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Diazocarbonyl derivatives of amino acids: unique chiral building blocks for the synthesis of biologically active compounds

Danil P. Zarezin, Valentine G. Nenajdenko*

Department of Chemistry, Lomonosov Moscow State University
Leninskie Gory 1, stroenie 3, 119991 Moscow, Russian Federation

This review deals with applications of chiral α-amino diazoketones, α-amino acid derivatives, in the synthesis of various biologically active compounds. General approaches to the synthesis of chiral α-amino diazoketones, including the Arndt – Eistert reaction, acylation of trimethylsilyldiazomethanes, *etc*., are discussed. Due to the presence of three functional groups, these building blocks can be used to produce a wide range of organic compounds with potential physiological activity, ranging from various heterocyclic compounds to peptidomimetics. Methods for the synthesis of β-amino acid-containing peptides and depsipeptides, amino acid derivatives and heterocyclic compounds with three- to seven-membered rings are considered.
The bibliography includes 226 references.

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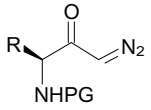
1. Introduction

Diazocarbonyl derivatives of amino acids (α-amino-α′-diazomethyl ketones, structure **I**) are valuable polyfunctional compounds. The presence of three functional groups (keto, diazo and protected amino groups) offers wide opportunities to organic chemists. Among the reactions involving diazocarbonyl derivatives of amino acids, the Wolff rearrangement and insertion reactions into C—H or X—H bonds (X = N, O, S)[1] are of particular importance. It should be noted that these compounds can be synthesized from natural amino acids in enantiomerically pure form. Since almost all biological molecules are chiral, optical activity is of great significance in the synthesis of complex organic compounds with physiological activity. In the past two decades, considerable attention has been paid to the synthesis of such compounds and their application for the preparation of compounds with high biological activity and, as a consequence, with high therapeutic potential. Diazocarbonyl compounds based on amino acids are especially widely used to synthesize β-amino acids and their derivatives, in particular, β-lactams, β-peptides (peptides with β-amino acid moieties). The β-lactam moiety is abundant in various antibiotics, including penicillin derivatives, cephalosporins, carbapenems and monobactams.[2] The β-lactam moiety is responsible for a similar mechanism of action of all β-lactam antibiotics, which relies upon inhibiting the bacterial cell wall synthesis. For β-amino acid-containing peptides, Seebach and Matthews[3] and Gellman and coworkers[4] showed that in some cases, the incorporation of β-amino acids into the peptide chain causes a change in physicochemical properties and biological activity of the peptide. Besides, such modifications of peptides give rise to

D P Zarezin. PhD student at the Division of Organic Chemistry of the Department of Chemistry, MSU.
e-mail: danzar@inbox.ru
Current research interests: multicomponent reactions, peptides.
V G Nenajdenko. Doctor of Chemical Sciences, Professor, Head of the same Division.
Telephone: +7(495)939 – 2276, e-mail: nenajdenko@gmail.com
Current research interests: organofluorine chemistry, chirality, peptide synthesis, cyclic imines, click chemistry, multicomponent reactions, alkenylation, heterocyclic compounds.

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Structure I



I

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new types of secondary and tertiary structure of the modified peptides, resulting in an increase in stability of the latter against proteases and, as a consequence, in the improvement of metabolic stability and oral biological activity of the agents.

Diazocarbonyl derivatives of amino acids are convenient reagents for the introduction of a β-amino acid moiety into the target molecule and can be employed to prepare valuable heterocyclic compounds with high therapeutic potential. This review is devoted to methods of synthesis of such substituted amino acids and their application for the preparation of biologically active compounds.

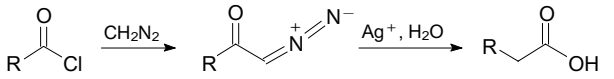
The following designations and abbreviations are used:
acac — acetylacetonate,
Anth — anthracenyl,
BINAP — 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl,
Boc — *tert*-butoxycarbonyl,
Cbz — benzyloxycarbonyl,
Cha — hexahydrophenylalanine,
cod — cycloocta-1,5-diene,
Cy — cyclohexyl,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCC — dicyclohexylcarbodiimide,
DIC — diisopropylcarbodiimide,
DIEA — diisopropylethylamine,
DMAP — 4-dimethylaminopyridine,
dr — diastereomeric ratio,
EDC — 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,
ee — enantiomeric excess,
Fmoc — 9-fluorenylmethoxycarbonyl,
Fu — furyl,
Hex — n-hexyl,
HOBt — 1-hydroxybenzotriazole,
IBCF — isobutyl chloroformate,
IC_{50} — half-maximal inhibitory concentration,
Ind — indolyl,
LDA — lithium diisopropylamide,
Ms — mesyl (methanesulfonyl),
MW — microwave radiation,
Naph — naphthyl,
NMM — *N*-methylmorpholine,
NPhth — phthalimido,
Ns — nosyl (4-nitrobenzenesulfonyl),
Nu — nucleophile,
PG — protecting group,
PMB — 4-methoxybenzyl,
PTSA — 4-toluenesulfonic acid,
Py — pyridine,
ROESY — rotating frame Overhauser effect spectroscopy,
rt — room temperature,
Sar — sarcosine,
SEM — 2-(trimethylsilyl)methoxymethyl ether,
TBAF — tetra-n-butylammonium fluoride,
TBDMS — *tert*-butyldimethylsilyl,
TBDPS — *tert*-butyldiphenylsilyl,
TBS — *tert*-butyldimethylsilyl,
TES — triethylsilyl,
Tf — triflate,
TFA — trifluoroacetic acid,
Th — thienyl,
TMS — trimethylsilyl,
Tol — tolyl (4-methylphenyl),
Ts — tosyl (4-methylbenzenesulfonyl),
Trt — trityl (triphenylmethyl).

2. Synthesis of chiral α-amino diazoketones

2.1. Arndt – Eistert reaction

The acylation of diazomethane allows the transformation of acid chlorides or mixed anhydrides of carboxylic acids into the corresponding diazoketones. This reaction is often referred to as the Arndt – Eistert reaction, although it is not quite correct because the classical Arndt – Eistert reaction consists of the following two reactions: acylation of diazomethane and the subsequent Wolff rearrangement of the resulting diazoketone catalyzed by silver salts to form a higher homologue of the starting acid (Scheme 1).[5]

Scheme 1



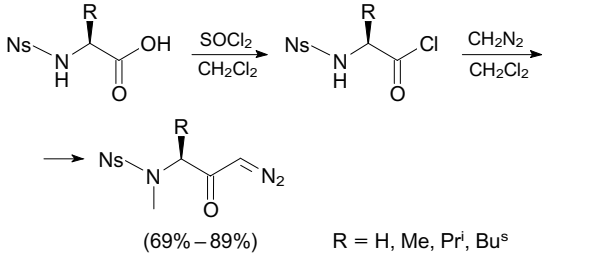
In the past two decades, the acylation of diazomethane was applied to synthesize β^3-amino acids. This reaction is currently the most commonly used method for the synthesis of diazocarbonyl derivatives of amino acids. This method was employed in >90% of publications devoted to the synthesis of diazo derivatives of amino acids, because it allows retention of the configuration of the starting acid.

The preparation of diazocarbonyl derivatives of amino acids can be divided into several steps: 1) amino group protection, 2) carboxyl group activation, 3) reaction with diazomethane or, in rare cases, with trimethylsilyldiazomethane. Each step is considered in detail below.

2.1.1. Protecting groups in the Arndt – Eistert reaction

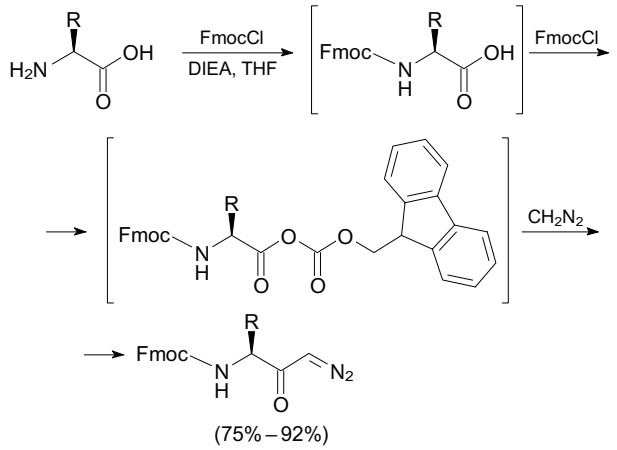
The Arndt – Eistert reaction requires amino group protection. A wide range of protecting groups (most often Fmoc, Boc and Cbz groups) are employed for this purpose. Belsito *et al.*[6] used N-nosylamino acids as the starting compounds in the Arndt – Eistert synthesis (Scheme 2). It should be noted that the presence of the strong electron-withdrawing nosyl group is responsible for a significant increase in the acidity of the NH group, thereby making it possible to prepare N-methylated β-amino acids, which present a potentially useful alternative to amino acids in the synthesis of peptide agents characterized by high lipophilicity and bioavailability.[7, 8]

Scheme 2



This research group[9] also performed the one-pot synthesis of *N*-Fmoc-α-amino diazoketones from α-amino acids, in which FmocCl served both for amino group

Scheme 3



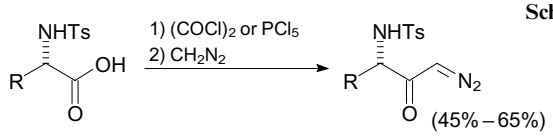
R = H, Me, Pr^i, Bu^i, Bu^s, Bn, $(CH_2)_2C(O)NH_2$, 3-indolylmethyl

protection and carboxyl group activation (Scheme 3). This approach was applied to a wide range of amino acids, including those containing reactive groups in the side chain. It should be emphasized that in the case of tryptophan, the protection of the indole NH group was not required. The synthesis was performed under an inert atmosphere in three steps without the isolation of intermediates. Initially, the amino group protection is provided by the reaction with FmocCl (1 equiv.) in the presence of a base. After completion of the reaction, the second equivalent of this reagent was added to activate the carboxyl group through the formation of the corresponding mixed anhydride, which reacted with diazomethane to form the desired diazo compound.

2.1.2. Carboxyl group activation in the Arndt – Eistert reaction

Amino acid chlorides are quite often used as the starting compounds in the Arndt – Eistert reaction due to their high reactivity and the ease of preparation. For example, α-amino diazoketones were synthesized from N-tosyl-protected amino acid chlorides (Scheme 4).[10,11] Amino acid chlorides were prepared *in situ* by the reaction with oxalyl chloride[10] or phosphorus pentachloride.[11]

Scheme 4

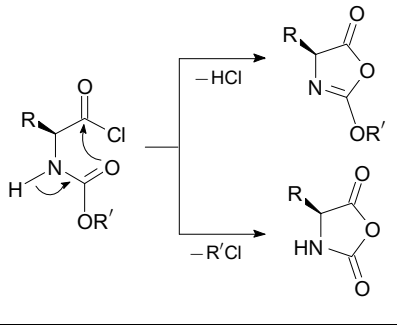


R = H, Me, Bn, $(CH_2)_2SMe$

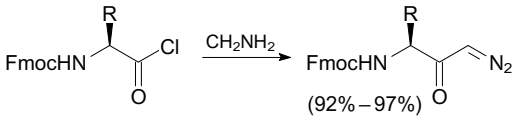
However, acid chlorides find little use in the Arndt – Eistert reaction involving N-acyl-protected (PG-Boc, Cbz, *etc.*) amino acids as the starting compounds. This is due to the fact that these reactions may be complicated by the reaction of acid chloride with the acid containing the N-acyl-protected amino group resulting in the formation of cyclic oxazolones and amino acid N-carboxyanhydrides (Scheme 5).[12 – 14]

Meanwhile, Fmoc-protected amino acid chlorides do not tend to form oxazolones under the conditions of the Arndt – Eistert reaction (Scheme 6).[15]

Scheme 5



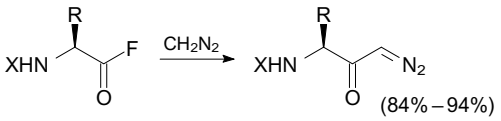
Scheme 6



R = Me, Pr^i, Bu^i, Bu^s, Bn

It is known that Boc-, Cbz-, Fmoc-protected amino acid fluorides are quite stable moisture-resistant rapid-acting acylating agents.[16] Therefore, amino acid fluorides were employed as the starting compounds in the Arndt – Eistert reaction (Scheme 7).[17] It should be noted that the acylation occurred at room temperature within 15 min to give target α-amino diazoketones in yields from 85% to 94%. However, this approach is of limited use because amino acid fluorides are difficult to prepare, requiring difficultly available and highly toxic fluorinating agents, such as cyanuric fluoride, tetramethylfluoroformamidinium hexafluorophosphate and sulfur diethylaminotrifluoride.

Scheme 7



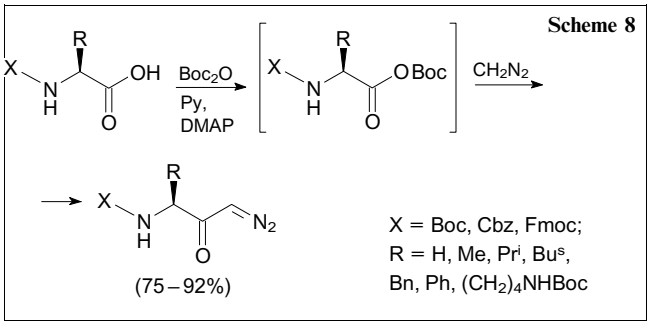
X = Fmoc, Boc, Cbz; R = Ph, Bu^s, CH_2Boc

Mixed anhydrides are most commonly used instead of α-amino acid chlorides in the acylation of diazomethane.[18] These compounds are prepared by the reaction of N-protected α-amino acids with chloroformates. Ethyl chloroformate,[19] isobutyl chloroformate[20,21] and 9*H*-fluoren-9-ylmethyl chloroformate are most widely employed in this reaction.[22] The nature of chloroformate has insignificant effect on the yields of the target products.

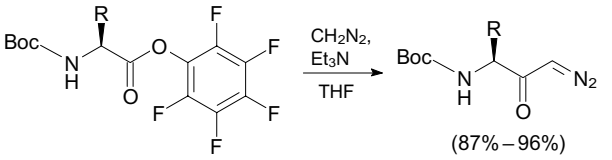
The *in situ* preparation of mixed anhydrides of amino acids is not limited to the reaction with chloroformates. For instance, the carboxyl group was successfully activated with di-*tert*-butyl pyrocarbonate (Boc_2O) (Scheme 8).[23] Diazomethane was acylated by Boc(Cbz,Fmoc)-α-amino acids using Boc_2O in the presence of pyridine and catalytic amounts of 4-dimethylaminopyridine (DMAP).

This research group[24,25] also employed Boc(Cbz)-α-amino acid pentafluorophenyl esters to synthesize α-amino diazoketones (Scheme 9). The reaction was performed in THF at room temperature in the presence of triethylamine.

Scheme 8



Scheme 9

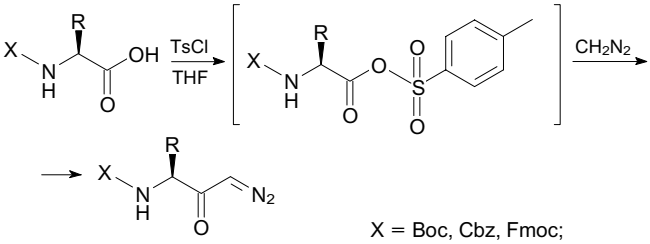


R = Me, Pr^i, Bn, Bu^s

An attempt to use amino acid 2,4,5-trichlorophenyl ester as an acylating agent failed.

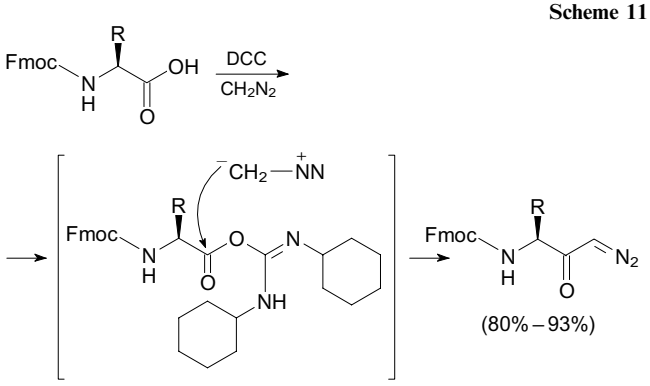
Vasanthakumar and Suresh Babu [26] used tosyl chloride (TsCl) to activate the carboxyl group in the synthesis of α-amino diazoketones. A series of amino diazoketones were prepared by the addition of a solution of TsCl and diazomethane in dichloromethane to a solution of N-protected amino acid in THF in the presence of pyridine (Scheme 10). The reaction proceeded through the formation of mixed carboxylic sulfonic anhydride, which was identified by IR spectroscopy (a band at 1825 – 1835 cm^{-1}). All diazomethane derivatives thus synthesized were isolated in good yields.

Scheme 10



Different carbodiimides [*e.g.*, dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)] are widely used as carboxyl group activating agents, particularly in the peptide synthesis (see Chapter 2 in the Handbook [27]). It is therefore quite natural that this approach has been applied to activate a carboxyl group in the synthesis of α-amino diazoketones (Scheme 11).[28] Target diazoketones were synthesized by the treatment of an equimolar mixture of Fmoc-α-amino acid and DCC with an ethereal solution of diazomethane. It should be noted that this reaction was performed without the addition of any base, which is essential when using Fmoc-α-amino acids as the starting compounds because of instability of the Fmoc group in the presence of bases.

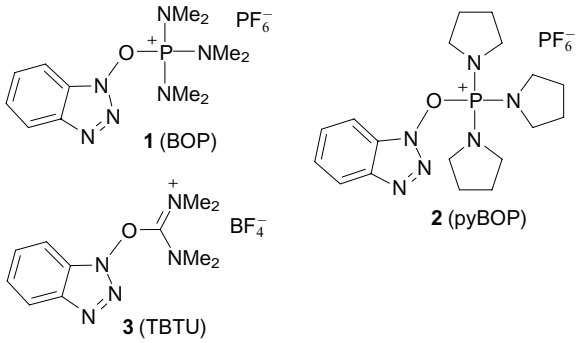
Scheme 11



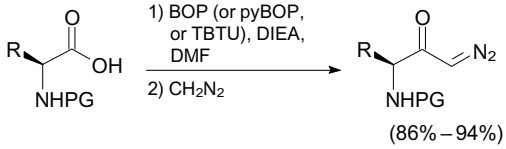
R = Me, Pr^i, Bu^i, Bn, Ph, CH_2Boc

It worth noting that onium salts, such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP, **1**), its pyrrolidine derivative (pyBOP, **2**) [29] and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU, **3**),[30] were also employed as carboxyl group activating agents in the acylation of diazomethane (Scheme 12).

Structures 1 – 3



Scheme 12



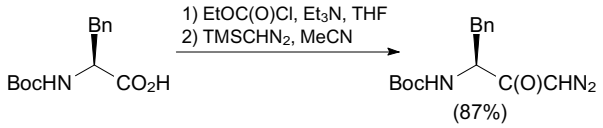
PG = Boc, Fmoc, Cbz; R = Me, Bn, Pr^i, Bu^s

However, despite good results, onium salts did not come into common use in the acylation of diazomethane because of their rather high cost and low atom-economy.

2.2. Acylation of trimethylsilyldiazomethane

Despite the extensive use of diazomethane in organic synthesis, this reagent is difficult to handle because it is very toxic, thermally unstable and potentially explosive.[31] Trimethylsilyldiazomethane ($TMSCHN_2$) is much more stable, thereby being a less explosive alternative to diazomethane.[32] The application of trimethylsilyldiazomethane, including for the synthesis of α-amino diazoketones, was reported.[30] An example is the synthesis of the diazocarbonyl derivative of L-phenylalanine (Scheme 13).[33] Although trimethylsilyl-

Scheme 13

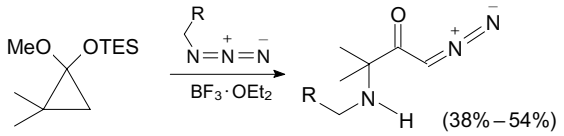


diazomethane is less reactive than diazomethane, the product yield was high.

2.3. Other methods

Another approach to the synthesis of α-amino-α′-diazomethyl ketones is based on the reaction of alkyl azides with (2,2-dimethyl-1-methoxycyclopropoxy)triethylsilane (Scheme 14).[34] Although the authors of the cited work prepared achiral diazo derivatives of amino acids, this reaction provides an alternative approach to the synthesis of diazoketones without using diazomethane.

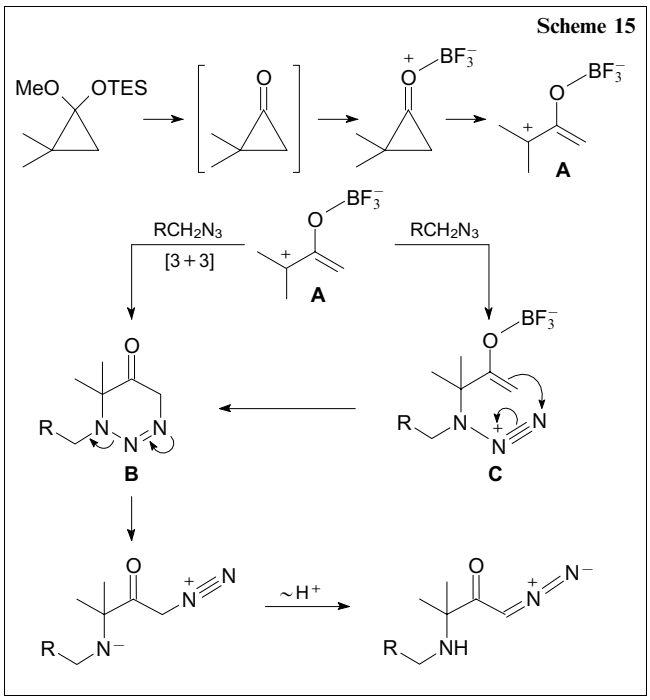
Scheme 14



R = Ph, 4-BrC_6H_4, 4-$MeO_2CC_6H_4$, 2-Naph, 9-Anth, Hex

The proposed reaction mechanism relies on the ability[35] of substituted cyclopropanones to undergo ring opening giving the 2-oxyallyl cation **A** (Scheme 15). Then the intermediate undergoes [3 + 3]-cycloaddition with alkyl azide to form 1,2,3-triazin-5-one **B**. The sequential ring opening and proton transfer afford the target diazo derivative. The stepwise process through the formation of the intermediate **C** is also possible.

Scheme 15

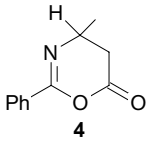


3. Synthesis of β-amino acid-containing peptides

Natural peptides have high physiological activity and regulate various biological processes. Therefore, these compounds are of great interest in medicinal chemistry. Presently, > 2% of marketed drugs are of peptide nature.[36] However, a considerable drawback of peptide drugs is their low metabolic stability and, as a consequence, low oral activity because they are easily cleaved in the body by peptidases. For this reason, most such drugs are formulated in injection vehicles, thereby significantly affecting their distribution. The introduction of a β-amino acid residue is known to considerably improve metabolic stability of the peptide. The effect of the β-amino acid moiety on the secondary structure of peptides and their resistance against peptidases were addressed in detail in a series of studies by Seebach *et al.*[37 – 39]

The synthesis of a tripeptide consisting of three β-aminobutanoic acid residues is one of the first attempts to prepare a nonracemic peptide containing a β-amino acid. Since attempts to perform the peptide synthesis using standard reagents, such as DCC and 1-hydroxybenzotriazole (HOBt), failed, Drey and Mtetwa[40] employed dihydro[1,3]oxazin-6-one **4**.

Structure 4

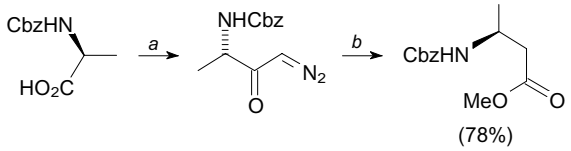


4

Required methyl 3-aminobutanoate was synthesized by the Arndt – Eistert reaction (Scheme 16).

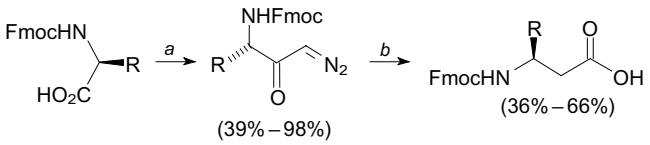
The homologation of amino acids containing functional groups such as azide and a C≡C triple bond was reported (Scheme 17).[41] The reactions with propargyl glycine and *O*-propargyl serine afford products in low yields (36% and 23%, respectively), which can be attributed to the reaction of silver trifluoroacetate (the catalyst for the Wolff rear-

Scheme 16



(*a*) 1) EtOC(O)Cl, Et_3N; 2) CH_2N_2, Et_2O; (*b*) AgOBz, Et_3N, MeOH

Scheme 17

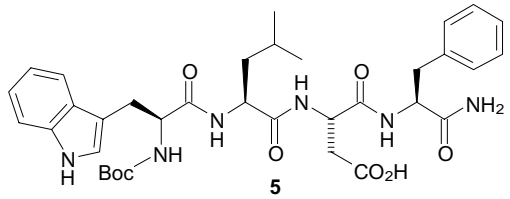


(*a*) 1) $Bu^iOC(O)Cl$, NMM; 2) CH_2N_2, THF; (*b*) AgO_2CCF_3, THF, H_2O; R = $(CH_2)_4N_3$, $CH_2C{\equiv}CH$, $CH_2OCH_2C{\equiv}CH$

rangement) with terminal alkyne. Azide-containing amino acid gives the product in an overall yield of 65%.

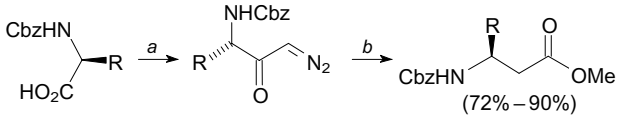
A similar β-amino acid synthesis was applied to modify the C-terminal tetrapeptide Boc-Trp-Leu-Asp-Phe-NH_2 (**5**) of gastrin. β-Amino acid derivatives were synthesized according to Scheme 18.[42]

Structure 5



5

Scheme 18

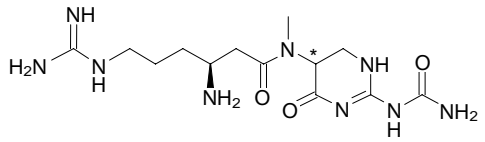


(*a*) 1) $Bu^iOC(O)Cl$, NMM; 2) CH_2N_2; (*b*) AgO_2CCF_3, Et_3N, MeOH; R = $CH_2C(O)Bn$, Bu^i, Ph

Rodriguez *et al.*[42] sequentially replaced leucine, aspartic acid and phenylalanine by appropriate homologues, the introduction of an additional CH_2 group having an insignificant effect on biological activity of the peptide. The evaluation of biological activity of the resulting molecules showed that the homoaspartic acid-containing tetrapeptide is most similar to Trp-Leu-Asp-Phe [the half-maximal inhibitory concentration (IC_{50}) was 0.75 and 0.5 μmol litre^{-1}, respectively].

Chiral diazocarbonyl derivatives of amino acids are convenient building blocks for the synthesis of β-amino acid-containing peptides. Xu *et al.*[43] synthesized analogues of the dipeptide antibiotics TAN-1057A(B) (structures **6a**,**b**) in order to enhance antimicrobial properties. Antibiotics of the TAN-1057A(B) series contain two key moieties, namely, homoarginine and 2,5-diamino-5,6-1*H*-dihydropyrimidin-4-one, which inhibit bacterial translation.

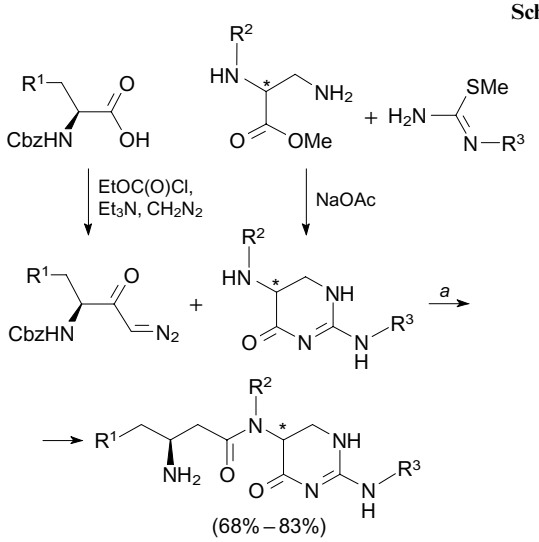
Structure 6



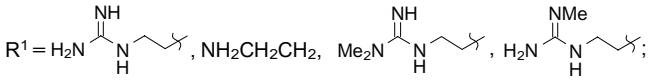
6a (TAN-1057A, *S* enantiomer),
6b (TAN-1057B, *R* enantiomer)

The antibiotics TAN-1057A(B) and their derivatives were synthesized by a procedure presented in Scheme 19.[44,45] It was shown that the replacement of the methyl group (R^2) by the ethyl one and well as the replacement of the guanidine moiety in homoarginine by primary amine (R^1) lead to a significant increase in selectivity but reduce inhibitory activity against bacterial translation. The dihydropyrimidinone core, which is a pharmacophore in the TAN-1057A(B) molecule, proved to be most sensitive to modifications. Xu and co-workers[46–48] and Williams and Yuan[49] applied a similar approach to the synthesis of the dipeptide antibiotic TAN-1057A(B) and its analogues.

Scheme 19



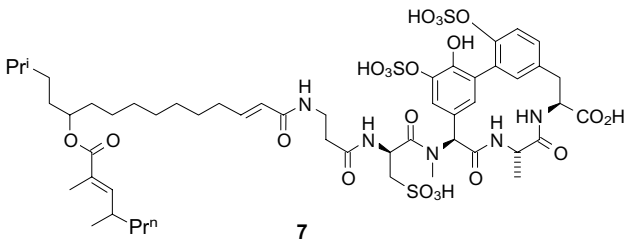
(*a*) 1) $AgClO_4$, Et_3N, DMF; 2) H_2, $PdCl_2$, Pd/C, MeOH;



R^2 = Me, Et; R^3 = $NH_2C(O)$, $MeNHC(O)$, $Me_2NC(O)$, EtC(O), Ac

Increasing demands for new antibiotics in modern medicine bring about a new term 'latent antibiotic' in pharmacology. A latent antibiotic is a naturally occurring compound, chemical modifications of which can impart antimicrobial activity to the resulting derivative. An example is arylomycin (**7**). Liu's research group[50] made attempts to enhance the efficiency of the latter compound.

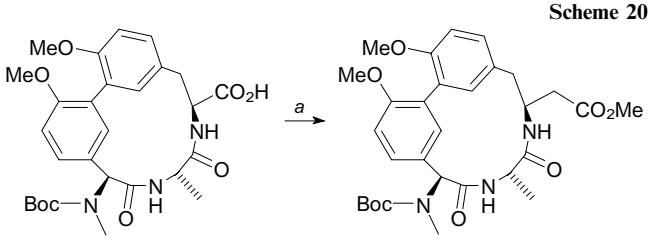
Structure 7



7

Liu and co-workers[50] modified the macrocyclic moiety of arylomycin by replacing the carboxyl group of tyrosine with phosphates and formamides and by replacing α-tyrosine with its β-analogue (Scheme 20). The authors suc-

Scheme 20

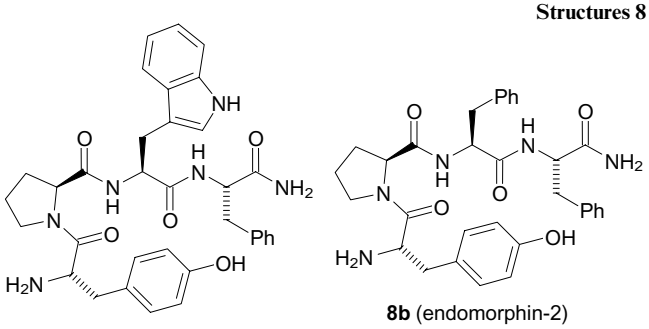


(*a*) 1) $Bu^iOC(O)Cl$, NMM; 2) CH_2N_2; 3) AgO_2CCF_3, MeOH

ceeded in improving efficiency of the natural antibiotic by a factor of 250 by the replacement of the tyrosine carboxyl group with diphenyl phosphate.

Recent pharmacological studies showed that endogenous peptides such as endomorphin-1, H-Tyr-Pro-Trp-Phe-NH_2, (**8a**) and endomorphin-2, H-Tyr-Pro-Phe-Phe-NH_2, (**8b**), may exhibit analgesic activity.

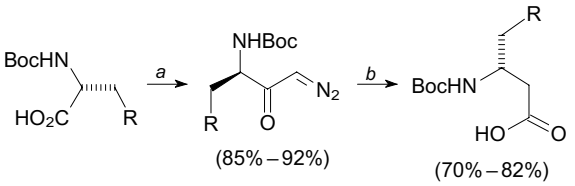
Structures 8



8a (endomorphin-1) **8b** (endomorphin-2)

These compounds represent a potential alternative to morphine, because they have agonist activity at the same μ-opioid receptors.[51] In order to enhance stability and analgesic activity of endomorphin-1, Cardillo *et al.*[52] synthesized its analogues, in which α-amino acids were replaced in turn with β^3-amino acids. β-Amino acids were synthesized according to Scheme 21. The skeleton of this β-peptide is more flexible; however, this does not lead to a significant change in its active conformation, and the mechanism of binding to the receptor remains unchanged. Hence, it is reasonable to expect that these compounds have similar biological activity. Podwysocka *et al.*[53] modified the tetrapeptide Tyr-D-Ala-Phe-Phe-NH_2 (TAPP), which is a ligand for the μ-opioid receptor, by replacing α-amino acids with β^3-amino acids (see Scheme 21).

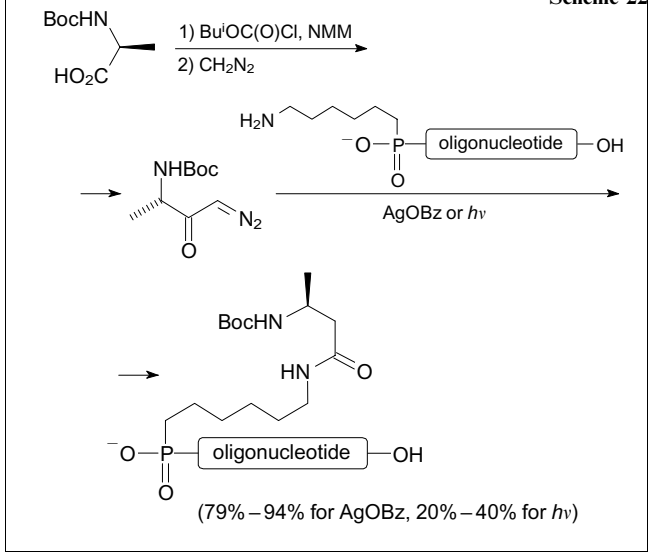
Scheme 21



(*a*) 1) EtOC(O)Cl, Et_3N; 2) CH_2N_2, Et_2O; (*b*) AgO_2CCF_3, Et_3N, THF, H_2O; R = 4-HOC_6H_4, 3-Ind, Ph

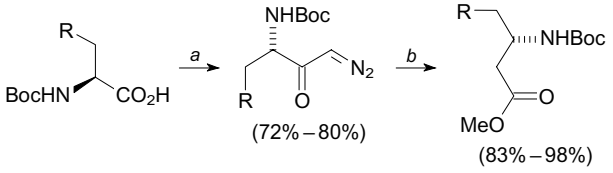
Biopolymers, including oligonucleopeptides, are of particular interest. These conjugates significantly extend the range of properties of synthetic nucleotides.[54] The conjugation of peptides to nucleotides essentially increases their cellular uptake [55] and facilitates binding to DNA.[56] Guibourdenche and Seebach [57] synthesized oligonucleopeptides by attaching different oligonucleotides to diazoketone. The Wolff rearrangement was performed in two ways: in the presence of a silver salt or under light irradiation. This approach was successfully applied to oligonucleotides containing up to eight nitrogen bases; when using oligonucleotides grafted onto solid support, up to 15 nitrogen bases (Scheme 22).

Scheme 22



Peptides containing one or several β-amino acids are often used as peptidase inhibitors. Aminopeptidases are exopeptidases that catalyze the cleavage of an amino acid sequence from the NH_2-terminus of the peptide. For example, the synthesis of a series of aminopeptidase inhibitors is based on peptide derivatives of diaminothiols, as well as leucine and phenylalanine homologues (Scheme 23).[58]

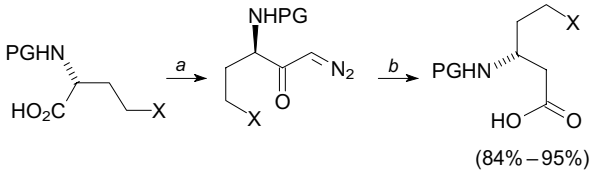
Scheme 23



(*a*) 1) $Bu^iOC(O)Cl$, NMM; 2) CH_2N_2; (*b*) AgOBz, MeOH; R = Ph, Pr^i

Unnatural β-dipeptide, an inhibitor of metallopeptidase *Tetanus neurotoxin* produced by anaerobic bacteria, was synthesized in a similar way (Scheme 24).[59]

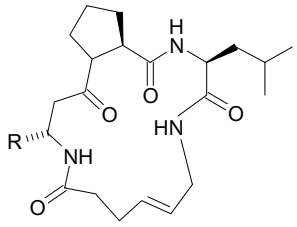
Scheme 24



(*a*) 1) EtOC(O)Cl, Et_3N; 2) CH_2N_2, Et_2O; (*b*) AgOBz, Et_3N, MeOH; X = C(O)NHTrt, PG = Boc; X = SO_2NHBu^t, PG = Cbz

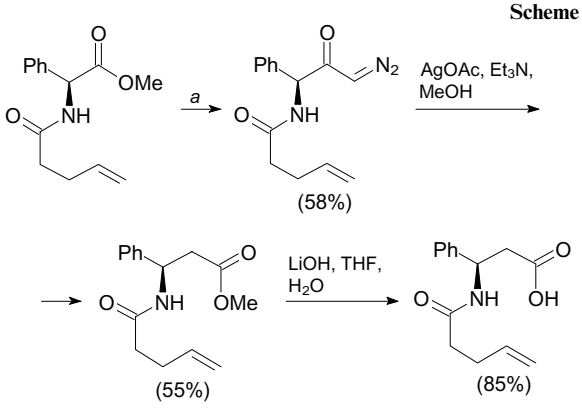
A combination of the amino acids α-L-proline and phenylglycine is responsible for the molecular conformation of many peptide drugs; however, the hydrogen bond between these amino acid residues is easily cleaved by endopeptidases, resulting in an irreversible conformational change.

Structures 9



9a,**b** R = Ph (**a**), Me (**b**)

Scheme 25

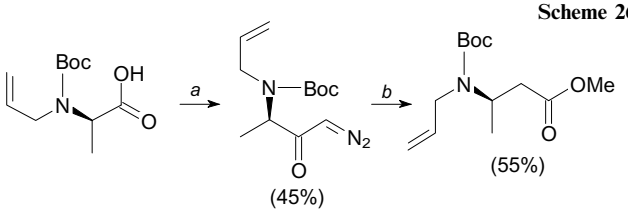


(*a*) 1) LiOH, THF, H_2O; 2) $Bu^iOC(O)Cl$, Et_3N; 3) CH_2N_2

To increase stability of this moiety against peptidases, Banerji *et al.*[60] synthesized cyclic peptide **9a** (R = Ph) by replacing phenylglycine with its β-analogue (Scheme 25).

A similar modification of the β-methyl-β-alanine – α-proline sequence was applied to synthesize cyclic peptide **9b** (R = Me).[61] For this purpose, *N*-Boc-*N*-allyl-β-methyl-β-alanine methyl ester was prepared from *N*-Boc-*N*-allyl-alanine by the Arndt – Eistert reaction (Scheme 26).

Scheme 26



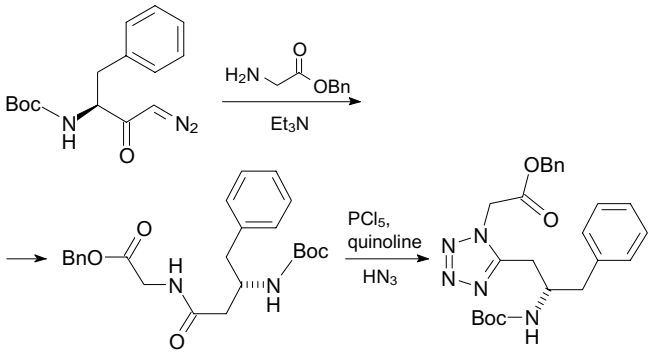
(*a*) 1) $Bu^iOC(O)Cl$, Et_3N; 2) CH_2N_2; (*b*) AgOAc, Et_3N, MeOH

A modification of the peptide chain in order to increase its stability can be accomplished by introducing a peptide bond bioisostere, *e.g.*, a tetrazole moiety. A β-dipeptide analogue, in which the peptide bond is replaced with a tetrazole moiety, was synthesized from phenylalanine-derived diazoketone (Scheme 27).[62] The resulting compound is a potential HIV protease inhibitor.

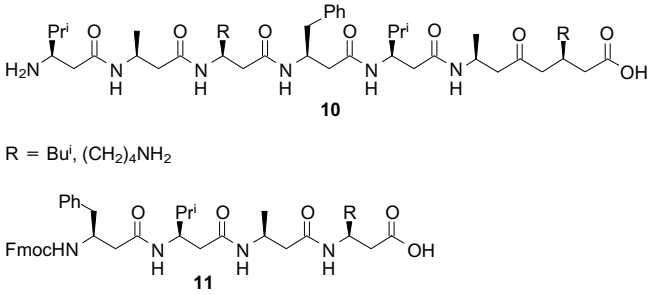
In recent years, the synthesis of unnatural oligopeptides, including those totally composed of β-amino acids, has attracted great interest. The peptide synthesis on solid support was performed for β-peptides containing 4 to 15 amino acids, *e.g.*, peptides **10** and **11**.[63]

This synthesis was carried out using Fmoc-protected amino acids, which were transformed by the Arndt – Eistert reaction into the corresponding homologues in yields from 38% to 75% (Scheme 28). In the case of amino acids containing functional groups in the side chain [R = $BocNH(CH_2)_4$, $Boc(CH_2)_2$], the yields of the products in the Wolff rearrangement step were moderate (38% and 47%, respectively). After deprotection of the nitrogen atom, the oligopeptide chain was assembled. The use of a solid support substantially simplifies and accelerates the peptide synthesis, because it allows one to use simple washing and filtration procedures instead of the laborious and time-consuming separation and purification of intermediate peptides.

Scheme 27



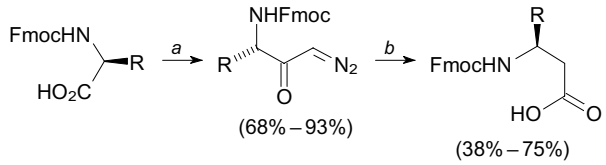
Structures 10, 11



R = Bu^i, $(CH_2)_4NH_2$

A β-amino acid can be introduced into a peptide in the Wolff rearrangement step. A series of diazoketones based on Boc-protected amino acids and peptides were synthesised [64] and then they were subjected to the Wolff rearrangement using O-protected amino acids and dipeptides as nucleophiles (Scheme 29).

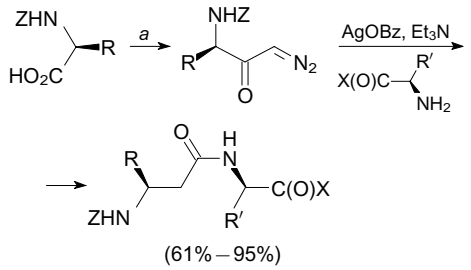
Scheme 28



(*a*) 1) $Bu^iOC(O)Cl$, NMM; 2) CH_2N_2, Et_2O;
(*b*) AgO_2CCF_3, Et_3N, THF, H_2O;
R = Me, Pr^i, Bu^i, Bn, $BocNH(CH_2)_4$, $Boc(CH_2)_2$, Bu^tOCH_2

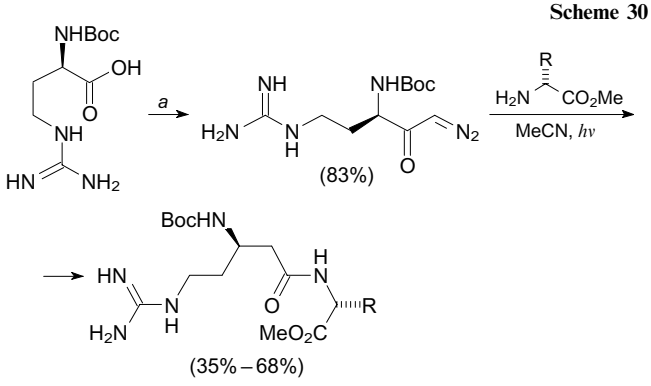
Bastiaans *et al.*,[65] synthesized a series of dipeptides containing β-arginine, which was produced from arginine by the Arndt – Eistert reaction (Scheme 30). A mixture of the resulting diazoketone and amino acid methyl esters was

Scheme 29



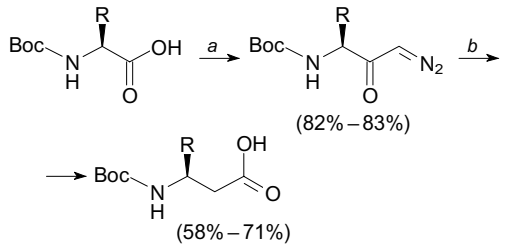
(*a*) 1) EtOC(O)Cl, Et_3N; 2) CH_2N_2, Et_2O; R = Me, Bu^i; R′ = Me, Pr^i, Bu^i; X = OBz, Sar-Leu-OMe; Z = Boc, Boc-Ala, Boc-Leu-Sar

Scheme 30



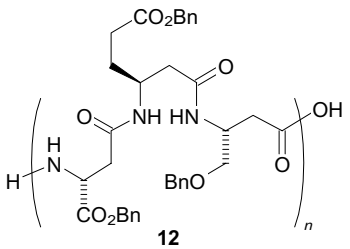
(*a*) 1) $Bu^iOC(O)Cl$, Et_3N; 2) CH_2N_2; R = Me, Pr^i, Ph

Scheme 31



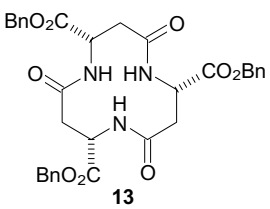
(*a*) 1) EtOC(O)Cl, Et_3N, THF; 2) CH_2N_2, Et_2O;
(*b*) AgO_2CCF_3, H_2O, THF; R = $(CH_2)_nCO_2Bn$, CH_2OBn; *n* = 0, 2

Structures 12 – 14

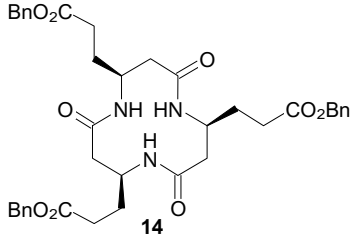


12

n = 1, 2



13



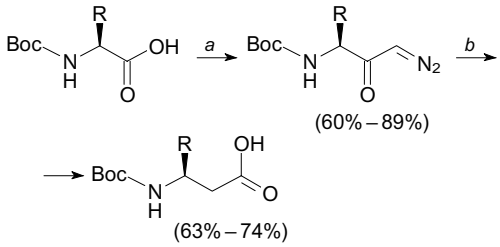
14

subjected to photolysis (λ = 300 nm) in dry acetonitrile, and the target dipeptides were isolated in yields from 35% to 68%.[66]

Homoserine, homoaspartic acid and homoglutamic acid are the most abundant natural β-amino acids (Scheme 31). Seebach's research team[67] synthesized cyclic and linear oligopeptides **12** – **14** based on derivatives of these β-amino acids and studied their secondary structure. For a series of cyclic and linear tri- and hexapeptides, it was shown that protecting groups at oxygen atoms affect the secondary structure of the peptide. Thus, after the removal of benzyl protecting groups, the peptide adopts 3_{14}-helical symmetry.

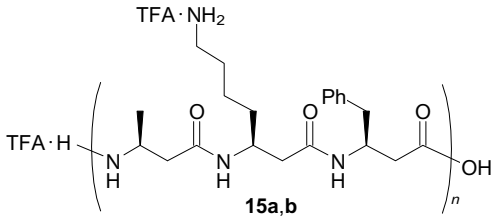
This research team[68] also demonstrated that the secondary structure of β-peptides depends on the constituent amino acids (Scheme 32). β-Hexapeptide **15a** and β-nonapeptide **15b** consisting of alternating β-methyl-β-alanine – homolysine – homophenylalanine sequences were shown to have a folded structure unlike helical symmetry of related peptides, in which homolysine is replaced with homoserine. In the cited study, this fact was attributed to partial destabilization of the helical secondary structure by hydrogen bonds formed by β-lysine.

Scheme 32



(*a*) 1) EtOC(O)Cl, Et_3N, THF; 2) CH_2N_2, Et_2O;
(*b*) AgO_2CCF_3, H_2O, THF;
R = $(CH_2)_2Ph$, $(CH_2)_3NHBoc$, $CH_2C_6H_4OBu^t$-4

Structures 15



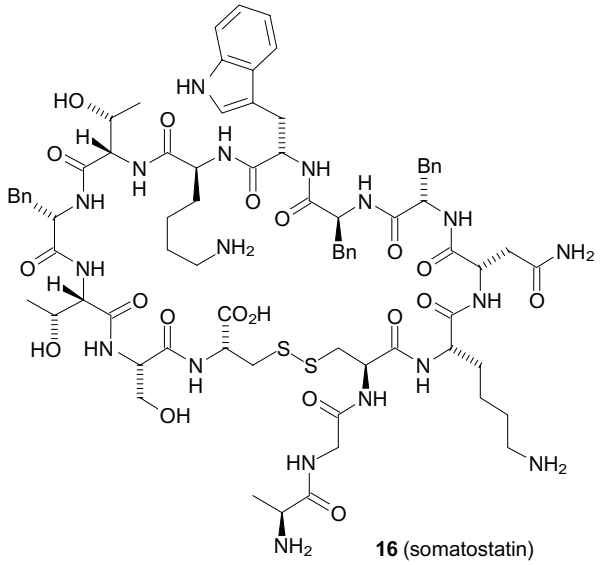
15a,**b**

n = 2 (**a**), 3 (**b**)

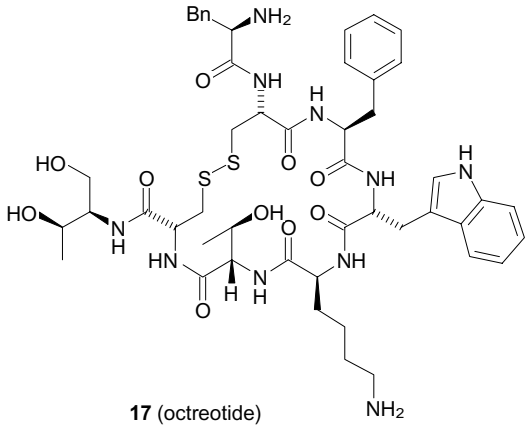
The secondary structure of cyclic β-peptides was studied in more detail in relation of tetrapeptides by means of physicochemical methods, including 2D ^1H ROESY experiments in different media, X-ray diffraction and computer simulation of 3D structures.[69]

Methods for the synthesis of cyclic peptides have been extensively developed in recent years. An increased interest in these methods is due to higher metabolic stability of cyclic peptides compared to their linear analogues.[70] The introduction of a β-amino acid moiety into a cyclic peptide would lead to enhancement of its metabolic stability. The effect of the β-amino acid moiety on the properties of cyclic peptides was addressed in a number of publications.[71 – 73] Seebach's research team[74 – 76] synthesized a series of cyclic β-tetrapeptides as analogues of the cyclic peptides somatostatin (**16**) and octreotide (**17**).

Structures 16, 17

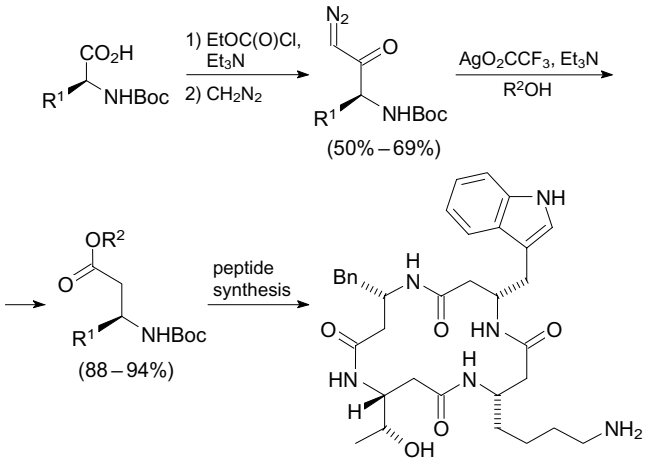


16 (somatostatin)



17 (octreotide)

Scheme 33



R^1 = Bn, $(CH_2)_4NHCbz$, indol-3-ylmethyl, (*R*)-1-benzyloxyethyl;
R^2 = H, Me

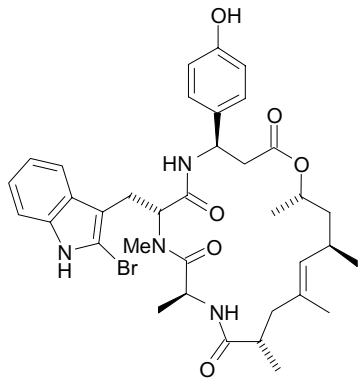
Octreotide is a cyclic α-octapeptide used to treat acromegaly and some other diseases and is an analogue of the natural tetradecapeptide somatostatin. Since octreotide shows low bioavailability, it was of interest to synthesize its β-analogue. The structure of a cyclic peptide consisting of β-amino acids was developed by molecular modelling. All β-amino acid building blocks required for the synthesis of the target β-tetrapeptide were prepared from diazocarbonyl compounds of appropriate *N*-Boc-α-amino acids: phenylalanine, tryptophan, lysine and threonine (Scheme 33).

4. Synthesis of β-amino acid-containing depsipeptides

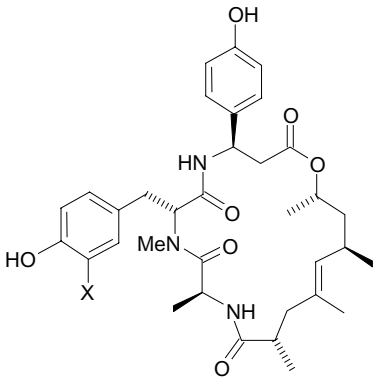
Depsipeptides are peptides containing one or several ester groups. In a more general sense, by depsipeptides are meant peptides containing components other than α-amino acids. Cyclic depsipeptides are highly promising as antitumour agents because many of them exhibit pronounced cytotoxic activity.[77,78] Most cyclic depsipeptides are produced by microorganisms. Jasplakinolide (**18**),[79] geodiamolides (**19**)[80] and chondramides (**20**)[81] isolated from marine sponges and mycobacteria were the first representatives of a large group of cyclodepsipeptides.

Becker and Kazmaier[82] made an attempt to modify the chondramide C structure by removing all methyl groups and stereogenic centres from the molecule and also by

Structures 18 – 20

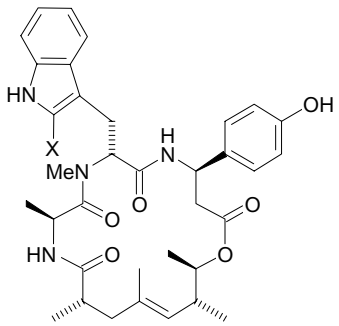


18 [(+)-jasplakinolide]



19 (geodiamolides A – C)

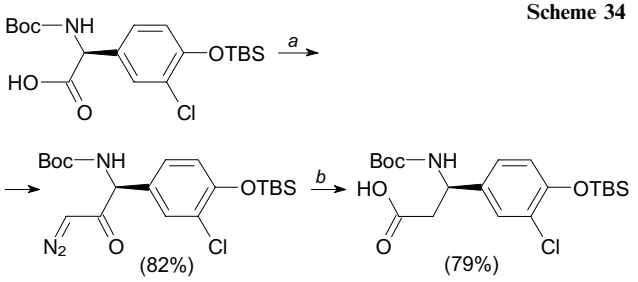
X = I (A), Br (B), Cl (C)



20 (chondramides C, D)

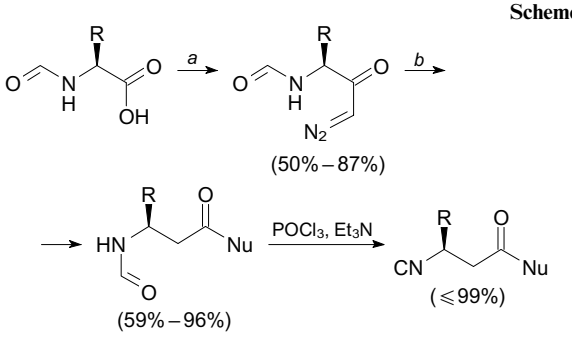
X = H (C), Cl (D)

Scheme 34

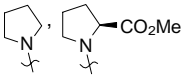


(*a*) 1) EtOC(O)Cl, Et_3N, THF, −20 °C; 2) CH_2N_2, −78 °C;
(*b*) AgOBz, SiO_2, EtOAc, 45 °C

Scheme 35



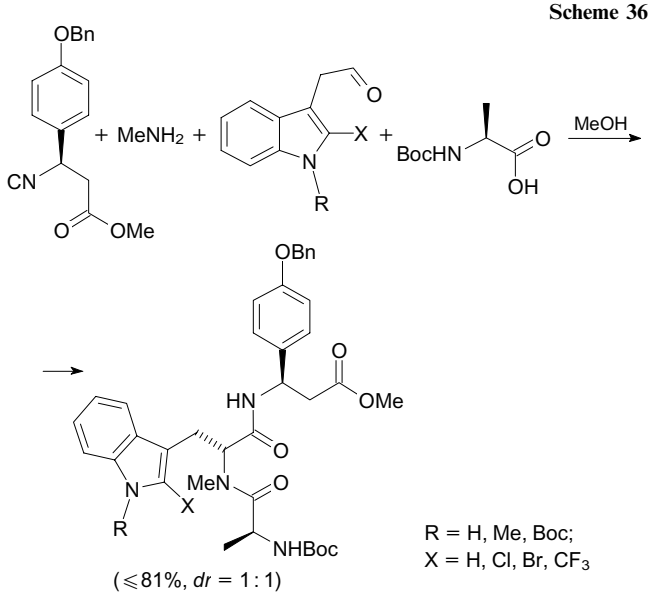
(*a*) 1) EtOC(O)Cl, Et_3N; 2) CH_2N_2; (*b*) AgOBz, NuH;
R = Me, Pr^i, Bu^s, Bu^i, Bn, Ph, $(CH_2)_2SMe$; Nu = OMe, OEt, OBu^t, OBn, NHBn,



introducing a halogen atom into the protected β-hydroxyphenylglycine moiety (Scheme 34). β-Hydroxyphenylalanine was synthesized by the Arndt – Eistert reaction followed by the Wolff rearrangement giving the target moiety in an overall yield of 65%. Biological activity of halogenated chondramide C is comparable with that of the natural depsipeptide.

Nenajdenko's research group[83] developed the synthesis of a new class of organic compounds — chiral derivatives of β-isocyanopropionic acids — from *N*-formyl-α-amino diazoketones. The Arndt – Eistert reaction involving *N*-formylamino acids affords diazoketones and the subsequent

Scheme 36

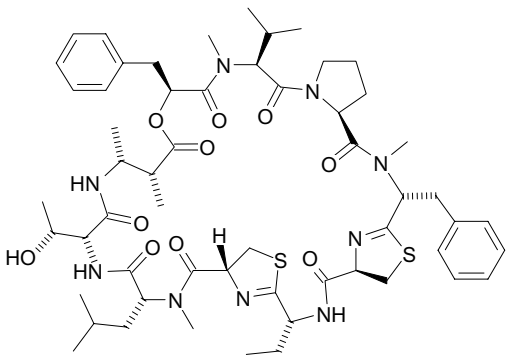


rearrangement of the latter in the presence of silver benzoate and different nucleophiles followed by dehydration provide a route to target β-isocyanopropionic acid derivatives (Scheme 35). These isocyanides are configurationally stable unlike isocyanoacetic acid derivatives, *i.e.*, isocyanides derived from α-amino acids.[84, 85]

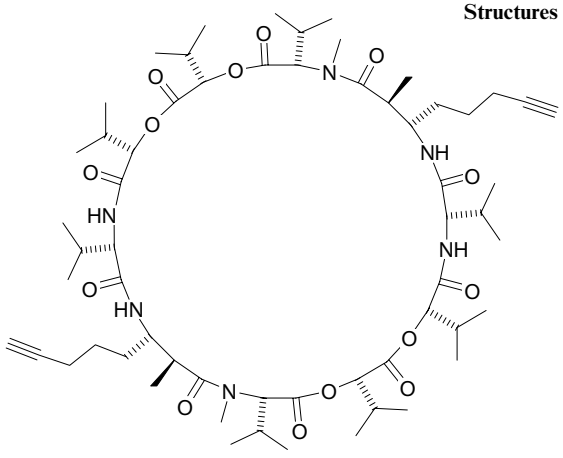
This approach was applied to the synthesis of peptide moieties of natural depsipeptides — jaspamides and chondramides (Scheme 36).[86] The Ugi reaction involving methyl 3-(4-benzyloxyphenyl)-3-isocyanopropanoate, which was prepared according to Scheme 35, indol-3-ylacetaldehyde, methylamine and N-Boc-protected alanine gave target peptides. It should be noted that this method allows easy variation of a substituent in position 2 of the indole ring, which in turn can change the biological activity of the final product.

Another approach to the preparation of a β-amino acid moiety was employed in the synthesis of another natural cyclic depsipeptide — grassypeptolide A (**21**).[87] This depsipeptide contains 3-amino-2-methylbutanoic acid, which was synthesized in high yield in two steps from N-protected alanine through the corresponding diazoketone (Scheme 37).

Structures 21, 22

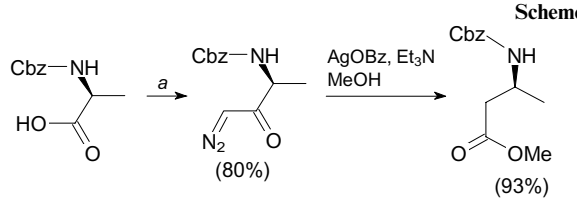


21 (grassypeptolide A)



22 (onchidin)

Scheme 37

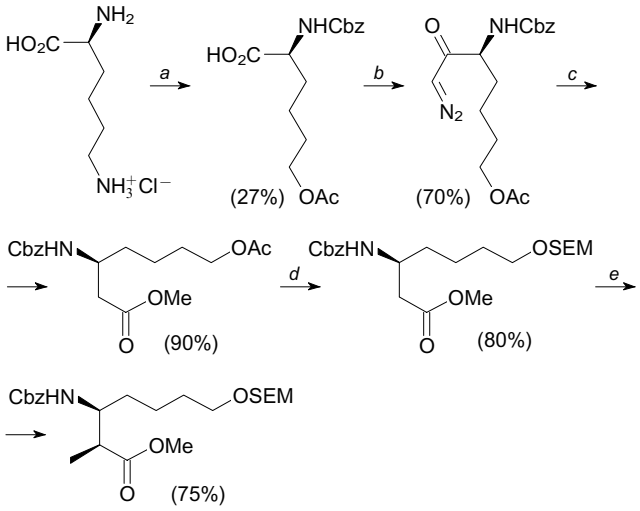


(*a*) 1) Bu^{i}OC(O)Cl, NMM; 2) CH_2N_2

Peng *et al.*[88] performed a total synthesis of onchidin (**22**) — a natural cyclic depsipeptide with high therapeutic potential (cytotoxicity IC_{50} = 8 μg ml^{-1}).

Onchidin includes nontrivial α-methyl-β-amino acid, which was synthesized from (*S*)-lysine hydrochloride (Scheme 38). The total synthesis involves nine steps, with the homologation of (*S*)-lysine by the Arndt – Eistert reaction followed by the Wolff rearrangement and the introduction of a methyl group in the α position being the key steps. Target β-amino acid was prepared in an overall yield of 10%. However, biological activity of the synthetic analogue of onchidin is significantly lower than that of the natural product, which was attributed to specific features of the secondary structure of the depsipeptide.

Scheme 38

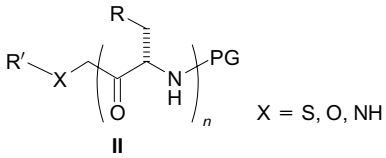


(*a*) LiOH, PhCHO; 2) CbzCl, NaOH, HCl; 3) AcOH, NaOAc, $NaNO_2$, 40 °C; (*b*) 1) Bu^{i}OC(O)Cl, Et_3N; 2) CH_2N_2, THF; (*c*) AgOBz, Et_3N, MeOH; (*d*) 1) K_2CO_3, MeOH, −5 °C; 2) SEMCl, DIEA, CH_2Cl_2; (*e*) – 1) LDA, LiCl, THF; 2) MeI, −78 °C

5. Synthesis of peptidomimetics

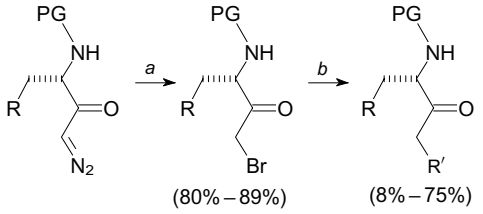
Peptidomimetics are peptide-like compounds containing non-peptide structural elements, which are able to mimic biological activity of natural peptide molecules. Peptidomimetics do not necessarily have classical peptide characteristics, such as enzymatically formed peptide bonds. Protease inhibitors constitute one of the largest and diverse classes of peptidomimetics. Generally, these peptidomimetics involve non-peptide and peptide components (structure **II**), the latter usually containing a β-amino acid moiety.

Structure II

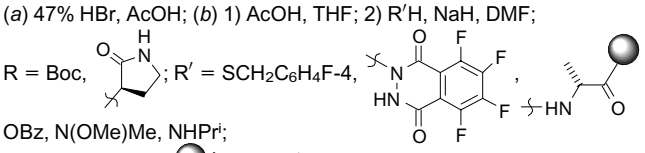


In medicine, protease inhibitors are used to treat various diseases such as ischemic heart disease, hepatitis A, emphysema, acute respiratory syndrome, HIV infections and many other. A number of studies addressed biological activity of inhibitors of caspase-3,[89 – 94] cysteine proteases,[95 – 101] serine proteases,[102, 103] elastases,[104] rhinoviruses,[105] tubulysins,[106] HIV proteases[107 – 109] and metalloproteases.[110] The synthesis of these compounds involves the preparation of diazoketone from the peptide component, the addition of hydrogen bromide to the diazoketone and subsequent anchoring of a non-peptide component *via* O-, S- or N-nucleophilic substitution of bromine (Scheme 39).

Scheme 39



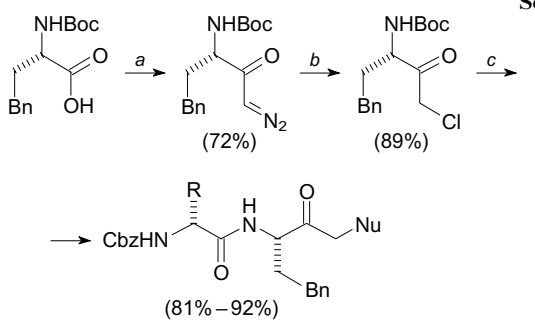
(*a*) 47% HBr, AcOH; (*b*) 1) AcOH, THF; 2) R′H, NaH, DMF;



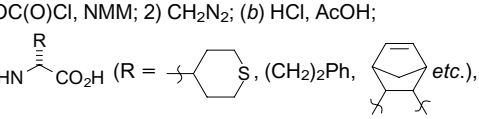
OBz, N(OMe)Me, NHPr^i;
PG = Boc, Fmoc; is support

The above-described synthetic scheme was applied[111] to prepare a series of new peptidomimetics, namely, pseudoprolyl homophenylalanyl ketones, acting as inhibitors of cysteine proteases FP-2 and FP-3 from *Plasmodium falcipa-*

Scheme 40



(*a*) 1) Bu^{i}OC(O)Cl, NMM; 2) CH_2N_2; (*b*) HCl, AcOH;

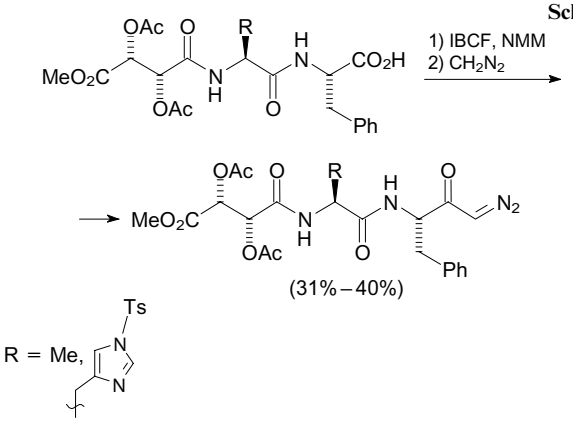
(*c*) 1) 

EDC, HOBt, Et_3N; 2) NuH; NuH = H_2O, NaOAc, AcSH, morpholine, $Ph(CH_2)_3SH$

rum (Scheme 40). The activity of these peptidomimetics was evaluated. A total of 22 compounds were synthesized, and the peptidomimetic containing Cbz-protected hydroxyproline linked to homophenylalanine was found to be most effective (IC_{50} = 80 nmol litre^{-1} against FP-2 and 60 nmol litre^{-1} against FP-3).

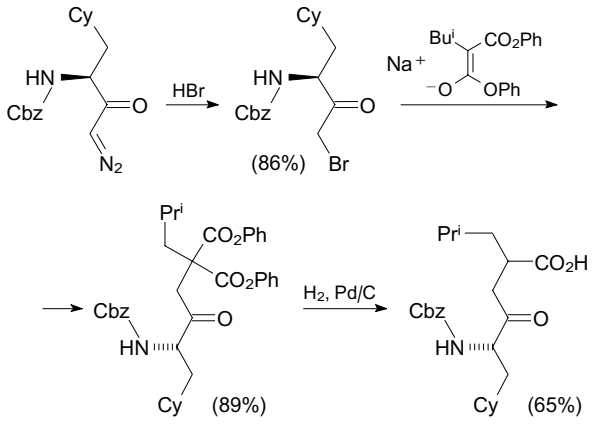
Since the form and distribution of the charge at the peptide bond are very similar to those in diazomethyl ketone, peptide-based diazoketones can act as protease inhibitors.[112, 113] Multiple tests using model reactions and microorganisms showed that the functional group in diazoketones is specific to thiol proteases and is inactive towards other protease classes. Wagner *et al.*[114] synthesized a series of diazoketone-containing cysteine proteases, so-called haptens, by the Arndt – Eistert reaction. Peptidyl diazomethyl ketones are among the most powerful inhibitors. Target peptidyl diazomethyl ketones were synthesized from appropriate peptides, the carboxyl groups of which were preactivated with isobutyl chloroformate, by the treatment with diazomethane (Scheme 41).

Scheme 41



In recent years, the concept of isosteric replacement of amide bonds in biologically active peptides has attracted considerable interest. This concept relies on the assumption that one or several amide bonds in peptides can be modified in such a way as to retain the conformation and receptor binding, but to prevent enzymatic hydrolysis. In particular, this concept was applied by Kaltenbronn *et al.*[115] to synthesize a renin inhibitor, which can be used to treat hypertension. 5-Amino-2-isobutyl-4-oxo-6-cyclohexylhexanoic acid derivative was synthesized from the diazocarbonyl derivative of 2-amino-3-cyclohexylpropanoic acid (Scheme 42).

Scheme 42

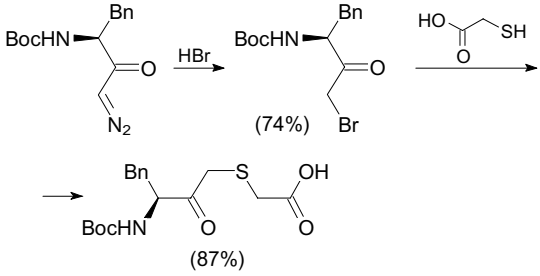


DeGraw *et al.*[116] described a similar method for the synthesis of peptidomimetics, which are more stable analogues of the pentapeptide thymopentin. α-Chloroketone was prepared from N-protected arginine-based diazoketone and then attached to a sodium malonate derivative followed by decarboxylation, resulting in the formation of the target peptidomimetic as a mixture of diastereomers in 24% and 27% yields (Scheme 43).

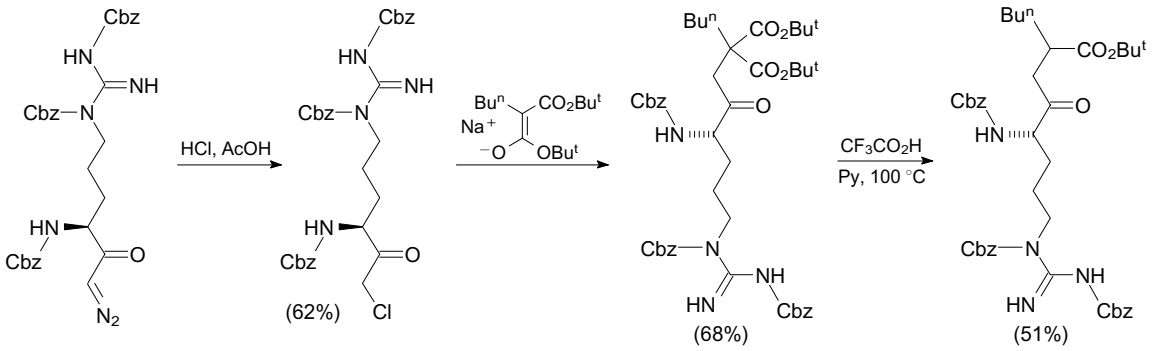
Another moiety of the renin inhibitor was modified by Raddatz *et al.*[117] in order to enhance its resistance to chymotrypsin, thereby improving oral activity. After the addition of sulfanylacetic acid to α-bromoketone, which was prepared from N-protected phenylalanine, the peptidomimetic was isolated in an overall yield of 64% (Scheme 44).

A moiety of the peptidomimetic, an inhibitor of the reuptake of the endocannabinoid anandamide, was synthesized.[118] Diazoketone was sequentially treated with hydro-

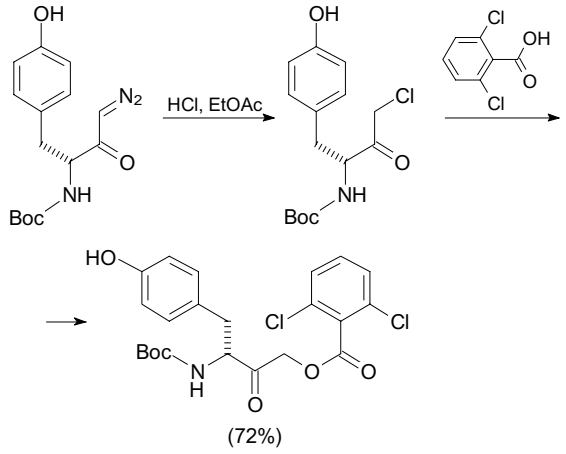
Scheme 44



Scheme 43



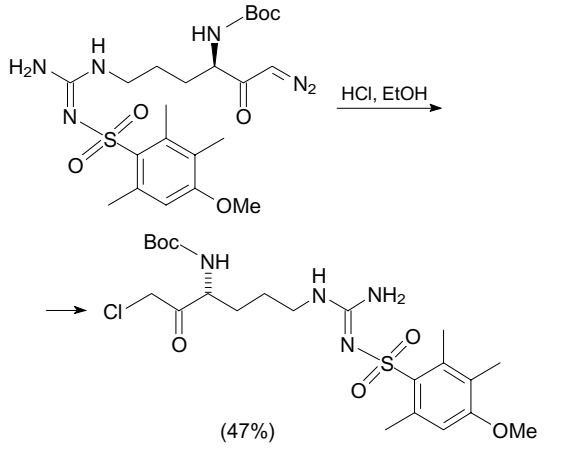
Scheme 45



chloric acid giving α-chloroketone and then with 2,6-dichlorobenzoic acid, resulting in the isolation of the target product in 72% yield (Scheme 45).

Peptide-based α-chloroketones can exhibit biological activity. Białas *et al.*[119] studied the secondary structure of peptide-based α-chloroketones as inhibitors of proteases, gingipains. Besides, peptide-containing α-chloroketones are used in the synthesis of linkers for anticancer drugs, because they can bind to the cancer cell surface. Generally, these linkers are coupled to a chromophore moiety. Sun *et al.*[120] developed a method for the synthesis of a new type of linkers bearing curcumin as a chromophore. This linker is based on the natural amino acid arginine, a derivative of which was converted into diazoketone and then treated with hydrochloric acid. Target α-chloroketone was obtained in 47% yield (Scheme 46).

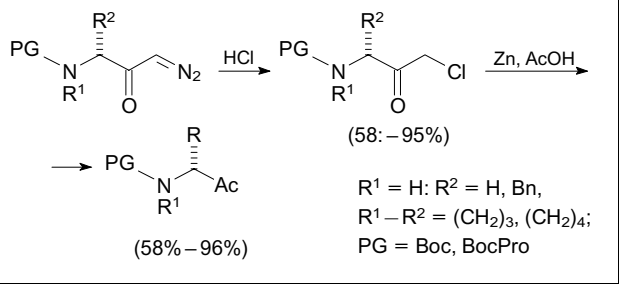
Scheme 46



A series of α-chloroketones were synthesized in a similar way [121] from amino acids and dipeptides. These chloroketones were used [122] to prepare α-aminoketones. The authors treated α-chloroketones with zinc metal in glacial acetic acid, resulting in the formation of target products in good to high yields (Scheme 47).

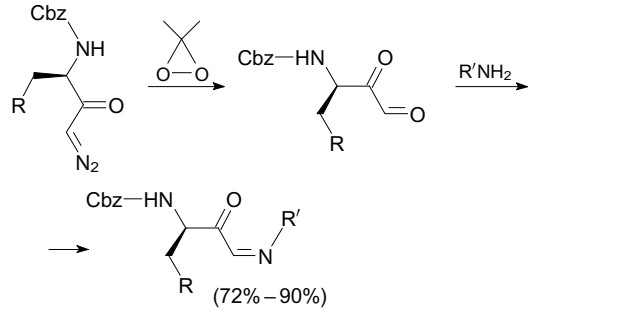
Other peptidomimetics — ketomethylenimino peptides acting as inhibitors of human leukocyte elastase, also known as human neutrophil elastase, — are used to treat various inflammatory and chronic diseases. A method was

Scheme 47



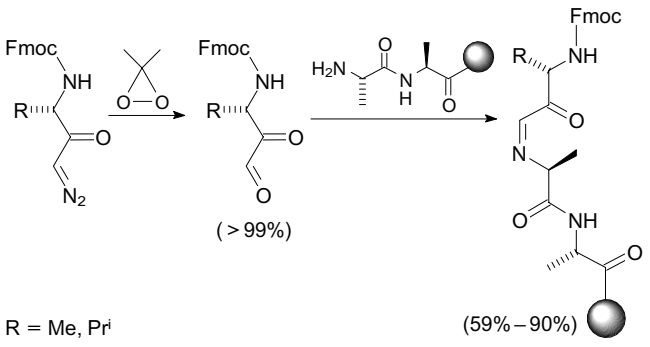
developed for the synthesis of ketomethylenimino peptides employing diazoketones as key intermediates.[123] Diazoketones were oxidized by dimethyldioxirane according to Groarke and then subjected to amination to prepare target peptidomimetics in high yields (Scheme 48).

Scheme 48



R = Me, Pr^i; R′ = Bu^n, Bn

Scheme 49

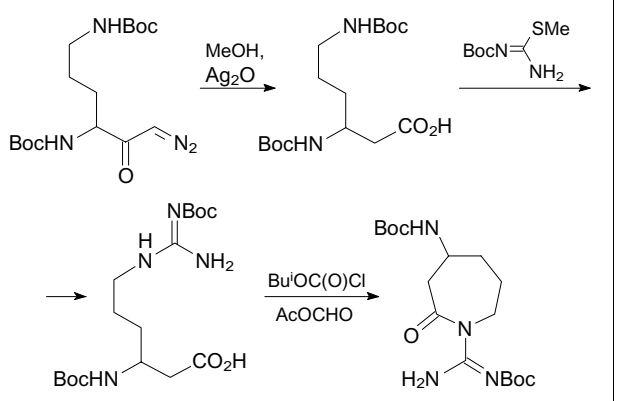


R = Me, Pr^i

A similar transformation was performed for a peptide immobilized on a polymer support to prepare ketomethylenimino peptides (Scheme 49).[124]

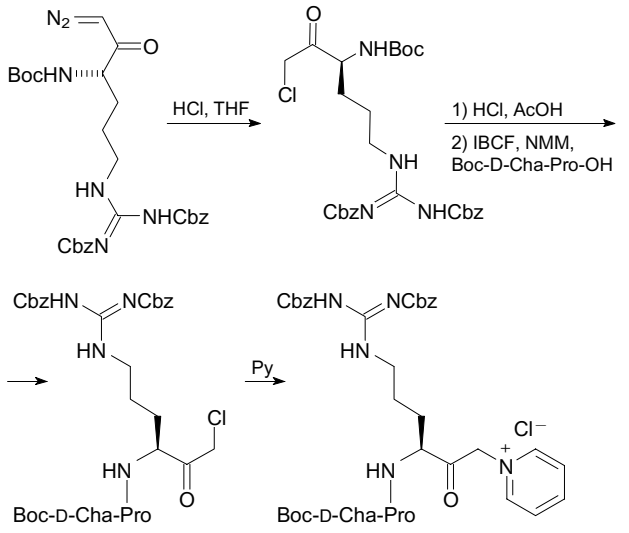
It was shown [125, 126] that peptidyl α-amino glyoxals and their hydrates can also exhibit biological activity and act as proteasomes and inhibitors of lysosomal cysteine proteases. These compounds are structurally similar to peptide aldehydes, resulting in their similar biological activity. Numerous inhibitors of interleukin-1β, known under the common name caspases, have peptide aldehyde nature. Apopain, papain, thrombin and trypsin are the most abundant caspases. Bajusz *et al.*[127] synthesized analogues of these compounds, in which α-aminoaldehyde was replaced with homoarginine lactam that was prepared from ornithine diazoketone in three steps (Scheme 50).

Scheme 50



Another approach to modification of caspases, in particular thrombin, was described by Steinmetzer and Konishi.[128] By analogy with prolyl endopeptidases, which contain, apart from a peptide component, an ammonium salt moiety, arginine involved in thrombin was transformed into pyridinium methyl ketone. Rather high biological activity of these compounds was attributed to the fact that the constant positive charge of the pyridinium salt stabilizes an intermediate enzyme – inhibitor complex (Scheme 51).

Scheme 51

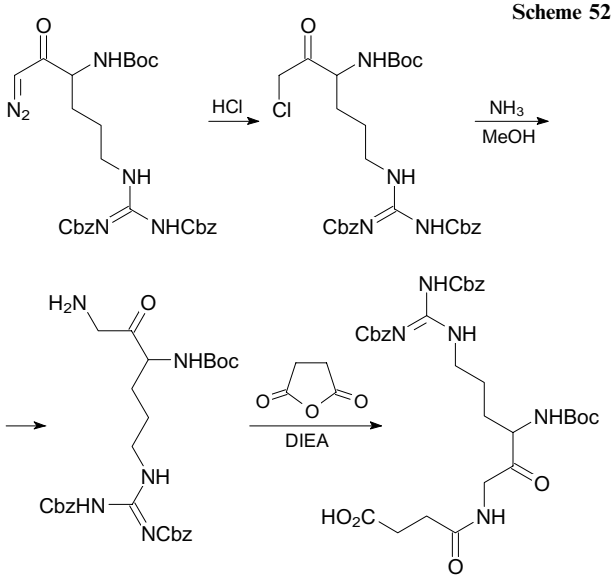


Besides, arginine involved in thrombin was modified as follows.[129] Diazoketone was transformed into α-chloroketone, which was sequentially treated with ammonia in methanol and succinic anhydride. The reaction product was employed in the solid-phase peptide synthesis without purification (the yields were not reported) (Scheme 52).

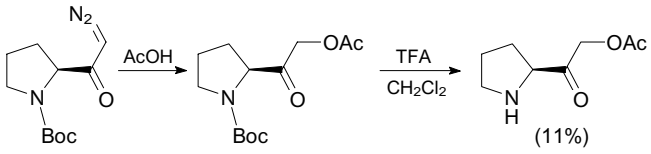
Wallen *et al.*[130] synthesized a series of prolyl-substituted oligopeptidases, which act as serine proteases in the body and can be used to treat Alzheimer's disease. One component of this oligopeptide was prepared from proline-based diazoketone. The target product was isolated in an overall yield of 11% (Scheme 53).

Another type of peptidomimetics was synthesized in high yields (72% – 76%) by condensation of α-amino keto azides with α-amino thioacids based on natural amino acids.[131] α-Amino keto azides were prepared from diazo-

Scheme 52

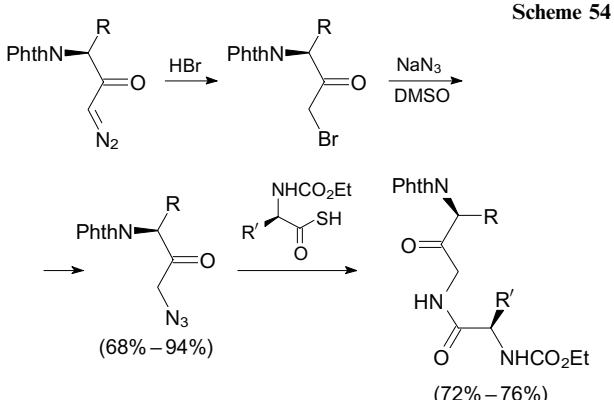


Scheme 53



carbonyl derivatives of natural amino acids by the sequential treatment with hydrobromic acid and sodium azide and were then studied in reductive acylation with N-protected aminothiocarboxylic acids. In this work, a series of peptide-like oxopropylacetamides were synthesized in good yields (Scheme 54).

Scheme 54

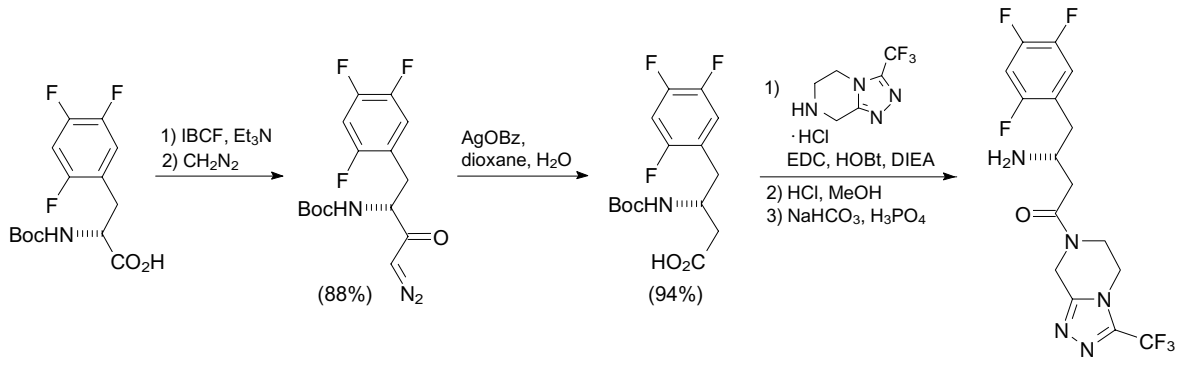


R = Bu^{i}, Bu^{s}, Bn; R′ = Bn, Bu^{s}

6. Synthesis of amino acid derivatives

Amino acids and their derivatives are of great interest in modern medicine. In past years, the range of amino acids, which served as the basis for the preparation of drugs, was significantly extended. For instance, sitagliptin phosphate, which is an β-amino acid derivative [3-amino-4-(2,4,5-trifluorophenyl)butanoic acid], is employed as a medication for diabetes. The synthesis of sitagliptin phosphate using α-amino diazoketone as a key intermediate was docu-

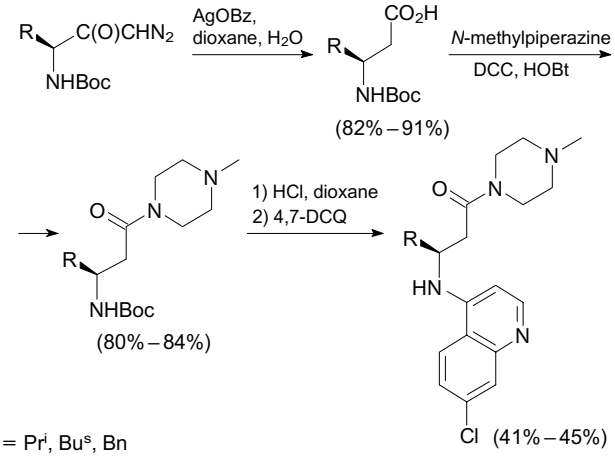
Scheme 55



mented.[132, 133] β-Amino acid was prepared by the Wolff rearrangement and then was condensed with triazolopyrazine followed by the treatment with hydrochloric and phosphoric acids to give sitagliptin phosphate (Scheme 55).

β-Amino acid derivatives containing 7-chloroquinoline and methylpiperazine moieties were synthesized from diazocarbonyl derivatives of amino acids, and their antiplasmodial activity and antimalarial selectivity were evaluated.[134] Starting β-amino acids were prepared by the Wolff rearrangement of α-amino diazoketones. The sequential treatment of β-amino acids with *N*-methylpiperazine in the presence of carboxyl group activators, hydrochloric acid and 4,7-dichloroquinoline (4,7-DCQ) produced target compounds. It should be noted that the β-amino acid derivative generated from isoleucine (R = Bu^s) exhibited the highest selectivity [the selectivity index (SI) was 2188] in the series of the synthesized compounds (Scheme 56).

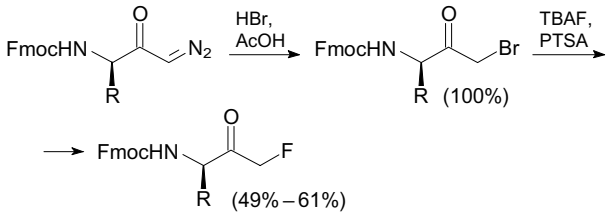
Scheme 56



R = Pr^i, Bu^s, Bn

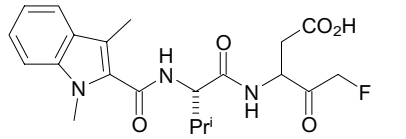
Fluoromethyl ketones and their peptide derivatives — peptidyl fluoromethyl ketones — comprise an important structural class of compounds in bioorganic and medicinal chemistry. These compounds served as the basis for the development of potential drugs for various diseases.[135] Roiban *et al.*[136] synthesized fluoromethyl ketone from diazocarbonyl derivatives of glycine and aspartic acid. The reaction of diazoketone with hydrobromic acid afforded bromoketones. The nucleophilic substitution of bromine using tetra-n-butylammonium fluoride (TBAF) in the presence of *p*-toluenesulfonic acid (PTSA) gave target fluoromethyl ketones (Scheme 57).

Scheme 57

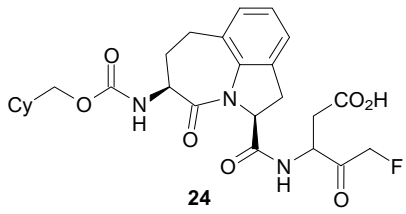


R = H, CH_2Boc

Structures 23, 24



23



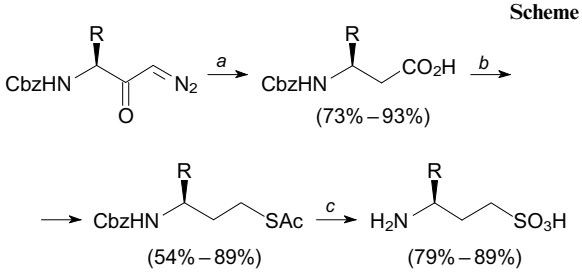
24

Peptidyl fluoromethyl ketones **23** and **24** were prepared in a similar way.[137, 138]

A number of compounds, *e.g.*, taurine, perform some biological functions of amino acids. These compounds are also referred to as (although not quite correctly) amino acids. Zheng and Xu[139] synthesized a series of chiral homotaurines from N-Cbz-protected α-amino diazoketones (Scheme 58). Homotaurine (3-aminopropane-1-sulfonic acid) is an important sulfur-containing amino acid. Homotaurine inhibits the formation of amyloid fibrils Aβ and can be used to treat Alzheimer's disease.[140]

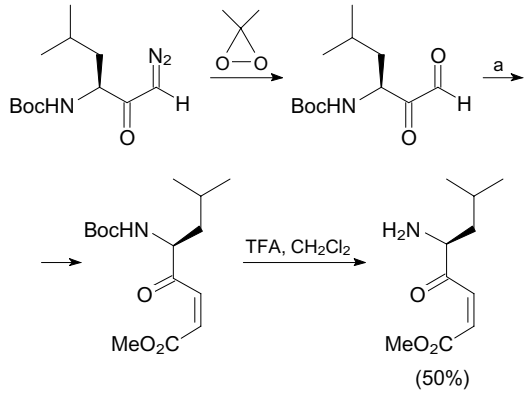
The synthesis of methyl (*Z*)-5-(*S*)-amino-7-methyl-4-oxooct-2-enoate as a potential inhibitor of leucine aminopeptidase was described (Scheme 59).[141, 142] N-Boc-Substituted α-amino diazoketone was oxidized by dimethyldioxirane to the corresponding glyoxal. The Horner – Wadsworth – Emmons reaction of the glyoxal followed by the treatment with trifluoroacetic acid gave the target inhibitor. It should be noted that there are other examples of the application of amino acid derivatives, generated from chiral α-amino diazoketones, as inhibitors of different enzymes.[141, 142]

Scheme 58



(*a*) AgOBz, dioxane, H_2O; (*b*) 1) EtOC(O)Cl, NMM; 2) $NaBH_4$; 3) MsCl, Et_3N; 4) HSAc, Cs_2CO_3; (*c*) 1) H_2O_2, HCO_2H; 2) H_2, Pd/C; R = Me, Bn, Pr^i, Bu^i, Bu^s, $CbzNH(CH_2)_4$, $4\text{-}BnOC_6H_4CH_2$

Scheme 59



(*a*) Bu^nLi, $(MeO)_2P(O)CH_2CO_2Me$

7. Synthesis of heterocyclic compounds

Chiral α-amino diazoketones are widely used as synthons for the preparation of various heterocyclic compounds, such as β-lactams, azitidinones, imidazoles, pyrazoles, thiazoles, piperidines and so on.

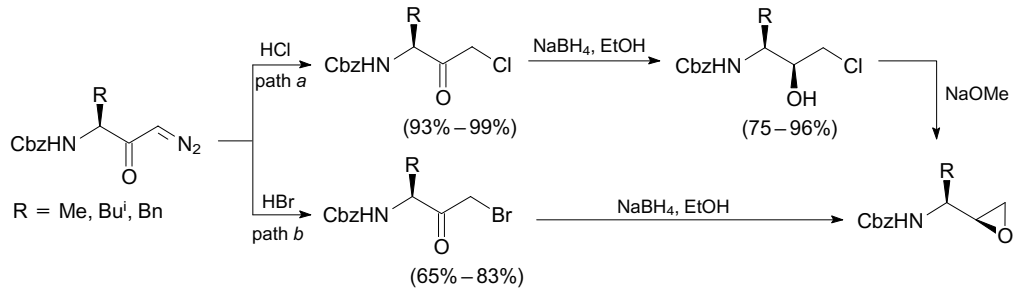
7.1. Synthesis of three-membered heterocyclic compounds

As shown above, α-amino diazoketones can be employed as the starting compounds for the synthesis of protected aminooxiranes.[143] The key step of this process involves the stereoselective reduction of α-haloketones, prepared from diazocarbonyl derivatives of amino acids, to haloamino alcohols, the treatment of which with a base affords target aminooxiranes (Scheme 60). It should be noted that the use of α-bromoketone as an intermediate for the synthesis of the target epoxide did not require additional treatment with a base. In the cited study, oxiranes were also synthesized from short peptides.

Heinsoo *et al.*[144] used the same method to synthesize aminooxiranes, but they employed Boc- and Fmoc-protected α-amino diazoketones as the starting compounds. These protecting groups were chosen because of their wide use in peptide synthesis. The resulting Boc- and Fmoc-protected aminooxiranes can serve as building blocks in peptide synthesis. The above-described approach to the synthesis of the oxirane ring from diazoketone was applied to prepare cyclic peptidomimetics containing a tyrosine moiety and acting as HIV-1 protease inhibitors (Scheme 61).[145, 146]

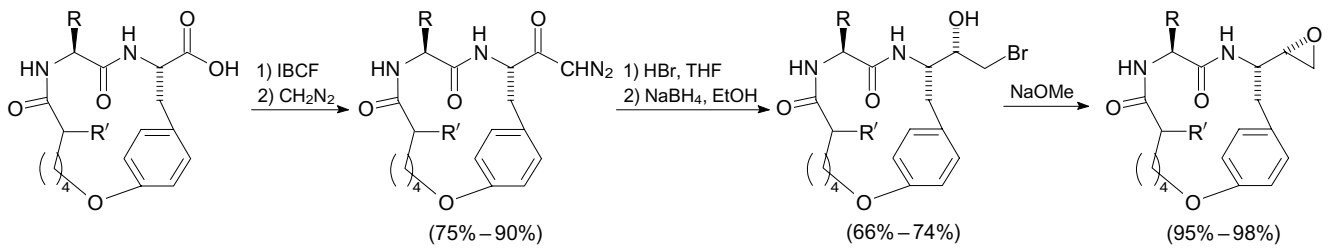
N-Protected aminooxiranes, produced from diazocarbonyl derivatives of amino acids, are building blocks in the synthesis of peptides containing an aminohydroxyethylene moiety.[147 – 149] The application of these peptides as inhibitors of different enzymes was addressed in a series of studies.[150 – 152] The aminohydroxyethylene moiety is gener-

Scheme 60



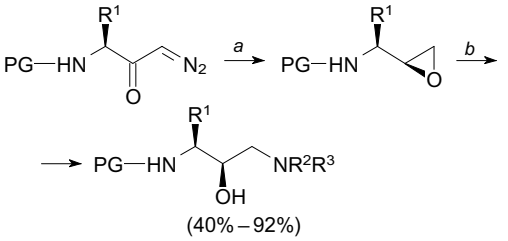
Path *a*: 68% – 88% yield, *erythro* : *threo* from 75 : 25 to 95 : 5; path *b*: 58% – 73% yield, *erythro* : *threo* from 67 : 33 to 80 : 20

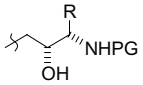
Scheme 61



R = Pr^i, Bu^n, CH_2OPr^n; R′ = H, NHBoc, NHAc

Scheme 62



(*a*) 1) HCl or HBr; 2) $NaBH_4$; 3) KOH, EtOH; (*b*) NHR^2R^3;
PG = Cbz, Boc; R^1 = Me, Pr^i, Bu^s,Bn;
R^2, R^3 = H, Bn, Ts, 

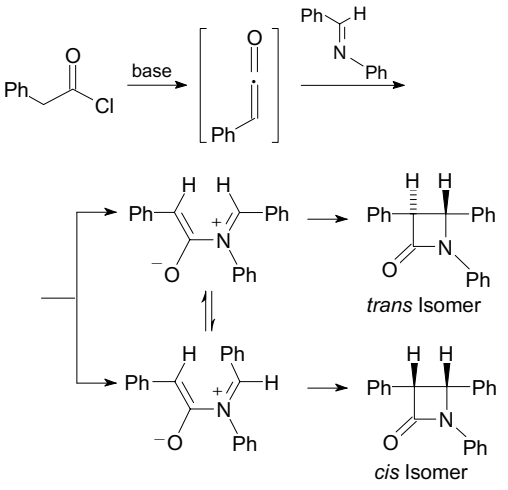
ated upon treatment of oxiranes with different amines (Scheme 62).

7.2. Synthesis of four-membered heterocyclic compounds

This section is devoted to application of diazocarbonyl derivatives of amino acids in the synthesis of four-membered heterocycles, such as β-lactams and azetidinones. A β-lactam moiety is a key structural unit of β-lactam antibiotics comprising one of the largest classes of antibiotics. Moreover, the wide use of antibiotics in medicine began with the discovery of penicillin, which is a representative of β-lactam antibiotics. Apart from their importance as structural components of β-lactam antibiotics, β-lactams have attracted considerable interest in organic synthesis as versatile chiral synthons. The β-lactam skeleton has found new pharmaceutical applications as an antagonist of LHRH (luteinizing hormone releasing hormone receptor),[153] a cholesterol uptake inhibitor[154] and an anticancer agent.[155] The ring strain of the β-lactam skeleton facilitates ring-opening reactions. This unique property was utilized to synthesize various compounds with high biological activity.

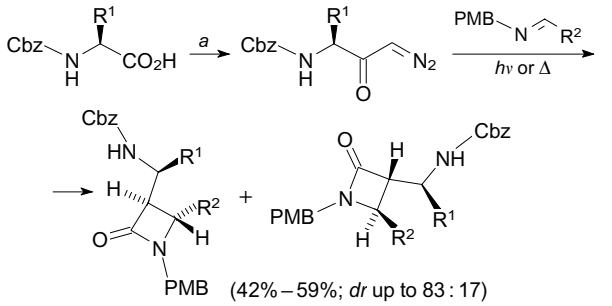
In 1907, many years before the discovery of antibacterial activity of penicillin, Staudinger[156] synthesized β-lactam by [2 + 2]-cycloaddition of diphenylketene with Schiff base (Scheme 63). In subsequent years, the synthetic scope of this reaction was significantly extended. Due to diversity of substrates and the ease of application, this reaction is considered as one of the most facile and efficient methods for the synthesis of β-lactams.

Scheme 63



Diazoketones serve as a convenient source for the *in situ* preparation of ketenes. It is therefore quite natural that these compounds are used in applied methods for the synthesis of β-lactams. Podlech's research team studied the synthesis of lactams by the Staudinger reaction starting from diazocarbonyl derivatives of β-amino acids for more than two decades. β-Lactams were synthesized from diazocarbonyl derivatives of amino acids by the photochemical or thermal Staudinger reaction[157] The photochemical reaction was performed in a quartz immersion photoreactor at −25 °C, while the thermal reaction was carried out at 160 °C in *o*-dichlorobenzene. β-Lactams were isolated in good yields as a diastereomeric mixture; in this mixture, the diastereomeric ratio is governed by steric hindrance of the starting amino acids and varies from 2 : 1 for alanine to 7 : 1 for valine (Scheme 64).

Scheme 64

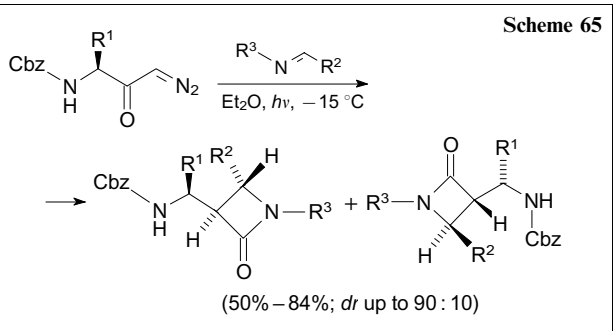


(*a*) 1) Et_3N, 2) EtOC(O)Cl; 3) CH_2N_2, Et_2O; R^1 = Me, Bn, Pr^i;
R^2 = Ph, 4-ClC_6H_4, (*E*)-PhCH═CH

Besides, the photochemical Staudinger reaction was applied to synthesize 4-acetoxy- and 4-formyl-substituted β-lactams as precursors of antibiotics based on bicyclic β-lactams.[158] Diazoketones, derivatives of N-benzyloxycarbonyl-protected amino acids, were used as the starting compounds. The target products were obtained in high yields. The diastereomeric ratio of β-lactams was up to 9 : 1 for *tert*-leucine and was independent of the structure of the imine used (Scheme 65).

A similar photochemical Staudinger reaction was used to study the diastereoselectivity of the formation of β-lactams.[159] N-Protected diazoketones, derivatives of natural

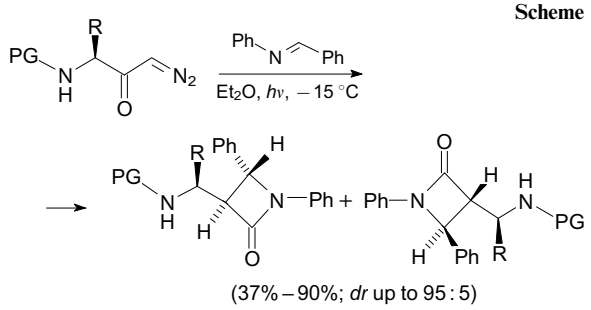
Scheme 65



R^1 = Me, Pr^i, Bu^t; R^2 = 4-$Me_2NC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, (*E*)-PhCH═CH, 2-Fu, 3-Th, Ph; R^3 = Bn, All, Bu^t

amino acids, such as alanine, valine, leucine, isoleucine, *tert*-leucine, ornithine, serine, *etc*., were chosen for this purpose. It was shown that the stereoselectivity of the formation of β-lactams depends mainly on the steric properties of diazoketone (*dr* = 95 : 5 for *tert*-leucine), while the diastereoselectivity cannot be significantly increased by varying the protecting group at the nitrogen atom of diazoketone. Nevertheless, the phthaloyl protecting group (NPG = NPhth) makes it possible to invert the diastereomeric outcome (*dr* = 17 : 83) (Scheme 66).

Scheme 66

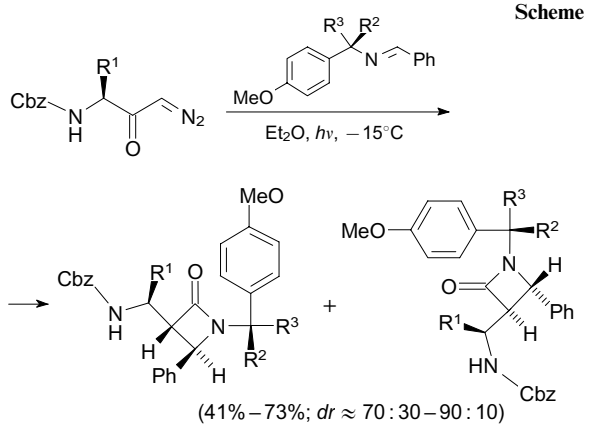


(37% – 90%; *dr* up to 95 : 5)

R = Me, Pr^i, Bu^i, Bu^s, Bu^t, Bn, CbzNH(CH$_2$)$_3$, BnOCH$_2$, TBDMSOCHMe; PG = Boc, Cbz, Fmoc; NPG = NPhth

The diastereomeric purity of β-lactams can be increased by employing chiral sterically hindered imines.[160] Thus, the introduction of the *p*-methoxyphenylethyl group (PMPE) or its analogues (R^2, R^3 ≠ H) as a substituent at the imine nitrogen atom allows an increase in diastereoselectivity of the reaction from 70 : 30 to 80 : 20 for alanine and from 70 : 30 to 83 : 17 for valine. In this case, the yield of the product decreases insignificantly. Besides, the PMPE group is synthetically convenient because it can be easily removed under oxidative conditions (Scheme 67).

Scheme 67

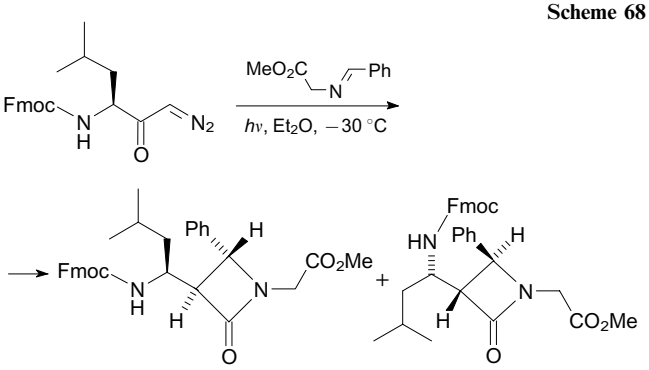


(41% – 73%; *dr* ≈ 70 : 30 – 90 : 10)

R^1 = Me, Pr^i, Bu^t; R^2, R^3 = H, Me

A natural amino acid-derived β-lactam moiety is often incorporated into the amino acid sequence of peptide drugs or peptidomimetics. This approach is used to enhance stability of peptides and peptidomimetics with retention of the conformation and biological activity. Maier *et al.*[161] introduced β-lactam into the peptide chain in order to mimic the conformationally labile tripeptide H-Pro-Leu-Gly-NH$_2$ (PLG), the conformation remaining unchanged and the biological activity being comparable with that of PLG (Scheme 68).

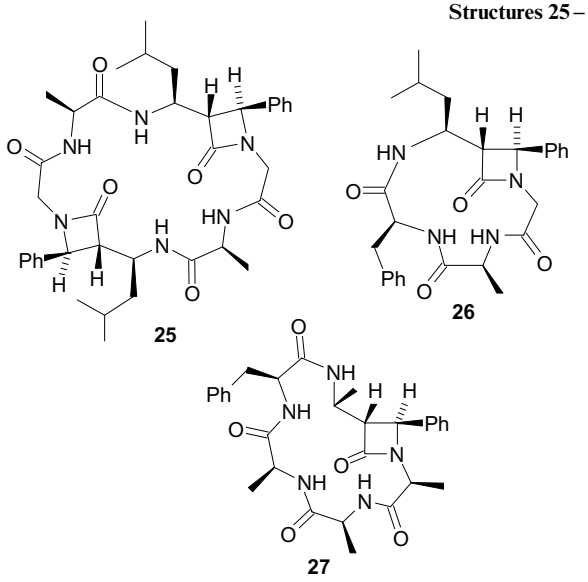
Scheme 68



(70%; *dr* = 70 : 30)

This method for the incorporation of β-lactam into the amino acid chain was applied also to cyclic peptidomimetics **25** – **27**.[162]

Structures 25 – 27

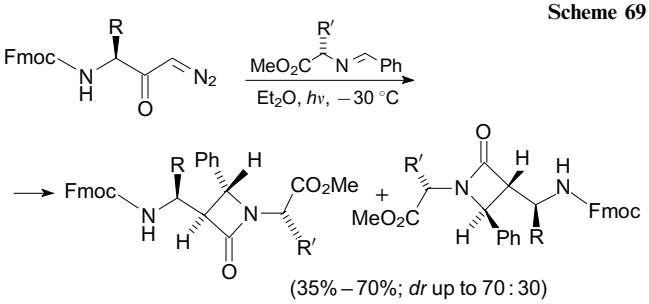


Target β-lactams were prepared from Fmoc-protected alanine- and leucine-based diazoketones by the photochemical Staudinger reaction. It was found that the amino acid for the transformation into the β-lactam moiety should be chosen considering its steric characteristics. A decrease in the size of the substituent in the side chain leads to a significant decrease in the product yield and the reaction diastereoselectivity: from 70% (*dr* = 70 : 30) for leucine to 35% (*dr* = 60 : 40) for alanine (Scheme 69).

β-Lactam can be incorporated into the amino acid sequence according to another procedure. Thus, the Staudinger reaction was performed using diazoketone produced from oligopeptide.[163] Diazoketones based on the N-protected dipeptides Cbz-Ala-Ala-CHN$_2$, Cbz-Ala-Val-CHN$_2$, Cbz-Ala-Leu-CHN$_2$ and some other were chosen. Compounds containing both β-lactam and a peptide were synthesized in high yields (Scheme 70).

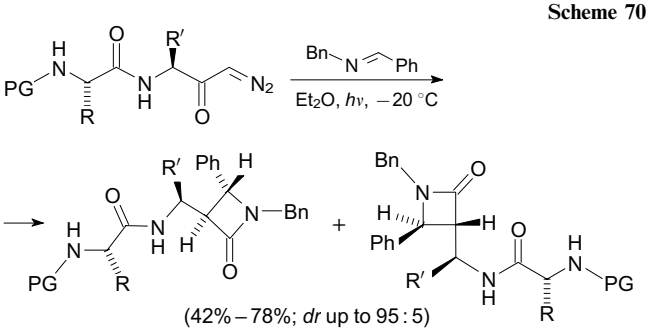
The main drawback of the photochemical Staudinger reaction is that the range of aldimines is limited exclusively

Scheme 69



R = Bu^i, Me; R′ = H, Bu^t

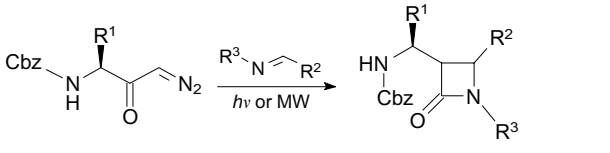
Scheme 70



PG = Boc, Cbz, Fmoc; R = Me, Bu^s, Bu^t; R′ = Me, Pr^i, Bu^i

to N-aryl- and N-benzyl-substituted derivatives. This issue was solved by performing the reaction under microwave irradiation rather than under photochemical conditions.[164] This made it possible to extend the range of substrates to N-furyl-, N-vinyl- and N-but-2-enyl-substituted imines. These reactions afford only *trans*-derivatives of β-lactams. For N-but-2-enyl derivatives, the product partially isomerized to *Z*-alkene (up to 28%). In this case, the diastereoselectivity was independent of the reaction conditions (Scheme 71).

Scheme 71



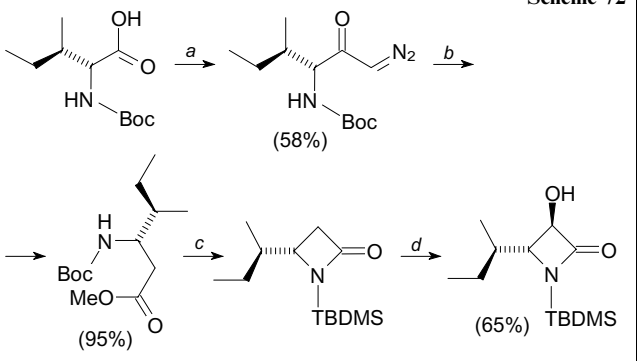
trans Isomer

(40% – 85%; dr up to 90 : 10)

R^1 = Bu^t, Me; R^2 = 2-Fu, CH$_2$=CH, MeCH=CHCH$_2$; R^3 = Bn, All

Ferguson *et al.*[165] developed another approach to the synthesis of β-lactams. Diazoketone derived from Boc-protected isoleucine was subjected to the Wolff rearrangement in the presence of silver benzoate, resulting in the formation of β-amino acid methyl ester. After Boc deprotection, the ester was transformed into the corresponding β-lactam in the presence of *tert*-butylmagnesium chloride as the base. Then β-lactam was transformed into α-hydroxy-β-lactam by the reaction with oxaziridine in the presence of lithium diisopropylamide (Scheme 72).

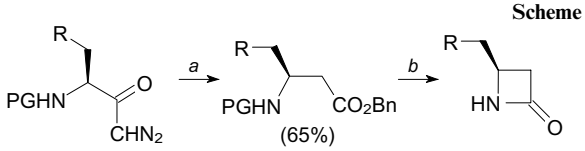
Scheme 72



(*a*) 1) Bu^{i}OC(O)Cl, NMM, Et$_2$O; 2) CH$_2$N$_2$; (*b*) AgOBz, Et$_3$N, MeOH; (*c*) 1) HCl; 2) TBDMSCl, DMAP, Et$_3$N; 3) Bu^{t}MgCl; (*d*) LDA, oxaziridine

The synthesis of monolactam inhibitors of cytomegalovirus protease was reported.[166, 167] These inhibitors contain the β-lactam ring as the key moiety, which was prepared from natural amino acids (serine and phenylalanine) by the sequential Arndt – Eistert reaction, Wolff rearrangement and β-lactam cyclization in the presence of Bu^{t}MgCl as the base (Scheme 73).

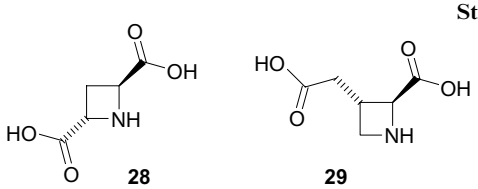
Scheme 73



(*a*) 1) AgOBz, Et$_3$N, THF; 2) BnBr, DBU, MeCN; (*b*) 1) HCl or H$_2$, Pd/C; 2) Bu^{t}MgCl; R = OBn, Ph; PG = Cbz, Boc

Azetidin-3-ones are bioisosteres of β-lactams but, unlike β-lactams, they are hydrolytically stable and, as a consequence, are highly stable against enzymes that cleave β-lactams.[168] It should be noted that four-membered rings, as conformationally restricting components, have attracted great interest in recent years due to high rigidity and physiological activity. For instance, natural (*S*)-azetidine-2-carboxylic acid derivatives **28** and **29** exhibit pronounced biological activity and are bioisostere analogues of glutamic acid and aspartate, respectively.[169]

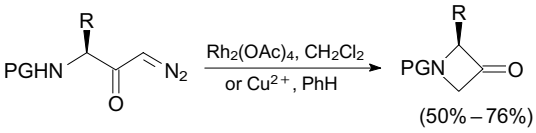
Structures 28, 29



The intramolecular insertion into the N—H bond studied by Rapoport and co-workers[170] provides one of the most convenient routes to azetidin-3-ones. The authors studied the transformation of different α-diazo-β-keto esters into various heterocyclic compounds in the presence of catalytic amounts of dirhodium tetraacetate [Rh$_2$(OAc)$_4$].[171] Recently, azetidin-3-ones were synthesized

starting from N-protected α-amino diazoketones. Diazocarbonyl derivatives of amino acids are easily transformed into the corresponding azetidin-3-ones in the presence of dirhodium tetraacetate [172, 173] or copper salts,[174, 175] In most cases, Ts and Boc protecting groups are employed; in one case, Cbz was used [176] (Scheme 74).

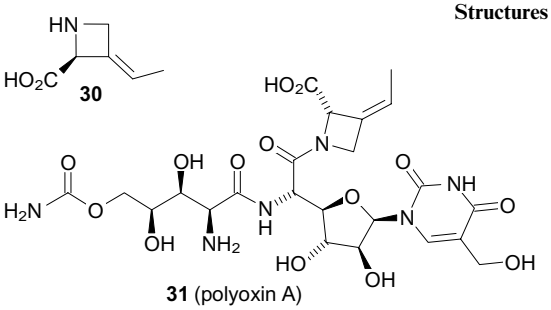
Scheme 74



RG = Ts, Boc, Cbz; R = Me, Pr^i, Bn, Ph

Hanessian *et al.*[177] accomplished the total synthesis of *cis*- (natural) and *trans*-polyoximic (unnatural) acids (**30**) from the diazocarbonyl derivative of D-serine. A polyoximic acid moiety is present in antifungal antibiotics, *e.g.*, polyoxin A (**31**).

Structures 30, 31



31 (polyoxin A)

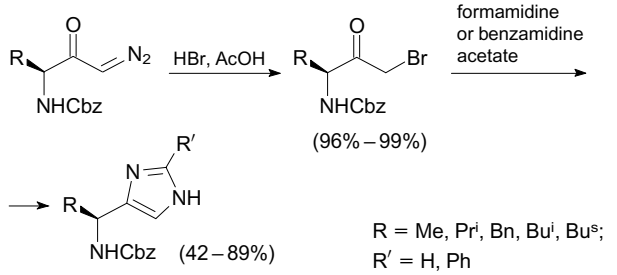
Polyoximic acid was synthesized as follows. The O-protected diazocarbonyl serine derivative was transformed into the corresponding azetidin-3-one under the action of rhodium acetate (Scheme 75). The next step involves the stereochemically controlled introduction of the ethylidene group. Hanessian *et al.*[177] found that *N*-methyl-*N*-methoxycarbonyl derivatives of Horner – Wadsworth – Emmons and Wittig reagents are excellently suitable for the synthesis of *cis* or *trans* isomers as the major products. Moreover, the *cis* and *trans* isomers were completely separated by chromatography. Sequential reduction of amide isomers with lithium aluminium hydride and sodium borohydride, bromination with carbon tetrabromide in the presence of triphenylphosphine and reduction with lithium borohydride followed by deprotection and oxidation with the Jones reagent gave target polyoximic acids.

7.3. Synthesis of five-membered heterocyclic compounds

Chiral α-amino diazoketones are convenient building blocks for the preparation of various five-membered heterocycles containing one or several heteroatoms, *e.g.*, pyrrolidines, imidazoles, thiazoles, pyrazoles and so on.

Imidazole derivatives, including chiral compounds, are rather abundant in nature. For example, the imidazole moiety is present in the natural essential amino acid histidine. Due to physiological activity, imidazole derivatives are applied in medicinal chemistry.[178] Hence, the development of efficient methods for the synthesis of chiral imidazole derivatives is a challenging problem. Bures and co-workers [179, 180] published studies devoted to the synthesis of chiral imidazoles from diazocarbonyl derivatives of natural amino acids. α-Amino diazoketones reacted with hydrobromic acid to form the corresponding α-bromoketones, which were treated with benzamidine or formamidine, resulting in the formation of target imidazole derivatives (Scheme 76).

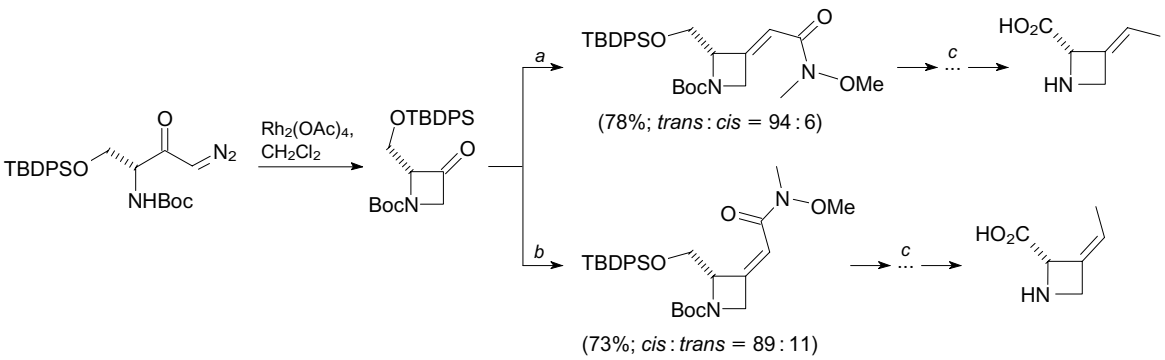
Scheme 76



R = Me, Pr^i, Bn, Bu^i, Bu^s;
R′ = H, Ph

Groarke *et al.*[181] proposed a quite different approach to the synthesis of chiral imidazoles from α-amino diazoketones. Previously, a method was developed for the synthesis of enantiomerically pure N-protected α-amino glyoxals from α-amino acids and dipeptides,[182] which provided the basis for the preparation of heterocyclic compounds. The

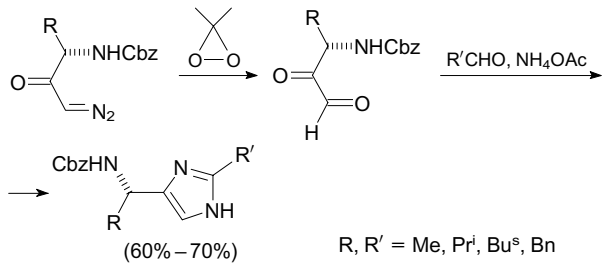
Scheme 75



(*a*) 1) NaH, THF; 2) diethyl (*N*-methoxy-*N*-methylcarbonylmethyl)phosphonate; (*b*) *N*-methoxy-*N*-methyl-2-(triphenylylphosphoranylidene)acetamide, MeOH; (*c*) 1) $LiAlH_4$; 2) $NaBH_4$, $CeCl_3 \cdot 7\,H_2O$ (*trans* isomer: 72% yield, *cis*: 75%); 3) CBr_4, PPh_3, CH_2Cl_2; 4) $LiBH_4$, DMSO (*trans*: 50%, *cis*: 63%); 5) TBAF, THF (*trans*: 94%, *cis*: 97%); 6) Jones reagent, acetone (*trans*: 40%, *cis*: 40%); 7) HCO_2H (100%)

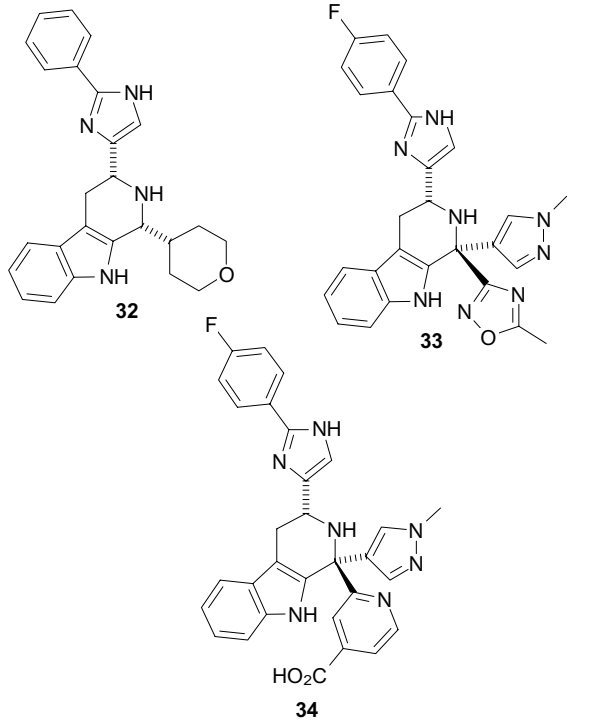
synthesis of chiral imidazoles involves the treatment of diazoketone with dimethyldioxirane giving α-amino glyoxal followed by the addition of a mixture of aldehyde and ammonium acetate (Scheme 77). The products were isolated in rather high yields (60% – 70%).

Scheme 77



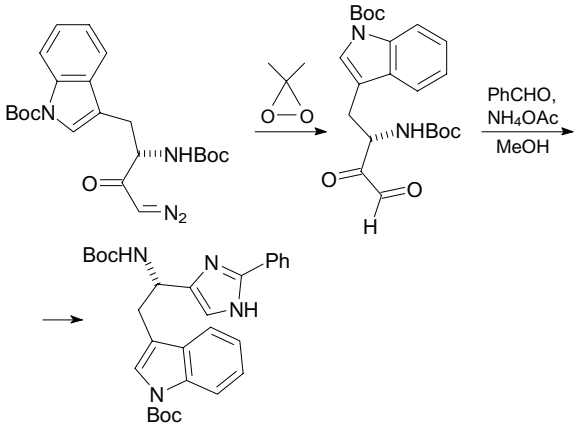
In 2016, this method was applied [183] to prepare antagonists of somatostatin receptor 3 (sstr3) (structures **32** – **34**), which are potential antidiabetic drugs. The imidazole moiety was synthesized through the formation of diazoketone followed by the treatment with dimethyldioxirane and the transformation of the resulting α-amino glyoxal into the target imidazole (Scheme 78).

Structures 32 – 34

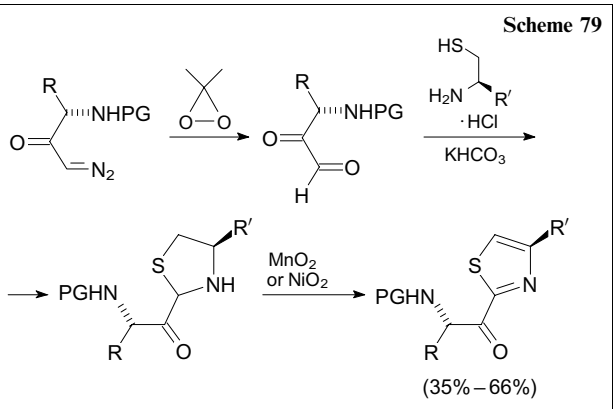


Like many heterocyclic compounds, the thiazole ring is a common pharmacophore group. Peptides containing serine, threonine and cysteine can undergo enzyme-mediated modification to form five-membered thiazole and oxazole heterocycles.[184] The presence of such five-membered heterocycles in peptide-like compounds is of interest due to a wide range of therapeutic properties, including antimicrobial, antiviral and anticancer activities. Chiral N-protected α-amino glyoxals derived from α-amino diazoketones [182] were used as the starting compounds in the synthesis of thiazoles.[185] The treatment of diazoketone with dimethyldioxirane afforded α-amino glyoxal, and then cysteine methyl ester hydrochloride or 2-aminoethanethiol in the presence of a base was added. The reaction gave thiazolidinones, which were oxidized *in situ* with manganese or nickel dioxide giving target thiazoles (Scheme 79). It should be noted that the reaction with manganese dioxide was sometimes accompanied by racemization.

Scheme 78



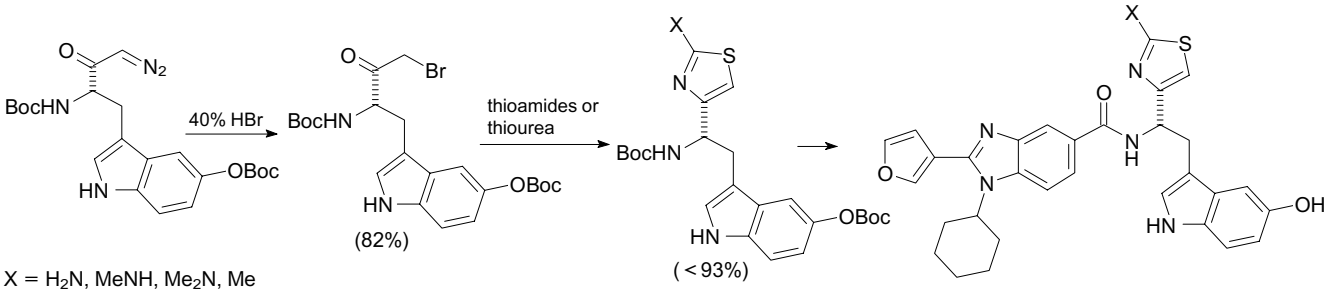
Scheme 79



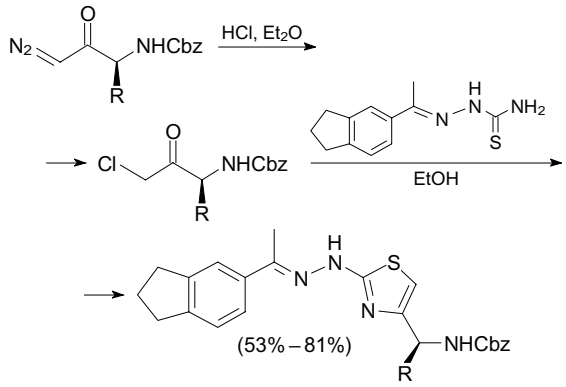
Beaulieu *et al.*[186] described a somewhat different approach to the synthesis of thiazoles starting from diazocarbonyl derivatives of amino acids. The authors synthesized a non-nucleoside allosteric inhibitor containing a thiazole moiety. The diazo derivative of amino acid was converted to bromoketone by the treatment with hydrobromic acid. The reaction of bromoketone with different thioamides or thiourea gave thiazole derivatives in yields of up to 93% (Scheme 80).

A similar approach was described by Maillard *et al.*[187] This research group synthesized 2-hydrazino-1,3-thiazole derivatives and evaluated their biological activity. Diazoketones were transformed into α-chloromethyl ketones by the treatment with HCl in diethyl ether. The condensation of the chloromethyl ketones with substituted thiosemicarbazone gave target 2-hydrazino-1,3-thiazoles in 53% – 81% yields (Scheme 81).

Scheme 80



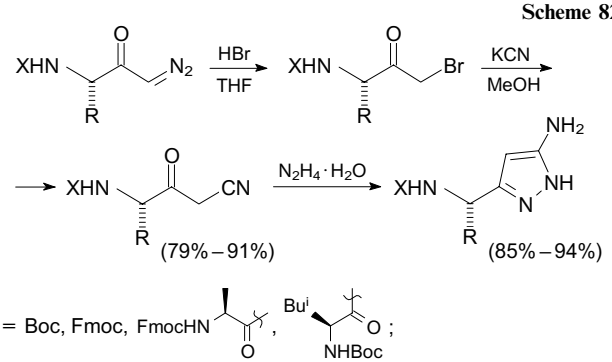
Scheme 81



Similar methods involving α-haloketones as intermediates were applied to prepare biologically active thiazole derivatives from chiral α-amino diazoketones.[188 – 190]

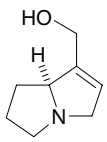
Apart from imidazoles and thiazoles, pyrazoles can also be synthesized from diazoketones. Sharnabai *et al.*[191] used diazoketones to prepare 5-aminopyrazole-containing peptidomimetics. Diazoketones derived from α-amino acid or dipeptide were treated with concentrated hydrobromic acid followed by the replacement of bromine in the resulting α-bromoketone with the cyano group and the reaction of the product with hydrazine hydrate (Scheme 82).

Scheme 82



The pyrrolizidine moiety, so-called necine, is present in numerous natural alkaloids. However, the construction of a necine-containing chiral molecule is a difficult problem. Boynton *et al.*[192] synthesized (−)-supinidine (**35**), a necine-based alkaloid, from (*S*)-glutamic acid.

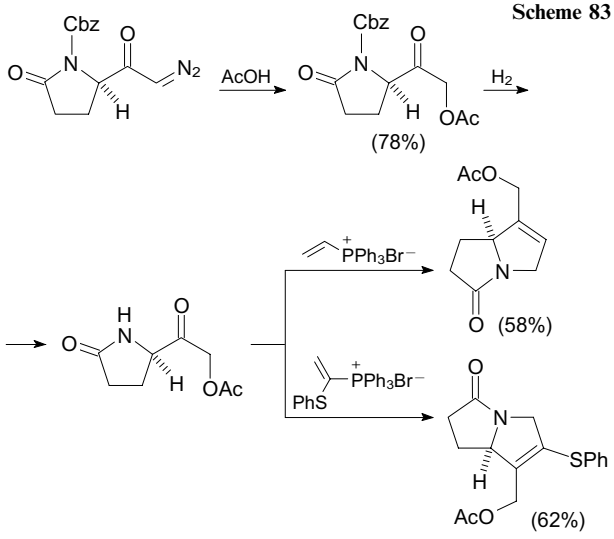
Structure 35



35 [(−)-supinidine]

N-Carboxybenzyl lactam derived from glutamic acid was transformed into diazoketone. The heating of the latter with acetic acid followed by deprotection afforded pyrrolidin-2-one, which was cyclized with vinylphosphonium salts to form (−)-supinidine derivatives in good yields (Scheme 83).

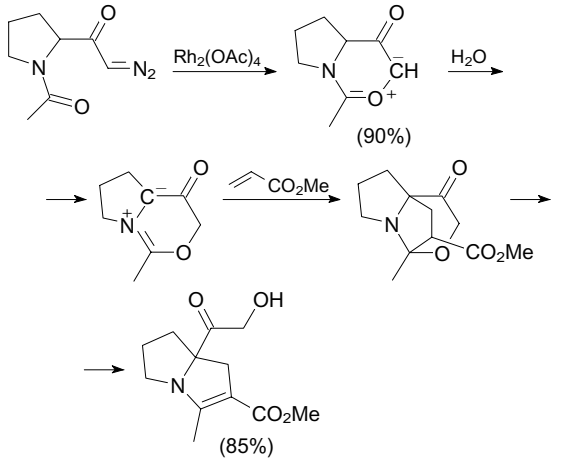
Scheme 83



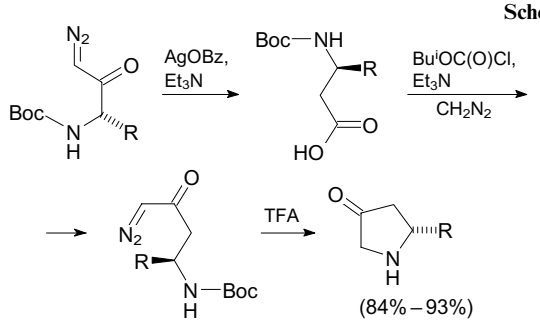
Another approach to the synthesis of the pyrrolizidine skeleton from diazoketones was reported by Padwa and coworkers,[193, 194] who considered dipole cascades. The first example of this synthesis involved the treatment of diazoketone derived from *N*-acetylproline with dirhodium tetraacetate giving 1,3-dipole, which was transformed into azomethine ylide. The 1,3-dipolar cycloaddition of azomethine ylide to methyl acrylate gave target dehydropyrrolizidine in 85% yield (Scheme 84).

Diazoketones were produced from β-amino acids through the intermolecular N−H insertion reaction and then transformed into chiral pyrrolidinones (Scheme 85) in high yields (84% – 93%).[195] This approach to the construc-

Scheme 84



Scheme 85

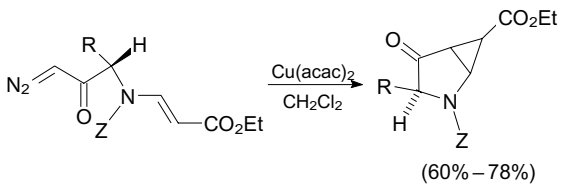


R = Me, Pr^i, Bn

tion of the pyrrolidinone moiety was applied by other authors.[196, 197]

Diazoketones produced from natural amino acids were successfully employed in the synthesis of chiral bicyclic pyrrolidine-containing donor-acceptor cyclopropanes.[198, 199] *N*-Vinyl diazoketones were treated with copper acetylacetonate giving bicyclic structures (Scheme 86) in good yields (60% – 78%). These compounds are often used as attractive building blocks.

Scheme 86



R = H, Me, Bn, TsOC$_6$H$_4$, Pr^i, Bu^i, Bu^s; Z = CO_2Et, Ts

The application of chiral diazo derivatives of amino acids in the synthesis of chiral derivatives of β-ketotriazoles,[200] selenazoles,[201] furanones[202, 203] and oxazolidinones[204, 205] (Scheme 87) was described in the literature.

7.4. Synthesis of six-membered heterocyclic compounds

Saturated mono- and polynuclear six-membered heterocyclic compounds serve as the basis for numerous natural compounds with a broad range of biological activities. Such compounds include natural poisons, pheromones, fungicides, neurotransmitters, tranquilizers and other agents. The alkaloids indolizidine (**36**) and monomorine (**37**) isolated from pheromones of Panamanian frogs and ants have attracted interest because they are very rare in nature.

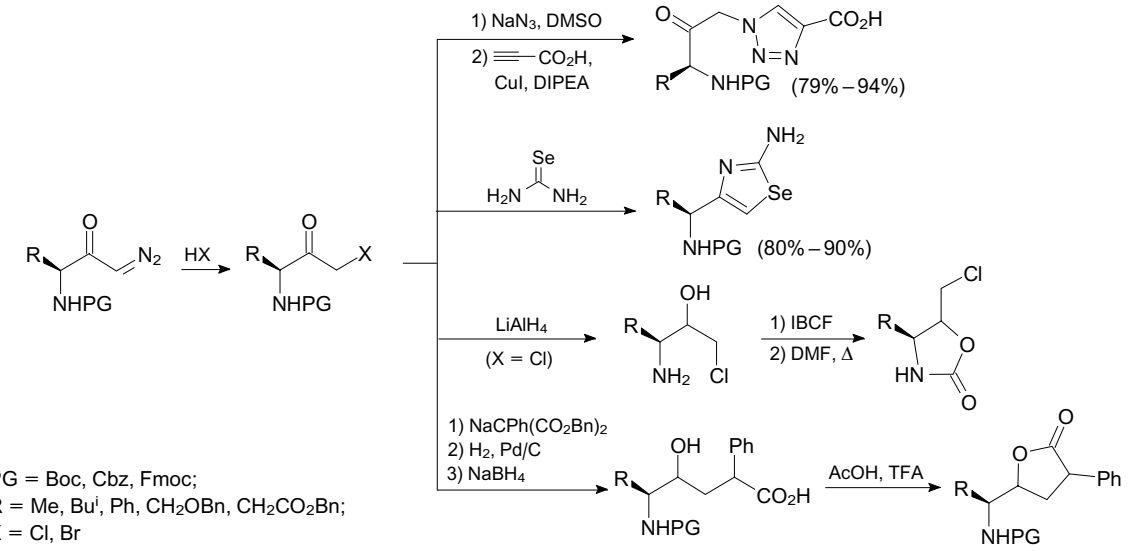
Structures 36, 37



36 [(–)-indolizidine] **37** [(+)-monomorine]

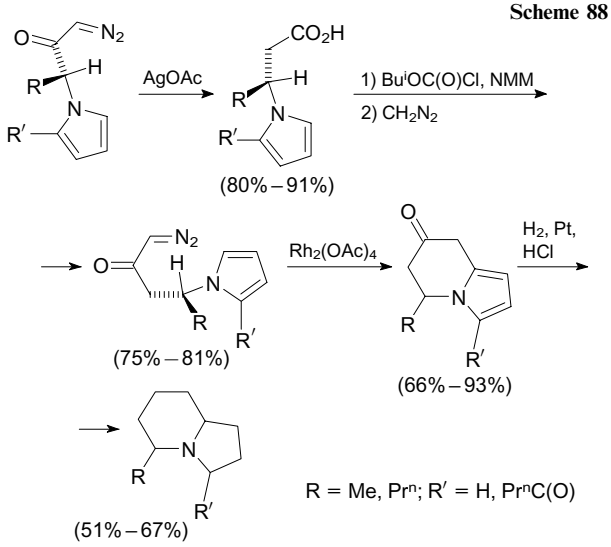
Jefford *et al.*[206] proposed a method for the preparation of these compounds from D-norvaline and L-alanine. The synthesis scheme includes the transformation of these amino acids into the corresponding 1-pyrrole derivatives, two sequential Arndt – Eistert reactions, cyclization of diazoketone in the presence of dirhodium tetraacetate and exhaustive reduction of the bicyclic compounds

Scheme 87



PG = Boc, Cbz, Fmoc;
R = Me, Bu^i, Ph, CH_2OBn, CH_2CO_2Bn;
X = Cl, Br

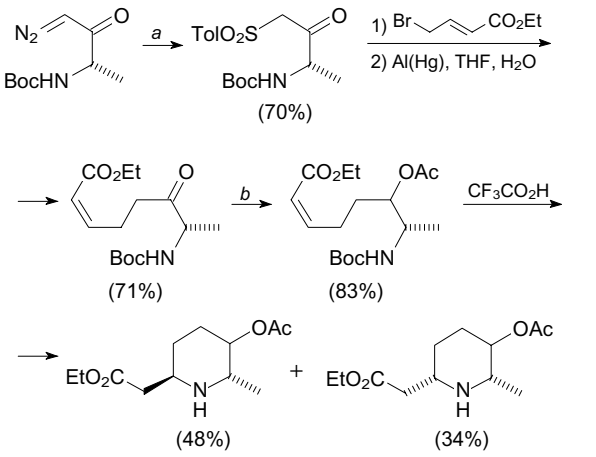
Scheme 88



(Scheme 88). Target indolizidine and monomorine were isolated in overall yields of 15% and 11%, respectively.

Numerous chiral 2,6-disubstituted piperidin-3-one-related alkaloids exhibit analgesic, antitumour and antimicrobial activities, thereby making them useful in pharmacology.[207] Sengupta and Mondal[208] developed a method for the synthesis of these compounds from alanine-derived diazoketone. The key step of the synthesis involves the intramolecular Michael reaction giving 2,6-disubstituted piperidin-3-ols as a mixture of diastereomers in a ratio of 7 : 5 (Scheme 89).

Scheme 89

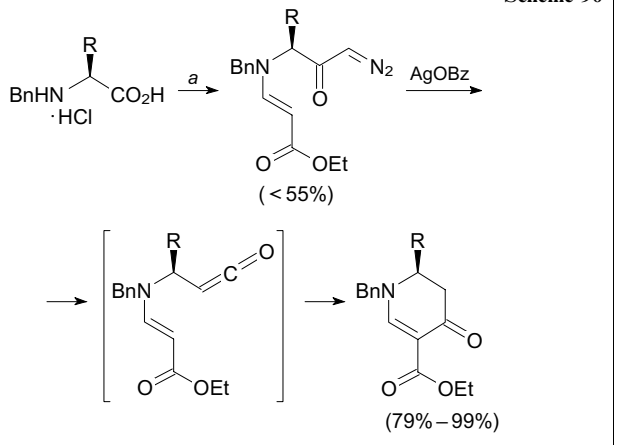


(*a*) 1) HBr; 2) $NaSO_2Tol$; (*b*) 1) $NaBH_4$, MeOH; 2) Ac_2O, Et_3N

The construction of the piperidine moiety was also described by Seki and Georg,[209] who proposed a new strategy for the synthesis from chiral *N*-vinyl-α-amino diazoketones. The starting diazo compounds were easily prepared by the Michael addition of N-benzylamino acids to ethyl propiolate. The Wolff rearrangement in the presence of silver benzoate gave target products in good yields (Scheme 90).

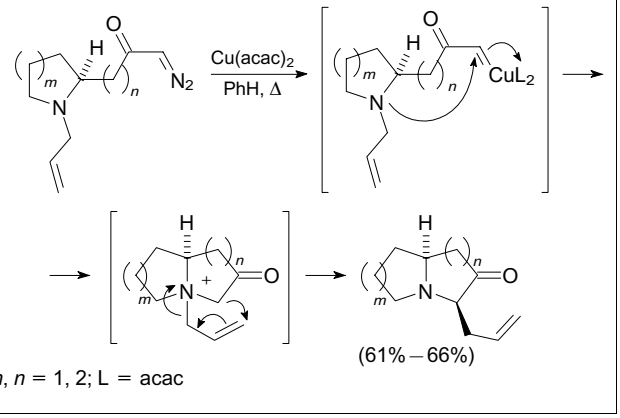
N-Allyl-α-amino diazoketones were applied in the synthesis of piperidine derivatives and other heterocyclic compounds.[210, 211] A series of cyclic, including bicyclic, amines were prepared in good yields through the intermolecular rearrangement of copper carbenoids produced from *N*-allyl-α-amino diazoketones (Scheme 91). The best yields (61% – 66%) were achieved with copper(II) acetylacetonate as the catalyst.

Scheme 90



(*a*) 1) ethyl propiolate, MeONa, MeOH; 2) IBCF, THF; 3) CH_2N_2; R = H, Me, Bu^i

Scheme 91

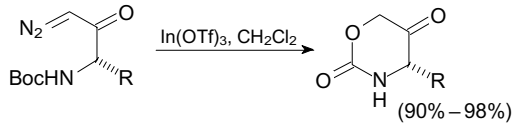


m, *n* = 1, 2; L = acac

Cyclic carbamates constitute a class of biologically active compounds traditionally synthesized from phosgene. This procedure has a number of drawbacks, such as low yields of products, sophisticated equipment and toxicity of the starting reagents. Jung and Avery[212] proposed an alternative method for the synthesis of cyclic carbamates without using phosgene. This method is based on the metal triflate-catalyzed intramolecular insertion of diazoketones. Different catalytic systems were examined. Indium, ytterbium and copper triflates ensured the best outcome (> 95%), and indium triflate was chosen as the catalyst. The final products were prepared from numerous natural and unnatural amino acids in nearly quantitative yields (Scheme 92).

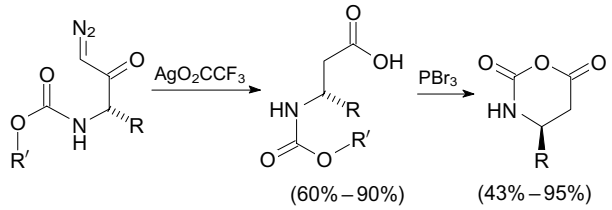
Cheng *et al.*[213] used diazoketones to synthesize cyclic N-carboxyanhydrides, which can be applied in peptide synthesis (Scheme 93). Previously, these compounds were produced from α-amino acids and phosgene according to the Fuchs – Farthing method.[214] However, as mentioned above,

Scheme 92



R = H, Me, Et, Pr^n, Bu^n, Hex, Bn, CH_2Bn, Ph

Scheme 93

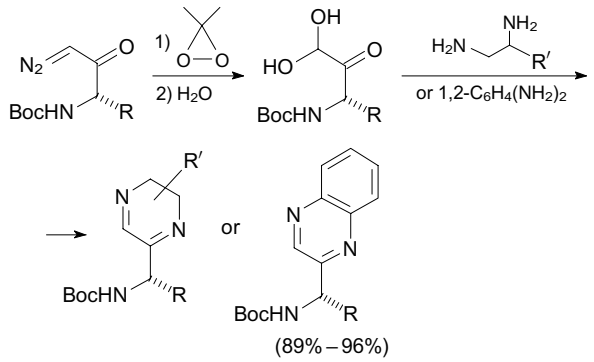


R = Me, Pr^i, Bu^i, Bn; R′ = Bn, Bu^t

the use of phosgene in the synthesis of natural compounds is highly undesirable. Phosphorus tribromide was employed to cyclize β-amino acids to the corresponding cyclic N-carboxyanhydrides. It was found that dichloromethane as the solvent and 0.6 equiv. PBr_3 are conditions of choice, both providing high conversion and minimizing side reactions. The best yields of the products were achieved at lower substrate concentrations (<0.1 mmol litre^{-1}) and in the presence of a base.

Unsaturated six-membered heterocycles can also be prepared from diazoketones. For instance, the oxidation of diazoketones with dimethyldioxirane was used in the synthesis of dihydropyrazines and quinoxalines.[215] N-Protected amino glyoxals were converted to hydrates and then treated with ethylenediamine or phenylenediamine (Scheme 94). This approach was successfully applied to dipeptides and substituted ethylenediamines.

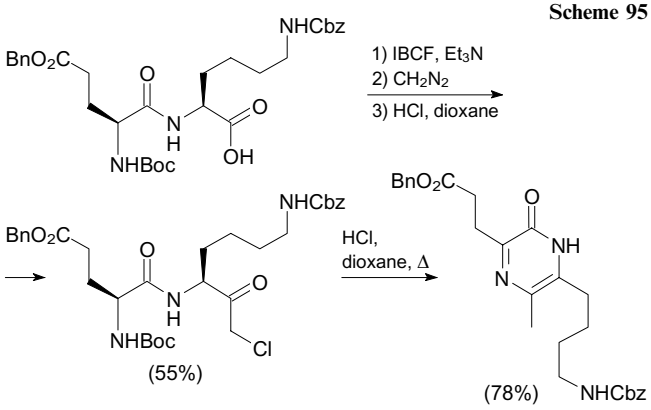
Scheme 94



R = Me, Pr^i, Bu^s, Bu^i, Bn, *N*-Cbz-L-Ala-L-Phe, *N*-Cbz-L-Phe-L-Ala, *N*-Cbz-L-Val-L-Phe, *N*-Cbz-L-Pro-L-Phe; R′ = H, Me, Ac

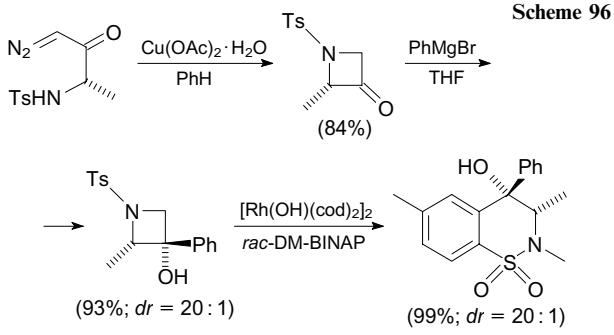
The construction of pyrazinone moieties from diazocarbonyl derivatives of peptides was reported.[216,217] The Arndt – Eistert reaction of the glutamic acid – lysine dipeptide gave a diazo derivative, which was converted, without isolation, to chloroketone by treating with hydrochloric acid. The repeated treatment with hydrochloric acid afforded target pyrazinones (Scheme 95).

Scheme 95



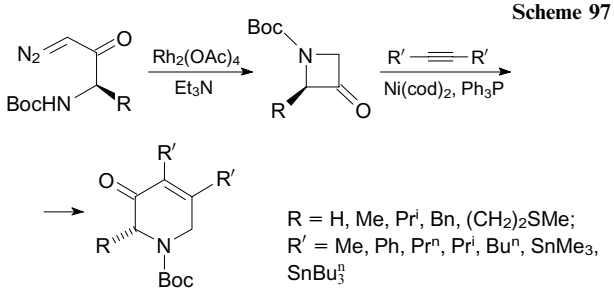
An interesting transformation of the four-membered heterocycle into six-membered benzosultam was reported by Ishida *et al.*[218] The reaction of diazoketone with copper acetate followed by the addition of the Grignard reagent afforded *N*-tosylazetidinol, which can undergo an intramolecular rearrangement in the presence of a rhodium complex and xylyl-substituted racemic BINAP {*rac*-DM-BINAP, 2,2′-bis[di(3,5-xylyl)phosphino]-1,1′-binaphthyl} to form benzosultam (Scheme 96).

Scheme 96



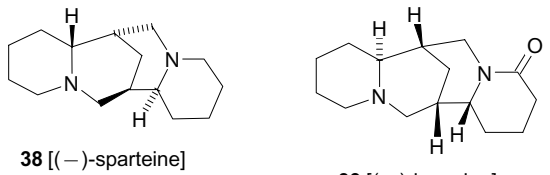
Ishida *et al.*[219] proposed a method for the synthesis of piperidinones from azetidinones. This synthetic strategy is based on carbon – carbon bond activation and involves the preparation of N-*tert*-butoxycarbonyl-protected azetidin-3-ones from appropriate diazoketones followed by their reaction with acetylenes in the presence of nickel complexes (Scheme 97). Target dehydropiperidinones were isolated in high yields (58% – 92%) with high enantiomeric excess (97% – 99% *ee*).

Scheme 97



The lupine alkaloid (−)-sparteine (**38**) is widely used in organic synthesis as a chiral basic catalyst. Its antipode, (+)-sparteine, can be synthesized from racemic lupanine (**39**). However, this method is complicated and involves numerous steps, which significantly limits the application of sparteine in chiral synthesis.

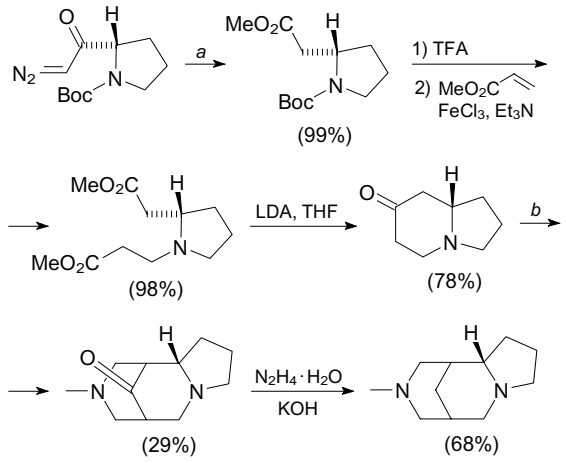
Structures 38, 39



38 [(−)-sparteine] **39** [(−)-lupanine]

Harrison *et al.*[220] proposed a method for the synthesis of sparteine and related cage structures from the diazo derivative of proline in five steps in an overall yield of 15%. Homoproline methyl ester was produced from N-protected proline-derived diazoketone by means of the Wolff rearrangement. After deprotection and condensation with methacrylate, the methyl ester was converted to dicarboxylic acid, which was treated with LDA giving bicyclic aminoketone. The Mannich reaction of the latter with methylamine and paraformaldehyde afforded tricyclic aminoketone, which was reduced to the target polycyclic compound according to the Kishner – Wolff reaction (Scheme 98).

Scheme 98



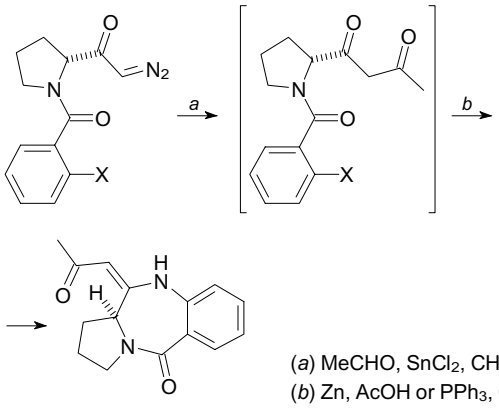
(*a*) $AgOBz$, Et_3N, MeOH; (*b*) $MeNH_2$, $(CH_2O)_n$, AcOH, MeOH

7.5. Synthesis of seven-membered heterocyclic compounds

Like most heterocyclic compounds, seven-membered heterocycles are quite widely used in modern medicinal chemistry. For example, benzodiazepine drugs contain a seven-membered heterocyclic moiety.[221]

Sorra *et al.*[222] proposed a new approach to the synthesis of the natural polynuclear heterocyclic compound fuligocandin isolated from fruit bodies of myxomycetes (Scheme 99). Fuligocandin was synthesized from N-*o*-nitrobenzylated proline, which was transformed into diazoketone, followed by its condensation with acetic anhydride in the presence of tin chloride. The resulting diketone was reduced, without isolation, with zinc in acetic acid, resulting

Scheme 99



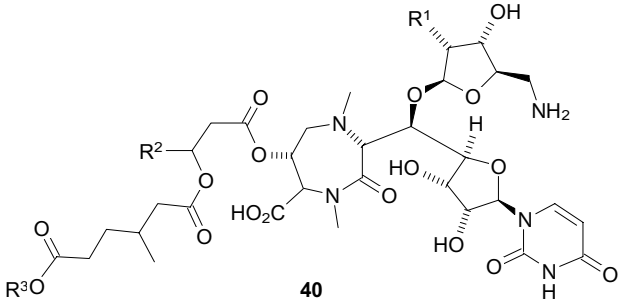
(*a*) $MeCHO$, $SnCl_2$, CH_2Cl_2; (*b*) Zn, AcOH or PPh_3, CH_2Cl_2; X = NO_2, N_3

in the diazepin-5-one ring closure to form target fuligocandin in 59% yield. This natural compound exhibits high cytotoxic activity against P388 leukemia cells.

Fuligocandin was synthesized from N-*o*-azidobenzylated proline by a similar procedure (see Scheme 99).[223] The seven-membered ring was constructed using the Staudinger reaction. The target natural heterocycle was prepared in 81% yield.

The antibiotics liposidomycins and caprazamycins (structures **40**) have a unique nucleoside-like structure and attract great interest.

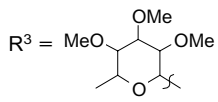
Structures 40



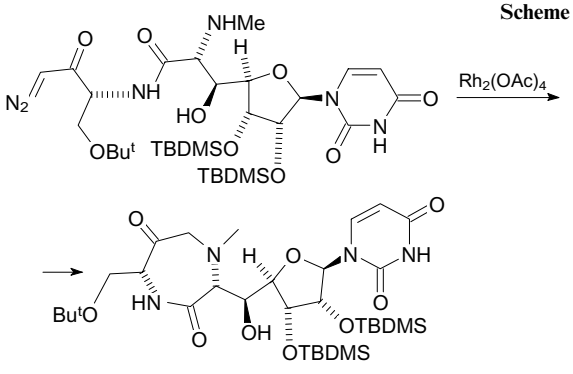
40

Liposidomycins: R^1 = H, SO_3H; R^2 = n-$C_{10}H_{21}$, $Pr^i(CH_2)_8$, $Bu^s(CH_2)_8$, R^3 = H

Caprazamycins: R^1 = H; R^2 = n-$C_{10}H_{21}$, n-$C_{11}H_{23}$, $Pr^i(CH_2)_9$;



Scheme 100

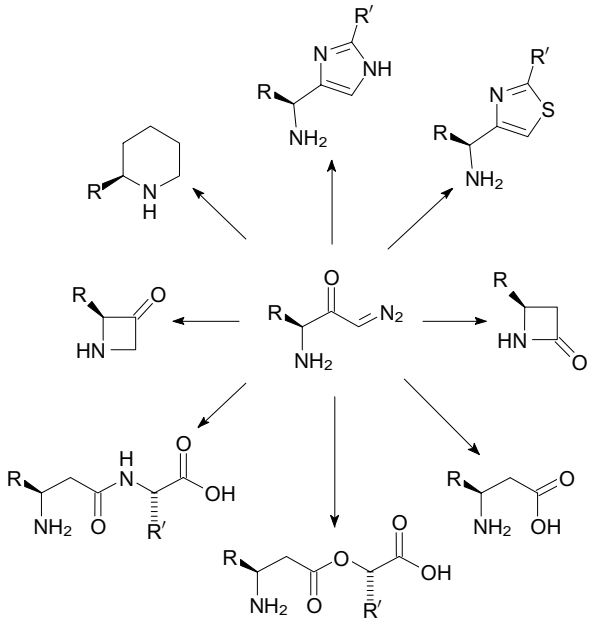


The diazepanone core of these compounds is often constructed using dirhodium tetraacetate-catalyzed intramolecular cyclization of diazoketones (Scheme 100).[224] The required product was isolated in 57% yield.

8. Conclusion

This review shows that chiral α-amino diazoketones have great importance in modern medicinal chemistry.[225, 226] Modifications of these compounds provide access to a wide range of chiral organic compounds with high biological activity. α-Diazocarbonyl derivatives of amino acids have great potential for the design of drugs of different nature. Moreover, a key advantage of α-amino diazoketones is their commercial availability, because they can easily be prepared from natural amino acids. It should be noted that α-amino diazoketones are key synthons for β-amino acid-containing β-lactams and peptides and are widely used in the synthesis of various chiral heterocyclic compounds with high therapeutic potential. Different synthetic applications of α-amino diazoketones are summarized in Scheme 101. Currently. the chemistry of α-amino diazoketones continues to grow.

Scheme 101



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