Potential of Amino Acid-Derived α-Amino Nitriles for Generating Molecular Diversity

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Abstract: This review covers some of the contributions of the authors to the peptidomimetic field. These contributions explore the potential of amino acid-derived α-amino nitriles for generating molecular diversity. Cyanomethyleneamino pseudopeptide analogues of several bioactive peptides and α-quaternary amino nitriles were obtained via a modified three component Strecker synthesis. Taking advantage of the reactivity of the cyano group and the diverse functionality of amino acid derivatives, cyanomethyleneamino pseudopeptides were transformed into carbamoylmethyleneamino and branched pseudopeptides or privileged heterocyclic scaffolds, such as: piperazine, pyrazino[1,2-*c*]pyrimidine, 1,4-benzodiazepine, and novel indole derivatives, including some spirocyclic compounds.

Keywords: Molecular diversity, diversity oriented synthesis, peptidomimetics, α-Amino nitriles, pseudopeptides, privileged scaffolds.

1. INTRODUCTION

Within the last two decades, the hit generation step in the drug discovery process has been broadly approached by means of high-throughput screening of diverse small molecule libraries generated by combinatorial chemistry. The most commonly used synthetic strategy to access these libraries has involved the appendage of different sets of building blocks to a common molecular skeleton. However, this strategy has led to limited structural diversity, because the diversity of building blocks upon a common scaffold produces compounds looking rather similar. Nowadays, it is accepted that gaining efficiency in the study of the chemical space of small molecules requires access to complex and diverse skeletons via diversity-oriented synthesis (DOS) [1]. Stereocontrolled multicomponent-coupling reactions, complexity-generating reactions (domino and tandem), and branching pathways are the most effective in DOS. Amino acid derivatives are highly valuable starting materials for these processes, due to their functional, stereochemical, and topographic diversity and ease of access.

α-Amino nitriles have maintained an important position in organic synthesis since 1850, when A. Strecker reported their preparation as intermediates for the synthesis of α-amino acids, via a three-components reaction between aldehydes, ammonia and HCN [2]. Since then, diverse versions of this reaction, between a carbonylic compound, an amine, and cyanide, have been one of the most used methods for the synthesis of precursors of non-proteinogenic amino acids [3]. During the last years, the attention has mainly been focused on the stereocontrol in the Strecker reaction, using chiral auxiliaries [3] or, more recently, chiral catalysts [4]. α-Amino nitriles are versatile bifunctional intermediates with multiple synthetic applications which are summarized in Scheme **1**. Thus, hydrolysis of the cyano group produces α-amino acids **A**, while, cyano reduction leads to 1,2-diamines **B**. Removal of a cyanide anion generates an intermediate iminium salt **C**, that may be trapped with nucleophilic reagents (**D**-**F**) or isomerize to an enamine **G**. α-Amino nitriles bearing an α-hydrogen (R^2 = H) can be deprotonated by strong bases to give the carbanion **H**, which can be trapped by diverse electrophiles. On the other hand, the cyanomethyleneamino [CH(CN)NH] group is present in the structure of some natural products such as the antitumorals saframycin A [5] and cyanosafracyn B [6]. This alkaloid is used as starting material for the semisynthesis of the recently approved antitumoral drug ecteinascidin (ET-743) [7].

At the beginning of the nineties, our research group proposed the cyanomethyleneamino moiety as a good peptide bond surrogate in the field of peptidomimetics, and developed an efficient methodology for the synthesis of Ψ[CH(CN)NH] pseudopeptides via a modified Strecker synthesis [8,9] (Scheme **2**). Later on, taking advantage of the functional, structural, and stereochemical diversity of readily accessible amino acid derivatives and of the high reactivity profile of the cyano group, we focused our attention on Ψ[CH(CN)NH] pseudopeptides as starting materials for the synthesis of other pseudopeptides and diversity of privileged scaffolds [10], such as piperazine, 1,4-benzodiazepine, pyrazino[1,2-*c*]pyrimidine, and indole derivatives. This review provides an overview of our work on the study of the potential of amino acid-derived α-amino nitriles in diversity-oriented synthesis, as summarized in Scheme **2**.

2. PSEUDOPEPTIDE SYNTHESIS

Pseudopeptides are peptide analogues modified at the peptide backbone, where, at least, one peptide bond has been replaced by an isosteric group [11]. These peptide bond surrogates are usually indicated by the Ψ Greek letter followed by the surrogate between brackets. These modifications have been mainly used to increase the peptide stability toward proteolytic enzymes, but, in many cases, they have also pro-

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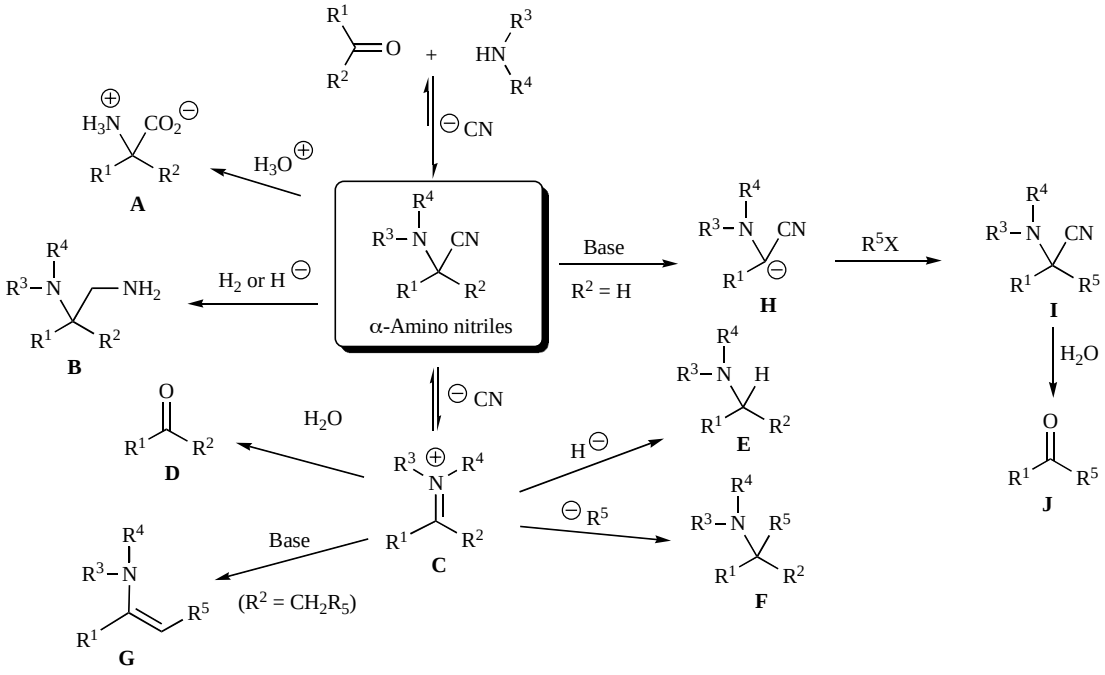


Scheme 1. Reactivity of α-amino nitriles.

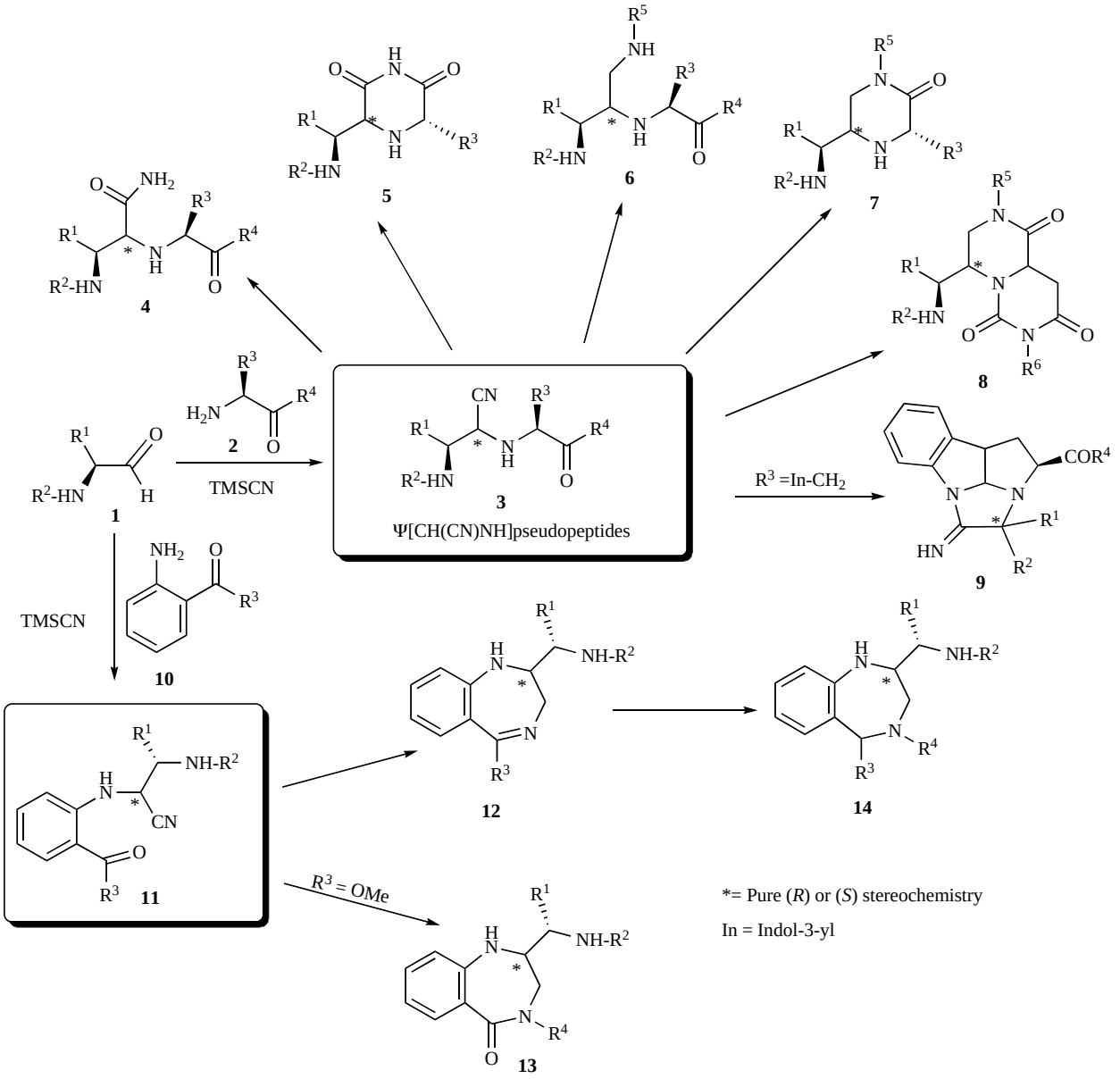
duced receptor selectivity and/or have changed the peptide functionality from agonist to antagonist. Some peptide bond surrogates have also been incorporated into peptidase inhibitors to mimic the enzyme-bound tetrahedral transition state of the scissile amide bond [11].

2.1. CYANOMETHYLENEAMINO PSEUDOPEPTIDES

The reduced peptide bond [CH_2NH] has been one of the peptide bond surrogates more successfully used in the design of metabolically stable agonists [12], antagonists [13] of natural peptides and peptidase inhibitors [14]. However, this surrogate causes an increase in flexibility and a decrease in the *H*-bonding properties of the peptide bond, by loss of the *H*-bonding acceptor amide carbonyl group [11]. Comparative semiempirical quantum mechanic calculations for simple models of the Ψ[CH(CN)NH] and the Ψ[CH_2NH] peptide bond surrogates showed that, from the electronic point of view, the Ψ[CH(CN)NH] surrogate is similar to the peptide bond [CONH], while, geometrically, it is similar to the tetrahedral transition state involved in peptidase hydrolysis, being, in any case, a better replacement for both than the Ψ[CH_2NH] [8]. These results were later experimentally confirmed with the synthesis and biological evaluation of several Ψ[CH(CN)NH] pseudopeptides, including analogues of: the C-terminal hexapeptide of neurotensin [NT(8-13), H-Arg-Arg-Pro-Tyr-Ile-Leu-OH] [15], the C-terminal tetrapeptide of cholecystokinin (CCK-4, H-Trp-Met-Asp-Phe-NH_2) [16], a potent and selective antagonist of CCK_1 receptors [17], and the N-terminal tripeptide of the insuline-like growth factor-1 (H-Gly-Pro-Glu-OH) [18]. On the other hand, the utility of the Ψ[CH(CN)NH] surrogate in the field of peptidase inhibitors was demonstrated with the synthesis of inhibitors of aminopeptidases B and M [19], that were equipotent with the known aminopeptidase inhibitor bestatin [20].

As abovementioned, we developed a modified Strecker reaction for the synthesis of Ψ[CH(CN)NH] pseudopeptides **3** [9], which, as shown in Scheme **3**, involves a Lewis acid-catalyzed condensation of an N-protected α-amino aldehyde (R^2-Xaa-H, **1**) with an N-deprotected α-amino acid or peptide (H-Yaa-R^4, **2**), followed by *in situ* addition of trimethylsilyl cyanide (TMSCN) upon the unstable intermediate imine **15**. Ψ[CH(CN)NH] Pseudopeptides were obtained as epimeric pairs at the generated [CH(CN)NH] stereogenic center in an (*R*):(*S*) ratio that, as shown in table 1, was mainly dependent on the nature and stereochemistry of the coupled amino acids. The main factor influencing the stereoselectivity was the homochirality or heterochirality of the starting amino acid derivatives [9]. No racemisation at the chiral centre of the starting α-amino aldehyde was observed when the formation of the peptide bond surrogate was carried out below 0ºC. However, up to 5% of racemisation was observed when the reaction was carried out at room temperature.

Taking as reference the reports of the Kunz's group on the influence of the solvent/catalyst system upon the stereochemical control in the TMSCN addition to Shiff bases derived from 1-amino-2,3,4,6-tetra-*O*-pivaloyl-β-D-galactose [21], we studied the possibility of controlling the stereoselectivity in the synthesis of Ψ[CH(CN)NH] pseudopeptides by varying the reaction conditions. MeOH/$ZnCl_2$, THF/$SnCl_4$, and CH_2Cl_2/$ZnCl_2$ were studied as solvent/catalyst pairs, but the results in stereoselectivity and yield were similar in the three cases. Neither an influence on the stereoselectivity was observed with the addition of cyclo L-phenylalanine-L-histidine as chiral catalyst, which at the time of our studies had been reported as a chiral organocatalyst for the asymmetric addition of HCN to aldehydes [22].

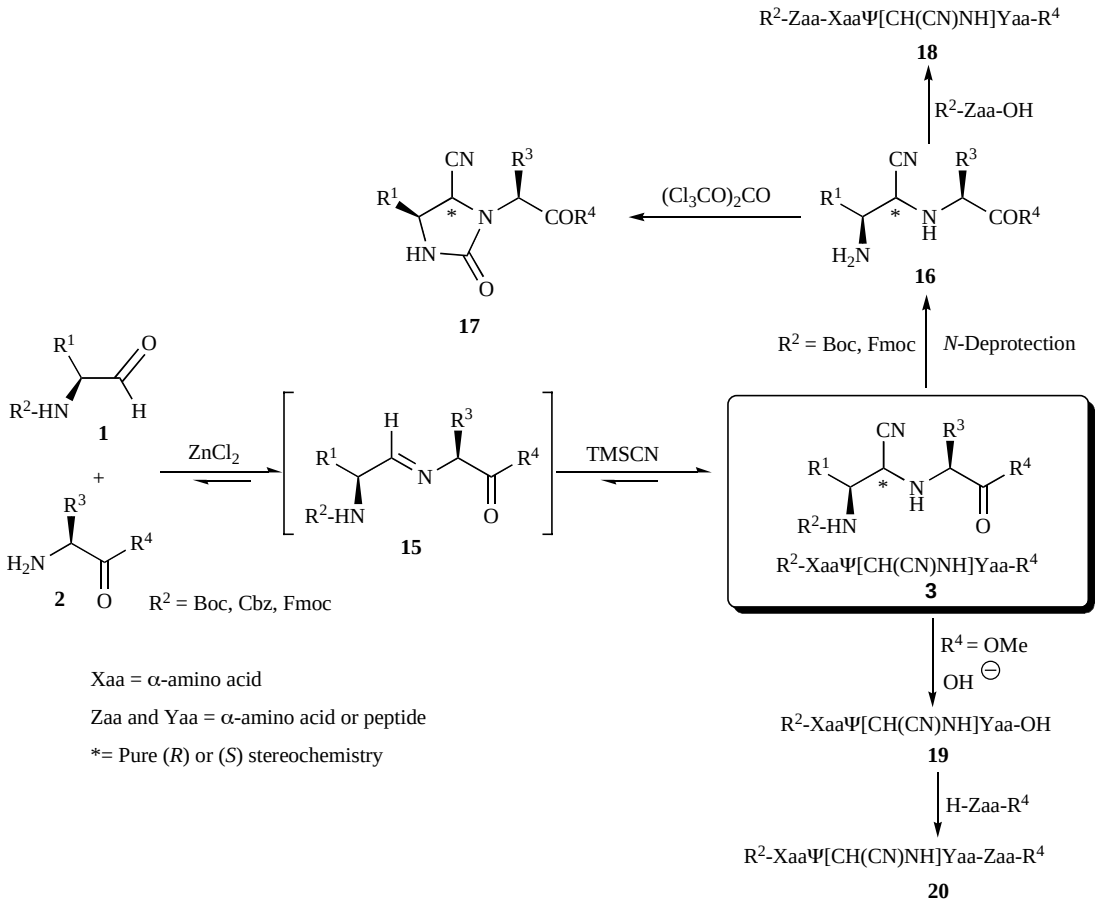


Scheme 2. Molecular diversity from amino acid-derived α-amino nitriles.

The assignment of absolute configuration at the [CH(CN)NH] chiral center was established on the basis of the $J_{4,5}$ value in the ^{1}H RMN spectra of the corresponding imidazolidin-2-ones **17**, which were obtained by *N*-deprotection, followed by reaction with bis(trichloromethyl)carbonate. The *threo*-imidazolidin-2-ones (*R*)-**17** showed a $J_{4,5}$ value of 3-4 Hz, consistent with a H_4,H_5 *trans* disposition, while, in the *erythro*-isomer (*S*)-**17**, the value of this constant was 8 Hz, indicative of a relative *cis* disposition for those protons [23]. In some pseudopeptides, this assignment was confirmed by NOE effects observed in NOE difference or NOESY 1 D spectra.

The synthesis of Ψ[CH(CN)NH] pseudopeptides is compatible with Boc, Cbz, and Fmoc *N*-protecting groups, and with OMe, OBzl, and O^{t}Bu *C*-protecting groups. As shown in Scheme **3**, pseudopeptides **3** can be easily extended at the *N*- and *C*-terminus applying standard methodologies of peptide synthesis. Thus, *N*-deprotection of pseudopeptides **3**, followed by coupling with an *N*-protected amino acid [9, 16, 18] or peptide [15] [R^2-Zaa-OH], using DCC/1-HOBt, HBTU or BOP as coupling agents, gives the corresponding *N*-extended pseudopeptides **18**. On the other hand, the use of an *N,C*-deprotected amino acid in the formation of the Ψ[CH(CN)NH] bond surrogate, allows to directly obtain *C*-deprotected pseudopeptides **19**, which can be also obtained by saponification of the methyl esters **3** (R^4 = OMe). The subsequent coupling of *C*-deprotected pseudopeptides **19** with a *C*-protected amino acid (H-Zaa-R^4), using DCC/1-HOBt as coupling reagents leads to *C*-extended pseudopeptides **20** [9].

Ψ[CH(CN)NH] Pseudopeptides can also be prepared by solid phase synthesis, using the Fmoc strategy and a *p*-



Scheme 3. Synthesis of Ψ[CH(CN)NH]pseudopeptides.

alcoxybenzyl-polystyrene resin (PAB-resin). This methodology was developed for the synthesis of analogues of the *C*-terminal hexapeptide of neurotensin [H-Arg-Arg-Pro-TyrΨ[CH(CN)NH]Ile-Leu-OH] [24]. The application of a Boc solid phase synthesis in a *p*-methoxyphenylacetamido-polystyrene resin (PAM-resin) was also studied, however, the Ψ[CH(CN)NH] peptide bond was not stable under HF required for the cleavage from the resin.

As starting materials for the synthesis of spirocyclic compounds, we were interested in quaternary α-amino nitriles **23** (Scheme **4**), whose preparation was initially attempted applying the reaction conditions developed for the Ψ[CH(CN)NH] bond coupling. Under these conditions, the main reaction product was the corresponding trimethylsilyl cyanohydrin derived from the starting ketone (**21**), obtaining α-amino nitriles **23** in very low yield [25]. However, the replacement of $ZnCl_2$ by ytterbium triflate as catalyst, and its addition after the formation of the intermediate imine **22**, allowed the synthesis of **23** in good yields (75-98%). Very recently, and with the same aim, D. Postel and col. have described a similar method for the synthesis of α-amino acid and ulose-derived quaternary α-amino nitriles, using $Ti(O^iPr)_4$ as catalyst [26], although they do not comment on our precedents.

Interestingly, Myers *et al.* have reported an ingenious construction of the pentacyclic skeleton of saframycin A (**24**) by the coupling of two units of a *N*-Fmoc-L-phenyl-alaninal derivative (**25**) and one of *N*-Fmoc-glycinal (**26**), including two consecutive Strecker reaction steps [27], as it is shown in the retrosynthetic direction in Scheme **5**.

2.2. CARBAMOYLMETHYLENEAMINO PSEUDOPEPTIDES

With the aim of counteracting the decrease in the H-bonding acceptor properties that produces the Ψ[CH_2NH] peptide bond surrogate, and to provide additional H-bonding interactions with receptors, Mohan *et al.* synthesized Ψ[$CH(CONH_2)NH$] pseudopeptides analogues of angiotensin II in 1991 [28]. These angiotensin analogues were prepared by *N*- and *C*-extension of H-ValΨ[$CH(CONH_2)$NH]His-OH pseudodipeptides, which had been obtained by concentrated H_2SO_4-mediated cyanohydration of the corresponding *N*-Boc-protected Ψ[CH(CN)NH] pseudodipeptides. This strong acid reaction medium is incompatible with the presence of peptide bonds and of most of the *N*- and *C*-protecting groups and, consequently, removal of the Boc-protecting group took place simultaneously with the cyanohydration. To avoid these drawbacks, we applied a phase-transfer catalyzed basic oxidative cyanohydration, previously developed for the hydration of cyanohydrins [29], to Ψ[CH(CN)NH] pseudopeptides **3a-f** for the synthesis of Ψ[$CH(CONH_2)$NH] pseudopeptides **27a-f** (Scheme **6**) [30]. This methodology was later unsuccessfully applied to the hydration of quaternary α-amino nitriles **23a-h**, which were

Table 1. Yield and Stereoselectivity of the Synthesis of R^2-XaaΨ[CH(CN)NH]Yaa-R^4

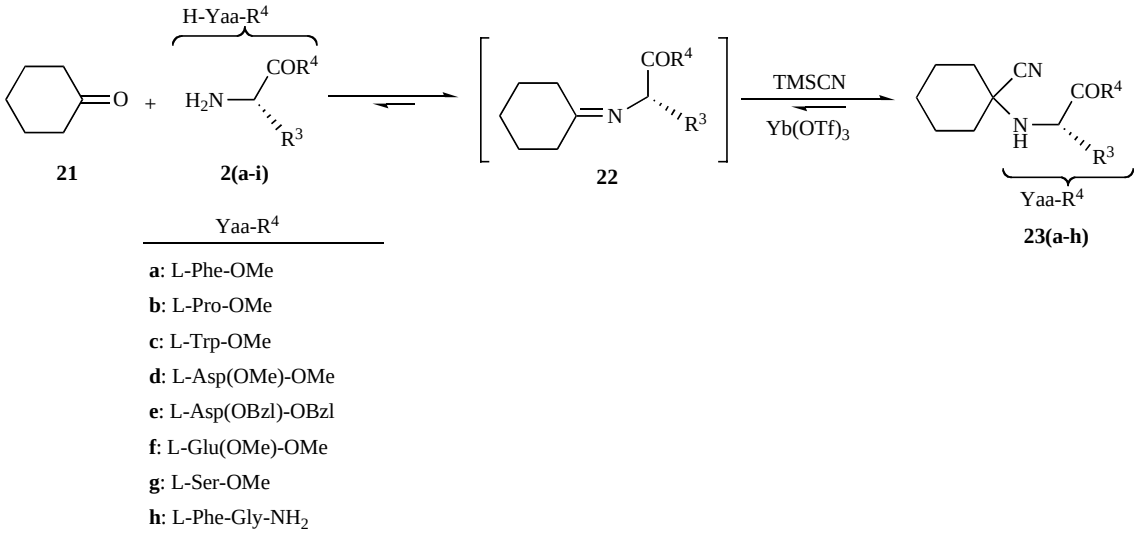
Pseudopeptide	R^2-Xaa	Yaa-R^4	Yield (%)[a]	Ψ[CH(CN)NH] (*R*)-3/(*S*)-3 ratio[b]
3a	Boc-L-Phe	L-Leu-OMe	95	1/1
3b	Cbz-L-Phe	L-Leu-OMe	90	1/1
3c	Boc-L-Phe	D-Leu-OMe	92	1/3
3d	Boc-L-Phe	L-Val-OMe	80	2/1
3e	Boc-L-Phe	L-Phe-OMe	82	1/1
3f	Boc-L-Phe	D-Phe-OMe	85	1/4
3g	Boc-L-Phe	L-Lys(Cbz)-OMe	76	1/1
3h	Boc-L-Phe	L-Glu(OMe)-OMe	88	1/1
3i	Boc-L-Phe	L-Pro-OMe	42	9/1
3j	Boc-L-Phe	L-Ala-L-Pro-OMe	55	1/1
3k	Boc-L-Phe	L-Leu-L-Pro-OMe	53	3/1
3l	Cbz-L-Leu	L-Leu	85	1/1
3m	Cbz-L-Trp	L-Phe	75	3/2
3n	Cbz-L-Trp	L-Phe-NH_2	65	3/2
3o	Boc-L-Trp	L-Phe-NH_2	60	3/2
3p	Cbz-L-Trp	L-Asp(OBzl)-L-Phe-NH_2	67	1/3
3q	Cbz-L-Trp	L-Nle-L-Asp(OBzl)-L-Phe-NH_2	89	1/1
3r	Boc-L-Nle	L-Asp(OBzl)-L-Phe-NH_2	65	1/3
3s	Boc-L-Asp(OBzl)	L-Phe-NH_2	45	1/2
3u	Cbz-L-Asp(O^{t}Bu)	L-Phe-NH_2	59	1/2
3v	Fmoc-L-Tyr(^{t}Bu)	L-Ile-L-Leu-O^{t}Bu	69	1/2
3x	Boc-L-Pro	L-Glu(OBzl)-OBzl	79	3/2
3y	Boc-Gly	L-Pro-L-Glu(OBzl)-OBzl	32	3/2

[a]Overall yield of (*R*)- and (*S*)-epimers. [b]Ratio determined by reversed-phase HPLC or NMR analysis of the crude reaction mixtures.

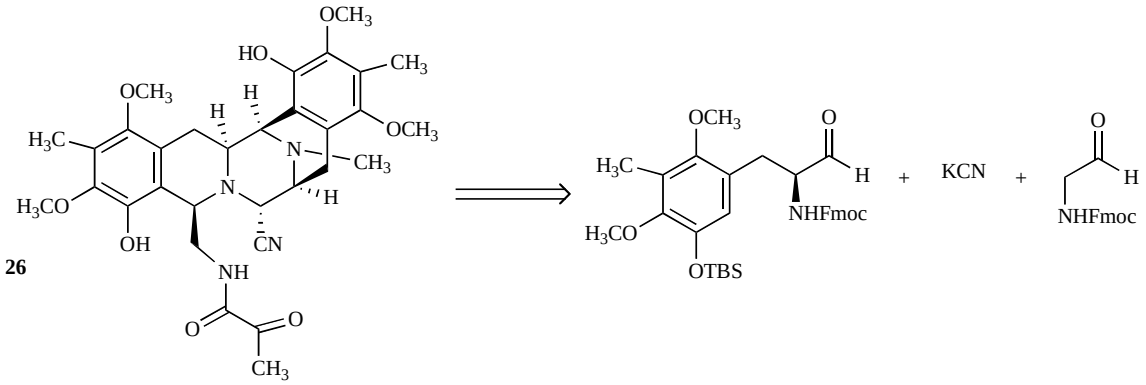
recovered unaltered from the reaction medium. The hydration of these amino nitriles required concentrated H_2SO_4 in CH_2Cl_2 solution to give the corresponding α-amino carboxamides **28a-h** [25]. Some of these compounds partially cyclised in the reaction media to their respective 2,6-dioxopiperazine derivatives **29**.

2.3. *C*-BACKBONE BRANCHED PSEUDOPEPTIDES

Branched peptides have been used for the preparation of multiple antigen peptides for immunological applications [31], for the synthesis of template assembled synthetic proteins(TASP) [32] and dendrimers [33], and for the introduction of conformational constrains into peptides through side-



Scheme 4. Synthesis of amino acid-derived α-quaternary amino nitriles.

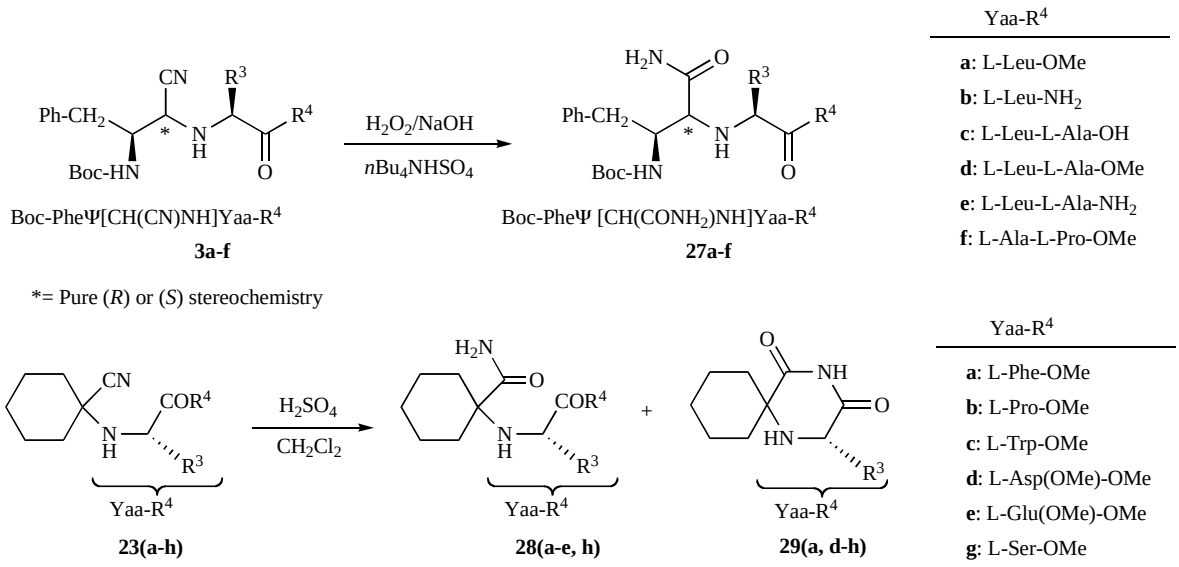


Scheme 5. Retrosynthesis of saframycin A according to reference [27].

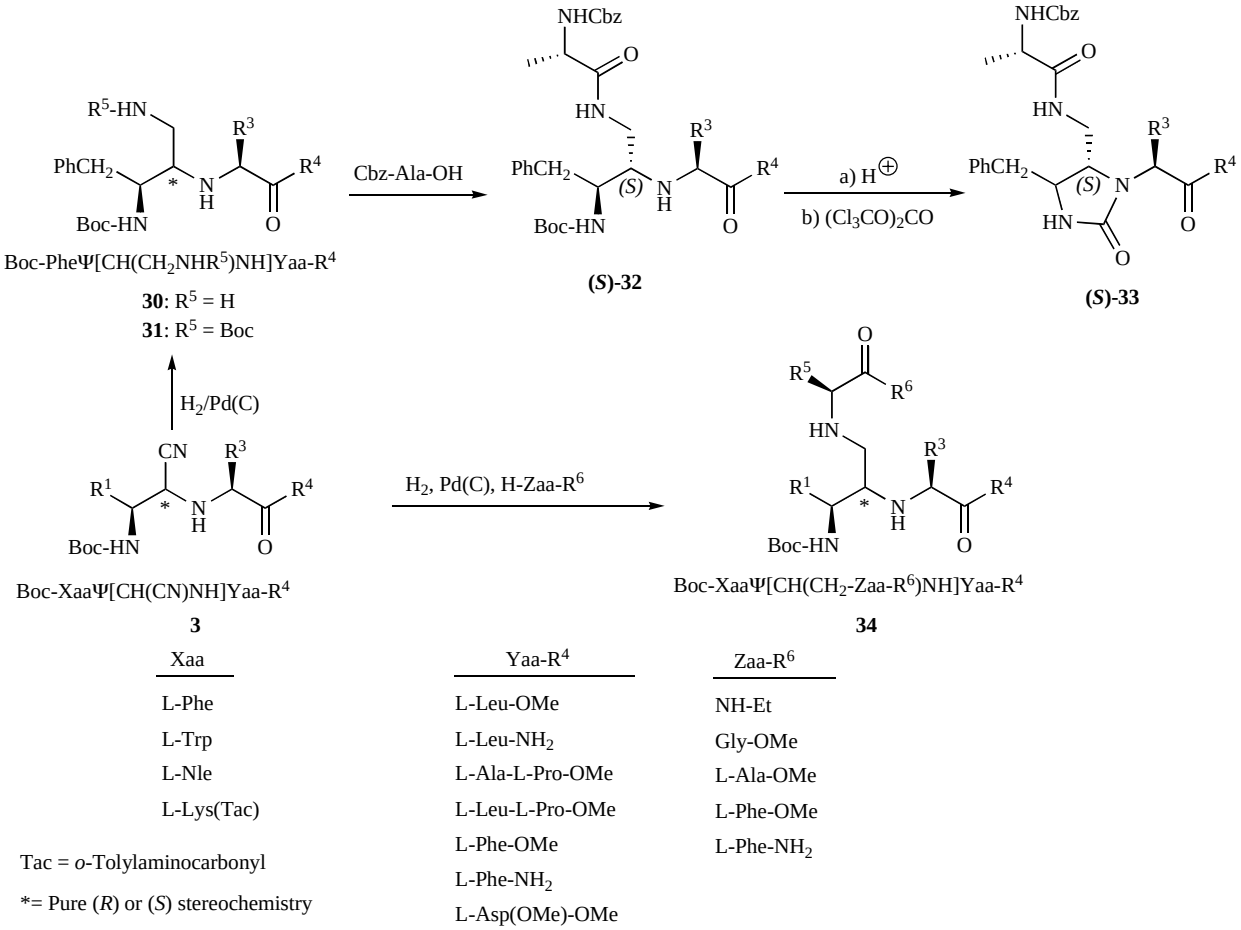
chain cyclizations [34]. Most classical procedures for branching or cyclization are only applicable to peptides containing reactive side chains, such as those of Asp, Glu, Lys or Cys [31-34]. In these cases, the branching or cyclization are only permissible in silent regions of peptides, but they may lead to inactive peptides when applied to active regions. To avoid this drawback, diverse strategies of *N*-backbone branching at the peptide bond have been proposed, involving *N*-alkylation with a functionalized carbon chain linker [35]. The cyano group can be considered as an amino precursor and, therefore, it may be a point of potential branching and extension of the peptide backbone. Taking into account this potential we studied the catalytic reduction of Ψ[CH(CN) NH] pseudopeptides as a source of *C*-backbone branched pseudopeptides.

As shown in Scheme **7**, the Pd(C) catalyzed hydrogenation of Ψ[CH(CN)NH] pseudopeptides **3** (Xaa = Phe), at room temperature and in the presence of AcOH, led to the corresponding Ψ[CH(CH_2NH_2)NH] pseudopeptides **30** [36]. Afterward, coupling of the epimer **(*S*)-30** with *N*-Cbz-L-Ala-OH, using DCC/HOBt as activating reagents, gave the *N*-extended derivatives **(*S*)-32**, whose absolute (*S*)-configuration was assigned on the basis of the $J_{4,5}$ value of the 2-oxoimidazolidine derivative **(*S*)-33**. However, the (*R*)-epimer **(*R*)-30** could not be *N*-extended under the same coupling conditions or using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) or benzotriazolyloxy tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) as coupling reagents. Pseudodipeptides **30** (R^4 = OMe or NH_2) were unstable at room temperature, cyclizing on standing to 2-oxopiperazine derivatives, as it will be commented in section 3.1. When the hydrogenation was carried out in the presence of di-*tert*-butyl-dicarbonate in neutral medium, the respective *N*-Boc-protected pseudopeptides **31** were obtained as single reaction products.

We also studied the possibility of backbone peptide branching by insertion of an amino acid derivative into Ψ[CH(CN)NH] pseudopeptides **3**, via catalytic hydrogenation in the presence of amino acid derivatives [37]. It is well known that catalytic hydrogenation of nitriles may give rise to a number of products, including primary, secondary and tertiary amines, imines, aldehydes, and amides. Despite the possible complexity of this reduction, its selectivity towards primary or secondary amines can be controlled with the hy-

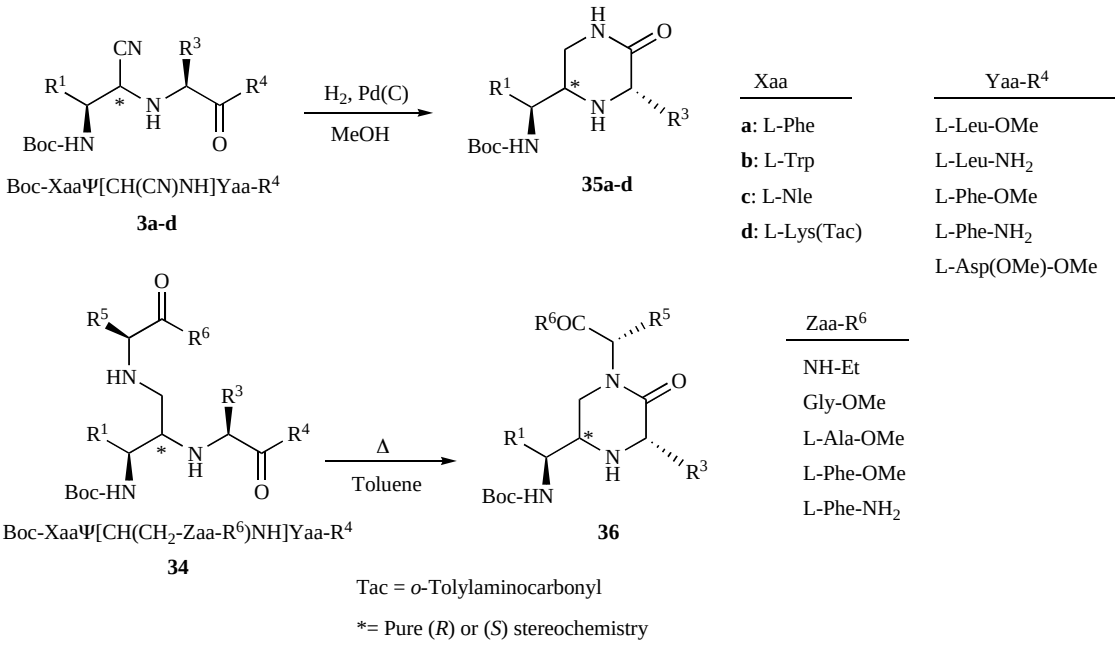


Scheme 6. Developed methods for the cyanohydration of α-amino nitriles.

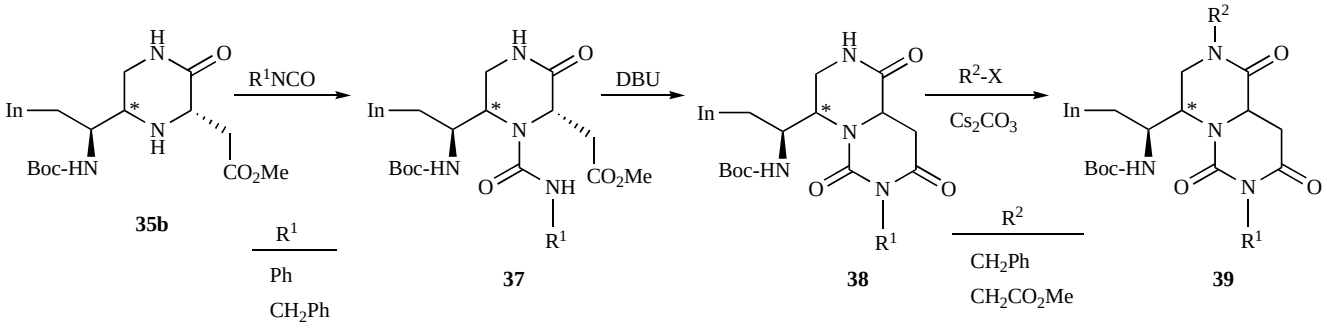


Scheme 7. Synthesis of *C*-backbone branched pseudopeptides.

drogenation conditions, such as catalyst, temperature, solvent, and addition of amines [38]. When the hydrogenation is carried out in the presence of primary amines, the formation of asymmetrical secondary amines competes with that of the symmetrical one. As shown in Scheme **7**, Ψ[CH(CN)NH] pseudopeptides **3** were selectively transformed into the branched peptides **34** by 10% Pd(C)-catalyzed hydrogenation in the presence of two equivalents of the *N*-deprotected amino acid derivatives H-Zaa-R^6.



Scheme 8. Synthesis of 2-oxopiperazines.



Scheme 9. Synthesis of 1,6,8-trioxo-perhydropyrazino[1,2-*c*]pyrimidines.

3. PRIVILEGED SCAFFOLD SYNTHESIS

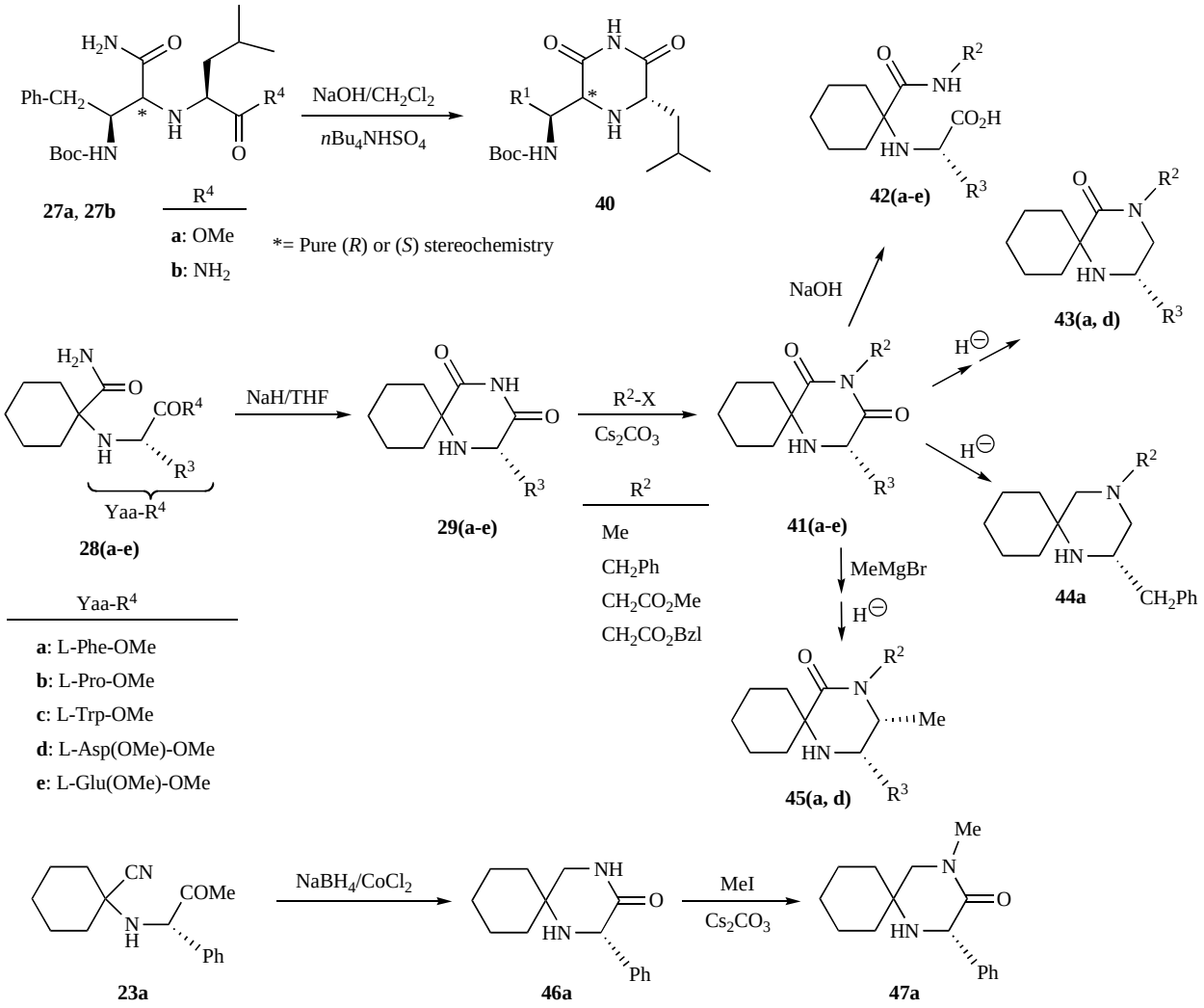
The concept of privileged scaffolds was introduced by Evans *et al*. in 1988, to define recurrent, generally heterocyclic, substructures present in diverse compounds with inherent affinity for diverse biological receptors [39]. Pyrrolidines, piperidines, piperazines, benzodiazepines, indoles, and biphenyls are among the most frequently found privileged scaffolds [40]. These structures have been widely used in the search of peptidomimetics, as scaffolds where amino acid side chains are attached in an appropriate orientation [40,41].

3.1. PIPERAZINE DERIVATIVES

As abovementioned, Ψ[CH(CH_2NH_2)NH] pseudodipeptides **30**, resulting from the hydrogenation of Ψ[CH(CN)NH] pseudodipeptides **3a-d**, cyclized on standing to give the 1-unsubstituted piperazines **35a-d** (Scheme **8**) [37]. Branched pseudopeptides **34** lactamized to the 1,3,5-trisubstituted piperazines **36**, by refluxing in toluene for a variable period of time dependent on the constituent amino acid residues [42]. The conformational analysis of simplified models of piperazines **36**, carried out by molecular dynamics, showed that these scaffolds could be good mimetics of γ–turns in peptides [42]. Therefore, to probe the suggested presence of a γ–turn in the bioactive conformations of the C-terminal tetrapeptide of cholecystokinin (CCK-4) and of some tripeptidic CCK_1 agonists, several CCK-4 analogues containing the 2-oxopiperazine skeleton **36** were prepared. The introduction of this conformational restriction led to a loss of 2 or 3 orders of magnitude in the affinity at CCK receptors. Based on these results, a γ–turn in the bioactive conformation of CCK-4 was discarded [42].

Aspartic acid-derived 2-oxopiperazines **35b** were used to explore the synthesis of bicyclic scaffolds to be applied in the search of analogues of perhydropyrido[1,2-*c*]pyrimidine-based selective CCK_1 antagonists [43]. As shown in Scheme **9**, the reaction of 2-oxopiperazines **35b** with isocyanates, followed by consecutive base-promoted cyclization and *N*-alkylation led to the 2,4,7-trisustituted-1,6,8-trioxo-perhydropyrazino[1,2-*c*]pyrimidines **39**.

Similarly to the abovementioned reactivity of quaternary α-amino carboxamides **28** in acid media (section 2.2), Ψ[CH($CONH_2$)NH] pseudodipeptides **27** demonstrated a high propensity to cyclize to the 2,6-dioxopiperazine derivatives **40** in the basic media of oxidative cyanohydration (Scheme **10**) [30]. On the other hand, the treatment of qua-

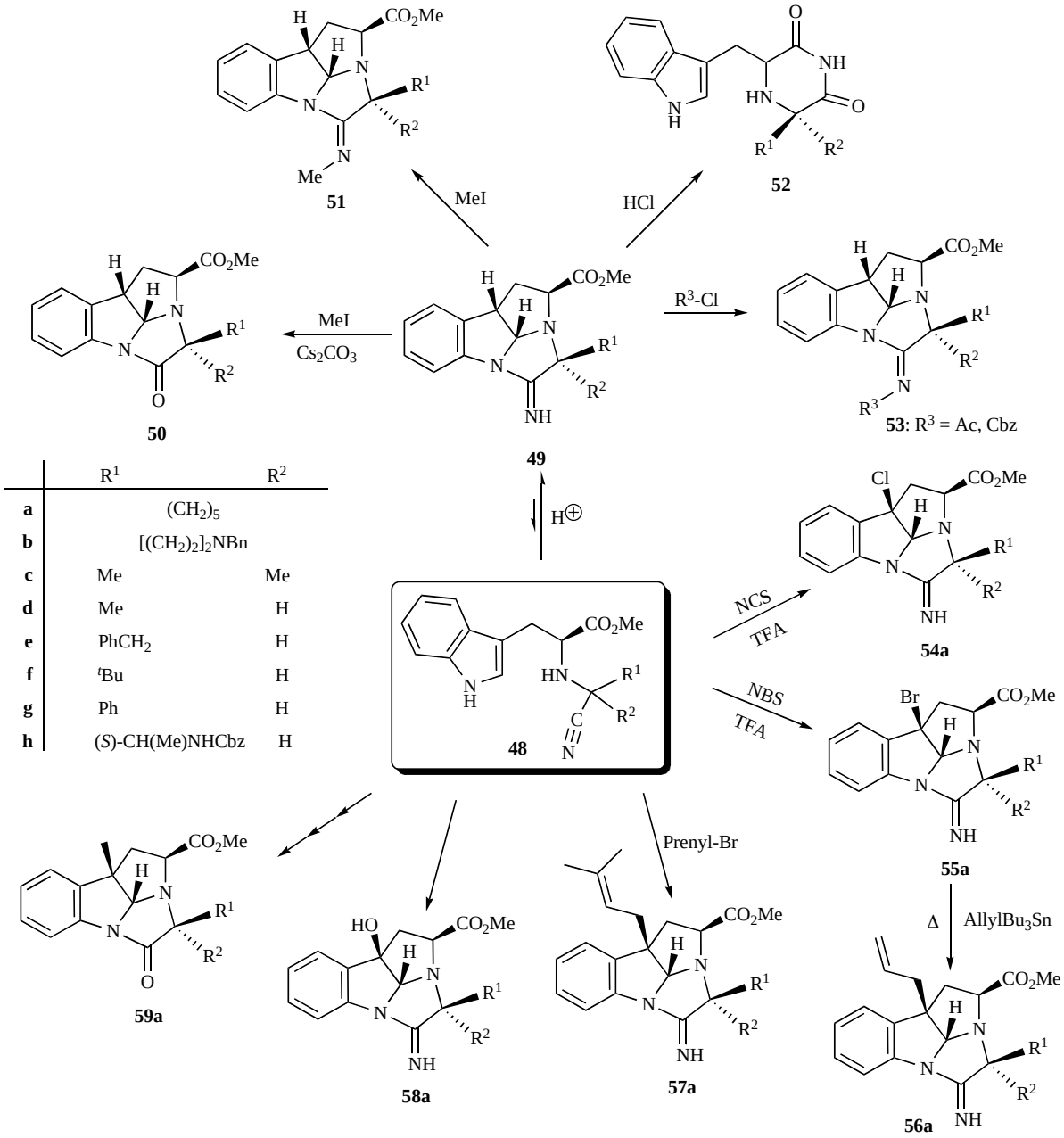


Scheme 10. Synthesis of spirocyclic piperazine derivatives.

ternary α-amino carboxamides **28(a-e)** with NaH, followed by alkylation, led to spirocyclic 1,5-disubstituted-2,6-dioxopiperazines **41(a-e)** [25], which, due to the rich reactivity of the imide group, can be transformed into: a) *N*-Carbamoylalkyl-α-amino acids **42**, by base-promoted hydrolysis [44]; b) 5-Oxopiperazines **43**, by reduction with $NaBH_4$, followed by TFA treatment [45]; c) Piperazines **44**, by reduction with $LiAlH_4$ [45]; or d) 4-Methyl-5-oxopiperazines **45**, by addition of MeMgBr, followed by TFA treatment [45]. Interestingly, as shown in Scheme **10**, the 3-oxopiperazine **47a** was regioselectively obtained by reduction of the α-amino nitrile **23a**, followed by *N*-alquilation. α-Amino nitrile **23a** could not be reduced by catalytic hydrogenation using either Pd(C) or Raney nickel as catalysts.

3.2. INDOLE DERIVATIVES

In the H_2SO_4-mediated hydration of the tryptophan-derived quaternary α-amino nitrile **48a** (Scheme **11**) the tetracyclic tautomer **49a**, containing the novel hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indole ring system, was obtained as main reaction product [46]. This unprecedented ring system could be considered as a hybrid of 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole and 2,3,9,9a-tetrahydroimidazo[1,2-*a*]indole, which are present in a growing class of indole alkaloids with a wide range of biological activities. The recurrent presence of indole-based heterocycles in natural products and in diverse compounds of therapeutic interest, along with the novelty of the mentioned tetracyclic ring system, pushed us to optimize the reaction conditions and to study the scope and stereoselectivity of the synthesis. Based on the Taniguchi and Hino's reports on the tautomerization of tryptophan and tryptamine derivatives to hexahydropyrrolo[2,3-*b*]indoles [47], we found that the tautomerization of amino nitriles **48** to the pyrroloimidazoindole **49** was quantitative in a 33% suspension of 85% H_3PO_4 in CH_2Cl_2 or in neat TFA [46]. As shown in Scheme **11**, this methodology was applied to a diversity of α-amino nitriles **a-h**, derived either from ketones(**a-c**) or from aldehydes (**d-h**) [48]. Two new stereogenic centres are sterespecifically or stereoselectively generated in the tautomerization, depending on the steric volume of the substituents and on the reaction temperature and time. Under kinetic control the 2-*exo*-diastereoisomer **49** was the sole or major reaction product. Under thermodynamic control, unhindered amino nitriles



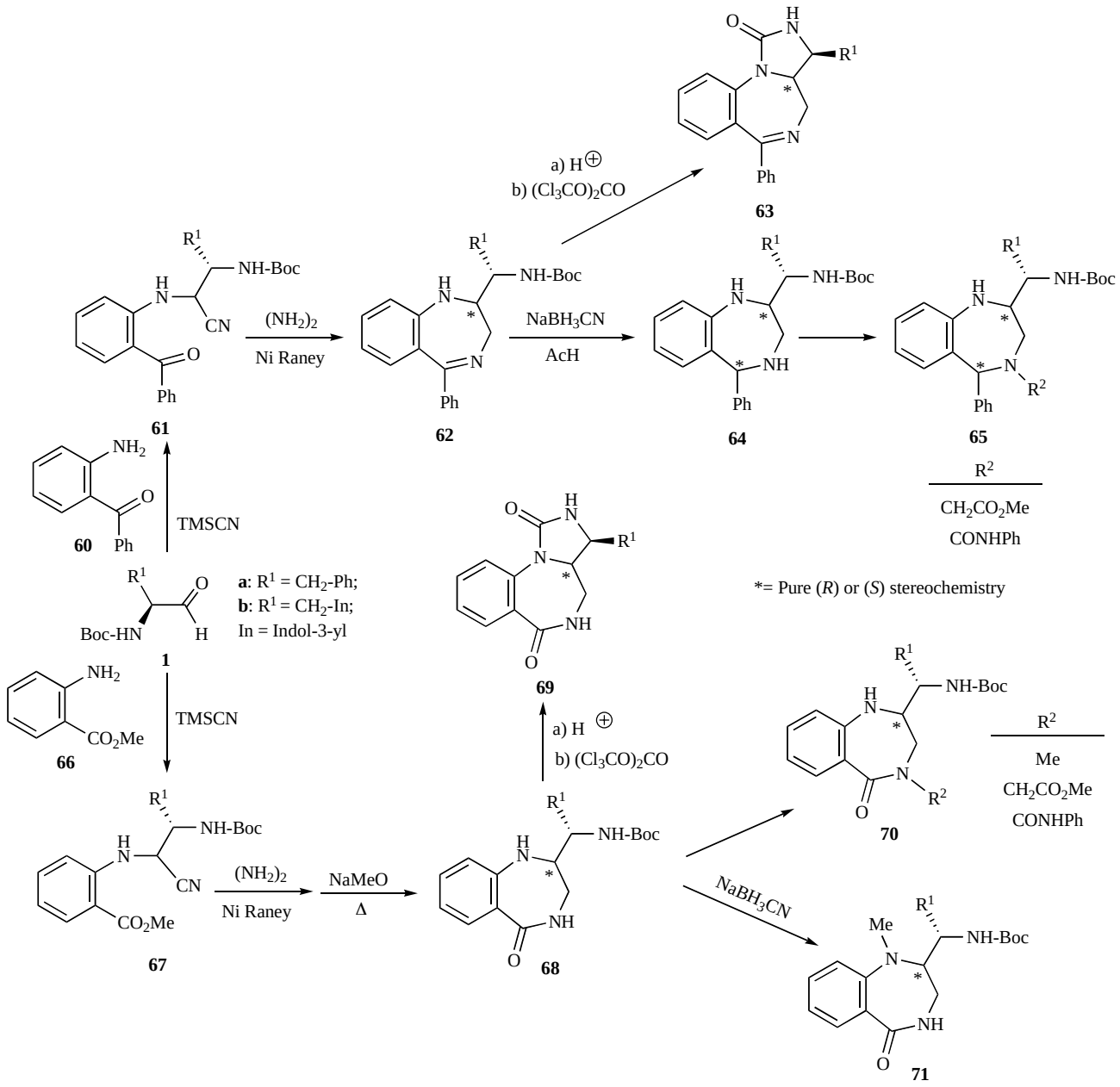
	R^1	R^2
a	$(CH_2)_5$	
b	$[(CH_2)_2]_2NBn$	
c	Me	Me
d	Me	H
e	$PhCH_2$	H
f	^{t}Bu	H
g	Ph	H
h	(*S*)-CH(Me)NHCbz	H

Scheme 11. Synthesis of indole derivatives.

also gave only the 2-*exo*-diastereoisomers **49**; however, in hindered amino nitriles the major reaction product was the 2-*endo*-isomer.

Hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles **49** have shown an interesting reactivity [46]. Thus, under standard conditions of *N*-methylation (MeI/Cs_2CO_3) the amidine group suffers alkylative hydrolysis to give the lactam derivative **50**, while the amidine methylation (**51**) requires treatment with MeI in the absence of base (Scheme **11**). Attempts to hydrolize the amidine **49** to the lactam **50**, by treatment with 1 N HCl, led to the 2,6-dioxopiperazine derivatives **52**. The *N*-Ac and *N*-Cbz protected derivatives of general formula **53** were obtained by treatment with acetyl chloride and benzyl chloroformate, respectively, in the presence of propylene oxide. However, diverse attempts of introducing the Boc-protection into the amidine group were unsuccessful.

Taking into account previous related studies on the building of the hexahydropyrrolo[2,3-*b*]indole ring system by cyclative addition of electrophiles to tryptophan derivatives [49], the introduction of substituents found in indole alkaloids (Me, OH, prenyl, substituted allyl) into the 10b position of the hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indole has been explored applying two alternative strategies: a) acid-induced cyclative addition of electrophiles to α-amino nitriles **48**, or b) replacement of subtituents previously introduced at position 10b. Thus, as shown in Scheme **11**, treatment of a solution of α-amino nitrile **48a** in 10% TFA/CH_2Cl_2 with *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) led to the respective 10b-halo-



Scheme 12. Synthesis of 1*H*-1,4-benzodiazepine derivatives.

hexahydropyrrolo[1',2',3':1,9a,9]imidazo[1,2-*a*]indoles **54a** and **55a** with complete 2-*exo*-stereoselectivity [50]. The 10b-allyl derivative **56a** was obtained from the 10b-bromo derivative **55a** by reaction with allyltributyltin in the presence of the free radical initiator AIBN in refluxing xylene. A similar 10b-bromo to 10b-prenyl replacement, by reaction with prenyltributylstannane to obtain **57a** did not take place. Nevertheless, this 10b-prenyl derivative was obtained from the α-amino nitrile **48a** by reaction with prenyl bromide in the presence of $Mg(NO_3)_2 \cdot 6H_2O$ in AcOH/AcONa buffer [50]. The TFA-mediated cyclative oxidation of α-amino nitrile **48a** with either H_2O_2 or dimethyldioxirane (DMDO) yielded the 10b-hydroxy-pyrroloimidazoindole **58a** [51]. Finally, the synthesis of the 10b-methyl derivative **59a** was approached by an strategy similar to that reported by the Nakagawa's group for the synthesis of the hexahydropyrrolo[2,3-*b*]indole-containing alkaloid physostigmine [52]. This strategy involved the introduction of a methylthiomethyl group by reaction with the Corey-Kim reagent [53], followed by successive TFA-mediated cyclation, alkylative hydrolysis of the amidine moiety as above commented, and catalytic hydrogenolysis of the 10b-methylthiomethyl to the 10b-methyl [51].

3.3. 1,4-BENZODIAZEPINE DERIVATIVES

Thinking that the use of a β-amino ester or β-amino ketone as the amino component in the Strecker synthesis, followed by appropriate cyano-carbonyl manipulation, could give access to diazepine derivatives, we devised the synthesis of the 1,4-benzodiapine derivatives shown in Scheme **12** as potential CCK receptors ligands [54,55]. Due to the low nucleophilic character of aromatic amines, the synthesis of α-amino nitriles derived from 2-amino-benzophenone (**60**) or

methyl antranilate (**66**) required longer reaction time and higher temperature, either in the formation of the imine (24 h, 65ºC) or in the addition of TMSCN (room temperature), than the synthesis of Ψ[CH(CN)NH] pseudopeptides commented in section 2.1. Unlike these pseudopeptides, *N*-aryl-α-amino nitriles **61** and **67** were resistant to catalytic hydrogenation, but both were effectively reduced by Raney nickel hydrogen transfer from hydrazine hydrate in refluxing MeOH. Under these conditions, the reduction of the benzophenone-derived amino nitrile **61** in situ led to the 5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepines **62**. The transformation of these benzodiazepines into their respective imidazo[3,4-*a*][1,4]benzodiazepine derivatives **63** allowed the assignment of absolute configuration at position 2. An additional point of diversity was introduced by $NaBH_3CN$-mediated reduction, followed by *N*-alkylation or *N*–acylation to give the 5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines **65** [54]. A parallel synthetic scheme was followed for the synthesis of 5-oxo-1,2,3,4-tetrahydro-1*H*-1,4-benzodiazepines **68**-**70**, except for the initial step of lactamization of the amino nitrile **67**, which, after the cyano reduction, required treatment with NaMeO in refluxing MeOH [55]. Furthermore, a methyl group was regioselectively introduced into position 1 of **71**, by $NaBH_3CN$/AcOH-mediated reductive alkylation of **68** with 35-40% methanolic solution of formaldehyde. The 1,4-benzodiazepine **68b** showed selective significant affinity at CCK_1 receptors (IC_{50} = 156.5±33.2 nM).

CONCLUSIONS

Although the reactivity of amino acid-derived α-amino nitriles has not been completely explored, this review illustrates the high potential of this reactive template on the generation of molecular diversity by simple hydration and reduction reactions, with particular incidence in the field of peptidomimetics and privileged scaffolds.

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