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Novel Solution- and Solid-Phase Strategies for the Parallel and Combinatorial Synthesis of Small-Molecular-Weight Compound Libraries

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Abstract. In this account dedicated to '100 years *Roche*' in CHIMIA, we present some of our strategies towards the synthesis of interesting novel amino-acid-derived building blocks; multigeneration synthesis of thiazole libraries in solution; a novel solid-phase approach towards highly substituted pyrimidines using a novel safety-catch linker principle and a multidirectional cleavage procedure; a versatile solid-phase synthesis of quinazolones taking advantage of the *Staudinger* phosphorylimine chemistry combined with a novel cyclization and cleavage strategy, and finally a novel solid-phase diketopiperazine synthesis combining the *Ugi* four-component reaction with a final ring-forming cleavage step.

1. Introduction

Due to the enormous progress made in genomic sciences and molecular biology, there is an ever-growing number of new biological targets with pharmacological interest emerging. To meet an increasing demand of novel and diverse small-molecular-weight compounds necessary for screening, combinatorial and parallel (or high-throughput) chemistry are currently in the focus of many pharmaceutical companies and academic institutions, as they are potentially interesting tools for the creation of novel and diverse compound collections [1–3]. Combinatorial and parallel chemistry combine organic chemistry in solution and on solid supports, robotics, data handling of large compound libraries with automated analytical and spectroscopic methods. In addition, there is a need of a large array of novel interesting and versatile building blocks.

Among the several possible approaches to carry out successfully combinatorial organic synthesis (COS), we primarily focused our attention on convergent assembly strategies performed in solution or preferentially on solid supports, which should give, more likely than linear strategies, access to small-molecular-weight 'drug-like' molecules. We selected primarily those reactions, assembly strategies, and reactive building blocks, which would allow for a high synthetic flexibility both in terms of arriving at a large number of pharmacologically relevant core structures and of easy subsequent derivatization. In addition, we focused on multicomponent [4] and multigeneration reaction approaches [4], which in combination with multidirectional resin cleavage [4][5] should allow for a rapid synthesis of compound collections in array format.

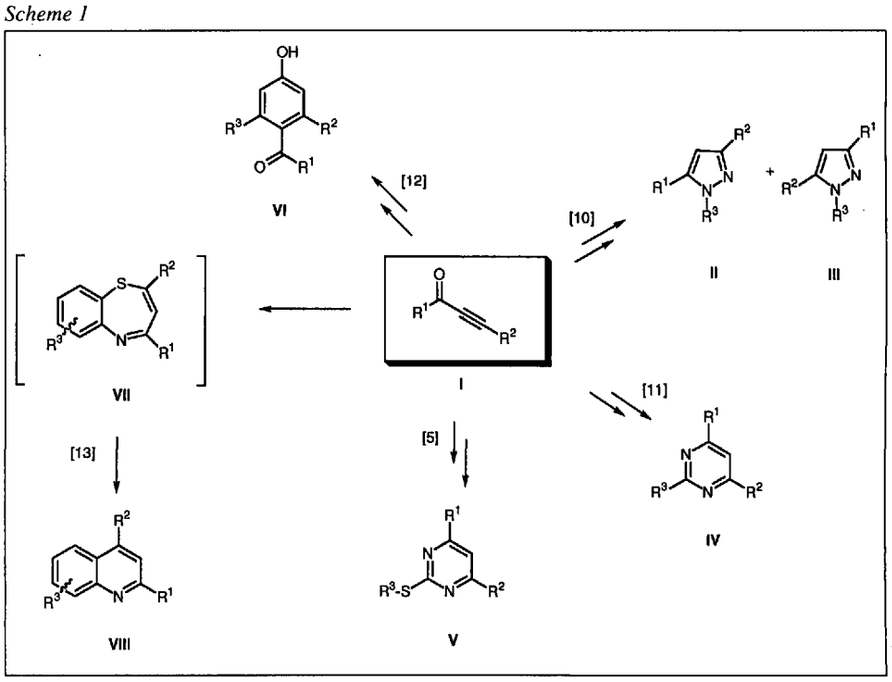
In the following chapters, we present some of our strategies towards the synthesis of interesting novel amino-acid-derived building blocks; multigeneration synthesis of thiazole libraries in solution; a novel solid-phase approach towards highly substituted pyrimidines using a novel safety-catch [6] linker principle and a multidirectional cleavage procedure; a versatile solid-phase synthesis of quinazolones taking advantage of the *Staudinger* phosphorylimine chemistry [7] combined with a novel cyclization and cleavage strategy, and finally a novel solid-phase diketopiperazine synthesis combining the *Ugi* four-component reaction [8] with a ring-forming cleavage step.

2. Building Blocks

2.1. *General Building Blocks*

As mentioned in the introduction, we focused mainly on convergent, multigeneration and multicomponent reactions to efficiently assemble diverse single com-

Scheme 1



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pound collections in array format. In order to have access to a large variety of pharmacologically relevant core structures, we selected multifunctional building blocks which could be employed in many different reactions. Among the bidentate nucleophiles, we selected in this account the use of thioureas and thiouronium salts, as their bis-acceptor counterparts the α-bromomethyl ketones and α-alkynyl ketones and as typical members of acceptor-donor species isocyanates, isothiocyanates, *ortho*-azidobenzoic acid derivatives, and amino acids. In addition, we used nucleophiles such as amines, alcohols, thiols, and carboxylates and acceptors like aldehydes and activated carboxylic acids.

As shown in *Scheme 1*, acetylenic ketones of type **I** [9] have been used to generate a diverse range of interesting core structures such as pyrazoles **II** and **III**, pyrimidines **IV** and **V** [11], highly substituted benzophenones **VI** *via* carbonyl-alkyne exchange (CAE) reaction [12], and quinolines **VIII** [13] *via* intermediate formation of **VII** followed by subsequent sulfur extrusion reaction.

2.2. *Novel Enantiomerically Pure Heterobiaryl-Alanine Analogues by Asymmetric Catalytic Hydrogenation*

For the synthesis of optically pure building blocks, we mainly focused on the synthesis of suitably protected non-coded amino acids as they can be synthesized reliably with a large variety of side chains. Catalytic asymmetric hydrogenation of α-amino-α,β-didehydroamino acids using chiral cationic diphosphinerhodium catalysts [14] has recently emerged as one of the most powerful tool for the synthesis of enantiomerically pure α-amino acids [15].

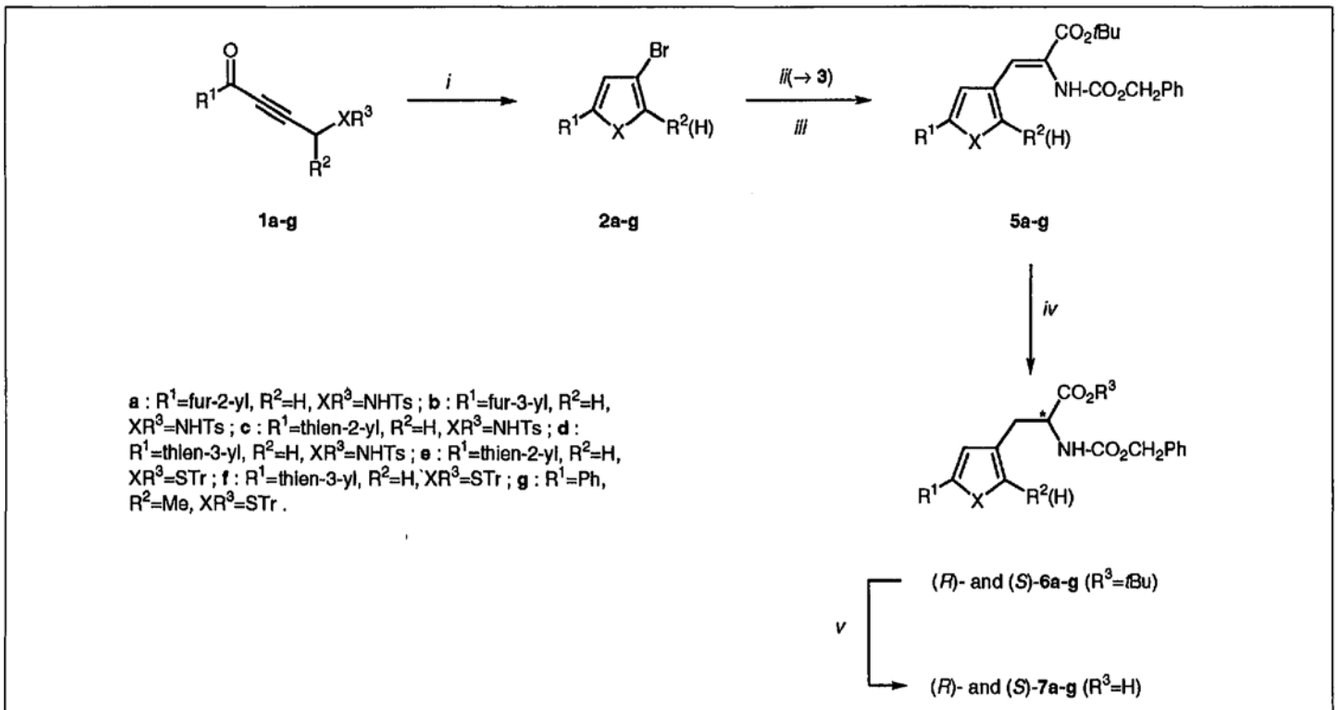
We describe in *Scheme 2* a fast entry into a series of novel five-membered heterobiaryl analogues of type **7** as substitutes for phenylalanine. The synthesis starts from acetylenic ketones **1a–g** which were cyclized with HBr/AcOH in CH_2Cl_2 [16] to the corresponding 3-bromopyrroles [17] and 3-bromothiophenes [18] **2a–g** in high yields. Subsequent lithiation with *tert*-butyllithium and treatment with formylpiperidine led to the corresponding aldehydes of type **3**. These were condensed with the phosphorylglycine derivative **4** [15] according to *U. Schmidt* [19] with *N,N,N',N'*-tetramethylguanidine (TMG) and charcoal to give the *N*-benzyloxycarbonyl-protected α-amino-α,β-didehydro *tert*-butyl esters (*Z*)-**5a–g** in good overall yields (*Table 1*). Subsequent asymmetric hydrogenation of the *tert*-butyl esters (*Z*)-**5** using [Rh(cod)Me-DuPhos]BF_4 (cod = cyclooctadiene, Me-DuPhos = 1,2-Bis(2,5-dimethylphospholano)benzene) [14] in MeOH at 40° under 60 bar H_2 pressure gave the *N*-protected amino-acid *tert*-butyl esters **6a–g** in high yields and excellent enantiomeric purities (97.5–99.3% ee, *Table 2*), which could be converted without any racemization to the final products

Table 1. *Preparation of* tert-*Butyl (Z)-α-amino-α,β-didehydro Esters* **5**

3-Bromo-heterobiaryl derivative	Product	(*E*/*Z*)-Ratio	Yield [%]
2a	5a	5/95 ((Z)>99)[a])	57
2b	5b	5/95 ((Z)>99)[a])	52
2c	5c	5/95 ((Z)>99)[a])	46
2d	5d	5/95 ((Z)>99)[a])	53
2e	5e	5/95 ((Z)>99)[a])	60
2f	5f	5/95 ((Z)>99)[a])	52
2g	5g	5/95 ((Z)>99)[a])	62

[a]) After isomerization of (*E*/*Z*)-**5**.

Scheme 2



i: HBr/AcOH (33%), CH_2Cl_2, 0°–r.t.; *ii*: *t*-BuLi, formylpiperidine, THF (→ **3**); *iii*: a) TMG, CH_2Cl_2, $(MeO)_2PO$–CH(NHZ)(CO_2t-Bu) (**4**), −30°–r.t.; b) TMG, charcoal, $CHCl_3$/MeOH (1:1); *iv*: H_2, MeOH, [Rh(cod)(all-*S*)- or (all-*R*)-Me-DuPhos]$^+BF_4^-$, 40°, 60 bar; *v*: TFA, CH_2Cl/H_2O, r.t.

7a–g. These novel amino acids constitute versatile building blocks, which can be used in many different ways for the construction of diverse compounds collections.

3. Parallel Solution Multigeneration Strategies

The successful production of multigeneration compound libraries by solution-phase chemistry in combination with the split methodology heavily depends on the choice of high-yielding reactions for each individual step, carefully chosen strategies for the chemical inactivation of highly reactive reagents and fast separation of inactivated or transformed reagents by automated separation technologies like liquid-phase extraction (LPE) or solid-phase extraction (SPE). An example of an efficient solution-phase synthesis suitable for a multigeneration compound library based on the 2-aminothiazole template is outlined in *Scheme 3*.

The synthesis is based on the *Hantsch* condensation [20] of thioureas **8** with 2-bromomethyl ketones **9** to give in high yields the 2-aminothiazoles **12**. The excess of **9** was trapped with *N*-(4-carboxyphenyl)thiourea **10** and removed by SPE. Subsequent treatment of thiazoles **12** with a series of amino-acid-derived isocyanates **13** gave the second generation of thiazoles **16** in essentially quantitative yields. Excess of **13** was trapped with 1,2-diaminoethane **14** and removed by SPE. Saponification gave the third generation of thiazole acids **17**, which could be efficiently transformed into the corresponding amides **19** by using EDCI (= 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride) and amine **18**. Again all the excesses of reagents could be either removed by LPE or SPE. This aminothiazole synthesis comprising four generations of products **12**, **16**, **17**, and **19** could be optimized in such a way that it could be fully automated and performed on a robotic system.

4. Novel Solid-Phase Multigeneration Strategies towards the Synthesis of Heterocycles

4.1. *Pyrimidines*

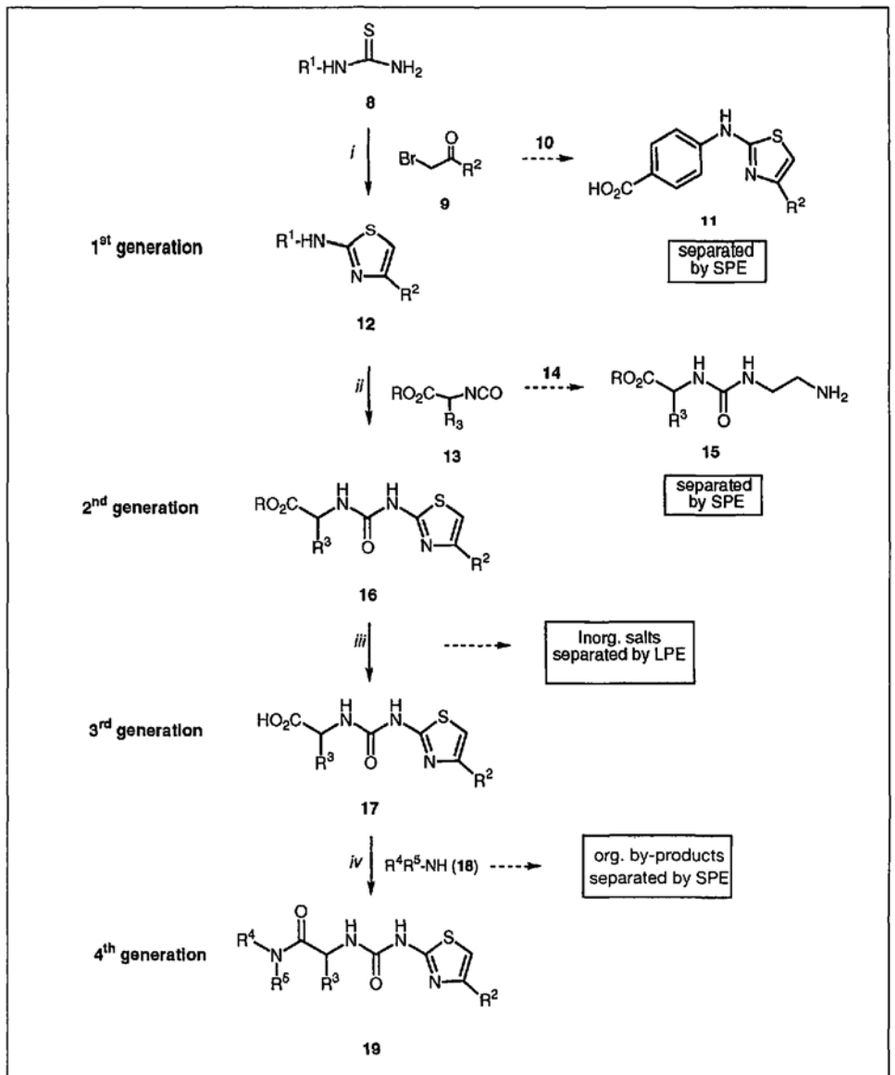
Next, we focused our attention on the solid-phase synthesis of pyrimidine derivatives due to the broad range of useful properties they display [21][22]. Our solid-phase multigeneration strategy towards novel 2,4,6-trisubstituted pyrimidines efficiently combines a new cyclocondensa-

Table 2. *Asymmetric Hydrogenation of* tert-*Butyl Esters* **5**

	Ligand	[5]/[C][a])	Product	Yield [%]	ee [%]	Abs. Config.
(*Z*)-**5a**	(all-*S*)-Me-DuPhos	100	**6a**	97.5	99.3	(*S*)
	(all-*R*)-Me-DuPhos	100		98.5	99.6	(*R*)
(*Z*)-**5b**	(all-*S*)-Me-DuPhos	100	**6b**	92	97.5	(*S*)
	(all-*R*)-Me-DuPhos	100		98.5	98.8	(*R*)
(*Z*)-**5c**	(all-*S*)-Me-DuPhos	100	**6c**	95	99.1	(*S*)
	(all-*R*)-Me-DuPhos	100		93	98.3	(*R*)
(*Z*)-**5d**	(all-*S*)-Me-DuPhos	100	**6d**	91	98.3	(*S*)
	(all-*R*)-Me-DuPhos	100		95.5	98.8	(*R*)
(*Z*)-**5e**	(all-*S*)-Me-DuPhos	100	**6e**	98.5	98.2	(*S*)
	(all-*R*)-Me-DuPhos	100		98.5	98.1	(*R*)
(*Z*)-**5f**	(all-*S*)-Me-DuPhos	100	**6f**	97.5	98.6	(*S*)
	(all-*R*)-Me-DuPhos	100		98	98.4	(*R*)
(*Z*)-**5g**	(all-*S*)-Me-DuPhos	100	**6g**	98.5	97.8	(*S*)
	(all-*R*)-Me-DuPhos	100		98.5	97.9	(*R*)

[a]) [5]/[C] = Molar ratio; C = catalyst.

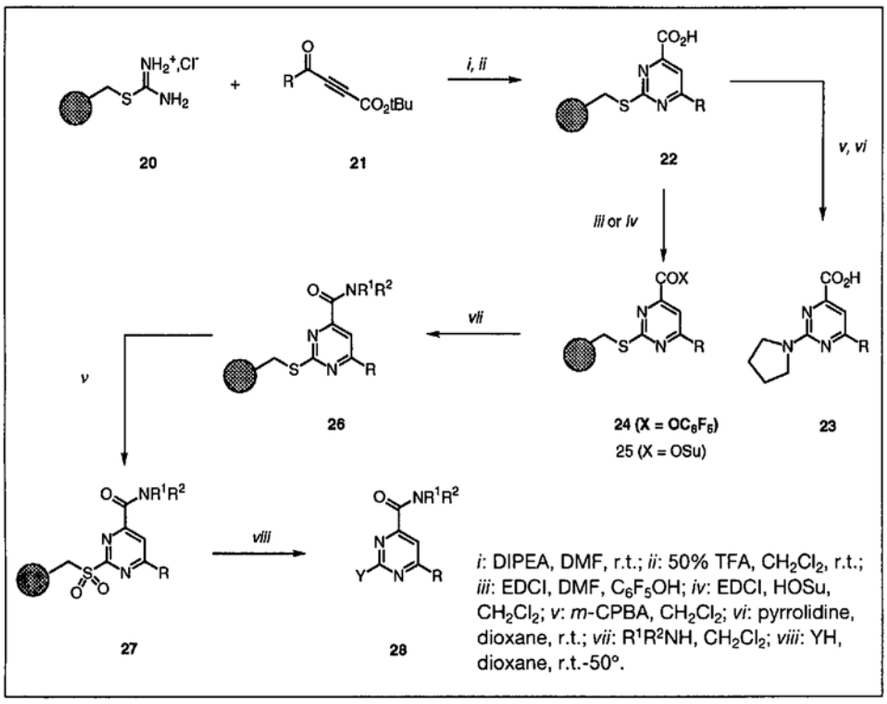
Scheme 3



i: EtOH, dioxane, 60°, followed by **10**; *ii*: toluene, 70°, followed by **14**; *iii*: 1M LiOH, EtOH, dioxane H_2O, r.t.; *iv*: EDCI, cat. DMAP, CH_2Cl_2, r.t.

10: *N*-(4-carboxyphenyl)thiourea; **14**: 1,2-diaminoethane.

Scheme 4



Scheme 5

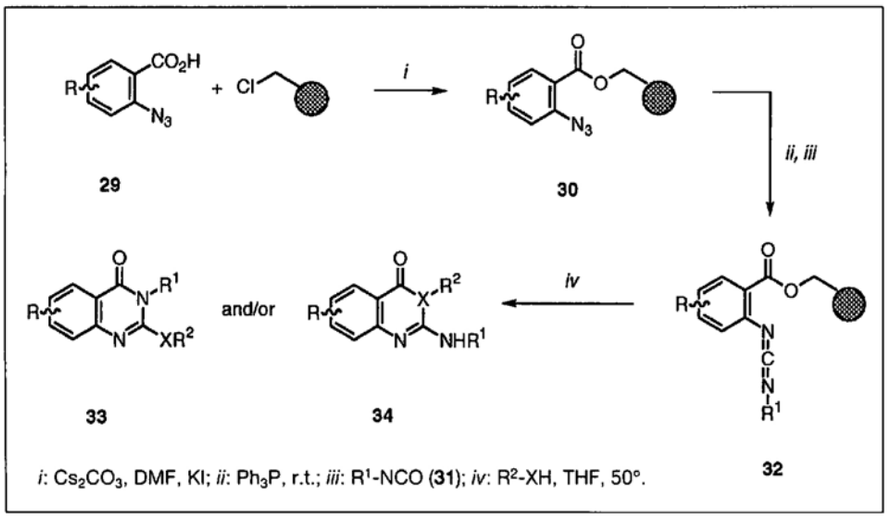
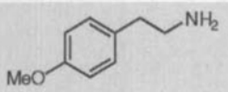


Table 3. *Preparation of* **28**

R	R^1R^2NH	Y	Product	Yield [%]	Purity [%]
Ph			**28a**	65	97
Ph			**28b**	46	95
Ph	$C_6H_{13}NH_2$		**28c**	62	98
Ph	cyclohexylamine	MeNH	**28d**	24	96

tion reaction of polymer-bound isothiourea **20** with highly functionalized acetylenic ketones of type **21** and the known nucleophilic displacement of the 2-sulfonyl group of pyrimidines [10][11] by various nucleophiles as the key cleavage step. Thus, when resin-bound thiouronium salt **20**, easily prepared by reaction of thiourea with commercially available high-loaded *Merrifield* resin (3.4 mmol/g) (purchased at *Senn Chemicals AG*) [5], was allowed to react with acetylenic ketones **21** in DMF in the presence of DIPEA (= *N*,*N*,-diisopropylethylamine) and followed by the cleavage of the *tert*-butyl ester group with TFA, the corresponding polymer-bound pyrimidine-4-carboxylic acids **22** were formed in high yields (determined by cleavage of the 2-alkylsulfonyl moiety from the resin with pyrrolidine, with pyrrolidine to form **23**, see *Scheme 4*). Conversion of the carboxylic acid **22** into the corresponding pentafluorophenyl esters **24** or hydroxysuccinimide derivatives **25** under standard conditions proceeded smoothly. Partitioning of the resin beads and parallel treatment with different primary and secondary amines gave the polymer-bound amides **26**. This reaction sequence could easily be followed by ATFT-IR (attenuated total reflexion method). As a key step in our sequence, we oxidized compounds **26** with *m*-CPBA in CH_2Cl_2 to form the intermediate 2-alkylsulfones **27**, which were again partitioned and subjected to a multidirectional cleavage [5] with different nucleophiles leading to the final products **28** in high yields and purities (*Table 3*).

The oxidation and cleavage step constitute a novel type of safety-catch linker strategy [6], which should be applicable to many other heterocyclic systems.

4.2. *Quinazolinones*

Another example for a succesful application of solid-phase chemistry constitutes the highly versatile synthesis of quinazolinones, which display interesting pharmacological properties. The developed strategy combines the aza-*Wittig* reaction with a multidirectional cleavage process (*Scheme 5*). Thus, alkylative esterification of substituted *o*-azidobenzoic acids **29** with high-loaded *Merrifield* resin (3.4 mmol/g) gave the polymer-bound *o*-azido esters **30**, which treated with a 1M PPh_3 solution in THF at room temperature gave the corresponding iminophosphoranes attached to the resin. Partitioning of the beads and reaction with different isocyanates **31** at room temperature smoothly formed the corresponding carbodiimides **32**. Additional partitioning and treatment with different nucleophiles (*e.g.* amines,

thiols) lead *via* intramolecular cyclization to quinazolines of type **33** (and/or **34** when primary non-sterically hindered amines were used) in good yields and high levels of purity, with simultaneous cleavage from the resin (*Table 4*). This strategy allows for a rapid synthesis of libraries of highly functionalized quinazolinones on the solid support [25].

5. Solid-Phase Multicomponent Reactions

The diketopiperazine scaffold has proven to be a versatile template in combinatorial chemistry due to four ring atoms which can be centers for the generation of molecular diversity [26]. Thus, we have developed a novel solid-phase synthesis that allows the generation of diketopiperazine libraries with four centers of diversity. The reported synthesis is based on the *Ugi* reaction of a polymer-bound amino acid followed by cyclization-assisted cleavage to give **38** as outlined in *Scheme 6*. Thus, *Rink* amine resin was charged with a protected amino acid to afford **35** after deprotection. Next, the resin-bound amino acid was divided up in separate reaction vessels and the *Ugi* reaction was performed treating each vessel individually with an aldehyde, an isocyanide, and an Fmoc-protected amino acid [4]. The reactions were terminated after 20 h by washing the resins **36** followed by deprotection to yield the resin-bound dipeptides **37**. In the final step, treatment of **37** in dioxane and warming up the reaction mixture resulted in cyclization-assisted cleavage and concomitant release of very pure diketopiperazines **38** [27]. Not surprisingly, the yields for this reaction sequence were usually moderate (*Table 5*), which is due to fact that the *Ugi* reaction was stopped arbitrarily and that there was the possibility of an alternate cyclization for **37** leading to resin-bound **39**.

6. Conclusion

In summary, we have shown novel solution- and solid-phase strategies towards small-molecular-weight non-peptidic compounds libraries. These strategies in combination with highly versatile building blocks like non-coded amino acids and acetylenic ketones will help speeding up the lead discovery process.

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Table 4. *Preparation of Quionazolines*

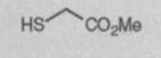
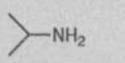
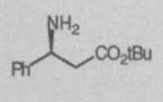
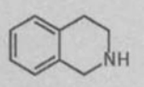
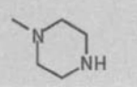
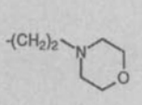
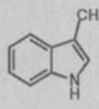
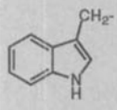
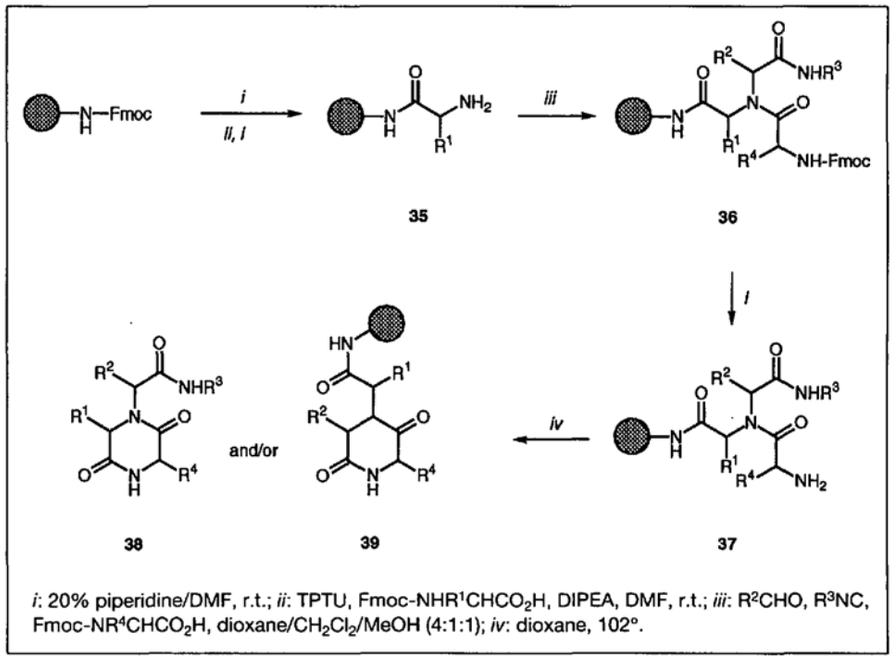
R	R^1	R^2XH	Product	Yield [%]	Purity [%]
H	C_3H_7		**33a**	42	98
H	C_3H_7		**33b**	56	100
H	C_3H_7		**33c**	59	98
H	C_3H_7		**33d**	71	97
H	C_3H_7		**33e**	85	98

Table 5. *Preparation of Diketopiperazines*

R^1	R^2	R^3	R^4	Product	Yield [%]	Purity [%]
H	i-C_3H_7	cyclohexane	$PhCH_2$	**38a**	24	97
Me	i-C_3H_7	cyclohexane	$MeS(CH_2)_2$	**38b**	41	90
H	i-C_3H_7			**38c**	24	91
H	$Ph(CH_2)_2$	cyclohexane	$iBuOCH_2$	**38d**	71	91
	Bu	cyclohexane	iBu	**38e**	9	91
Me	i-C_3H_7	i-C_3H_7	MeO_2CCH_2	**38f**	32	83

Scheme 6



i: 20% piperidine/DMF, r.t.; *ii*: TPTU, Fmoc-NHR^1CHCO_2H, DIPEA, DMF, r.t.; *iii*: R^2CHO, R^3NC, Fmoc-NR^4CHCO_2H, dioxane/CH_2Cl_2/MeOH (4:1:1); *iv*: dioxane, 102°.

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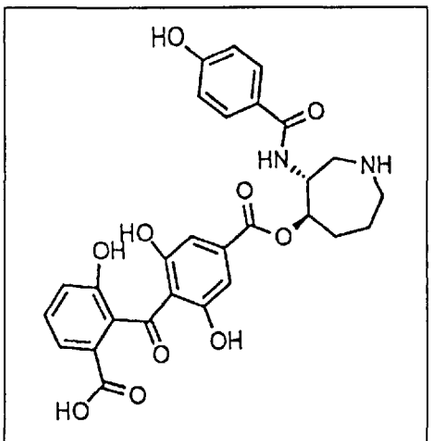
Total Synthesis of Enantiomerically Pure (–)-Balanol

Pierre Barbier* and **Josef Stadlwieser**

Abstract. The total synthesis of enantiomerically pure (–)-Balanol (**1**), using tri-*O*-acetyl-D-glucal as a chiral template for the central azepane fragment is described.

(–) Balanol (**1**, Azepinostatin), a potent inhibitor of protein kinase C enzymes, was isolated from the culture filtrates of different fungi (*Verticillium balanoides*, *Fusarium merismoides*) and its structure was elucidated by spectroscopic methods and chemical degradation [1][2]. Furthermore, the potential medical use of **1** was claimed in a recent patent [3]. The structural complexity as well as its biological activity make **1** a challenging synthetic target. Recently, independent syntheses of **1** were published by different groups [4–6].

In this communication, we wish to report a new synthesis of enantiomerically pure **1**, using tri-*O*-acetyl-D-glucal (**2**) as chiral template for the central azepane fragment of **1**. The synthesis of **15**, a fully protected and properly functionalized building block for the central azepane moiety, is outlined in *Scheme 1*.



(–)-Balanol (**1**)

The elaboration of **30**, a suitably protected building block for the highly functionalized benzophenone fragment of **1**, is outlined in *Scheme 2*. It is noteworthy, that direct alkylation of **16** with benzyl bromide under different conditions failed.

An alternative synthesis of **20**, starting from 3-hydroxyphthalic acid [9], proved to be less convenient.

The total synthesis of **1** was finally completed by assembling the individual building blocks **15**, **30** and **31** [10], followed by removal of the protective groups according to *Scheme 3*.

All compounds were fully characterized by spectroscopic methods (^{1}H-NMR, IR, MS) and microanalyses.

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