, K. *Br. J. Dermatol.* **2004**, *150*, 1213.

(24) (a) Wank, H.; Rogers, J.; Davies, J.; Schroeder, R. *J. Mol. Biol.* **1994**, *236*, 1001. (b) Ando, T.; Matsuura, K.; Izumi, R.; Noda, T.; Take, T.; Nagata, A.; Abe, J. *J. Antibiotics* **1971**, *24*, 680. (c) Izumi, R.; Noda, T.; Ando, T.; Take, T.; Nagata, A. *J. Antibiotics* **1972**, *25*, 201.

(25) (a) Hawkes, G. E.; Randall, E. W.; Hull, W. E.; Gattegno, D.; Conti, F. *Biochemistry* **1978**, *17*, 3986. (b) Yoshioka, H.; Aoki, T.; Goko, H.; Nakatsu, K.; Noda, T.; Sakakibara, T.; Take, A.; Nagata, A.; Abe, J.; Nakamiya, T.; Shiba, T.; Kaneko, T. *Tetrahedron Lett.* **1971**, 2043. (c) Thomas, M. G.; Chan, Y. A.; Ozanick, S. G. *Antimicrob. Agents Chemother.* **2003**, *47*, 2823. (d) Noda, T.; Take, T.; Nagata, A.; Wakamiya, T.; Shiba, T. *J. Antibiotics* **1972**, *25*, 427. (e) Wakamiya T.; Shiba, T. *J. Antibiotics* **1975**, *28*, 292.

(26) Jordan, D. C.; Yamamura, Y.; McKague, M. E. *Can. J. Microbiol.* **1969**, 1005.

(27) (a) Vos, S.; Berrisford, D. J.; Avis, J. M. *Biochemistry* **2002**, *41*, 5383. (b) Wallis, M. G.; Streicher, B.; Wank, H.; von Ahsen, U.; Clodi, E.; Wallace, S. T.; Famulok, M.; Schroeder, R. *Chem. Biol.* **1997**, *4*, 357.

(28) Bycroft, B. W.; Cameran, D.; Croft, L. R. Hassanali-Walji, A.; Johnson, A. W.; Webb, T. *Nature* **1971**, *231,* 301.

(29) Nomoto, S.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1709.

(30) (a) Waksman, S. A.; Woodruff, H. B. *J. Bacteriol.* **1943**, *46*, 299. (b) Jackson, M. D.; Gould, S. J.; Zabriskie, T. M. *J. Org. Chem.* **2002**, *67*, 2934.

(31) (a) Rane, D. F.; Girijavallabhan, V. M.; Ganguly, A. K.; Pike, R. E.; Saksena, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 3201. (b) Andruszkiewicz, R. *J. Antibiotics* **1994**, *47*, 380. (c) Andruszkiewicz, R.; Zieniawa, T.; Ciimara, H.; Kasprzak, L.; Borowski, E. *J. Antibiotics* **1994**, *47*, 715. (d) Cooper, R.; Horan, A. C.; Gentile, F.; Gullo, V.; Loebenberg, D.; Marquez, J.; Patel, M.; Pua Truumess, I. *J. Antibiotics* **1988**, *41*, 13.

(32) (a) Inukai, M.; Isono, F.; Takahashi, S.; Enokita, R.; Sakaida, Y.; Haneishi, T. *J. Antibiotics* **1989**, *42*, 662. (b) Isono, F.; Inukai, M.; Takahashi, S.; Haneishi, T.; Kinoshita, T.; Kuwano, H. *J. Antibiotics* **1989**, *42*, 667. (c) Isono, F.; Katayama, T.; Inukai, M.; Haneishi, T. *J. Antibiotics* **1989**, *42*, 674. (d) Isono, F.; Sakaida, Y.; Takahashi, S.; Kinoshita, T.; Nakamura, T.; Inukai, M. *J. Antibiotics* **1993**, *46*, 1203. (e) Howard, N. I.; Bugg, T. D. H. *Bioorg. Med. Chem.* **2003**, *11*, 3083.

(33) Chatterjee, S.; Nadkarni, S. R.; Vijayakumar, E. K. S.; Patel, M. V.; Ganguli, B. N.; Fehlhaber, H.-W.; Vertesy, L. *J. Antibiotics* **1994**, *47*, 595.

(34) (a) Chen, R. H.; Buko, A. M.; Whittern, D. N.; McAlpine, J. B. *J. Antibiotics* **1989**, *42*, 512. (b) Fernandes, P. B.; Swanson, R. N.; Hardy, D. J.; Hanson, C. W.; Coen, L.; Rasmussen, R. R.; Chen, R. H. *J. Antibiotics* **1989**, *42*, 521. (c) Kimura, K.; Bugg, T. D. H. *Nat. Prod. Rep.* **2003**, *20*, 252.

(35) (a) Bodanszky, A. A.; Bodanszky, M. *J. Antibiotics* **1970**, *23*, 149. (b) Kong, F.; Carter, G. T. *J. Antibiotics* **2003**, *56*, 557. (c) Vertesy, L.; Ehlers, E.; Kogler, M.; Kurz, M.; Meiwes, J.; Seibert, G.; Vogel, M.; Hamman, P. *J. Antibiotics* **2000**, *53*, 816.

(36) (a) Hausmann, W.; Borders, D. B.; Lancaster, J. E. *J. Antibiotics* **1969**, *22*, 207. (b) Martin, J. H.; Hausmann, W. K. *J. Am. Chem. Soc.* **1960**, *82*, 2079.

(37) Fujino, M.; Inoue, M.; Ueyanagi, J.; Miyake, A. *Bull. Chem. Soc. Jpn.* **1963**, *38*, 515.

(38) (a) Uchida, I.; Shigematsu, N.; Ezaki, M.; Hashimoto, M. *Chem. Pharm. Bull.* **1985**, *33*, 3053. (b) Schmidt, U.; Mundinger, K.; Mangold, R.; Lieberknecht, A. *J. Chem Soc., Chem. Commun.* **1990**, 1216.

(39) (a) Morimoto, K.; Shimada, N.; Naganawa, H.; Takita, T.; Umezawa, H. *J. Antibiotics* **1982**, *35*, 378. (b) Nakamura, Y.; Shin, C. *Chem. Lett.* **1992**, 49. (c) Morimoto, K.; Shimada, N.; Naganawa, H.; Takita, T.; Umezawa, H. *J. Antibiotics* **1981**, *34*, 1613. (d) Schmidt, U.; Riedl, B. *J. Chem Soc., Chem. Commun.* **1992**, 1186.

(40) (a) Shiroza, T.; Ebisawa, N.; Furihata, K.; Endo, T.; Seto, H.; Otake, N. *Agric. Biol. Chem.* **1982**, *46*, 865. (b) Shin, C.-G.; Ikeda, M.; Yonezawa, Y. *Agric. Biol. Chem.* **1985**, *49*, 2243. (c) Shiroza, T.; Ebisawa, N.; Kojima, A.; Furihata, K.; Shimazu, A.; Endo, T.; Seto, H.; Otake, N. *Agric. Biol. Chem.* **1982**, *46*, 1885.

(41) (a) Shigematsu, N.; Setoi, H.; Uchida, I.; Shibata, T.; Terano, H.; Hashimotop, M. *Tetrahedron Lett.* **1988**, *29*, 5147. (b) Shibata, T.; Nakayama, O.; Okuhara, M.; Tsurumi, Y.; Terano, H.; Kohsaka, M. *J. Antibiotics* **1988**, *41*, 1163.

(42) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941.

(43) (a) Clark, W. D.; Corbett, T.; Valeriote, F.; Crews, P. *J. Am. Chem. Soc*. **1997**, *119*, 9285. (b) Grieco, P. A.; Reilly, M. *Tetrahedron Lett.* **1998**, *39*, 8925.

(44) (a) Bastiaans, H. M. M.; van der Baan, J. L.; Ottenheijm H. C. J. *J. Org. Chem.* **1997**, *62*, 3880. (b) Maryanoff, B. E.; Greco, M. N.; Zhang, H.-C.; Andrade-Gordon, P.; Kauffman, J. A.; Nicolaou, K. C.; Liu, A.; Brungs, P. H. *J. Am. Chem. Soc.* **1995**, *117*, 1225. (c) Maryanoff, B. E.; Zhang, H.-C.; Greco, M. N.; Glover, K. A.; Kauffman, J. A.; Andrade-Gordon, P. *Bioorg. Med. Chem*. **1995**, *3*, 1025.

(45) Berer, N.; Rudi, A.; Goldberg, I.; Benayahu, Y.; Kashman, Y. *Org. Lett*. **2004**, *6*, 2543.

(46) (a) Kretsinger, J. K.; Schneider, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 7907. (b) Schneider, J. P.; Lear, J. D.; DeGrado, W. F. *J. Am. Chem. Soc.* **1997**, *119*, 5742.

(47) Liu, F.; Lewis, R. N. A. H.; Hodges, R. S.; McElhaney, R. N. *Biochemistry* **2002**, *41*, 9197.

(48) Padmanabhan, S.; York, E. J.; Stewart, J. M.; Baldwin, R. L. *J. Mol. Biol.* **1996**, *257*, 726.

(49) Groebke, K.; Renold, P.; Tsang, K. Y.; Allen, T. J.; McClure, K. F.; Kemp, D. S. *Proc. Natl. Acad. Sci.* **1996**, *93*, 4025.

(50) Seebach, D.; Studer, A.; Pfammatter, E.; Widmer, H. *Helv. Chim. Acta* **1994**, *77*, 2035.

(51) Lougheed, T.; Zhang, Z.; Woolley, G. A.; Borisenko, V. *Bioorg. Med. Chem.* **2004**, *12*, 1337.

(52) Wang, D.; Guo, L.; Zhang, J.; Jones, L. R.; Chen, Z.; Pritchard, C.; Roeske, R. W. *J. Peptide Res*. **2001**, *57*, 301.

(53) Jarvo, E. R.; Copeland, G. T.; Papanoiannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc*. **1999**, *121*, 11638.

(54) (a) Thumshirn, G.; Hersel, U.; Goodman, S. L.; Kessler, H. *Chem. Eur. J.* **2003**, *9*, 2717. (b) Poethko, T.; Schottelius, M.; Thumshirn, G.; Hersel, U.; Herz, M.; Henriksen, G.; Kessler, H.; Schwaiger, M.; Wester, H.-J. *J. Nucl. Med*. **2004**, *45*, 892. (c) Poethko, T.; Schottelius, M.; Thumshirn, G.; Herz, M.; Haubner, R.; Henriksen, G.; Kessler, H.; Schwaiger, M.; Wester, H.-J. *Radiochim. Acta* **2004**, *92*, 317. (d) Schottelius, M.; Poethko, T.; Herz, M.; Reubi, J. C.; Kessler, H.; Schwaiger, M.; Wester, H.-J. *Clinical Cancer Res*. **2004**, *10*, 3593.

(55) Smith, C. J.; Sieckman, G. L.; Owen, N. K.; Hayes, D. L.; Mazuru, D. G.; Kannan, R.; Volkert, W. A.; Hoffman, T. J. *Cancer Res.* **2003**, *63*, 4082.

(56) Pheng, L. H.; Dumont, Y.; Fournier, A.; Chabot, J.-G.; Beaudet, A.; Quirion, R. *Br. J. Pharmacol*. **2003**, *139*, 695.

(57) (a) Patacchini, R.; Giuliani, S.; Turini, A.; Navarra, G.; Maggi, C. A. *Eur. J. Pharmacol*. **2000**, *398*, 389. (b) Weisshoff, H.; Nagel, A.; Zschunke, A.; Mügge, C. *FEBS Lett.* **2001**, *491*, 299.

(58) Wilczynski, A.; Wang, X. S.; Joseph, C. G.; Xiang, Z.; Bauzzo, R. M.; Scott, J. W.; Sorensen, N. B.; Shaw, A. M.; Millard, W. J.; Richards, N. G.; Haskell-Luevano, C. *J. Med. Chem*. **2004**, *47*, 2194.

(59) (a) De Luca, S.; Ragone, R.; Bracco, C.; Digilio, G.; Aloj, L.; Tesauro, D.; Saviano, M.; Pedone, C.; Morelli, G. *ChemBioChem* **2003**, *4*, 1176. (b) De Luca, S.; Morelli, G. *J. Peptide Sci*. **2004**, *10*, 265.

(60) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem*. **2001**, *3*, 612.

(61) (a) Pascal, R.; Sola, R.; Jouin, P. *Methods Enzymol, Comb. Chem. Part B* **2003**, *369*, 182. (b) Hoffmann, M.; Burkhart, F.; Hessler, G.; Kessler, H. *Helv. Chim. Acta* **1996**, *79*, 1519. (c) Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett*. **1998**, *39*, 1295.

(62) (a) For a review, see: Souers, A. J.; Ellman, J. A. *Tetrahedron* **2001**, *57*, 7431. (b) Golebioswki, A.; Klopfenstein, S. R.; Shao, X.; Chen, J. J.; Colson, A.-O.; Grieb, A. L.; Russell, A. F. *Org. Lett*. **2000**, *2*, 2615.

(63) (a) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Comb. Chem*. **2001**, *3*, 578. (b) Nezfi, A.; Ostresh, J. M.; Giulianotti, M.; Houghten, R. A. *Tetrahedron Lett.* **1998**, *39*, 8199.

(64) (a) Marastoni, M.; Bazzaro, M.; Bortolotti, F.; Salvadori, S.; Tomatis, R. *Eur. J. Med. Chem*. **1999**, *34*, 651. (b) Mohan, R.; Chou, Y. L.; Lumma, W. C.; Erhardt, P. W.; Shaw, K. J. *J. Med. Chem*. **1991**, *34*, 2402. (c) Moore, S.; Patel, R. P.; Atherton, E.; Kondo, M.; Meienhofer, J. *J. Med. Chem*. **1976**, *19*, 766. (d) Herranz, R.; Vinuesa, S.; Castro-Pichel, J.; Pérez, C.; García-López, M. T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1825. (e) Chang, P. K.; Sciarini, L. J.; Handschumacher, R. E. *J. Med. Chem.* **1973**, *16*, 1277.

(65) Rosowsky, A.; Vaidya, C. M.; Bader, H.; Wright, J. E.; Teicher, B. A. *J. Med. Chem*. **1997**, *40*, 286.

(66) Greenlee, W. J.; Allibone, P. L.; Perlow, D. S.; Patchett, A. A.; Ulm, E. H.; Vassil, T. C. *J. Med. Chem*. **1985**, *28*, 434.

(67) Astles, P. C.; Harris, N. V.; Morley, A. D. *Bioorg. Med. Chem*. **2001**, *9*, 2195.

(68) Delaet, N. G. J.; Robinson, L. A.; Wilson, D. M.; Sullivan, R. W.; Bradley, E. K.; Dankwardt, S. M.; Martin, R. L.; Van Wart, H. E.; Walker, K. A. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2101.

(69) (a) Chapman, J.; Pickett, N. L.; Kolawole, G.; Motevalli, M.; O'Brien, P. *Acta Cryst*. **2000**, *C56*, 501. (b) Anagnostopoulos A.; Hadjispyrou, S. *J. Inorg. Biochem*. **1995**, *57*, 279. (c) Kozlov, Y. M.; Babich, V. A. *Zh. Obshch. Khim.* **1980**, *50*, 1116. (d) Kozlov, Y. M.; Babich, V. A.; Gorelov, I. P.; Kapustnikov, A. I. *Zh. Obshch. Khim.* **1982**, *52*, 658. (e) Kozlov, Y. M.; Babich, V. A. *Zh. Obshch. Khim.* **1981**, *51*, 1115. (f) Schnabelrauch, M.; Wittmann, S.; Rahn, K.; Möllmann, U.; Reissbrodt, R.; Heinisch, L. *Biometals* **2000**, *13*, 333. (g) Geisser, B.; Alsfasser, R. *Eur. J. Inorg. Chem*. **1998**, 957. (h) Enyedy, E. A.; Csova, H.; Lázár, I.; Micera, G.; Garriba, E.; Farkas, E. *J. Chem. Soc., Dalton Trans*. **2002**, 2632.

(70) (a) Matilla, A.; Tercero, J. M.; Dung, N.-H.; Viossat, B.; Pérez, J. M.; Alonso, C.; Martín-Ramos, J. D.; Niclós-Gutiérrez, J. *J. Inorg. Biochem.* **1994**, *55*, 235.

(71) (a) Moradell, S.; Lorenzo, J.; Rovira, A.; Robillard, M. S.; Avilés, F. X.; Moreno, V.; Llorens, R.; Martínez, M. A.; Reedijk, J.; Llobet, A. *J. Inorg. Biochem*. **2003**, *96*, 493. (b) González, M. L.; Tercero, J. M.; Matilla, A.; Niclós-Gutiérrez, J.; Fernández, M. T.; López, M. C.; Alonso, C.; González, S. *Inorg. Chem*. **1997**, *36*, 1806.

(72) (a) Seo, M. S.; Sohn, Y. S.; Yang, B. S.; Nam, W.; Kim, K. M. *Inorg. Chem. Commun.* **2004**, *7*, 1178. (b) Boer, J.; Blount, K. F.; Luedtke, N. W.; Elson-Schwab, L.; Tor, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 927.

(73) (a) Eaton, C. N.; Denny, G. H.; Rayder, M. A.; Ly, M. G.; Babson, R. D. *J. Med. Chem*. **1973**, *16*, 289. (b) Strazzolini, P.; Malabarba, A.; Ferrari, P.; Grandi, M.; Cavalleri, B. *J. Med. Chem.* **1984**, *27*, 1295. (c) Yu, J. *Curr. Opin. Investig. Drugs* **2001**, *2*, 1623.

(74) (a) McGill, A. D.; Zhang, W.; Wittbrodt, J.; Wang, J.; Schlegel, H. B.; Wang, P. G. *Bioorg. Med. Chem*. **2000**, *8*, 405. (b) Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. *Chem. Rev*. **2002**, *102*, 1091.

(75) Batova, A.; Diccianni, M. B.; Omura-Minamisawa, M.; Yu, J.; Carrera, C. J.; Bridgeman, L. J.; Kung, F. H.; Pullen, J.; Amylon, M. D.; Yu, A. L. *Cancer Res*. **1999**, *59*, 1492.

(76) (a) Pesti, J. A.; Yin, J.; Zhang, L.-H.; Anzalone, L.; Waltermire, R. E.; Ma, P.; Gorko, E.; Confalone, P. N.; Fortunak, J.; Silverman, C.; Blackwell, J.; Chung, J. C.; Hrytsak, M. D., Cooke, M.; Powell, L.; Ray, C. *Org. Proc. Res. Develop*. **2004**, *8*, 22. (b) Serebruany, V. L.; Malinin, A. I.; O'Connor, C. M.; Gurbel, P. A. *Am. Heart J.* **2003**, *146*, 91. (c) Murphy, J.; Wright, R. S.; Gussak, I.; Williams, B.; Daly, R. N.; Cain, V. A.; Pieniaszek, H. J.; Sy, S. K. B.; Ebling, W.; Simonson, K.; Wilcox, R. A.; Kopecky, S. L. *Am. J. Cardiovascular Drugs* **2003**, *3*, 101. (d) Batt, D. G.; Houghton, G. C.; Daneker, W. F.; Jadhav, P. K. *J. Org. Chem*. **2000**, *65*, 8100. (e) Zhang, L.-H.; Anzalone, L.; Ma, P.; Kauffman, G. S.; Storace, L.; Ward, R. *Tetrahedron Lett*. **1996**, *37*, 4455. (f) Mousa, S. A.; Bozarth, J. M.; Lorelli, W.; Forsythe, M. S.; Thoolen, M. J. M. C.; Slee, A. M.; Reilly, T. M.; Friedman, P. A. *J. Pharmacol. Exp. Therapeutics* **1998**, *286*, 1277.

(77) (a) Hosoya, K.; Ishimitsu, T. *Cardiovascular Drug Rev.* **2002**, *20*, 93. (b) Wang, J.-M.; Wang, Y.; Zhu, Z.-S.; Zhang, M.-C.; Zou, Y.; Li, J.-J.; Li, M.-J.; Jiang, X.-J.; Li, X.-Y. *Life Sci.* **2004**, *75*, 407.

(78) Carroll, C. D.; Johnson, T. O.; Tao, S.; Lauri, G.; Orlowski, M.; Gluzman, I. Y.; Goldberg, D. E.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3203.

(79) Cheng, M.; De, B.; Pikul, S.; Almstead, N. G.; Natchus, M. G.; Anastasio, M. V.; McPhail, S. J.; Snider, C. E.; Taiwo, Y. O.; Chen, L.; Dunaway, C. M.; Gu, F.; Dowty, M. E.; Mieling, G. E.; Janusz, M. J.; Wang-Weigand, S. *J. Med. Chem*. **2000**, *43*, 369.

(80) Shreder, K.; Zhang, L.; Goodman, M. *Tetrahedron Lett*. **1998**, *39*, 221.

(81) (a) Falorni, M.; Giacomelli, G. *Synlett* **1996**, 143. (b) Hays, S. J.; Bigge, C. F.; Novak, P. M.; Drummond, J. T.; Bobovski, T. P.; Rice, M. J.; Johnson, G.; Brahce, L. J.; Coughenour, L. L. *J. Med. Chem*. **1990**, *33*, 2916. (c) Harris, E. W.; Ganong, A. H.; Monaghan, D. T.; Watkins, J. C.; Cotman, C. W. *Brain Res*. **1986**, *382*, 174. (d) Harris, N. C.; Davies, J. *Brain Res.* **1992**, *594*, 176. (e) Bigge, C. F.; Hays, S. J.; Novak, P. M.; Drummond, J. T.; Johnson, G.; Bobovski, T. P. *Tetrahedron Lett.* **1989**, *30*, 5193.

(82) (a) Hammond, J. R. *Arch. Pharmacol*. **2000**, *361*, 377. (b) Rongen, G. A.; Smits, P.; Donck, K. V.; Willemsen, J. J.; De Abreu, R. A.; Belle, H. V.; Thien, T. *J. Clin. Invest*. **1995**, *95*, 658. (c) Wainwright, C. L.; Parratt, J. R.; Belle, H. V. *Br. J. Pharmacol*. **1993**, *109*, 592.

(83) (a) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem*. **1994**, *37*, 3443. (b) Duffy, J. L.; Kevin, N. J.; Kirk, B. A.; Chapman, K. T.; Schleif, W. A.; Olsen, D. B.; Stahlhut, M.; Rutkowski, C. A.; Kuo, L. C.; Jin, L.; Lin, J. H.; Emini, E. A.; Tata, J. R. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 2423. (c) Gauthier, D. R., Jr.; Ikemoto, N.; Fleitz, F. J.; Szumigala, R. H., Jr.; Petrillo, D.; Liu, J.; Reamer, R. A.; Armstrong, J. D., III; Yehl, P. M.; Wu, N.; Volante, R. P. *Tetrahedron: Asymmetry* **2003**, *14*, 3557.

(84) (a) Ojima, I.; Habus, I. *Tetrahedron Lett.* **1990**, *31*, 4289. (b) van Maanen, H. L.; Kleijn, H.; Jastrzebski, J. T. B. H.; Verweij, J.;

Kieboom, A. P. G.; van Koten, G. *J. Org. Chem.* **1995**, *60*, 4331. (c) Brown, M. J.; Overman, L. E. *J. Org. Chem.* **1991**, *56*, 1933.

(85) (a) Kavrakova, I. K.; Lyapova, M. J. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1580. (b) Kavrakova, I. K.; Lyapova, M. J. *Org. Prep. Proc. Int.* **1996**, *28*, 333.

(86) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P.; Meervelt, L. V.; Mischenko, N. *Tetrahedron Lett.* **1997**, *38*, 4671.

(87) (a) DeMong, D. E.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 3529. (b) DeMong, D. E.; Williams, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 8561.

(88) Viso, A.; Fernández de la Pradilla, R.; López-Rodríguez, M. L.; García, A.; Flores, A.; Alonso, M. *J. Org. Chem.* **2004**, *69*, 1542. (b) Viso, A.; Fernández de la Pradilla, R.; García, A.; Alonso, M.; Guerrero-Strachan, C.; Fonseca, I. *Synlett* **1999**, 1543.

(89) (a) Davis, F. A.; Deng, J. *Org. Lett.* **2004**, 6, 2789. (b) Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*, 621.

(90) Polniaszek, R. P.; Bell, S. J. *Tetrahedron Lett.* **1996**, *37*, 575.

(91) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583.

(92) Ooi, T.; Kameda, M.; Fujii, J.-I.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397.

(93) (a) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992.

(94) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.

(95) Hartwig, W.; Mittendorf, J. *Synthesis* **1991**, 939.

(96) (a) Jones, R. C. F.; Crockett, A. K.; Rees, D. C.; Gilbert, I. H. *Tetrahedron: Asymmetry* **1994**, *5*, 1661. (b) Gilbert, I. H.; Rees, D. C.; Crockett, A. K.; Jones, R. C. F. *Tetrahedron* **1995**, *51*, 6315.

(97) Bycroft, B. W.; Chhabra, S. R.; Grout, R. J.; Crowley, P. J. *J. Chem. Soc., Chem. Comm.* **1984**, 1156.

(98) Shiba, T.; Ukita, T.; Mizuno, K.; Teshima, T.; Wakamiya, T. *Tetrahedron Lett.* **1977**, *31*, 2681.

(99) (a) Lowe, G.; Parker, J. *Chem. Commun.* **1971**, 577. (b) Golding, B. T.; Smith, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 702. (c) Herdeis, C.; Nagel, U. *Heterocycles* **1983**, *20*, 2163.

(100) Robinson, A. J.; Lim, C. Y. *J. Org. Chem.* **2001**, *66*, 4141.

(101) (a) Vartak, A. P.; Young, V. G.; Johnson, R. L. *Org. Lett.* **2005**, *7*, 35. (b) Obata, N.; Niimura, K. *J. Chem. Soc., Chem. Commun.* **1977**, 238.

(102) Ozaki, Y.; Iwasaki, T.; Miyoshi, M.; Matsumoto, K. *J. Org. Chem.* **1979**, *44*, 1714.

(103) Álvarez-Ibarra, C.; Csáky̆, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478.

(104) Belokon, Y. N.; Chernoglazova, N. I.; Batsanov, A. S.; Garbalinskaya, N. S.; Bakhmutov, V. I.; Struchkov, Y. T.; Belikov, V. M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1987**, *36 part 2*, 779.

(105) (a) Zeitler, K.; Steglich, W. *J. Org. Chem.* **2004**, *69*, 6134. (b) Schumann, S.; Zeitler, K.; Jäger, M.; Polborn, K.; Steglich, W. *Tetrahedron* **2000**, *56*, 4187.

(106) Chen, Y.; Yudin, A. K. *Tetrahedron Lett.* **2003**, *44*, 4865.

(107) (a) Rasmussen, K. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1287. (b) Casarrubios, L.; Pérez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358. (c) Rasmussen, K. G.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1401.

(108) (a) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676.

(109) (a) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368. (b) Moran, M.; Bernardinelli, G.; Müller, P. *Helv. Chim. Acta* **1995**, *78*, 2048.

(110) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099.

(111) Aires-de-Sousa, J.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **1996**, *37*, 3183.

(112) Ha, H.-J.; Suh, J.-M.; Kang, K.-H.; Ahn, Y.-G.; Han, O. *Tetrahedron* **1998**, *54*, 851.

(113) Lee, K.-D.; Suh, J.-M.; Park, J.-H.; Ha, H.-J.; Choi, H.-G.; Park, C. S.; Chang, J. W.; Lee, W. K.; Dong, Y.; Yun, H. *Tetrahedron* **2001**, *57*, 8267.

(114) (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (b) Davis, F. A.; Zhang, Y.; Rao, A.; Zhang, Z. *Tetrahedron* **2001**, *57*, 6345. (c) Osborn H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (d) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39.

(115) Yang, X.-F.; Zhang, M.-J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2002**, *67*, 8097.

(116) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223. (b) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813. (d) Palomo, C.; Cossío, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Román, P.; Luque, A.; Martínez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360.

(117) (a) Endo, M.; Droghini, R. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2483. (b) Moyna, G.; Williams, H. J.; Scott, A. I. *Synth. Commun.* **1997**, *27*, 1561.

(118) Fukuyama, T.; Keith Frank, R.; Jewell, C. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 2122.

(119) (a) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783. (b) Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1990**, *31*, 977.

(120) Ojima, O. *Acc. Chem. Res.* **1995**, *28*, 383.

(121) (a) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Benito, A.; Khamrai, U. K.; Eikeseth, U.; Linden, A. *Tetrahedron* **2000**, *56*, 5563. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Benito, A.; Cuerdo, L.; Fratila, R. M.; Jiménez, A.; Lonaz, I.; Miranda, J. I.; Pytlewska, K. R.; Micle, A.; Linden, A. *Org. Lett.* **2004**, *6*, 4443.

(122) (a) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Mielgo, A. *Chem. Commun.* **1996**, 633. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I. *Russ. Chem. Bull.* **1996**, *45*, 2463.

(123) Brown, D.; Brown, G. A.; Andrews, M.; Large, J. M.; Urban, D.; Butts, C. P.; Hales, N. J.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2014.

(124) (a) Viso, A.; Fernández de la Pradilla, R.; García, A.; Guerrero-Strachan, C.; Alonso, M.; Flores, A.; Martínez-Ripoll, M.; Fonseca, I.; André, I.; Rodríguez, A. *Chem. Eur. J.* **2003**, *9*, 2867. (b) Viso, A.; Fernández de la Pradilla, R.; Guerrero-Strachan, C.; Alonso, M.; Martínez-Ripoll, M.; André, I. *J. Org. Chem.* **1997**, *62*, 2316.

(125) Alker, D.; Harwood: L. M.; Williams, E. *Tetrahedron Lett.* **1998**, *39*, 475.

(126) Meyer, R.; Schöllkopf, U.; Böhme, P. *Liebigs Ann. Chem.* **1977**, 1183.

(127) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969.

(128) Lin, Y.-R.; Zhou, X.-T.; Dai, L.-X.; Sun, J. *J. Org. Chem.* **1997**, *62*, 1799.

(129) (a) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 855. (b) Dai, L.-X.; Lin, Y.-R.; Hou, X.-L.; Zhou, Y.-G. *Pure Appl. Chem.* **1999**, *71*, 1033.

(130) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228.

(131) (a) Dumez, E.; Szeki, A.; Jackson, R. F. W. *Synlett* **2001**, 1214. (b) Ambroise, L.; Dumez, E.; Szeki, A.; Jackson, R. F. W. *Synthesis* **2002**, 2296.

(132) (a) Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, 1, 4275. (b) Hannesian, S.; Sharma, R. *Heterocycles* **2000**, *52*, 1231.

(133) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1998**, *63*, 5627.

(134) Obrecht, D.; Karajiannis, H.; Lehmann, C.; Schönholzer, P.; Spielgler, C.; Müller, K. *Helv. Chim. Acta* **1995**, *78*, 703.

(135) Langlois, N.; Le Nguyen, B. K. *J. Org. Chem.* **2004**, *69*, 7558.

(136) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401.

(137) Fondekar, K. P. P.; Volk, F.-J.; Khaliq-uz-Zaman, S. M.; Bisel, P.; Frahm, A. W. *Tetrahedron: Asymmetry* **2002**, *13*, 2241.

(138) Li, B.-F.; Yuan, K.; Zhang, M.-J.; Wu, H.; Dai, L.-X.; Wang, Q.-R.; Hou, X.-L. *J. Org. Chem.* **2003**, *68*, 6264.

(139) Seo, R.; Ishizuka, T.; Abdel-Aziz, A. A.-M.; Kunieda, T. *Tetrahedron Lett.* **2001**, *42*, 6353.

(140) (a) Rossen, K.; Sager, J.; DiMichele, L. M *Tetrahedron Lett.* **1997**, *38*, 3183. (b) Rossen, K.; Pye, P. J.; DiMichele, L. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 6823.

(141) (a) Pfammatter, E.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1323. (b) Juaristi, E.; Quintana, D.; Lamatsch B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553. (c) Schanen, V.; Cherrier, M.-P.; de Melo, S. J.; Quirion, J.-C.; Husson, H.-P. *Synthesis* **1996**, 833.

(142) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59*, 3123. (b) Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Urchegui, R.; Linden, A. *J. Org. Chem.* **1996**, *61*, 4400. (c) Palomo, C.; Ganboa, I.; Cuevas, C.; Boschetti, C.; Linden, A. *Tetrahedron Lett.* **1997**, *38*, 4643. (d) Palomo, C.; Aizpurua, J. M.; Cabré, F.; Cuevas, C.; Munt, S.; Odriozola, J. M. *Tetrahedron Lett.* **1994**, *35*, 2725.

(143) (a) Castellanos, E.; Reyes-Rangel, G.; Juaristi, E. *Helv. Chim. Acta* **2004**, *87*, 1016. (b) Chu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. J.; Woo, N.-T.; Olmstead, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 1800.

(144) Dunn, P. J.; Häner, R.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5017.

(145) (a) Merino, P.; Lanaspa, A.; Merchán, F. L.; Tejero, T. *Tetrahedron Lett.* **1997**, *38*, 1813. (b) Merino, P.; Lanaspa, A.; Merchán, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*, 629.

(146) Snider, B. B.; Gu, Y. *Org. Lett.* **2001**, *3*, 1761.

(147) You, S.-L.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 1681.

(148) (a) Fabiano, E.; Golding, B. T.; Sadeghi, M. M. *Synthesis* **1987**, 190. (b) Golding, B. T.; Howes, C. *J. Chem Res. (S)* **1984**, 1. (c) Otsuka, M.; Kittaka, A.; Iimori, T.; Yamashita, H.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1985**, *33*, 509. (d) Kogan, T. P.; Rawson, T. E. *Tetrahedron Lett.* **1992**, *33*, 7089.

(149) (a) Turner, J. J.; Sikkema, F. D.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Synlett* **2001**, 1727. (b) Schmidt, U.; Mundinger, K.; Riedl, B.; Haas, G.; Lau, R. *Synthesis* **1992**, 1201. (c) Luo, Y.; Blaskovich, M. A.; Lajoie, G. A. *J. Org. Chem.* **1999**, *64*, 6106. (d) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267. (e) Eastwood, F. W.; Perlmutter, P.; Yang, Q. *Tetrahedron Lett.* **1994**, *35*, 2039. (f) Cherney, R. J.; Wang, L. *J. Org. Chem.* **1996**, *61*, 2544.

(150) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc*. **1985**, *107*, 7105.

(151) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc*. **1988**, *110*, 2237.

(152) Warshawsky, A. M.; Patel, M. V.; Chen, T.-M. *J. Org. Chem*. **1997**, *62*, 6439.

(153) Atherton, E.; Meienhofer, J. *J. Antibiotics* **1972**, *25*, 539.

(154) Nakamura, Y.; Hirai, M.; Tamotsu, K.; Yonezawa, Y.; Shin, C.-G. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 1369.

(155) Mattingly, P. G.; Miller, M. J. *J. Org. Chem*. **1980**, *45*, 410.

(156) Baldwin, J. E.; Adlington, R. M.; Birch, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 256.

(157) Baldwin, J. E.; Adlington, R. M.; Mellor, L. C. *Tetrahedron* **1994**, *50*, 5049.

(158) (a) Baldwin, J. E.; Farthing, C. N.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett*. **1996**, *37*, 3761. (b) Farthing, C. N.; Baldwin, J. E.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett*. **1996**, *37*, 5225.

(159) (a) Solomon, M. E.; Lynch, C. L.; Rich, D. H. *Tetrahedron Lett*. **1995**, *36*, 4955. (b) Solomon, M. E.; Lynch, C. L.; Rich, D. H. *Synth. Commun*. **1996**, *26*, 2723.

(160) (a) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309. (b) Xu, J. *Tetrahedron: Asymmetry* **2002**, *13*, 1129. (c) Korn, A.; Rudolph-Böhner, S.; Moroder, L. *Tetrahedron* **1994**, *50*, 1717. (d) Burgaud, B. G. M.; Horwell, D. C.; Padova, A.; Pritchard, M. C. *Tetrahedron* **1996**, *52*, 13035. (e) Nakajima, K.; Takai, F.; Tanaka, T.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1577.

(161) Garner, P.; Park, J. M. *Org. Synth*. **1997**, *70*, 18. (*Coll. Vol. 9*, p 300)

(162) Guibourdenche, G.; Roumestant, M. L.; Viallefont, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2041.

(163) (a) Chhabra, S. R.; Mahajan, A.; Chan, W. C. *J. Org. Chem*. **2002**, *67*, 4017. (b) Chhabra, S. R.; Mahajan, A.; Chan, W. C. *Tetrahedron Lett.* **1999**, *40*, 4905.

(164) Falorni, M.; Giacomelli, G.; Satta, M.; Cossu, S. *Synthesis* **1994**, 391.

(165) Falorni, M.; Porcheddu, A.; Giacomelli, G. *Tetrahedron: Asymmetry* **1997**, *8*, 1633.

(166) Rao, S. L. N. *Biochemistry* **1975**, *14*, 5218.

(167) (a) Olsen, R. K.; Hennen, W. J.; Wardle, R. B. *J. Org. Chem*. **1982**, *47*, 4605. (b) Schneider, F. *J. Liebigs Ann. Chem*. **1937**, *529*, 1.

(168) (a) Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266. (b) Lee, E.-S.; Jurayj, J.; Cushman, M. *Tetrahedron* **1994**, *50*, 9873. (c) Zhang, L.-H.; Kauffman, G. S.; Pesti, J. A.; Yin, J. *J. Org. Chem*. **1997**, *62*, 6918. (d) Noguchi, N.; Kuroda, T.; Hatanaka, M.; Ishimaru, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 633. (e) Burger, K.; Spengler, J.; Hennig, L.; Herzschuh, R.; Essawy, S. A. *Monatsh*. *Chem*. **2000**, *131*, 463.

(169) (a) Deng, J.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett*. **1996**, *37*, 2261. (b) Englund, E. A.; Gopi, H. N.; Appella, D. H. *Org. Lett*. **2004**, *6*, 213. (c) Schirlin, D.; Altenburger, J.-M. *Synthesis* **1995**, 1351.

(170) Seki, M.; Shimizu, T.; Inubushi, K. *Synthesis* **2002**, 355.

(171) Cardillo, G.; Orena, M.; Penna, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1991**, *47*, 2263.

(172) (a) Rossi, F. M.; Powers, E. T.; Yoon, R.; Rosenberg, L.; Meinwald, J. *Tetrahedron* **1996**, *52*, 10279. (b) Knapp, S.; Kukkola, P. J.; Sharma, S.; Dhar, T. G. M.; Naughton, A. B. J. *J. Org. Chem*. **1990**, *55*, 5700.

(173) Gonda, J.; Helland, A.-C.; Ernst, B.; Bellus, D. *Synthesis* **1993**, 729.

(174) (a) McKennis, H., Jr.; Yard, A. S. *J. Am. Chem. Soc*. **1958**, *23*, 980. (b) Wenner, W. *J. Org. Chem*. **1948**, *13*, 26.

(175) (a) Mérour, J. Y.; Coadou, J. Y. *Tetrahedron Lett*. **1991**, *32*, 2469. (b) Gubert, S.; Braojos, C.; Sacristán, A.; Ortiz, J. A. *Synthesis* **1991**, 318. (c) Demaine, D. A.; Smith, S.; Barraclough, P. *Synthesis* **1992**, 1065-. (d) Jucker, E.; Rissi, E. *Helv. Chim. Acta* **1962**, *45*, 2383.

(176) McCort, G. A.; Pascal, J. C. *Tetrahedron Lett*. **1992**, *33*, 4443.

(177) (a) Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3041. (b) Martres, M.; Gil, G.; Méou, A. *Tetrahedron Lett*. **1994**, *35*, 8787. (c) Kyburz, E.; Els, H.; St. Majnoni; Englert, G.; von Planta, C.; Fürst, A.; Plattner, Pl. A. *Helv. Chim. Acta* **1966**, *49*, 359.

(178) Davoli, P.; Forni, A.; Moretti, I.; Prati, F. *Tetrahedron: Asymmetry* **1995**, *6*, 2011.

(179) Nadir, U. K.; Krishna, R. V.; Singh, A. *Tetrahedron Lett*. **2005**, *46*, 479.

(180) (a) Muñiz, K.; Nieger, M. *Synlett* **2003**, 211. (b) Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc*. **1977**, *99*, 3420.

(181) Li, G.; Kim, S. H.; Wei, H.-X. *Tetrahedron Lett*. **2000**, *41*, 8699.

(182) (a) Li, G.; Wei, H.-X.; Kim, S. H.; Carducci, M. D. *Angew. Chem., Int. Ed*. **2001**, *40*, 4277. (b) Wei, H.-X.; Siruta, S.; Li, G. *Tetrahedron Lett*. **2002**, *43*, 3809. (c) Wei, H.-X.; Kim, S. H.; Li, G. *J. Org. Chem*. **2002**, *67*, 4777. (d) Pei, W.; Timmons, C.; Xu, X.; Wei, H.-X.; Li, G. *Org. Biomol. Chem*. **2003**, *1*, 2919.

(183) Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem*. **1998**, *63*, 2045.

(184) Hennings, D. D.; Williams, R. M. *Synthesis* **2000**, 1310.

(185) (a) Lee, S.-H.; Yoon, J.; Nakamura, K.; Lee, Y.-S. *Org. Lett*. **2000**, *2*, 1243. (b) Lee, S.-H.; Yoon, J.; Chung, S.-H.; Lee, Y.-S. *Tetrahedron* **2001**, *57*, 2139.

(186) (a) Chuang, T.-H.; Sharpless, K. B. *Org. Lett*. **2000**, *2*, 3555. (b) Chuang, T.-H.; Sharpless, K. B. *Org. Lett*. **1999**, *1*, 1435.

(187) (a) Price, V. E.; Greenstein, J. P. *J. Biol. Chem*. **1948**, *173*, 337. (b) Labia, R.; Morin, C. *J. Org. Chem*. **1986**, *51*, 249. (c) McCord, T. J.; Foyt, D. C.; Kirpatrick, J. L.; Davis, A. L. *J. Med. Chem*. **1967**, *10*, 353. (d) Shadid, B.; van der Plas, H. C.; Boesten, W. H. J.; Kamphuis, J.; Meijer, E. M.; Schoemaker, H. E. *Tetrahedron* **1990**, *46*, 913.

(188) Sagiyan, A. S.; Avetisyan, A. E.; Djamgaryan, S. M.; Djilavyan, L. R.; Gyulumyan, E. A.; Grigoryan, S. K.; Kuz'mina, N. A.; Orlova, S. A.; Ikonnikov, N. S.; Larichev, V. S.; Tararov, V. I.; Belokon, Y. N. *Russ. Chem. Bull.* **1997**, *46*, 483.

(189) Es-Sayed, M.; Gratkowski, C.; Krass, N.; Meyers, A. I.; Meijere, A. *Synlett* **1992**, 962.

(190) Belov, V. N.; Funke, C.; Labahn, T.; Es−Sayed, M.; Meijere, A. *Eur. J. Org. Chem*. **1999**, 1345.

(191) Estermann, H.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1824.

(192) (a) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem*. **2003**, *1*, 3708. (b) Burke, A. J.; Davies, S. G.; Hedgecock, C. J. R. *Synlett* **1996**, 621.

(193) Durham, T. B.; Miller, M. J. *J. Org. Chem*. **2003**, *68*, 35.

(194) Chung, H.-K.; Kim, H.-W.; Chung, K.-H. *Heterocycles* **1999**, *51*, 2983.

(195) (a) Fernández-Megía, E.; Paz, M. M.; Sardina, F. J. *J. Org. Chem*. **1994**, *59*, 7643. (b) Fernández-Megía, E.; Sardina, F. J. *Tetrahedron Lett*. **1997**, *38*, 673.

(196) Riemer, C.; Bayer, T.; Schmitt, H.; Kessler, H. *J. Peptide Res.* **2004**, *63*, 196.

(197) Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2787.

(198) Wardrop, D. J.; Burge, M. S. *Chem. Commun*. **2004**, 1230.

(199) Verstappen, M. M. H.; Ariaans, G. J. A.; Zwanenburg, B. *J. Am. Chem. Soc*. **1996**, *118*, 8491.

(200) Robinson, A. J.; Stanislawski, P.; Mulholland, D. *J. Org. Chem*. **2001**, *66*, 4148.

(201) Kuwano, R.; Okuda, S.; Ito, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2773.

(202) (a) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett*. **2002**, *43*, 4495. (b) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Eur. J. Org. Chem*. **2003**, 2635. (c) Shin, C.-G.; Watanabe, K.; Ohmatsu, H.; Yoshimura, J. *Tetrahedron Lett*. **1978**, 4535.

(203) Felder, E.; Maffei, S.; Pietra, S.; Pitrè, D. *Helv. Chim Acta* **1960**, *43*, 888.

(204) Aebischer, B.; Frey, P.; Haerter, H. P.; Herrling, P. L.; Mueller, W.; Olverman, H. J.; Watkins, J. C. *Helv. Chim. Acta* **1989**, *72*, 1043.

(205) (a) Bruce, M. A.; St. Laurent, D. R.; Poindexter, G. S.; Monkovic, I.; Huang, S.; Balasubramanian, N. *Synth. Commun*. **1995**, *25*, 2673. (b) Beard, T. M.; Turner, N. J. *Chem. Commun*. **2002**, 246.

(206) Komeda, H.; Harada, H.; Washika, S.; Sakamoto, T.; Ueda, M.; Asano, Y. *Eur. J. Biochem*. **2004**, *271*, 1580.

(207) Kukula, P.; Prins, R. *J. Catal.* **2002**, *208*, 404.

(208) Rossen, K.; Weissman, S. A.; Sager, J.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 6419.

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