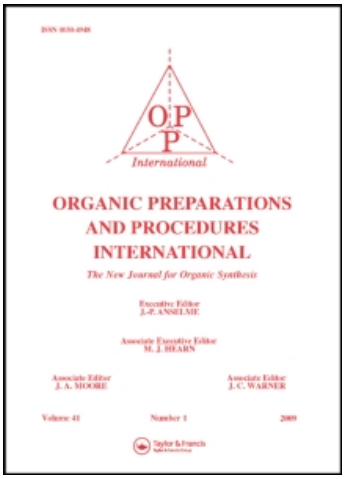

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

RECENT PROGRESS IN SOLID PHASE HETEROCYCLE SYNTHESES. A REVIEW

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To cite this Article Corbett, Jeffrey W.(1998) 'RECENT PROGRESS IN SOLID PHASE HETEROCYCLE SYNTHESES. A REVIEW', Organic Preparations and Procedures International, 30: 5, 489 — 550
To link to this Article: DOI: 10.1080/00304949809355320
URL: http://dx.doi.org/10.1080/00304949809355320

ORGANIC PREPARATIONS AND PROCEDURES INT., 30 (5), 489-550 (1998)

RECENT PROGRESS IN SOLID PHASE HETEROCYCLE SYNTHESES. A REVIEW

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INTRODUCTION

The capability of synthesizing pharmaceutically useful compounds utilizing solid phase chemistry, as exemplified in 1992 by Ellman in his benzodiazepine synthesis, has resulted in an explosion in the solid phase synthesis of other heterocyclic systems.[1-3] This review will only cover advances made in the field of solid supported heterocycle synthesis since the beginning of 1997 through March, 1998, and will not cover peptide, nucleoside and glucoside libraries. Two previous reviews have covered heterocyclic solid phase synthesis for material published prior to 1997. Complete descriptions of the individual properties of the different resins mentioned in this review are available in leading references 4-7 and in the papers cited therein illustrating the original work. Furthermore, it is not the purpose of this review to explicitly show every compound made, but rather to represent the scope and limitations of the synthetic routes delineated in the respective papers. The interested reader is directed to the original manuscripts for a more detailed description of the work.

I. COMPOUNDS CONTAINING ONE HETERO ATOM

1. Lactones, Lactams, β-Lactams and β-Sultams

Le Hetet and coworkers have synthesized γ- and δ-lactones from resin formed epoxides (*Fig.* 1).[8] The epoxides were generated by treating Merrifield resin-bound alkenoic esters **1** with *m*-chloroperoxybenzoic acid (*m*-CPBA). The resulting epoxides **2** were then treated with either sodium

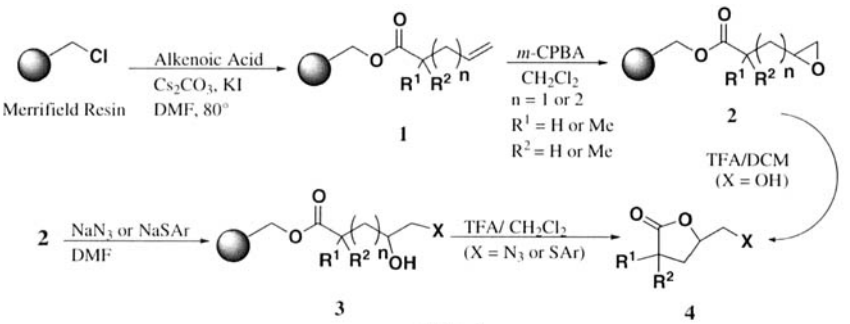


Fig. 1

azide, sodium phenylsulfide, or sodium *p*-methylphenylsulfide in dimethylformamide (DMF) to give **3**. Cleavage of secondary alcohols **3** from the resin afforded the derivatized lactones **4**. Alternately, treatment of epoxides **2** with trifluoroacetic acid (TFA) in methylene chloride delivered lactones **4** (X = OH).

Hanessian has recently reported on the preparation of a lactone on Wang resin using a novel *p*-alkoxybenzyl ether linkage.[9,10] Ethyl ester **6**, prepared by treating trichloroacetimidate functionalized Wang resin **5** with ethyl 6-hydroxyhexanoate, was alkylated with allyl iodide to deliver **7** (*Fig.* 2). Ozonolysis of **7** afforded aldehyde **8**, which was reduced with $NaBH_4$ under sonication to give resin bound lactone **9**. Treatment of **9** with 10% TFA afforded lactone **10**.

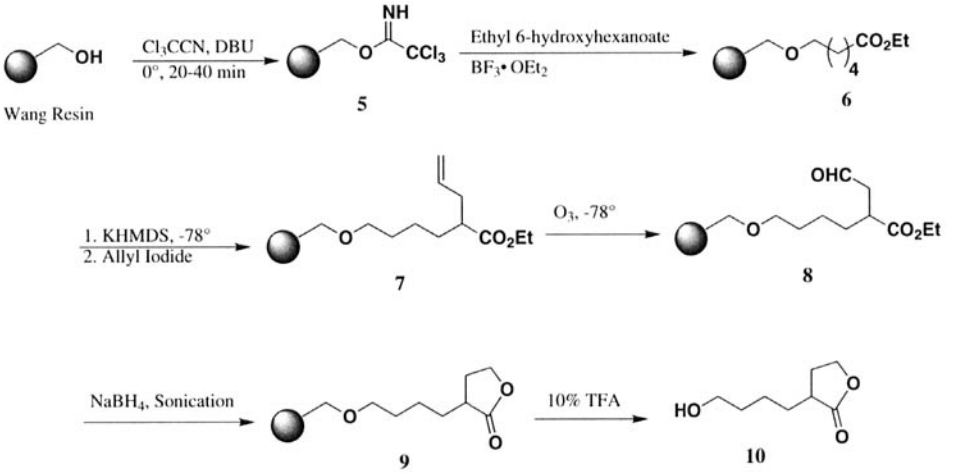
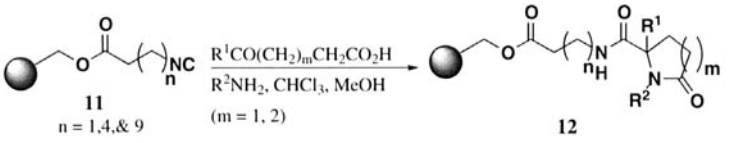


Fig. 2

Short and Mjalli have reported the preparation of 5- and 6-membered lactams from resin-bound isocyanides (*Fig.* 3).[11] Wang resin derivatized isocyanides **11** were exposed to a mixture of



Compound	m	R^1	R^2	R^3
13a	1	Me	Bn	$(CH_2)_{10}CO_2H$
13b	1	Me	*n*-$C_{11}H_{23}$	$(CH_2)_5CO_2H$
13c	1	Me	$CH_2C{\equiv}CH$	$(CH_2)_5CO_2H$
13d	1	CO_2H	Ph	$(CH_2)_{10}CO_2H$
13e	1	Me	Bn	$(CH_2)_2CO_2H$
13f	2	Me	Bn	$(CH_2)_2CO_2H$
13g	2	Me	Bn	$(CH_2)_{10}CO_2H$
13h	1	Me	*n*-Bu	$(CH_2)_{10}CO_2H$

10% TFA | CH_2Cl_2

13a-h

Fig. 3

ω-ketoacids and primary amines in 3:1 $CHCl_3$/MeOH to afford the resin bound intermediates **12**, which upon cleavage in acid afforded lactams **13a-h** in 60-98% yield.

A solid phase synthesis of seven-member ring lactams was developed by Picopio and coworkers.[12] Mitsunobu displacement of cinnamyl alcohol resin **14** with sulfonamide **15** gave **16** (*Fig.* 4).[13] Removal of the sulfonamide was accomplished upon treatment of **16** with *n*-butylamine in methylene chloride, and acylation of the intermediate amine with (±)-*N*-Boc-allyl glycine **17** gave amide **18**. Treatment of **18** with Grubb's ruthenium catalyst **19** in 1,2-dichloroethane afforded a solution of **20** in 16% yield from sulfonamide **15**.

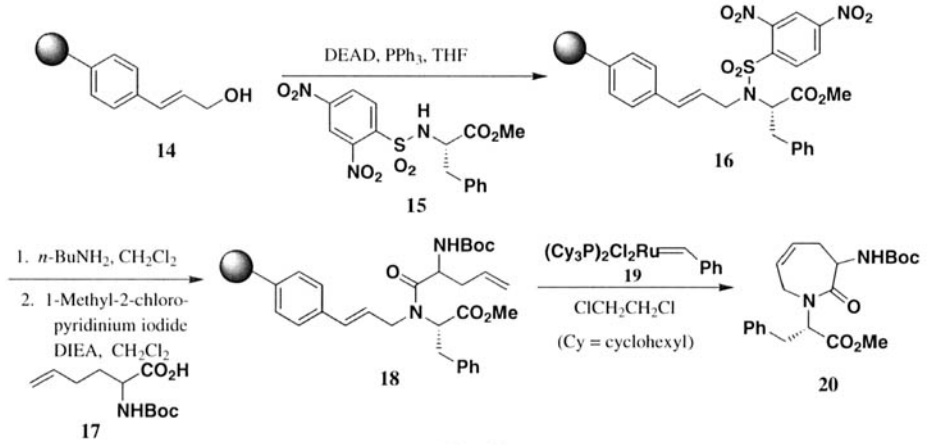


Fig. 4

Several reports have recently appeared describing the synthesis of β-lactams. In work performed by Ruhland and coworkers, *N*-Fmoc-*L*-alanine was attached to either Sasrin, Wang or ArgoGel-MB-OH resins to give **21** (*Fig.* 5).[14] Removal of the *N*-(9-fluorenylmethoxycarbonyl) (Fmoc) protecting group, formation of an intermediate imine upon treatment with a *p*-substituted aryl aldehyde and exposure of the resulting imine to phenoxy ketene afforded the [2+2] cycloaddition adducts **22**. The products then underwent Suzuki or Heck reactions to afford variously substituted β-lactams **23**.

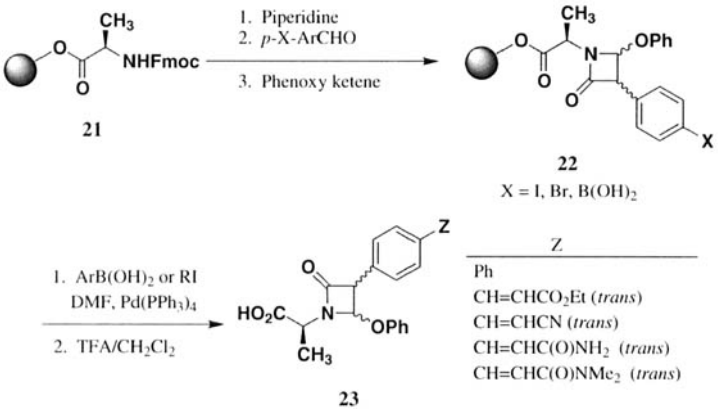
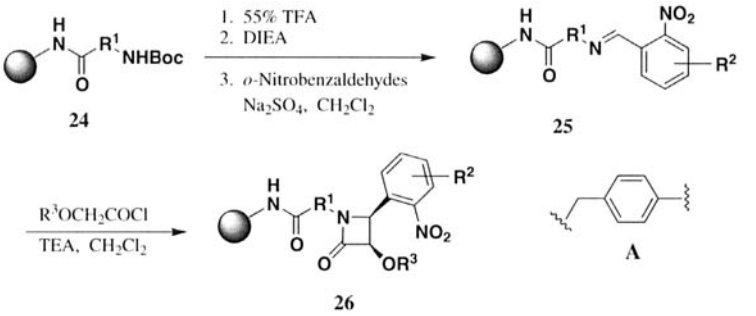


Fig. 5

β-Lactams were also synthesized by Pei and coworkers as intermediates in the synthesis of quinolines (*Fig.* 6).[15] The synthesis utilized 4-methylbenzhydrylamine (MBHA) resin derivatized with various *N*-Boc amino acids **24**. Removal of the Boc protecting group from the resin-bound amino acid, generation of the free amine with diisopropylethylamine (DIEA), and formation of an intermediate imine with *o*-nitrobenzaldehydes gave **25**. Reaction with an *in situ* generated ketene using triethylamine (TEA) furnished a variety of *cis*-β-lactams **26** in undisclosed yield. For a definition of the variable units, see *Fig.* 6. *cis*-β-Lactams **26** were not cleaved from the resin, but were used to prepare quinolines (See *Fig.* 29).



R^1	R^2	R^3
-CH_2-	H	Phenyl
CH_3CH	H	Phenyl
See **A** above	H	Phenyl
PhCH	6,7-Methylenedioxy	4'-Chlorophenyl
1,4-Disubstituted phenyl	6-Chloro	CH_3CO
1,4-Disubstituted phenyl	6-Chloro	CH_3
1,4-Disubstituted phenyl	6-Chloro	Phenyl
1,4-Disubstituted phenyl	6-Chloro	H
1,4-Disubstituted phenyl	6-Chloro	4'-Chlorophenyl
CH_3CH	H	4'-Chlorophenyl
$(CH_3)_2CHCH$	8-Methoxy	Phenyl
$(CH_3)_2CHCH$	8-Methoxy	CH_3CO
$(CH_3)_2CHCH$	8-Methoxy	4'-Chlorophenyl
See **A** above	6,7-Dimethoxy	Phenyl
See **A** above	6,7-Dimethoxy	4'-Chlorophenyl
HO_2CCH_2CH	6-Hydroxy	4'-Chlorophenyl

Fig. 6

Another β-lactam synthesis was recently reported wherein a soluble-resin-bound imine was treated with enolates and with ketenes.[16] Carboxylic acid **27** was formed upon heating succinic anhydride and the soluble polymer polyethylene glycol monomethylether of molecular weight 5000 (MeOPEG) in methylene chloride containing a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) at reflux. Treating **27** with *N*-(4-hydroxyphenyl)-*O*-benzylcarbamate, dicyclohexylcarbodiimide (DCC) and *N,N*-dimethylaminopyridine (DMAP) gave **28**, which was hydrogenated with 10% palladium on carbon to deliver aniline **29**. The imines **30** were formed upon heating aniline **29** with

aldehydes **31** at 90°. Benzaldehyde gave high yields of the desired imine **30**, while 2-thiophenecarboxaldehyde and *trans*-cinnamaldehyde gave the desired imine **30** and approximately 30% starting material. Reacting imine **30** with the titanium enolate of 2-pyridylthioesters **32a,b** in methylene chloride at room temperature and cleavage gave β-lactams **33 a,b**. Imine **30** also underwent a cycloaddition in methylene chloride at room temperature with the ketenes generated from acid chlorides **34a,b** to give β-lactams **35a,b**. The β-lactams were removed from the resin either by acid catalyzed methanolysis or under basic conditions with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methylene chloride.

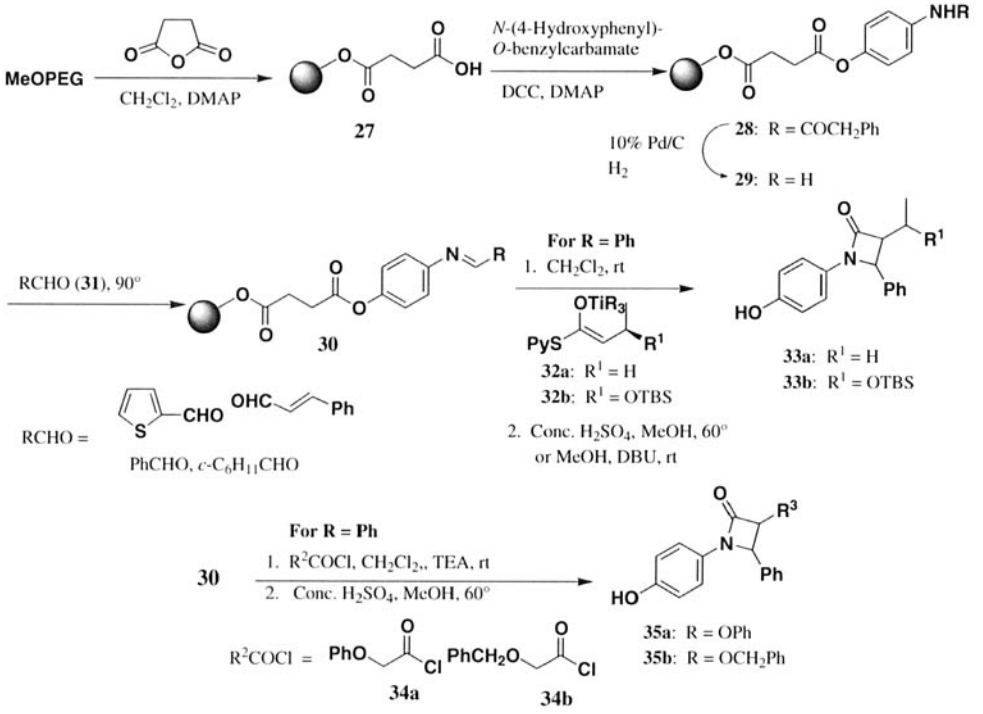


Fig. 7

A [2+2] cycloaddition between a resin-bound imine and an *in situ* formed sulfene has been used by Gordeev to synthesize β-sultams.[17] An *N*-Fmoc protected amino acid was attached to either Sasrin or TentaGel™ S-NH_2, equipped with the photocleavable α-methyl-6-nitroveratryl alcohol linker, resins **36**. Removal of the Fmoc group and condensation with benzaldehyde derivatives generated the intermediate imine **37** (*Fig.* 8).[18,19] Imine **37** was suspended in pyridine and THF at -78° and methyl (chlorosulfonyl)acetate **38** was then added. The mixture was stirred at -78° for 3 hours, and then at room temperature for 24 hours before being worked up to afford a 1:1 mixture of *trans*-diastereomeric β-sultams **39** (only one diastereomer is shown in *Fig.* 8). Sasrin-supported β-sultams were cleaved with 2% TFA to afford β-sultams **40** in 58-90% yield. TentaGel™-supported β-sultams were cleaved with 365 nm light in isopropanol (IPA) to give β-sultams **40** in 19-39% yield. The Fmoc ester of (chlorosulfonyl)acetate **41** was also used in a [2+2] cycloaddition reaction with imines **37** to

give the Fmoc-protected β-sultam **42**. Removal of the Fmoc ester with DBU gave the carboxylic acid **43** which, upon cleavage from Sasrin resin with mild acid, furnished **44**. In order to introduce more diversity into the system, the pentafluoroester derivative of carboxylic acid **43** (R^1 = Me, R^2 = Ph) was coupled to phenethylamine in 1-methyl-2-pyrrolidinone (NMP) to afford amide **45** in 37% yield.

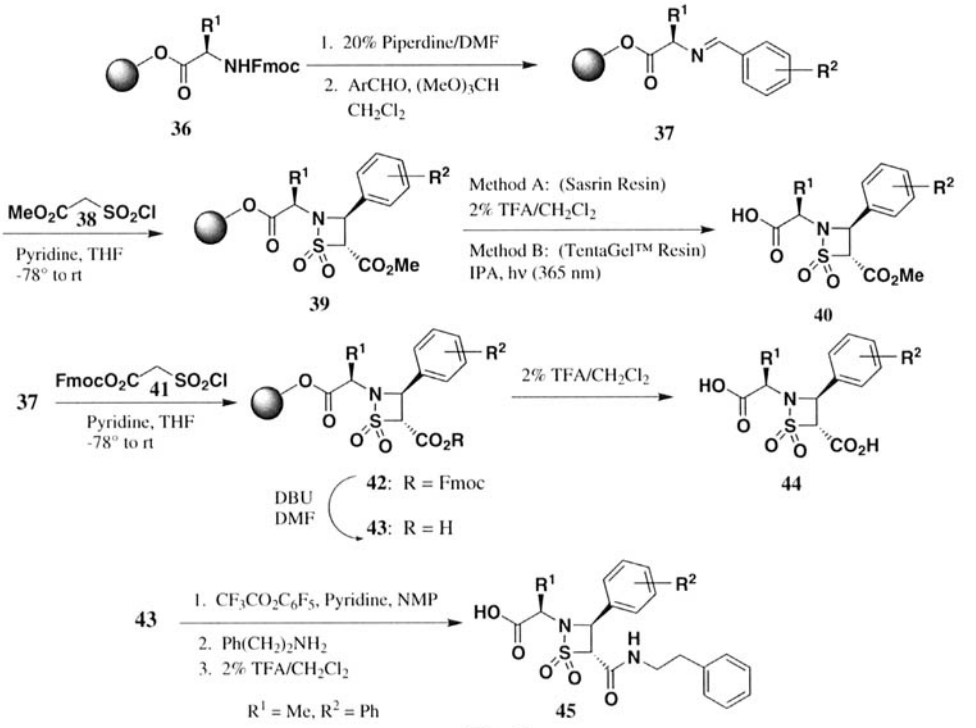


Fig. 8

2. Dihydropyrans and Pipecolinic Acids

The ring metathesis reaction used by Piscopio and coworkers in the synthesis of a lactam has also been used to synthesize dihydropyrans and two pipecolinate derivatives (see *Fig.* 4).[12] In the synthesis of a dihydropyran, olefin **48** was obtained by a Wittig reaction between polystyrene methylenetriphenylphosphonium resin **46** and aldehyde **47** (*Fig.* 9).[13] Resin **48** was suspended in methylene chloride and treated with 5 mol% of Grubb's catalyst **19** to afford, after filtration and concentration, the desired dihydropyran **49** in 43% overall yield (73% yield for the last step).

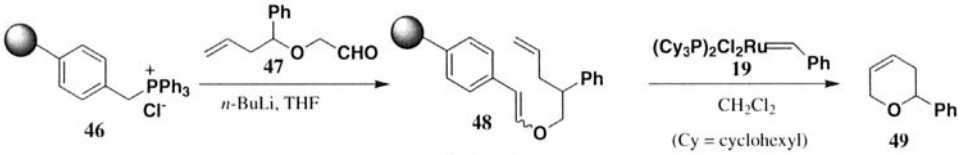


Fig. 9

The ring metathesis reaction used to synthesize pipecolinate derivatives is shown in *Fig.* 10.[12] Cinnamyl alcohol resin **50** underwent a Mitsunobu coupling with sulfonamide **51** to afford

intermediate **52**. When **52** was treated with 5 mol% of catalyst **19**, sulfonamide **53** was obtained upon filtration and concentration in 62% yield. In a sequence of reactions similar to those described in *Fig.* 4, **52** was sequentially treated with *n*-butylamine to remove the dinitrosulfonate group, coupled to *p*-methoxyphenylacetic acid and then cyclized with 5 mol% **19** in methylene chloride to give **54** in 22% yield from sulfonamide resin **52**.

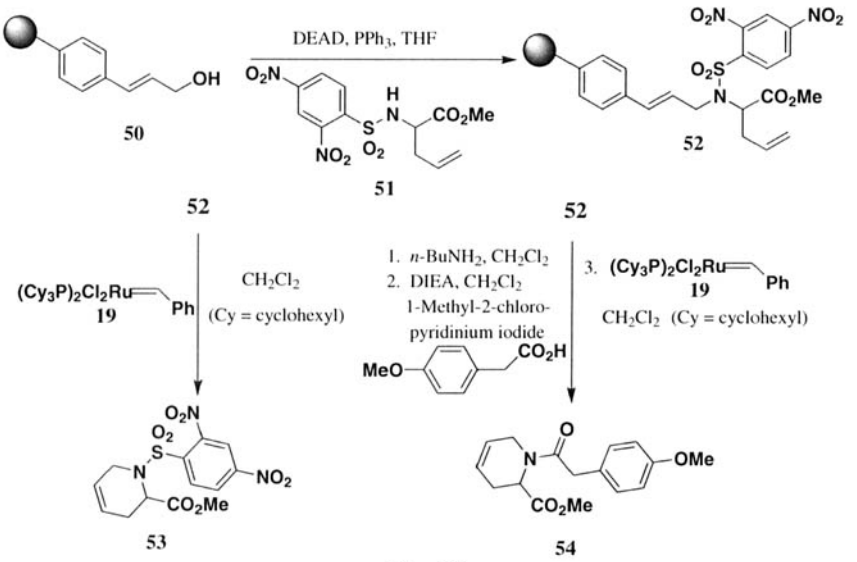


Fig. 10

3. Furans, Benzofurans, Tetrahydrofurans and Thiophenes

Routledge and coworkers reported on the use of a radical reaction on solid phase to construct furan rings.[20] These workers tested the ability of an aminobromomethyl ether, prepared from **55**, on either carboxylated polystyrene divinyl benzene copolymer (**56a**) or TentaGel™ resin (**56b**) to undergo 5-*exo* cyclization (*Fig.* 11).[21] The nitro group of **56a,b** was reduced with stannous chloride to give **57a,b**. Utilization of the divinyl benzene derivatized polymer **57a** required greater than one equivalent of AIBN in order for the cyclization to progress to completion to afford **58a**. However, use of the TentaGel™ derivatized polymer **57b** required only 6 mol% AIBN for the reaction to go to completion to cleanly afford **58b** as the only product. To further investigate the usefulness of solid phase radical cyclizations, intramolecular cyclizations of radicals onto alkynes was also explored. Carboxylated TentaGel™ resin was derivatized with 2-butyne-1,4-diol to afford the resin bound alcohol **59** which was converted into resin-bound iodoacetylenic ethers **60a-d** upon treatment with alkenes and *N*-iodosuccinimide, in the presence of a catalytic amount of acid, in 38-50% yield.[22] Cyclization of **60a-d** with 5 mol% AIBN and tributyltin hydride followed by cleavage afforded a mixture of the (*E*)- and (*Z*)-alkylidene tetrahydrofurans **61a-d** in 63-80% isolated yields based upon the loading of the iodoacetylenic ethers **60**.

Gowravaram and Gallop developed an approach to synthesizing furans which utilized the rhodium catalyzed formation of an isomünchone which undergoes [2+3] cycloaddition with alkynes.[23]

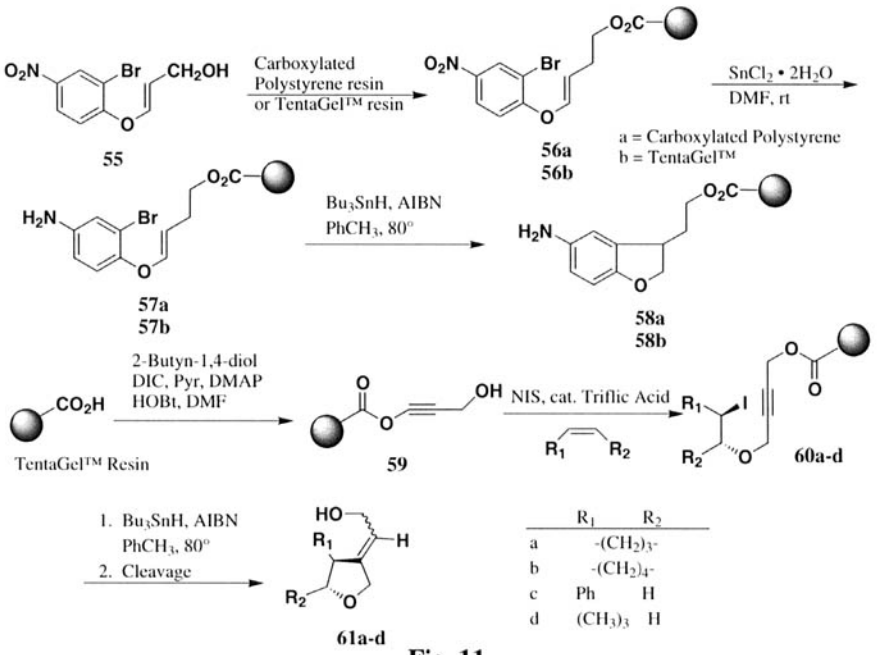


Fig. 11

This approach is known as a tracerless synthesis since there is no vestigial remnant of the polymeric linkage site remaining on the final product. Acylation of TentaGel™-NH_2 resin with carboxylic acids afforded amides **62** (*Fig.* 12). Treatment of **62** with ethyl malonyl chloride afforded imides **63**, which were then converted to the diazoimides **64** upon exposure to tosyl azide and triethylamine. Reacting the diazoimides **64** with $Rh_2(OAc)_4$ and various activated alkynes gave, upon isolation of the filtrate, solutions of the desired furans **65**.[24] Purification by flash chromatography to remove unreacted acetylenes afforded the pure furans **65** in 50-70% yield.

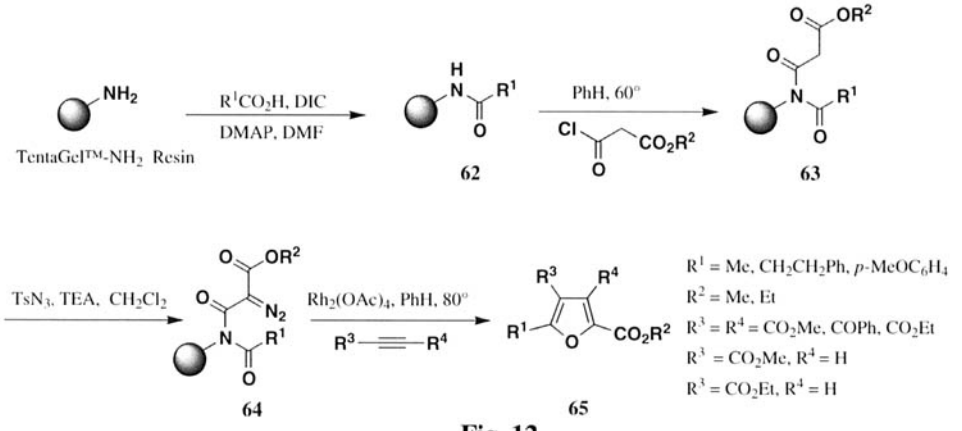


Fig. 12

Kurth and coworkers have extensively studied the solid phase synthesis of furans and this work was recently reviewed.[25] Solid phase furan syntheses were also reviewed by Nefzi and will not

be expounded upon further in this review.[4] Two new reports of benzofuran syntheses have appeared, however. The first of these was work performed by Zhang and Maryanoff in which a Heck coupling was used to construct the desired benzofuran nucleus (*Fig.* 13).[26] The same chemistry was applied to

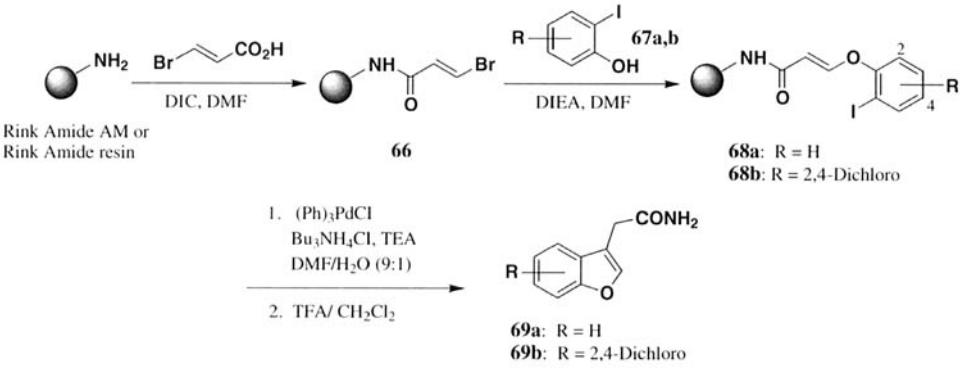


Fig. 13

the synthesis of indoles, as will be discussed in *Fig.* 18. Rink amide or Rink amide AM resin was acylated with γ-bromocrotonic acid, using 1,3-diisopropylcarbodiimide (DIC) as the coupling agent, giving **66** which was subsequently treated with *o*-iodophenols **67a,b** to deliver aryliodides **68a,b**. Treating **68a,b** with (triphenylphosphine)palladium (II) chloride, tetrabutylammonium chloride and triethylamine effected the desired ring closure to generate resin-bound benzofuran which was cleaved with TFA to afford benzofurans **69a,b**, in 83 and 81% yields, respectively.

The synthetic approach of Zhang and Maryanoff allows for the synthesis of various aryl substitutions on the benzofuran nucleus. However, it does not demonstrate the derivatization of the 2-position of benzofurans. A route described by Fancelli and coworkers would allow for the synthesis of 2-substituted benzofurans.[27] The synthesis involves coupling an alkyne to a resin-bound *o*-iodophenoxybenzoic acid ester **71**, obtained by attaching benzoic acid derivative **70** to TentaGel™ resin using diethyl azodicarboxylate (DEAD). Cyclization of phenol **71** onto an alkyne in 1,1,3,3-tetramethylguanidine (TMG) followed by saponification from the resin generates the benzofurans **72** in 67-90% yield (*Fig.* 14).

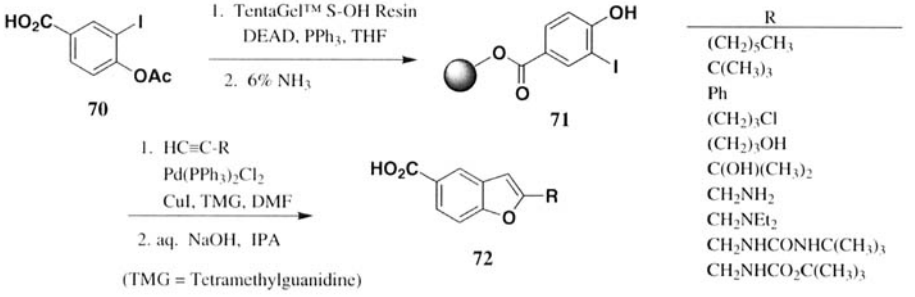
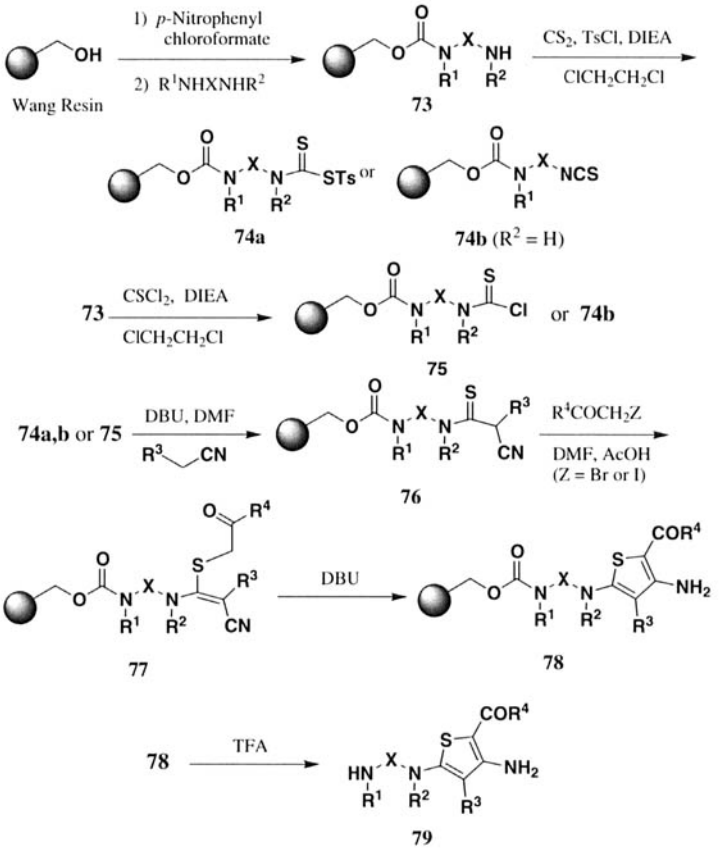


Fig. 14

Stephensen and Zaragoza have used thiocarbamoyl derivatives and isothiocyanates in the synthesis of tetrasubstituted thiophenes (*Fig.* 15).[28] Wang resin was initially derivatized with various diamines to generate amines **73**,[24,29] which were then treated with carbon disulfide and tosyl chloride in the presence of base to afford either the *S*-tosyl thiocarbamoyl derivative **74a** or isothiocyanate **74b**



$R^1NH\text{-}X\text{-}NHR^2$	R^3	R^4
H2NCH2CH2NH2	Cyano	Phenyl
$H_2NCH_2C(CH_3)_2CH_2NH_2$	Cyano	Phenyl
$H_2NCH_2CH_2CH_2CH_2NH_2$	Cyano	Phenyl
Piperazine	Cyano	Phenyl
$H_2NCH_2CH_2NH_2$	4-Chlorophenylsulfonyl	Phenyl
$H_2NCH_2C(CH_3)_2CH_2NH_2$	4-Chlorophenylsulfonyl	Phenyl
$H_2NCH_2CH_2CH_2CH_2NH_2$	4-Chlorophenylsulfonyl	Phenyl
$H_2NCH_2C(CH_3)_2CH_2NH_2$	Methanesulfonyl	4-Biphenyl
$H_2NCH_2C(CH_3)_2CH_2NH_2$	Benzoyl	Phenyl

Fig. 15

(when R^2 = H). Similarly, treatment of resin **73** with thiophosgene and base gave either **75** or **74b**. Exposure of resins **74a,b** or **75** to activated acetonitriles and DBU generated thioamides **76**. Alkylation of the thioamides **76** was effected under mildly acidic conditions with α-haloketones to afford **77**,

which, upon treatment with amine bases, afforded resin-bound thiophenes **78**. Thiophenes **78** were cleaved from the resin upon treatment with TFA to furnish thiophenes **79** in 53-85% purity. Some limitations associated with this synthesis are: (1) No thiophene was isolated when aliphatic haloketones or haloacetic esters were used in the alkylation of **76**. (2) Using amino acids, instead of diamines, resulted in obtaining products with much lower purity.

4. Pyrrolidine

Pearson and Clark have synthesized pyrrolidines by a [4+2] cycloaddition between 2-aza-allyl anions and alkenes (*Fig.* 16).[30] To a dihydropyran derivatized 2% crosslinked polystyrene resin **80** was attached either *p*-hydroxybenzaldehyde or 1,n-diols using pyridinium *p*-toluenesulfonic acid (PPTS), which were subsequently oxidized with 2-iodoxybenzoic acid (IBX) in DMSO/THF, to

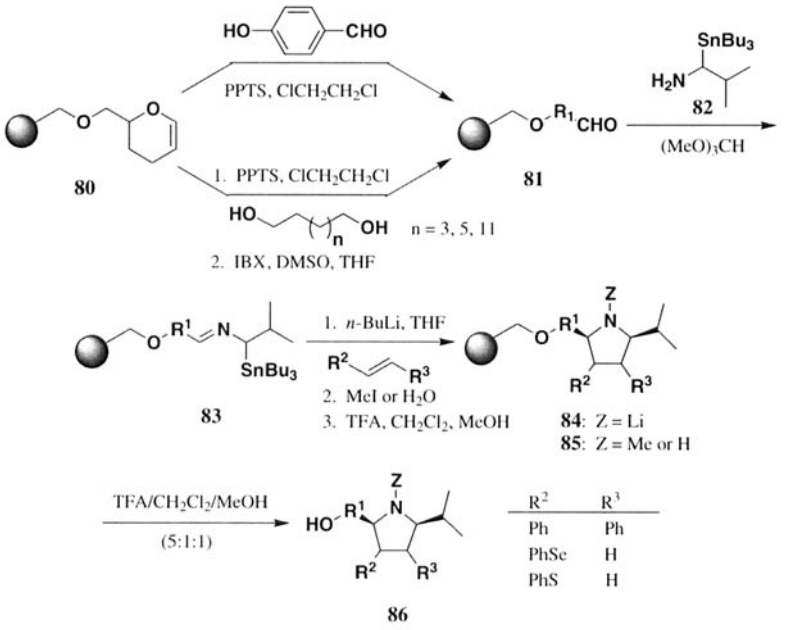


Fig. 16

afford aldehydes **81**.[31,32] It was found that the yields of aldehydes **81** using the 2-iodoxybenzoic acid oxidation system were routinely greater than from Swern and pyridine/sulfur trioxide oxidations. Imines **83** were formed by condensing aldehydes **81** with α-aminostannane **82** in the presence of trimethylorthoformate. A mixture of imines **83** and alkenes were treated with *n*-BuLi at -42° to afford the *N*-lithiopyrrolidines **84** *via* an intermediate aza-allyl anion. The *N*-lithiopyrrolidines **84** were quenched with various electrophiles to afford the *cis*-2,5-substituted pyrrolidines **85**, except for one case which resulted in a mixture of *cis-/trans*-2,5-substituted pyrrolidines. Cleavage of pyrrolidines **85** from the resin was achieved upon treatment with acid to deliver pyrrolidines **86** in 32-50% yield. The general usefulness of this reaction remains unclear since only a single α-aminostannane was utilized and only highly activated olefins were used in this synthesis of pyrrolidines.

An encoded library of mercaptoacyl pyrrolidines was prepared by workers at Affymax, and screened for activity in an angiotensin-converting enzyme assay.[33] The chemistry used to synthesize the pyrrrolidines was published in 1996,[34] and was not modified for the present publication.[33] Therefore, the synthesis mercaptoacyl pyrrolidines will not be reviewed here and the interested reader is directed to the original paper.

5. Indoles, Oxindoles and Spiroindolines

Fagnola and coworkers have shown that resin-bound iodoanilines can be coupled with alkynes using a palladium catalyst to synthesize 5-carboxy-2-substituted indoles (*Fig.* 17).[35,36] 3-Iodo-4-acetamidobenzoic acid (**87**) was coupled to TentaGel™ resin to give ester **88**. Coupling various alkynes to **88** was achieved in tetramethylguanidine using a palladium catalyst to form the intermediate adduct **89**, which spontaneously cyclized to afford the desired resin-bound 2-substituted indole **90**. Cleaveage of **90** was effected with mild base to generate **91** in 48-95% yield.

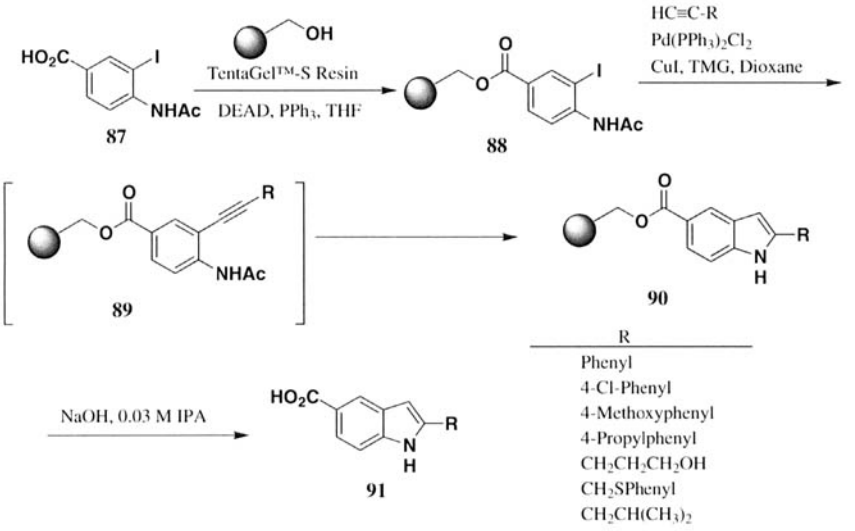


Fig. 17

Maryanoff and coworkers have reported the construction of trisubstituted indoles using a Heck-type cyclization, as was reported in *Fig.* 13 for the construction of benzofurans.[37] As in the work of Fagnola, Maryanoff's synthesis commences with an *N*-Fmoc-*o*-iodoaniline derivative **92a**, which was attached to Rink Amide resin using DCC and 1-hydroxybenzotriazole (HOBt) to give **93** (*Fig.* 18). It was also found that aniline **92b** could also be attached to Rink Amide resin without protection of the aniline to afford aniline **94**. After removal of the Fmoc group from **93** with piperidine, the aniline **94** was acylated with either acetyl chloride or isobutyryl chloride to give **95**. Amides **95** were then treated with palladium acetate and a variety of disubstituted alkynes to afford trisubstituted indoles **96a-n**. It was found that tetrabutylammonium chloride was more effective than lithium chloride during the annulation of silylalkynes onto **95**. Cleavage was effected with TFA to give indoles **97a-n** in 38-100% yield. It was found that when unsymmetrical alkynes were used in the

Heck-type coupling/cyclization reaction, the more sterically demanding group usually occupied the 2-position. When a trimethylsilyl-substituted alkyne was used, the acidic conditions used in cleavage from the resin resulted in protonolysis of the indole to afford the 2-unsubstituted indole. The synthesis was used to prepare 17 different indoles.

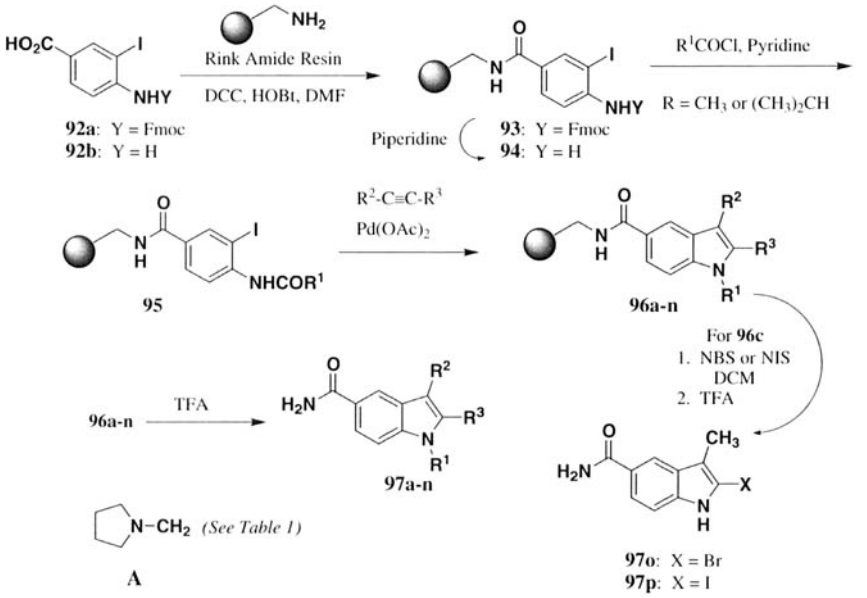


Fig. 18

The subunits listed under R^3 in Table 1 which are marked with an asterisk afforded, after cleavage from the resin, the desilylated material, and not the trimethylsilyl derivatives. It was possible to treat **96c** with either *N*-bromosuccinimide or *N*-iodosuccinimide in methylene chloride and isolate, after cleavage from the resin with TFA, the 2-halo-3-methylindole derivatives **97o,p** in 88 and 91% yield, respectively (*Fig.* 18).

Collini and Ellingboe have also reported the solid phase synthesis of trisubstituted indoles, based upon a solution phase synthesis of 2,3-disubstituted indoles utilizing two palladium coupling reactions, from an *o*-iodoanilinobenzoic acid (*Fig.* 19).[38,39] The synthesis is notable in that it allows for the regiospecific incorporation of different groups into the 2- and 3-positions of the indole nucleus. This was achieved by coupling *o*-iodoanilinobenzoic acid **98**, prepared in four steps from 4-amino-3-nitrobenzoic acid, to chloromethyl Wang resin **99** to give **100**. Heck-type coupling of terminal alkynes to **100** followed by trifluoroacetylation of the aniline gave intermediates **101**. Trifluoroacetylation of aniline **100** prior to coupling to the terminal alkyne produced only the 2-substituted indole **102**, where R^2 was H. Cyclization of **101** to the indole **102** occurred upon treatment with palladium tetrakistriphenylphosphine and a vinyl triflate. Finally, alkylation of the indole N-H was achieved with alkyl halides using sodium hydride in DMF to produce **103**. The isolated and purified yields of 22 trisubstituted indoles **104** ranged from 33-81%.

TABLE 1. Indoles Prepared by Method in *Fig. 18*

Compound	R^1	R^2	R^3
97a	H	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$
97b	H	CH_3	*t*-Bu
97c	H	CH_3	$Si(CH_3)_3$ *
97d	H	CH_3	C_6H_5
97e	H	C_6H_5	$Si(CH_3)_3$ *
97f	H	$CO_2CH_2CH_3$	C_6H_5
97g	H	$HOCH_2CH_2$	$Si(CH_3)_3$ *
97h	H	$ClCH_2CH_2$	$Si(CH_3)_3$ *
97i	H	*m*-$CH_3OC_6H_4CH_2CH_2$	$Si(CH_3)_3$ *
97j	H	**A** (See *Fig.* 18)	**A** (See *Fig.* 18)
97k	CH_3CO	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$
97l	CH_3CO	CH_3	$Si(CH_3)_3$ *
97m	CH_3CHCO	CH_3	*t*-Bu
97n	CH_3CHCO	CH_3	$Si(CH_3)_3$ *

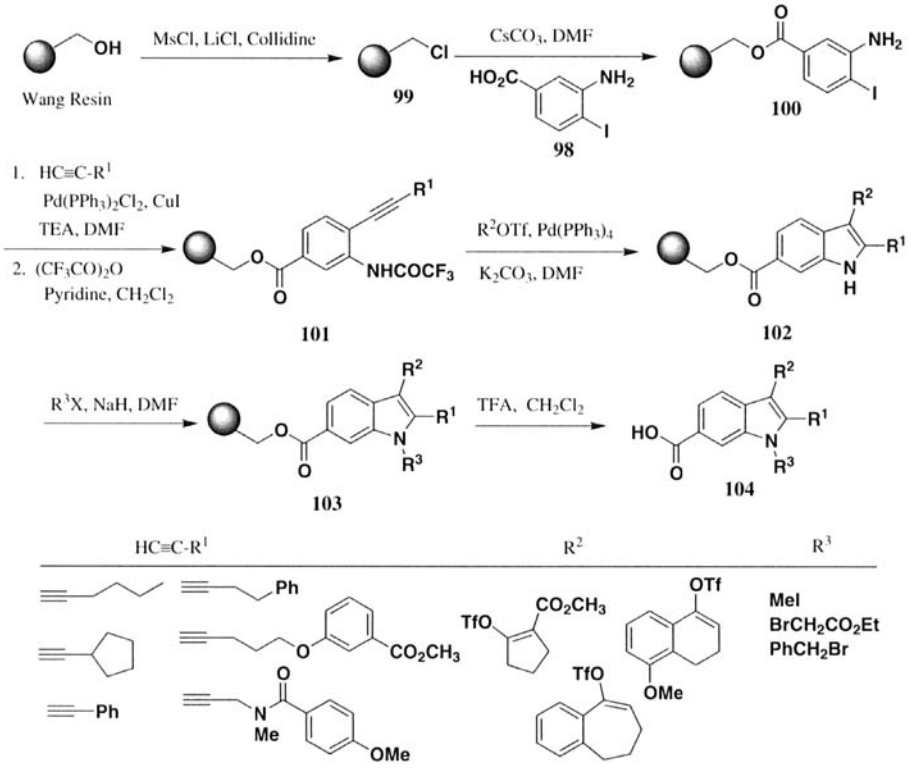


Fig. 19

A Heck cyclization has also been used by Arumugam and coworkers to synthesize oxindoles from a resin-bound *o*-iodoaniline derivative.[40] Alkylation of 3-iodo-4-nitrophenol **105** with ethyl bromoacetate followed by saponification gave carboxylic acid **106** in 95% yield (*Fig.* 20). Rink amide resin was acylated with **106** under standard peptide coupling conditions, followed by stannous chloride mediated reduction of nitro compound **107** to afford *o*-iodoaniline **108**. The anilino nitrogen was reductively alkylated with three different aldehydes using sodium triacetoxyborohydride under sonication to give the secondary anilines **109a-c**. Acylation of **109a-c** with three crotonyl chlorides delivered amides **110**, which were treated with palladium acetate triphenylphosphine and silver carbonate in DMF to afford various ratios of the (*E*)- and (*Z*)-3-alkyl(or aryl)idene-2-oxindoles **111**. Acidic cleavage from the resin gave the desired oxindoles **112** in satisfactory yields only when crotonyl chloride or cinnamoyl chloride was used (65-82%), and not when acryloyl chloride was used (10-17%). In order to incorporate more diversity into the molecules, it was found that soft-nucleophiles could be added to the (*E*)- and (*Z*)-3-alkyl(or aryl)idene-2-oxindole **111** ($R^1 = CH_2CH(CH_3)_2$, R^2 = Ph). For instance, 1,4-conjugate addition of phenyl sulfide, benzyl sulfide or ethyl malonate to **111** (R^1 =

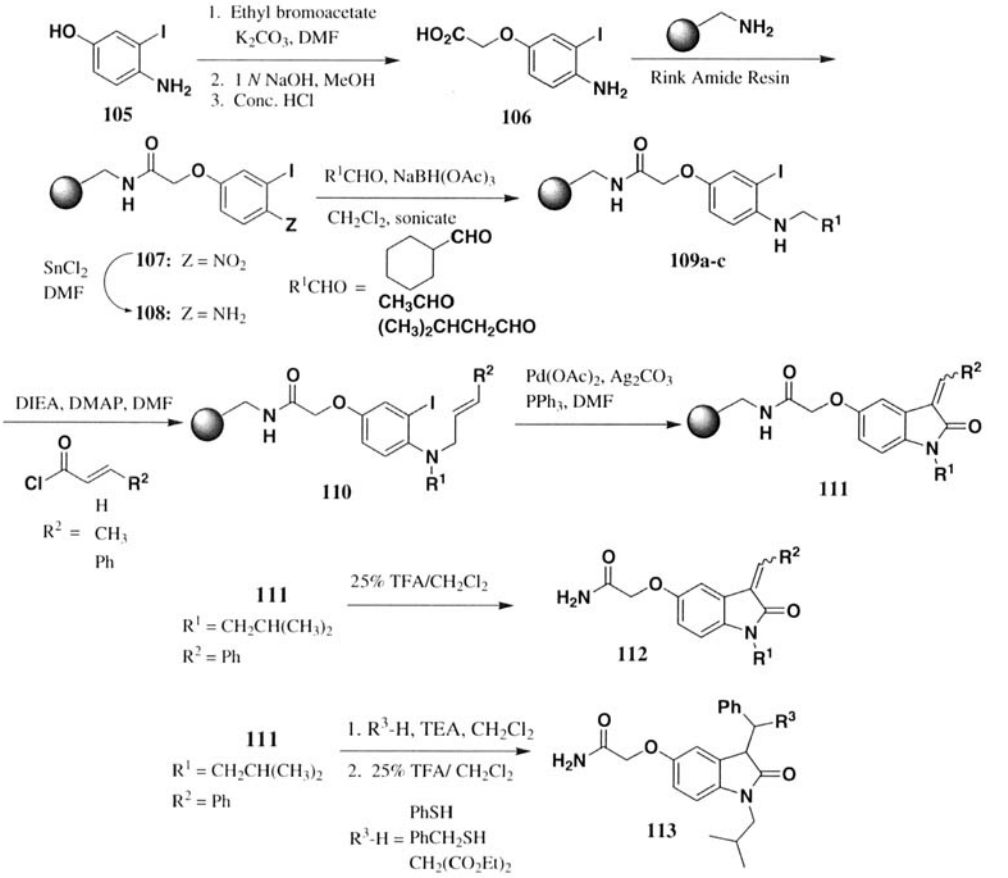


Fig. 20

$CH_2CH(CH_3)_2$, R^2 = Ph), using triethylamine in methylene chloride, followed by acidic cleavage generated diastereomeric mixtures of the trisubstituted oxindoles **113** in 80 to 90% yield.

A spiroindoline synthesis has been reported by Cheng and Chapman based upon the Fisher indole reaction.[41] Since the conditions used in the synthesis of spiroindolenes in the Fisher indole synthesis required the use of strong acids, such as TFA, an acid stable resin was needed.[42] Therefore, TentaGel™ S HMB resin was used. Dimethyl acetal protected piperidine-4-carboxaldehyde (**114**) was coupled to the resin using a succinic anhydride derived linker and the acetal group was removed to give aldehyde **115** (*Fig.* 21). Exposure of **115** to a variety of arylhydrazines in the presence of TFA gave indolenine intermediates **116**, which were reduced with sodium triacetoxyborohydride to give resin bound spiroindolines **117**. Following acylation of spiroindolines **117** with acetic anhydride, the material was cleaved from the resin using a triethylamine/methanol mixture to afford 16 different spiroindoline methyl esters **118** in 83-95% yield. It was found that solvent choice was critical in the Fisher indole reaction, and methylene chloride was the only solvent which gave desired products.

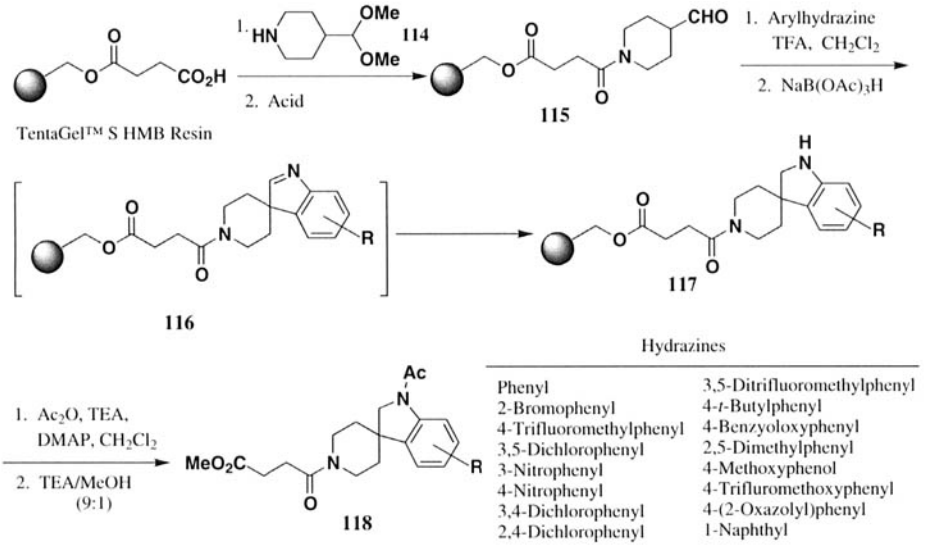


Fig. 21

6. Dihydropyridones and 1H-[2]Pyridinones

Wang and Wilson have demonstrated the use of Danishefsky's diene in a solid phase tandem Mannich-Michael reaction with resin-bound aldimines.[43] A Mitsubobu reaction between Wang resin and *p*-hydroxybenzaldehyde (**119**) gave resin-bound aldehyde **120** (*Fig.* 22). Overnight exposure of aldehyde **120** to amines, using trimethyl orthoformate as solvent, gave high yields of resin-bound imines **121**. In the case of aniline, repeated exposure of aldehyde **120** was required in order to drive the reaction to completion. Treating imine **121** with Danishefsky's diene and the Lewis acid ytterbium triflate ($Yb(OTf)_3$) in anhydrous THF gave the desired resin-bound 2,3-dihydro-4-pyridones **122**. **122** was removed from the resin with TFA to give **123** in 60-90% yield.

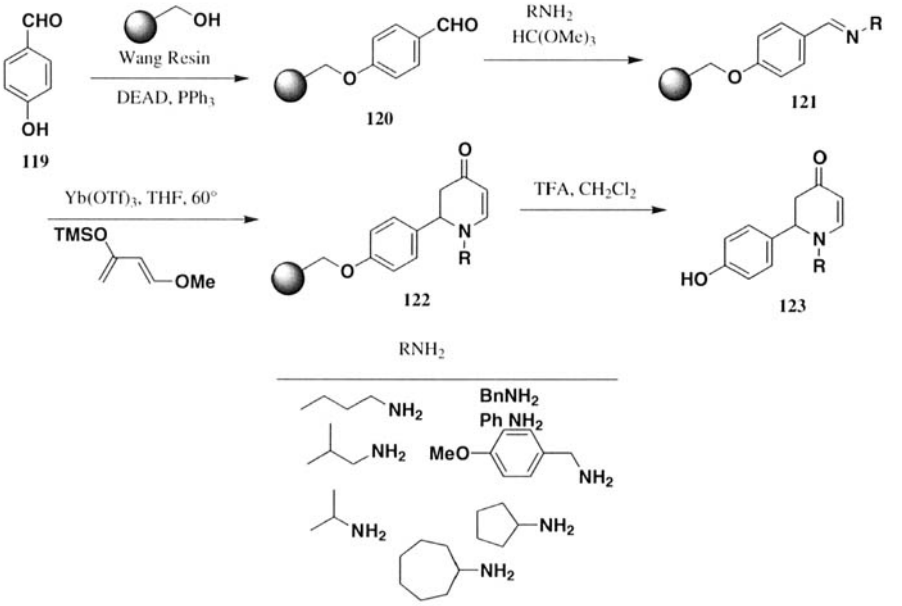


Fig. 22

A resin-bound acyl-pyridinium complex was used in a synthesis of dihydropyridones.[44] The chloroformate functionalized hydroxymethylated polystyrene resin **124** was reacted with a pre-mixed solution of 4-methoxypyridine (**125**) and a Grignard reagent in THF to give dihydropyridone **127** *via* the intermediate iminium salt **126** (*Fig.* 23). Dihydropyridone **127** could be saponified from the support to afford dihydropyridones **128** in 31-67% yield and with purities generally above 90%. It also proved possible to derivatize **127** by the 1,4-addition of organocuprates. For instance, treating **127** with the cuprate obtained from combining alkyl magnesium chloride, cuprous iodide and boron

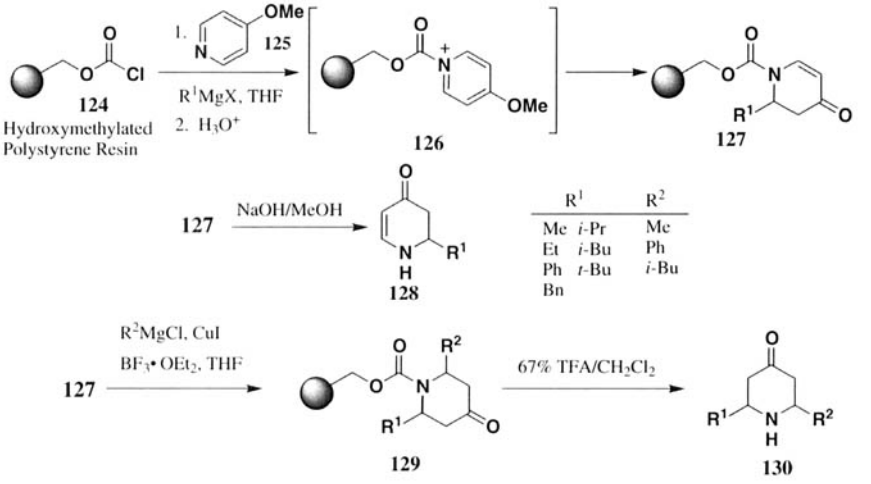


Fig. 23

trifluoride etherate gave **129**. Cleavage of **129** from the resin was effected with 67% TFA in methylene chloride to give **130** in 27-32% yield with purities above 85%.

Considerable work has been performed by Bolton and coworkers on the solid phase synthesis of 1H-[2]pyridinones.[45] Carboxylic acid **131** was coupled to Wang resin to give the cyclization precursor **132** (*Fig.* 24). Cyclization to the pyridinone ring system occurred upon treatment of **132** with a palladium catalyst and an aryl iodide containing cuprous iodide to give *trans*-**133a**. Similarly, cyclization to a pyridinone occurred upon exposing **132** to cobalt octacarbonyl in the presence of *N*-methylmorpholine *N*-oxide (NMO) to afford *trans*-**133b.** Cleavage of **133a** and **133b** from the resin with TFA and esterification with diazomethane delivered pyridinones **134a** and **134b**. The synthesis of another pyridinone ring system was accomplished by treating **135** with a palladium catalyst and an aryl iodide, followed by cobalt octacarbonyl to give **136** as a 5:1 mixture of diastereomers, with the *cis*-isomer predominating. Cleavage with TFA and esterification with diazomethane afforded methyl esters **137**. Cyclization of **135** with the cobalt catalyst gave *cis*-**138**, which was reduced on the solid phase with 50 mol% of $[(PPh_3)CuH]_6$ to give, after cleavage and esterification, *cis*-**139**. Similarly, reducing *trans*-**133b** with $[(PPh_3)CuH]_6$ gave, after cleavage and esterification, *trans*-**140**. The authors also demonstrated that other sulfonamides can be used in the synthesis and an amino acid (phenylalanine) could be attached to Wang resin before attaching **131**, thereby extending the diversity of compounds synthesized by this route.

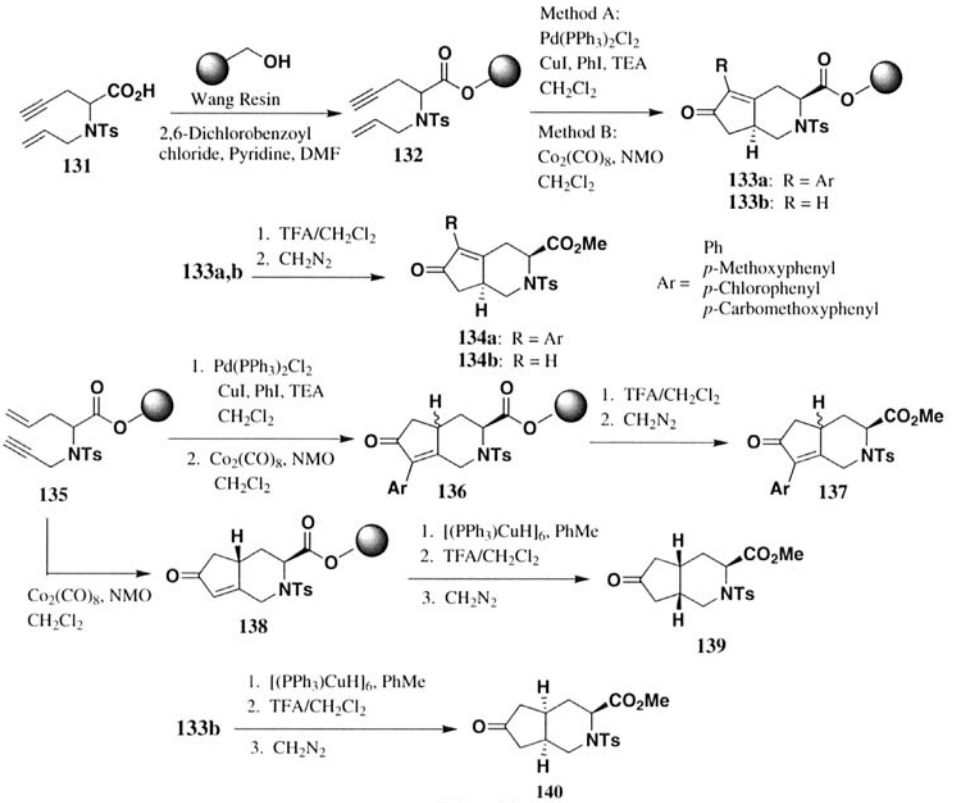


Fig. 24

7. Tetrahydroquinolines, Isoquinolines and Quinolines

A multi-component Grieco condensation reaction has been applied by Armstrong to the solid phase synthesis of a library of tetrahydroquinolines.[46] The Grieco three component reaction consists of condensing an aniline, cyclopentadiene and benzaldehyde to furnish a *cis*-fused tetrahydroquinoline (*Fig.* 25).[47] Armstrong chose to tether the aniline moiety to the solid phase. This was achieved by coupling *p*-nitrobenzoic acid (**141**) to Wang resin and reducing the nitro group to the desired aniline **142** using stannous chloride. Combining **142** with benzaldehyde and cyclopentadiene in acetonitrile containing 1% TFA, followed by cleavage from the resin delivered **143**. Using this chemistry, a library of 80 tetrahydroquinolines was synthesized wherein **142** was condensed with five olefins and eight aldehydes. The most efficient olefin was cyclopentadiene, while 2,4-dimethylstyrene was the worst. Also, acetaldehyde and valeraldehyde failed to afford any tetrahydroquinolines.

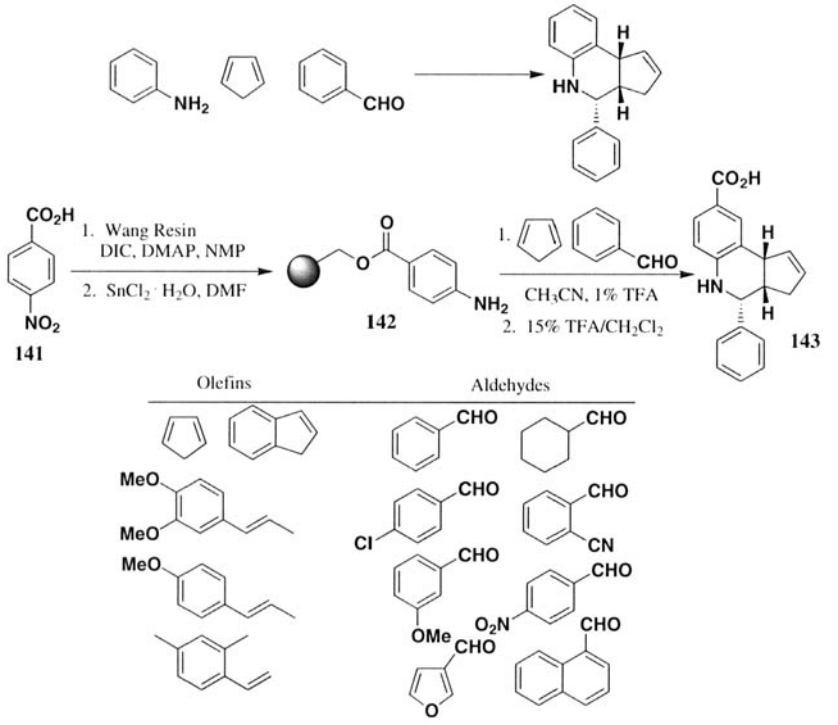


Fig. 25

2-Arylquinoline-4-carboxylic acid derivatives have been synthesized by Gopalsamy and Pallai by applying the Doebner quinoline synthesis to the solid phase.[48,49] Rink resin was derivatized with three different amino acids using the coupling agent 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) to give amines **144** (*Fig.* 26). Acylation of amine **144** with pyruvyl chloride gave pyruvic amide **145** which was subsequently heated at reflux in benzene with a preformed solution of benzylidene **146** to afford resin-bound 2-arylquinoline-4-carboxylamides **147**. The 2-arylquinoline-4-carboxamides **147** were cleaved from the resin upon treatment with 50%

TFA to give **148** in 62-92% yield. It also proved possible to condense pyruvic amide **145** with an excess of an equimolar mixture of anilines **149** and benzaldehydes **150** to give resin bound amides **147** in comparable yield and purity to the method employing the preformed benzylidene **146**.

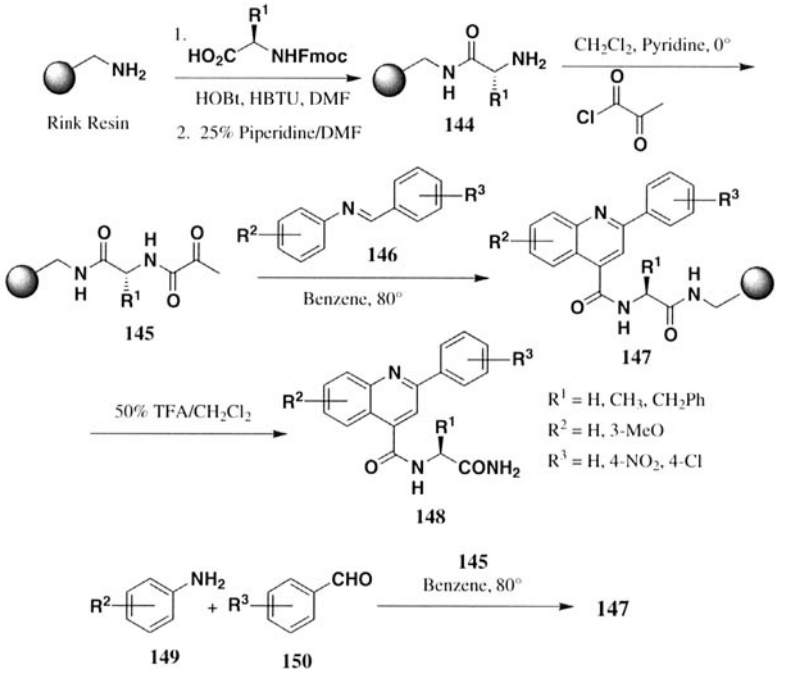


Fig. 26

A unique vinylsulfonylethyl ether linker on a hydroxymethylated polystyrene resin was used to synthesize a set of *N*-alkylated 5- and 6-alkoxy-1,2,3,4-tetrahydroisoquinolines from a tetrahydropyranyl protected tetrahydroisoquinoline.[50] Heinonen and Lonnberg functionalized hydroxymethyl polystyrene resin with divinyl sulfone (**151**) to give vinylsulfonylethyl ether resin **152** (*Fig.* 27). As a model reaction to define reaction conditions and to determine loading levels, 5-ethoxy-1,2,3,4-tetrahydroisoquinoline **153** was attached to resin **152** to give the tertiary amine **154**. The authors failed to give any information regarding the conditions used for coupling isoquinoline **153** to resin **152**. Treating **154** with iodomethane in DMF gave the intermediate quaternary salt which, when exposed to disopropylethylamine in methylene chloride, gave a solution of **155** with the yield varying from 210-270 μmol/g. Even though it was found that the highest yield of **155** occurred when quaternization was run for one hour and release of **155** from the resin was run for 18 hours (giving 270 μmol/g yield), it was more convenient to run the quaternization step for 0.5 hours and the release for 0.5 hours (giving 250 μmol/g yield). It was also found that **154** could be quaternized not only with iodomethane, but with ethyl iodide, 1-iodopropane, and benzyl bromide.

With the reaction times for the manipulation of **154** deduced, 5- or 6-(tetrahydropyran-2-yloxy)-1,2,3,4-tetrahydroisoquinoline **156** was attached to resin **152** to give **157**. The tetrahydropyran

protecting group was removed with TFA to give phenols **158**. Attempts to run a Mitsunobu reaction on phenols **158** initially failed until it was found that the reactions could be performed using tributyl phosphine/1,1'-(azodicarbonyl)dipiperidine to deliver ethers **159**.[51] Four different alcohols were used in the Mitsunobu reaction and quaternization was performed using only iodomethane. Release from the resin was effected with diisopropylethylamine to afford isoquinolines **160** in 80-100% yield, except for compounds which contained R^1OH = $MeCHCHCH_2OH$ and Me_2CHCH_2OH which were obtained in 40 and 25% yields, respectively.

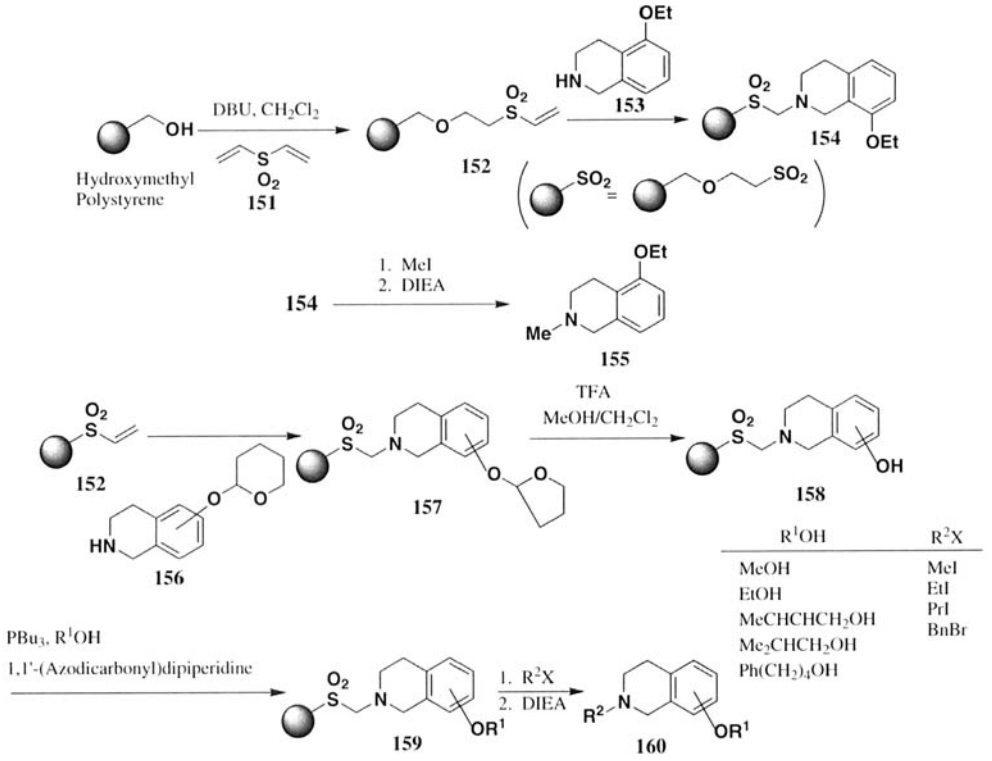


Fig. 27

A traceless solid phase route to isoxazolinoisoquinolines has recently been reported by Kurth.[52] This work is an extension of a previous solid phase synthetic route to isoxazolinoisoquinolines performed by the Kurth group.[53] The resin-bound acid chloride **161**, prepared from unfunctionalized polystyrene-2% divinylbenzene copolymer resin as described in a previous publication,[53] was acylated with isoquinoline in the presence of trimethylsilylcyanide to give the Reissert condensation product **162**.[53] Alkylation of C-1 with alkyl and benzyl halides in THF at -78° using lithium diisopropyl amide (LDA) gave **163a-e** and hydrolysis with aqueous potassium hydroxide in THF delivered the C-1-substituted quinolines **164a-e** in 59 and 50% yield for **164b** and **164c** (R^1 = ethyl or benzyl), respectively. 1,3-Dipolar cycloaddition reactions were then explored. Resin-bound Reissert adduct **165**, prepared as described for **162** using 4-phenylisoquinoline instead of isoquinoline, was alkylated with

allyl bromide or methallyl bromide to furnish **166d,e**. Treatment of olefins **166d,e** with nitrile oxide **167** or **168**, generated *in situ* from a mixture of nitropropane or $C_6H_5CH_2NO_2$, phenyl isocyanate and triethylamine, generated intermediates **169a-c** which were hydrolyzed from the resin to cleanly afford the isoxazolinoisoquinolines **170a-c** solely as the *exo*-adducts in 27, 24, and 23% yield, respectively. The same 1,3-dipolar cycloaddition reaction conditions were applied to **163d,e** to give **171a-c** which where then hydrolyzed from the resin to afford **172a-c** in 25, 26 and 21% yield, respectively. In an

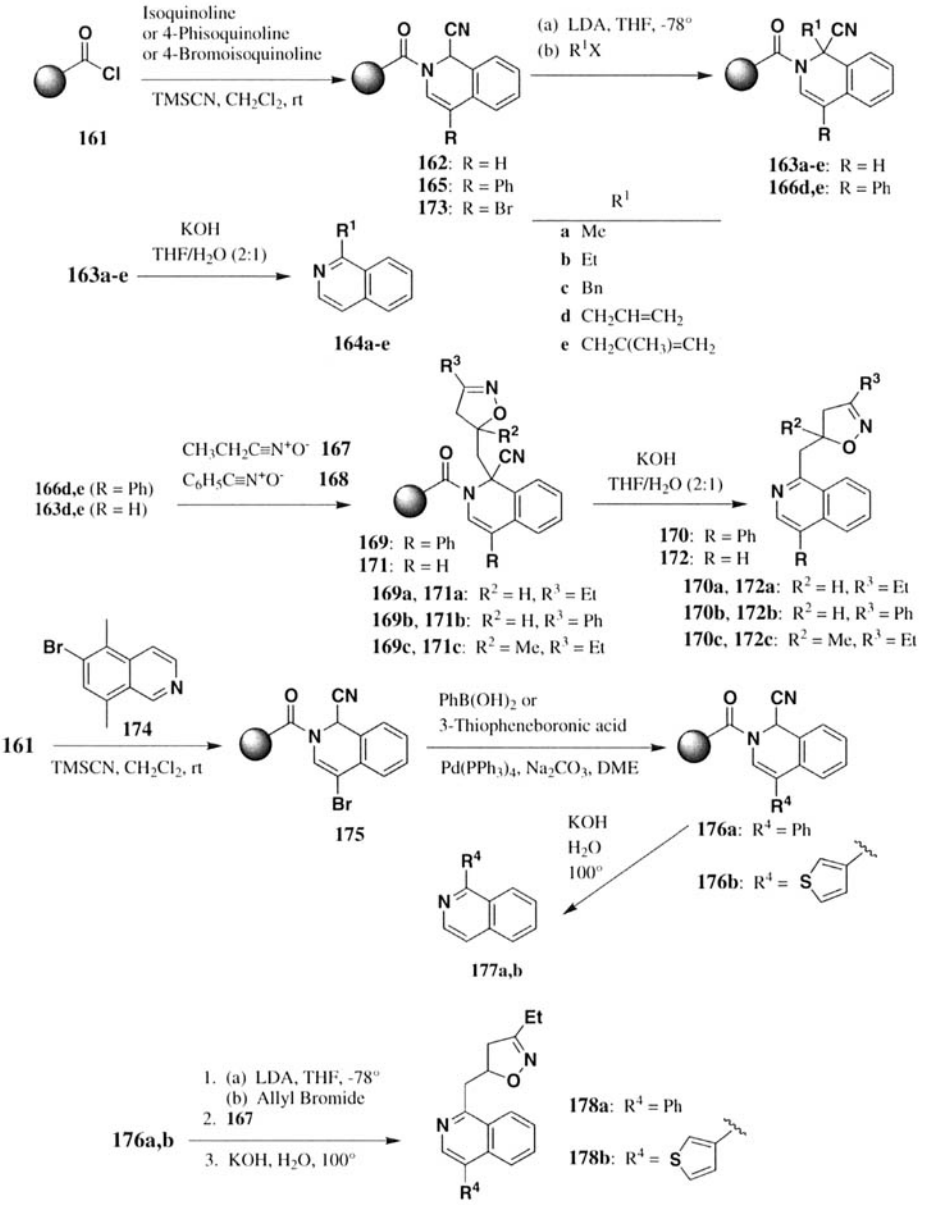
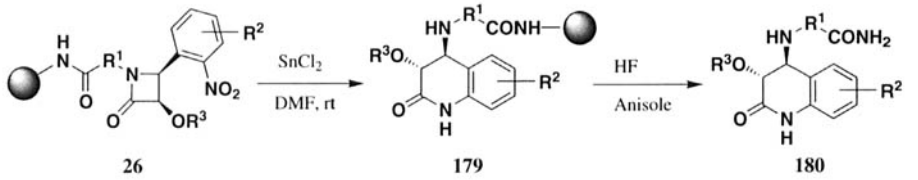


Fig. 28

effort to further enhance the structural diveristy of the products being formed, 4-bromoisoquinoline was attached to resin **161** as described above to give **173**. All efforts to effect a Suzuki coupling between **173** and arylboronic acids failed. The reason for the failure was ascribed to the vinyl bromide **173** being too electron rich. To circumvent the problem associated with Suzuki couplings to **173**, 6-bromo-5,8-dimethylisoquinoline (**174**) was synthesized and attached to resin **161** under conditions described above to deliver **175**. Suzuki couplings between phenylboronic acid or 3-thiopheneboronic acid and **175** using $Pd(PPh_3)_4$ in 1,2-dimethoxyethane (DME) containing sodium carbonate gave **176a,b**. Hydrolysis from the resin using KOH in water at 100° gave **177a,b** in 89 and 69% overall yield, respectively. Finally, **176a,b** was alkylated with allyl bromide, reacted with nitrile oxide **167** and hydrolyzed from the resin to afford **178a,b** in 19 and 17% yield, respectively.

As described earlier in *Fig.* 6, Pei and coworkers synthesized β-lactams as intermediates in the solid phase synthesis of 4-amino-3,4-dihydro-2(1H)-quinolinones.[15] The nitro group of β-lactam **26**, prepared as described in *Fig.* 6, was reduced with stannous chloride to give resin bound dihydroquinolinone **179** (*Fig.* 29). For a definition of the different R-groups in *Fig.* 29, see *Fig.* 6. Removal of **179** from MBHA resin was achieved using a hydrogen fluoride/anisole mixture to give **180** in 68-100% yield and in purities above 85%. Using the chemistry described in *Fig.* 6 and *Fig.* 29, a library of 4,140 dihydroquinolinones was prepared.



26 179 180

Fig. 29

II. COMPOUNDS CONTAINING MORE THAN ONE HETERO ATOM

1. Tetrahydroquinoxalin-2-ones, Benzimidazolones, Quinazolinones and Quinazolines

Two syntheses of 1,2,3,4-tetrahydroquinoxalin-2-ones have appeared recently in the literature.[54,55] Work described by Lee and coworkers describes the synthesis of 7-carboxamide-3,4-dialkyl-1,2,3,4-tetrahydroquinoxalin-2-ones (*Fig.* 30), in unknown enantiomeric purity. The synthesis was similar to a solution phase synthesis reported by TenBrink and coworkers, wherein an *ipso*-fluoro displacement is used to introduce an amino acid into an aromatic group.[56] 4-Fluoro-3-nitrobenzamide resin **182** was obtained by coupling 4-fluoro-3-nitrobenzoic acid (**181**) to Rink amide resin using *O*-(7-azabenzotriazol-1-yl)-N,N,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HATU) (*Fig.* 31). Treating **182** with methyl or ethyl amino acid esters for 3 days in DMF containing DIEA resulted in an *ipso*-fluoro displacement and formation of **183**. The extent of fluorine displacement was monitored by cleavage of **184** from resin **183** with TFA. Reduction of the nitro group of **183** was achieved using conditions reported by Pavia, namely with a stannous chloride/water

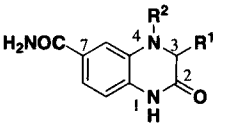
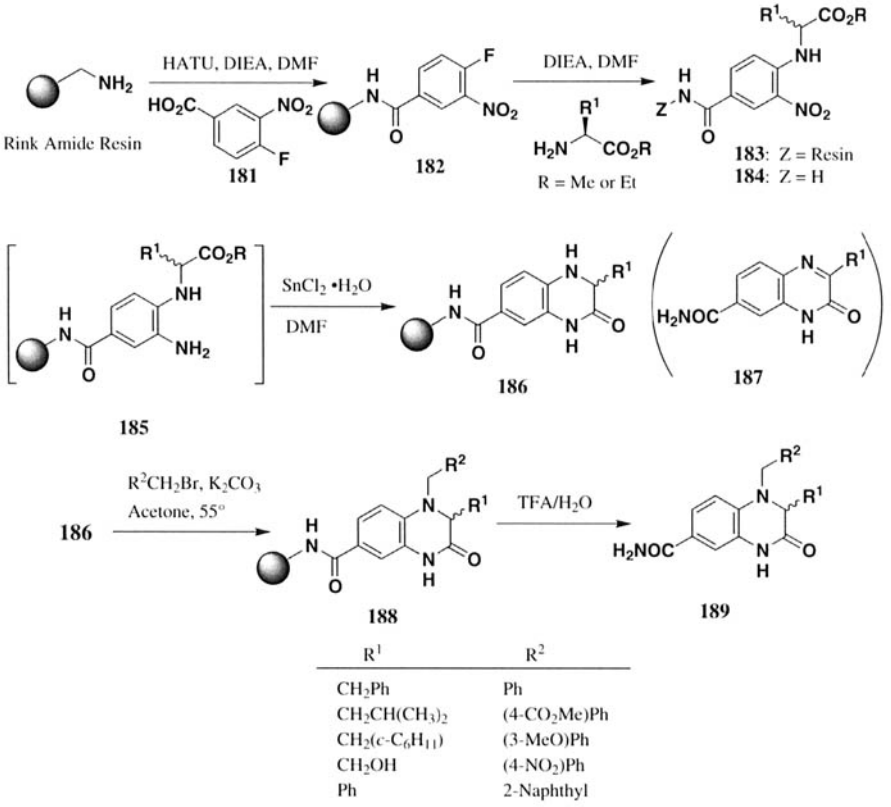


Fig. 30

mixture in DMF to afford **186** *via* the aniline intermediate **185**.[57] The authors presumed that the aniline intermediate **185** spontaneously cyclized to give **186** since, upon cleavage with TFA, no aniline was observed. It was also found that approximately 25% of material cleaved from resin **186** had aromatized to give 3-alkyl-quinoxalin-2-ones **187**. The oxidation was more prone to occur when R^1 = cyclohexylmethyl, isobutyl and benzyl, and least likely when R^1 = phenyl and hydroxymethyl. Alkylation of resins **186** with alkyl bromides in potassium carbonate in acetone at reflux gave **188**. Cleavage of **188** with TFA gave amides **189**, in unknown enantiomeric purity, in 32-93% yield.



R^1	R^2
CH_2Ph	Ph
$CH_2CH(CH_3)_2$	(4-CO_2Me)Ph
CH_2(c-C_6H_{11})	(3-MeO)Ph
CH_2OH	(4-NO_2)Ph
Ph	2-Naphthyl

Fig. 31

The approach developed by Corbett and coworkers also involved the *ipso*-fluoro displacement reaction of a resin bound 4-fluoro-3-nitrobenzoate with an amino acid ester.[55] In particular, 4-fluoro-3-nitrobenzoic acid (**181**) was attached to Wang resin (not shown) or to bromomethyl Wang resin to give **190** (*Fig.* 32). Various chiral amino acid esters were used in an *ispo*-fluoro displacement on resin-bound 4-fluoro-3-nitrobenzoate **190** to give **191**. The nitro group of **191a-g** was reduced using aqueous stannous chloride in DMF at 80° to give benzopiperazinone **192**. Treating resin **192** with TFA gave benzopiperazinones **193a-g**. Chiral HPLC analysis of **193b** indicated that it had partially racemized, yielding material with a 50% ee. Assuming that racemization occurred during reduction of **191b** by enolization of the ester under the acidic conditions used, cesium salts of

carboxylic acids were used to synthesize **192** *via* the carboxylic acids **194**. As with **191**, stannous chloride reduction of **194a-g** gave **192 a-g**. Cleavage of **192** with TFA gave **193a-g**, which had poor chemical purity and poor optical purity when synthesized from amino acid salts.

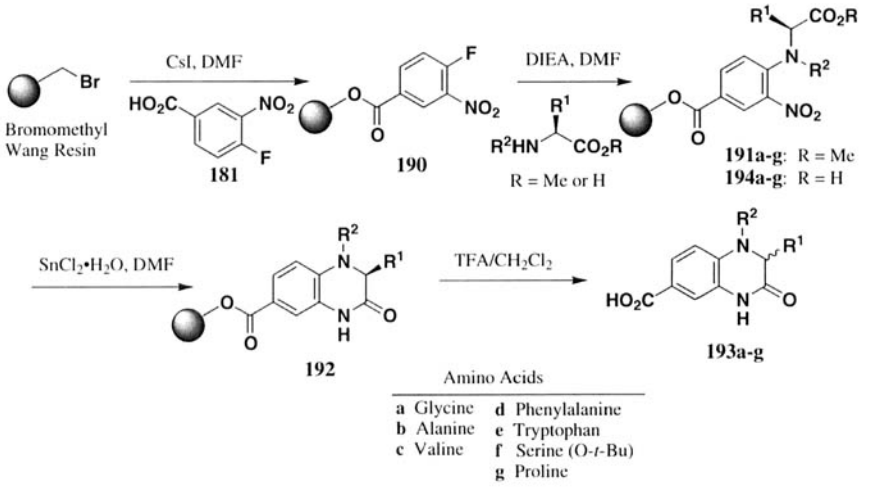


Fig. 32

The remainder of the synthesis was then conducted using amino acid esters since no advantage was gained using the amino acid salts. Using **192b** as an example to exemplify further chemistry, it proved possible to acylate the aniline nitrogen with chloroformates and chlorothioformates to give **195** (*Fig.* 33). Cleavage of **195** (X = O, R = allyl) from the resin afforded enantiomerically pure **196**, having an ee of 99% in 69% yield from **192b**. The yield for other derivatives of **196** was 34-69% from

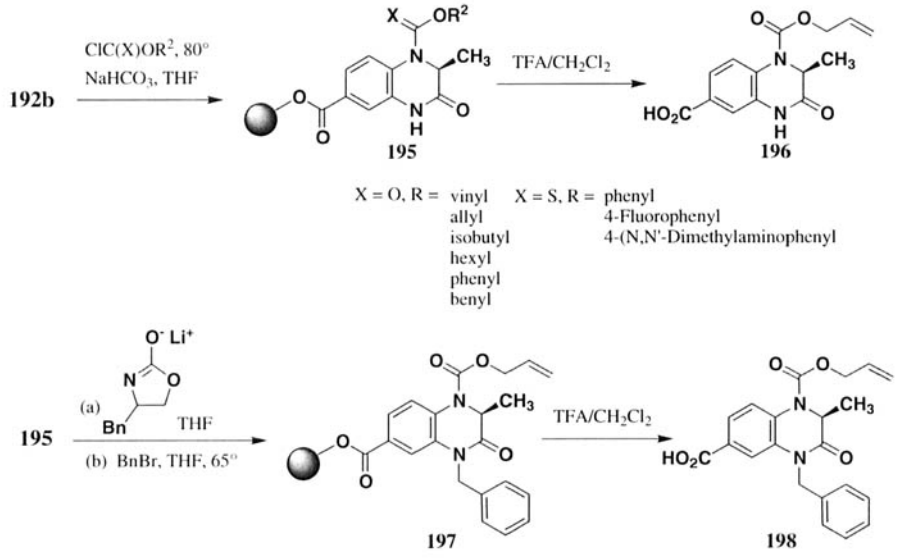


Fig. 33

192b. It proved possible to alkylate the anilide nitrogen of **195** (X = O, R = allyl) with benzyl bromide to give **197**. Cleavage from the resin with TFA gave **198** in 45% yield from **192b**.

In order to add more diversity to the compounds being synthesized, four different amino acid derivatized Wang resins **199** were coupled to **181** to give intermediate **200** (*Fig.* 34). *ipso*-Fluoro displacement proceeded with *L*-alanine methyl ester to afford *o*-fluoronitrobenzoate **201**. Stannous chloride reduction gave **202** which was then acylated to provide carbamate **203**. Cleavage from the resin gave **204** in 17-50% yield from Wang resin.

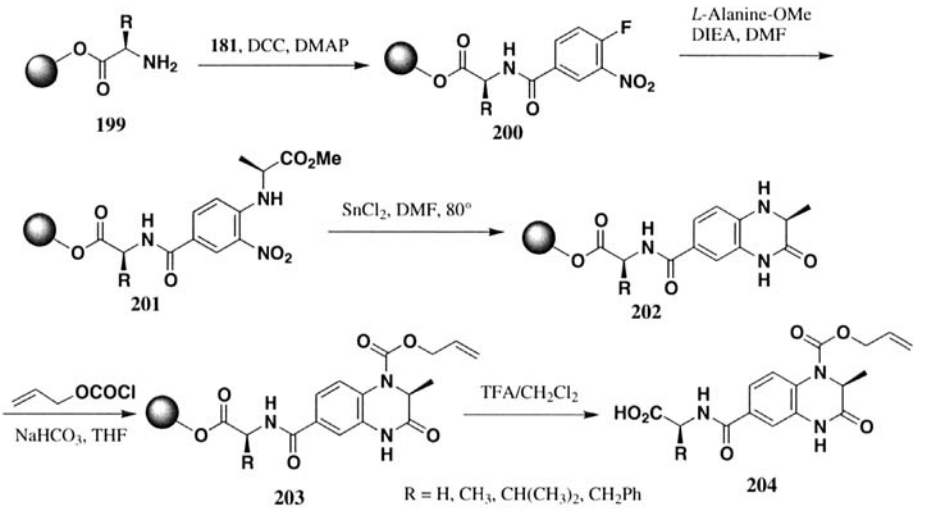


Fig. 34

Mayer and coworkers have taken amino acid derivatized Wang resins **205** and converted them to resin-bound anthranilamides **206** by coupling **205** with either an *o*-nitrobenzoic acid **207**, followed by reduction of the nitro group with stannous chloride, or an isatoic anhydride **208** (*Fig.* 35).[58] The anthranilamides **206** were condensed with an aldehyde in dimethylacetamide containing 5% acetic acid to afford dihydroquinazolinones **209**. Dihydroquinazolinones **209** could be cleaved from the resin to afford dihydroquinazolinones **210**, or oxidized with potassium permanganate in acetone and cleaved to give 2-substituted quinazolines **211**. The authors also demonstrated that a traceless approach to dihydroquinazolinones and 2-substituted quinazolines could be achieved by using Rink resin instead of Wang resin. The traceless synthesis proceeded under identical conditions to that already discribed to afford **212**.

Wang and Hauske have reported the synthesis of 3,4-dihydroquinazolines *via* an aryl iminophosphorane. They have found that aryl iminophosphoranes **214** were synthesized when Wang resin functionalized with substituted aminobenzoic acids **213** was treated with triphenylphosphine and DEAD in THF (*Fig.* 36). This chemistry was then applied to the solid phase synthesis of dihydroquinazolines from resin-bound 2-nitrocinnamic acid **216** (*Fig.* 37). In particular, carboxylic acid **215** was attached to Wang resin, and the nitro group was reduced with stannous chloride hydrate in DMF to afford **216**. When aniline **216** was treated with PPh_3 and DEAD, cinnamyl iminophosphorane **217**

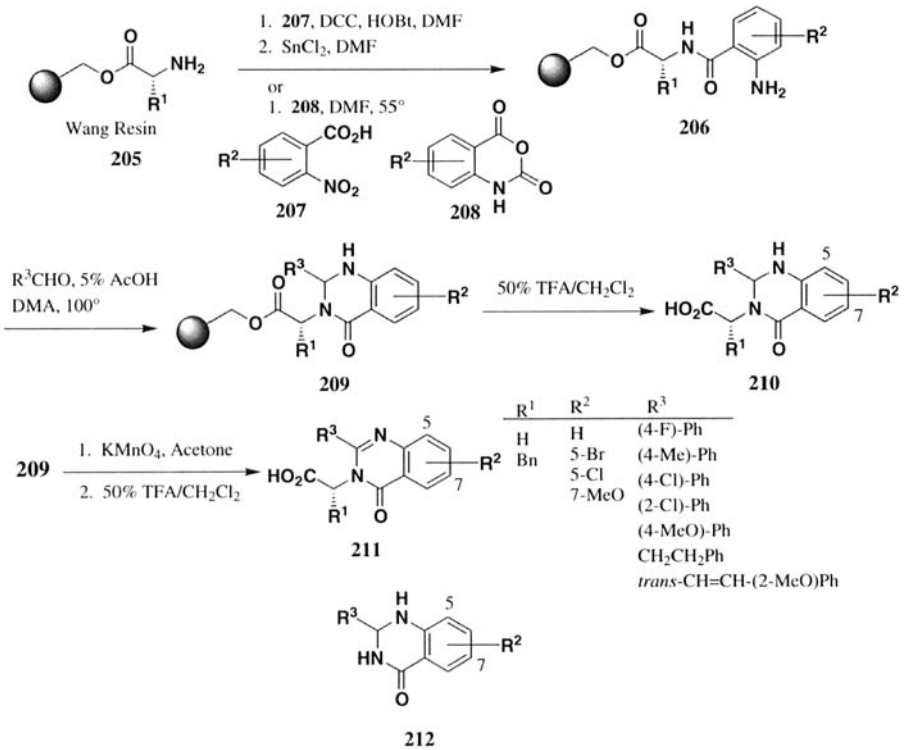


Fig. 35

was cleanly formed in high yield. The aza-Wittig reaction between *m*-substituted aryl isocyanates **218** and iminophosphorane **217** proceeded to give carbodiimides **219**, as confirmed by a distinct IR absorption. Heating a secondary amine at 80° with **219** gave **221** *via* intermediate **220**. Cleavage of **221** from the resin with moist TFA gave ureas **222** in unspecified yield and purity.

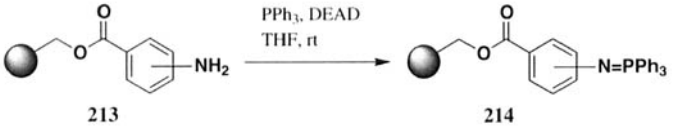


Fig. 36

Quinazoline-2,4-diones containing an asymmetric center have been prepared from chiral amino acids.[60] Sasrin supported amino acids **223a** are coupled to *o*-methoxycarbonyl aryl isocyanates **224a** or the activated carbamate derivative **224b** to afford ureas **225** (*Fig.* 38). Alternately, isocyanate or carbamate derivatized amino acids **223b** are treated with **224c** to give **225**. It was found that quinazoline-2,4-dione formation could be induced upon heating **225** in NMP containing 5% tetramethylguanidine to give **226**. Cleavage of **226** with 1% TFA delivered **227** with purities above 90%. The N-H of **226** could be derivatized by alkylation with alkyl halides in NMP containing TMG, or by Mitsunobu reactions with alcohols to give, after cleavage, **228** in purities ranging from 79-94%.

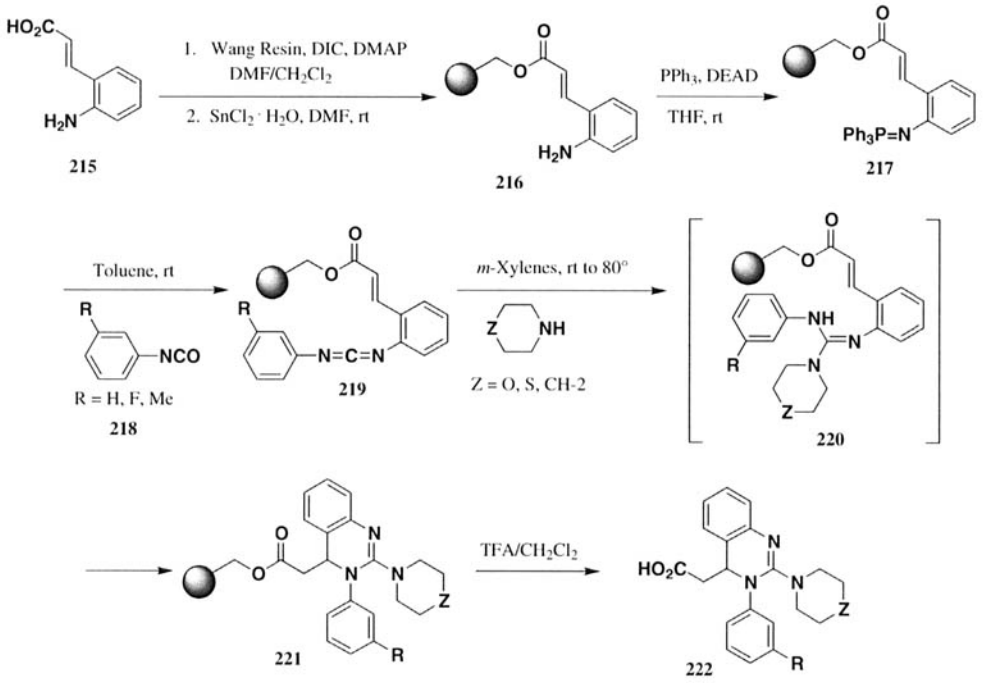
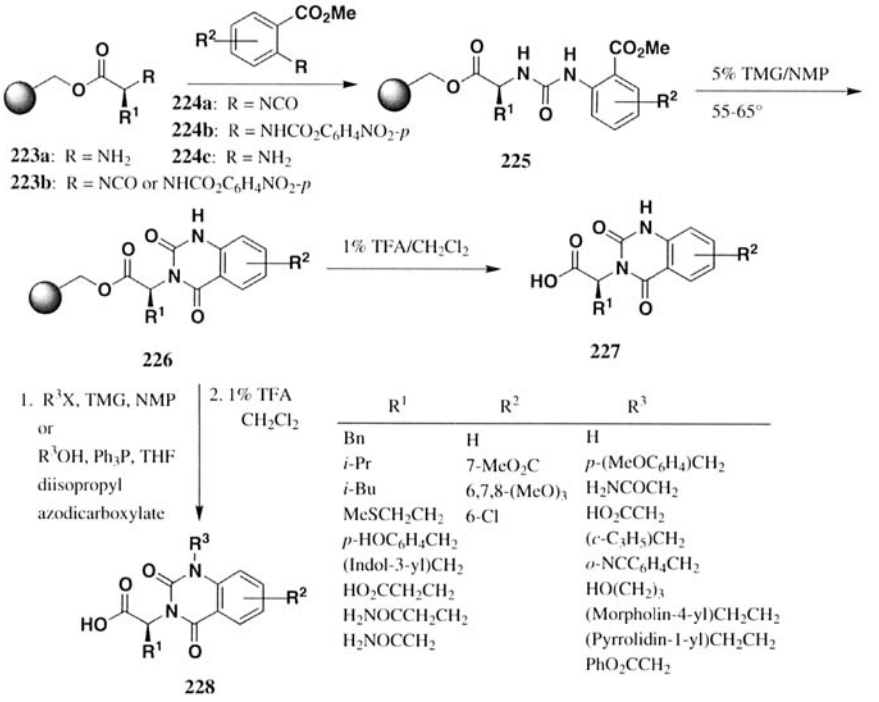


Fig. 37



R^1	R^2	R^3
Bn	H	H
i-Pr	7-MeO_2C	*p*-$(MeOC_6H_4)CH_2$
i-Bu	6,7,8-$(MeO)_3$	H_2NCOCH_2
$MeSCH_2CH_2$	6-Cl	HO_2CCH_2
p-$HOC_6H_4CH_2$		(*c*-C_3H_5)CH_2
(Indol-3-yl)CH_2		*o*-$NCC_6H_4CH_2$
$HO_2CCH_2CH_2$		$HO(CH_2)_3$
$H_2NOCCH_2CH_2$		(Morpholin-4-yl)CH_2CH_2
H_2NOCCH_2		(Pyrrolidin-1-yl)CH_2CH_2
		PhO_2CCH_2

Fig. 38

2. Diazepine, Benzodiazepine and Tetrahydro-β-Carbolines

Houghten and coworkers have disclosed the synthesis of eight dipeptidomimetics containing a 1,3,4,7-tetrasubstituted perhydro-1,4-diazepine-2,5-dione ring system.[61] The amine of *N*-Fmoc, O-*t*-Bu protected aspartic acid functionalized *p*-methylbenzhydrylamine resin **229** was deprotected and reductively aminated with a variety of substituted benzaldehydes using sodium cyanoborohydride in DMF containing 1% acetic acid (*Fig.* 39) to give **230**. Coupling *N*-Fmoc protected amino acids to the resulting secondary amine of resin bound aspartic acid derivatives **230** was found to occur when double couplings were performed with HATU, and then only phenylalanine and methionine gave good yields of the coupled products **231**.[62] A more hindered amino acid, such as valine, afforded low yields of the desired amides **231** (as evidenced by the purity of the final product **234** being 15%). Removal of the Fmoc-protecting group and reductive amination with benzaldehyde gave secondary amines **232** which, following removal of the *t*-Bu ester protecting group with 60% TFA, underwent an intramolecular cyclization to afford the desired heterocycle **233**. Hydrogen fluoride treatment removed **233** from the resin to give **234** in 15-87% purity and unspecified yield. When reductive amination of **229** failed, a major by-product (5-15%) was dimerization of the resulting carboxylic acid, obtained upon removal of the *t*-butyl ester.

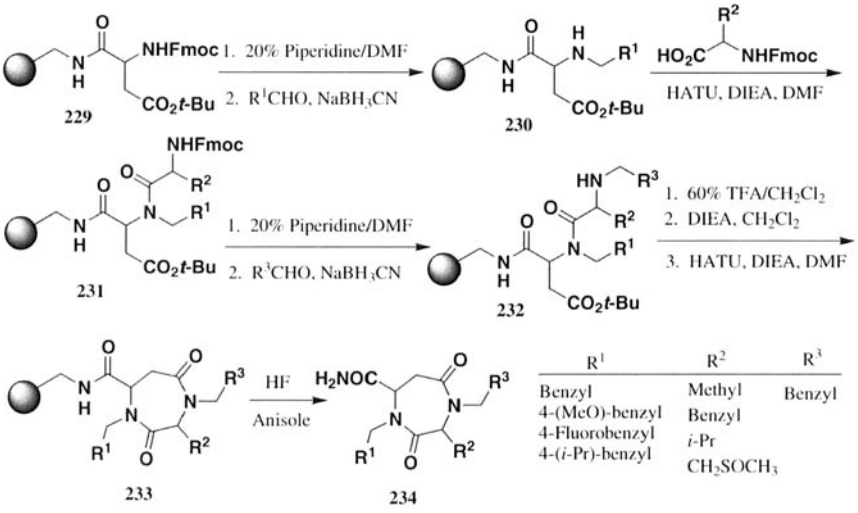


Fig. 39

1,4,7-Trisubstituted perhydro-1,4-diazepine-2,5-diones have also been synthesized by Krchnak and Weichsel.[63] The chemistry explicitly shown consists of coupling symmetrical secondary amines (not shown) or secondary *N*-Fmoc amino alcohols **235** to trityl derivatized TentaGel™ resin to give **236** (*Fig.* 40). The authors state that the synthesis was also performed on Rink functionalized TentaGel™ resin, although this work is not shown in the paper. Furthermore, they claim that primary amines or Fmoc-protected primary amino alcohols could be attached to trityl resin and the products used in the synthesis of diazepines, although this work is also not shown. Removal of the Fmoc group

from **236**, coupling *N*-Fmoc O-allyl protected aspartic acid and removal of another Fmoc group gave **237**. Reductive amination of **237** with aldehydes introduced the third diversity element into the system and gave **238**. Acylation of **238** with bromoacetic acid, activated with tetramethylfluoroformamidinium hexafluorophosphate (TFFH),[64] gave primary bromides **239**, which were treated with various amines and anilines in 2 *M* dimethylsulfoxide to yield the tetrasusbtituted intermediate **240**. Alloc deprotection was effected with either palladium (tetrakis)triphenylphosphine or saponification with 0.5% sodium hydroxide in methanol/water (20:80) and cyclization occurred upon overnight treatment with diphenylphosphoryl azide (DPPA) to afford **241**. Trifluoracetic acid vapor effected cleavage from the resin gave 1,4,7-trisubstituted perhydro-1,4-diazepine-2,5-diones **242** in 76-96% yield. Using this chemistry, a library of 2,720 compounds was synthesized by the split/mix technique.

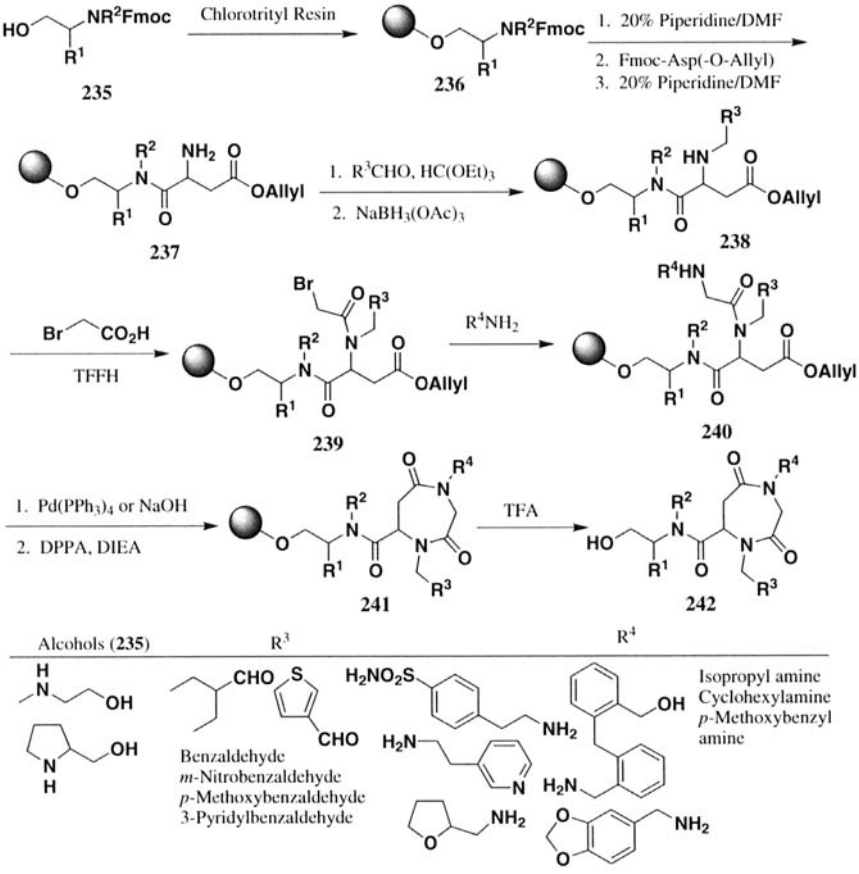


Fig. 40

A library consisting of 120 tetrahydro-1,4-benzodiazepine-2-ones containing three points of diversity was synthesized by Bhalay and coworkers.[65] Wang resin was coupled to fumaryl chloride to yield fumarate **243**. **243** was coupled to 24 anilino alcohols **244**, synthesized from commercially available anthranilate esters, to give **245**. Activation of benzylic alcohols **245** by transformation into their

mesylate with methanesulfonyl chloride followed by nucleophilic displacement with one of five primary amines furnished **246**. Finally, saponification with sodium methoxide in THF/MeOH afforded the intermediate methyl ester **247** which underwent Michael addition/cyclization to the desired tetrahydro-1,4-benzodiazipine-2-ones **248** in yields above 72%.

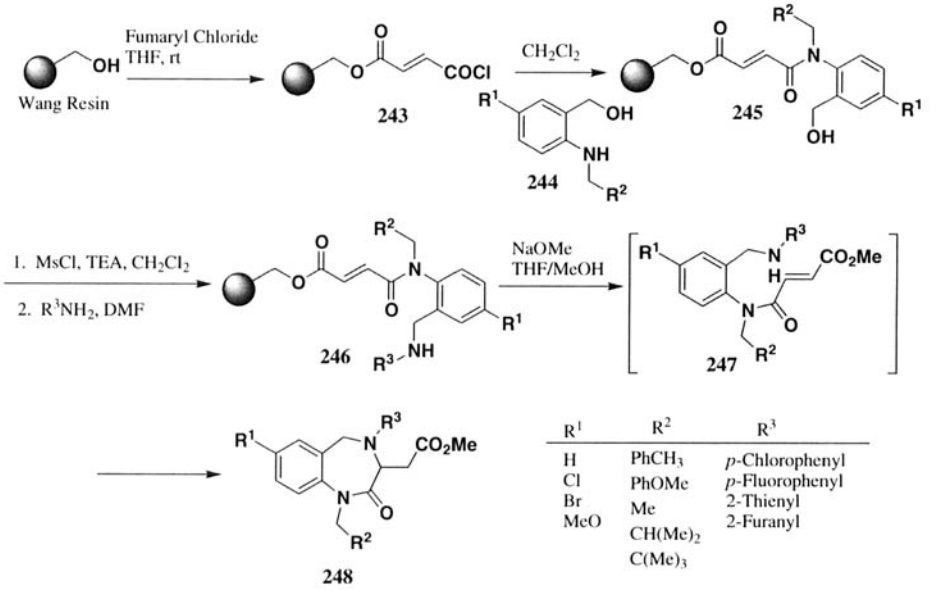


Fig. 41

A previously reported tracerless synthesis of 1,4-benzodiazepines using a germanium or silicon linkage to the solid support was further expanded upon by Ellman.[66,67] Aminomethylpolystyrene derivatized resin **249a** (Z = Si), bearing the arylsilane functionalized aromatic unit, undergoes a Stille coupling to either aromatic or aliphatic acid chlorides using $Pd_2dba_3{\cdot}CHCl_3$ to produce **250a** (*Fig.* 42). Removal of the ((2-(4-biphenyl)isopropyl)oxy)carbonyl (Bpoc) group with 3% TFA, acylation of the resulting aniline with α-*N*-Fmoc amino acid fluorides and Fmoc removal yields **251a**. Formation of resin-bound 1,4-benzodiazepine **252a** proceeds upon exposure of **251a** to 5% acetic acid at 65°. Deprotonation with a lithiated oxazolidinone and alkylation with alkyl halides gives **253a**. Cleavage of the silane linked derivative **253a** is achieved by first removing any amino acid side chain protecting groups with TFA and then cleaving the material from the resin with anhydrous hydrogen fluoride to give benzodiazepines **254**. It has been found that significant amounts of silyl-containing benzodiazepines **255** are formed under these conditions, however.

Since the formation of **255** was a serious side reaction, a germanium linker was investigated in an effort to identify a linker which could be efficiently cleaved with TFA. The preparation of the germanium linker is outlined in *Fig.* 43. Protecting the aniline of 4-bromoaniline (**256**) with a 2-(4-methylphenyl)isopropyl carbamate (Mpc) group, and lithium-halogen exchange with subsequent trapping of the resultant anion with (6-((triethylsilyl)oxy)hexylgermane (**257**) gave **258**. Ortho-metallation and quenching with trimethyltin chloride afforded stannane **259**. Removal of the silyl ether and

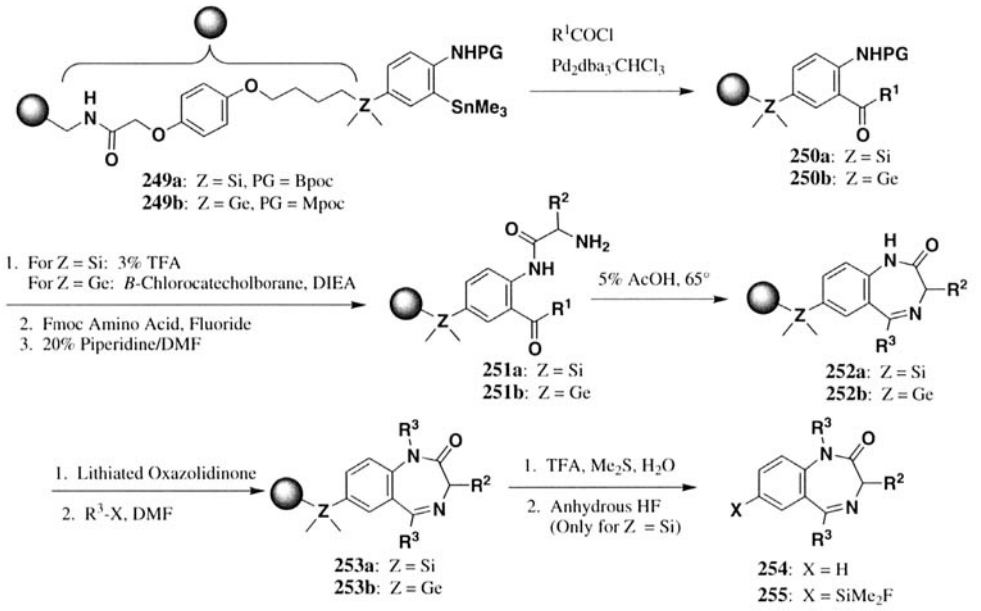


Fig. 42

Mitsunobu coupling to phenol **260** produced germane **261**. Aminomethylpolystyrene resin was then attached to **261** in *N*-methylpyrrolidinone (NMP) to afford resin-bound germanyl linker **262**.

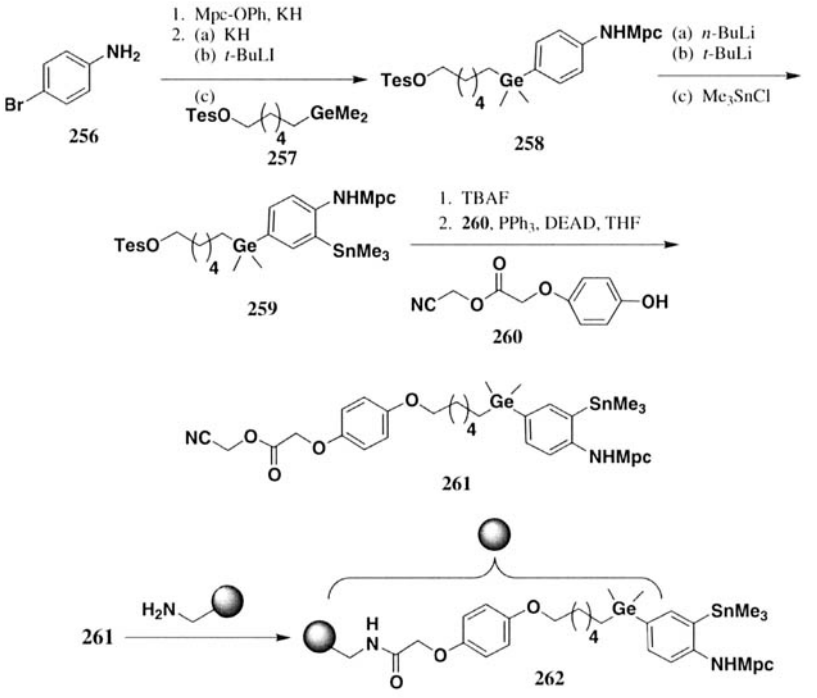


Fig. 43

The synthesis of the germanyl linked benzodiazepines is shown in *Fig.* 42. The only difference in the synthesis of the germanyl derivatives is that *B*-chlorocatecholborane was used to remove the Mpoc protecting group from **250b**. Resin-bound germanyl benzodiazepine **253b** could be cleaved from the resin with TFA or bromine to afford **263** or **264** (*Fig.* 44). The yields of some bromine derivatized benzodiazepines ranged from 47-59%, while a sampling of compounds **263** ranged from 58-68%.

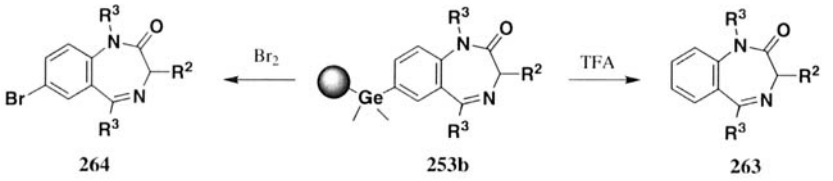


Fig. 44

The 4-hydroxythiophenol linker has been used in the synthesis of tetrahydro-β-carboline-3-carboxamides and of tetrahydro-β-carboline-2,3-bis-lactams.[68,69] *L*-Boc-tryptophan was coupled to resin **265** to give **266**. Removal of the Boc group and heating indole **266** with an aldehyde in toluene at 80° gave the Pictet-Spengler product **267** as a mixture of diastereomers with the *trans*-diastereomer typically predominating. α,β-Unsaturated aldehydes and benzaldehydes bearing electron donating subsitutuents failed to give the desired tetrahydro-β-carboline **267**. Aminolysis of **267** with sub-stoichiometric amounts of primary amines gave the desired tetrahydro-β-carbolines **268** after concentration. The synthesis of tetrahydro-β-carboline-2,3-bis-lactams was demonstrated on **267** where R = Ph. Acylation of **267** with either *N*-Boc glycine or *N*-Boc-β-alanine using benzotriazole-1-yl-oxy-tris-

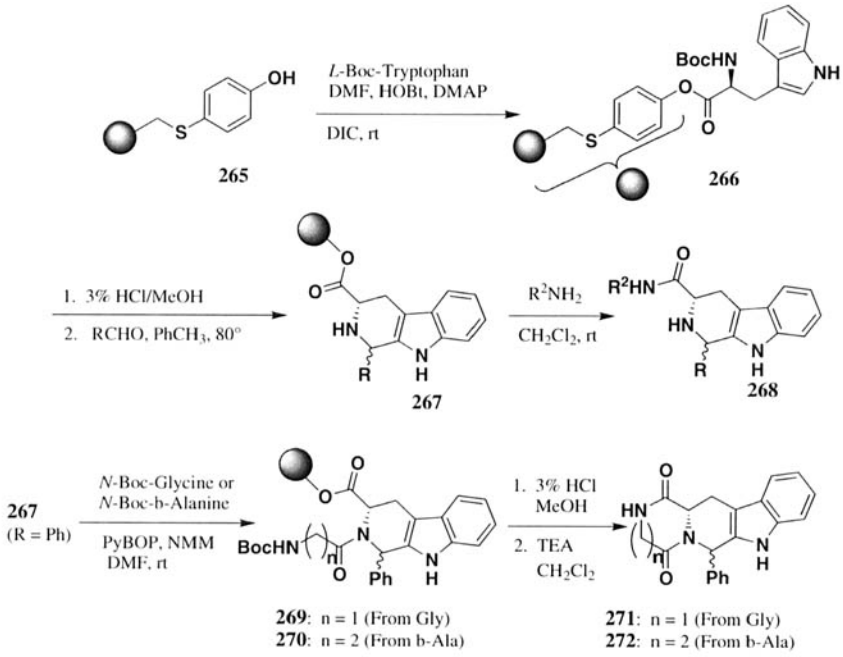


Fig. 45

pyrrolidino-phosphonium hexafluorophosphate (PyBOP) gave **269** and **270**. Removal of the Boc groups with 3% hydrochloric acid in methanol and cyclization with excess triethylamine in methylene chloride at room temperature gave the six-membered lactam **271** and the seven-membered lactam **272** from **269** and **270**, respectively.

An extensive amount of work has been published by Ellman and coworkers covering the development of 1,4-benzodiazepine-2,5-dione libraries.[70] Resin-bound benzaldehyde **274** is prepared by treating 4-hydroxy-2,6-dimethoxybenzaldehyde **273** with Merrifield resin (*Fig.* 46). The reductive amination of **274** with α-amino acid esters delivered **275**, without racemization of the amino ester. Acylation of **275** required double coupling with anthranilic acids using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) in NMP to give **276**. Other coupling agents failed to give the desired product. The lithium salt of acetanilide **277** was used to induce cyclization of **276** to give intermediate **278**, which was not isolated but rather alkylated to afford benzodiazepine **279**. The final product was removed from the solid support upon treatment with a trifluroacetic acid/dimethylsulfide/water mixture to give **280**. Compounds containing a bromide (R^1 = Br) have also been subjected to Suzuki couplings allowing access to more complex benzodiazepines **280**.

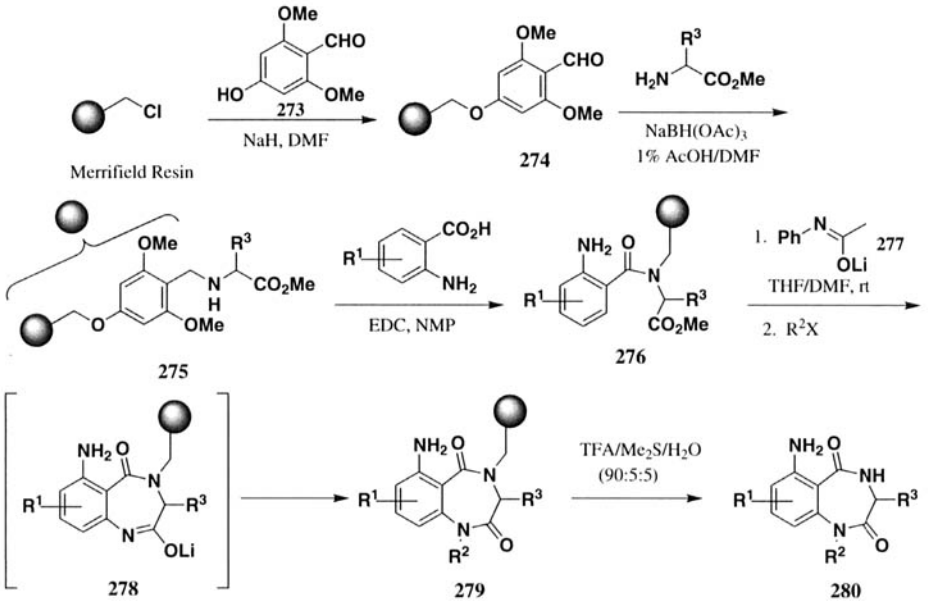
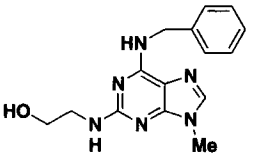


Fig. 46

3. Purines, Pyrimidines and Pyridines

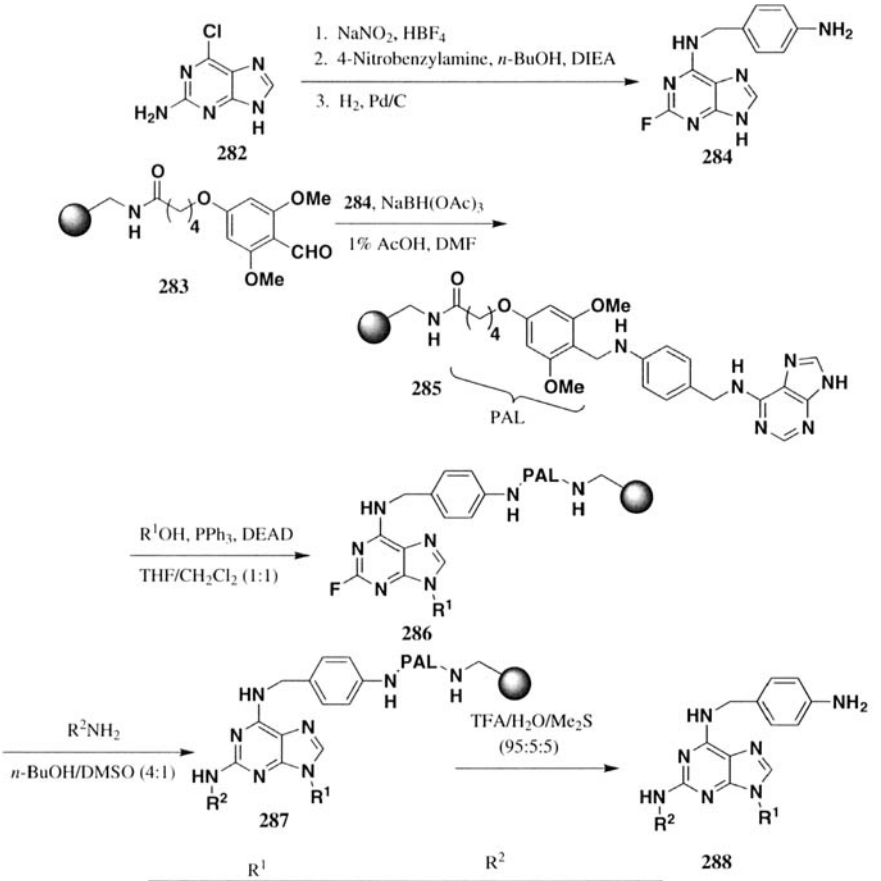
Schultz and coworkers have synthesized large libraries of 2,9-disubstituted purines on the solid phase in an effort to identify inhibitors of CDK/cyclin protein kinases.[71,72] It was thought that **284** could be used to synthesize derivatives of olomoucine (**281**), a known inhibitor of the protein kinase CDK2 (*Fig.* 47). **284** was synthesized in three steps from commer-cially available 2-amino-6-

chloropurine (**282**) by diazotization in aqueous fluoroboric acid, amination with 4-nitrobenzylamine and hydrogenation (*Fig.* 48). Crowns **283** functionalized with the benzaldehyde precursor of the PAL linker were reductively aminated with **284** to afford purine **285**.[73] Mitsunobu reaction of alcohols R^1OH with purine **285** gave nine different *N*-alkylated purines **286**. Displacement of the fluorine with ten primary amines R^2NH_2 in *n*-butanol/DMSO (4:1) provided **287** which was then cleaved from the resin with TFA to give purines **288** in 51-85% yield.



Olomoucine (**281**)

Fig. 47



R^1	R^2
Ethanol	Butylamine
Me_2NCH_2CHOH	2-Aminoethanol
Isopropanol	1,3-Diaminopropane
BnOH	4-Methoxybenzylamine
2-(2-Thienyl)ethanol	2-Fluorobenzylamine
2-(3-Thienyl)ethanol	2-(2-Aminoethyl)pyridine
3-Hydroxyfuran	(S)-(-)-2-Amino-3-phenyl-1-propanol
4-(2-Hydroxyethyl)morpholine	Cyclohexylamine
(+/-)-1-Phenyl-1-propanol	2-(Methylamino)ethanol
	(+/-)-2-Amino-3-methyl-1-butanol

Fig. 48

An approach to 2,6-disubstituted purines has been developed by Nugiel and coworkers.[74] Merrifield resin was functionalized with Ellman's tetrahydropyran linker **289** and 2,6-dichloropurine was loaded onto the resin upon treatment with 0.5 equivalents of camphorsulfonic acid in 1,2-dichlorobenzene to give **290** (*Fig.* 49).[31] The selective displacement of one chloride from **290** with either one of seven primary or secondary amines or with 3-benzyloxybenzyl alcohol or phenylhydrazine in *n*-butanol at room temperature gave the 6-subsituted purines **291a-g** in 90-96% yield. More stringent conditions were required to effect synthesis of 2,6-disubtituted purines. In particular, heating a neat amine with **291a-g** gave the desired purines **292**. When purines **291h,i,** containing an ether and hydrazine linkages, were exposed to these nucleophilic displacement conditions, no desired product was observed. Finally, **293** was obtained in 53-90% yield from **292** upon treatment with acid.

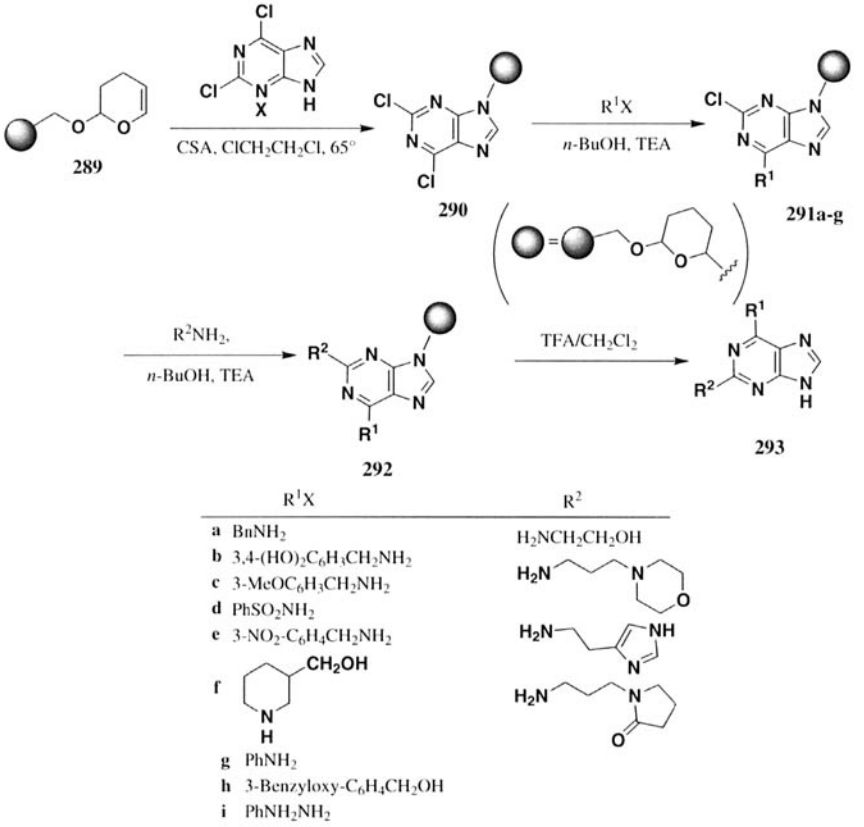


Fig. 49

The nucleophilic displacement of a resin-bound sulfonated pyrimidine has been used to synthesize 2,5-disubstituted-4-trifluoromethylpyrimidines.[75] Resin-bound pyrimidine **295** was prepared by coupling commercially available 2-chloro-4-trifluoromethyl pyrimidine-5-carboxylate (**294**) to NovaSyn™ TG thiol resin. Oxidation of sulfide **295** to sulfone **296** was performed using *m*-CPBA in methylene chloride. Treating **296** with various amines gave **297** in 50-96% yield; the poorest yield was obtained using aniline. Carboxylic acid **298** was prepared by saponification of **295**

in sodium

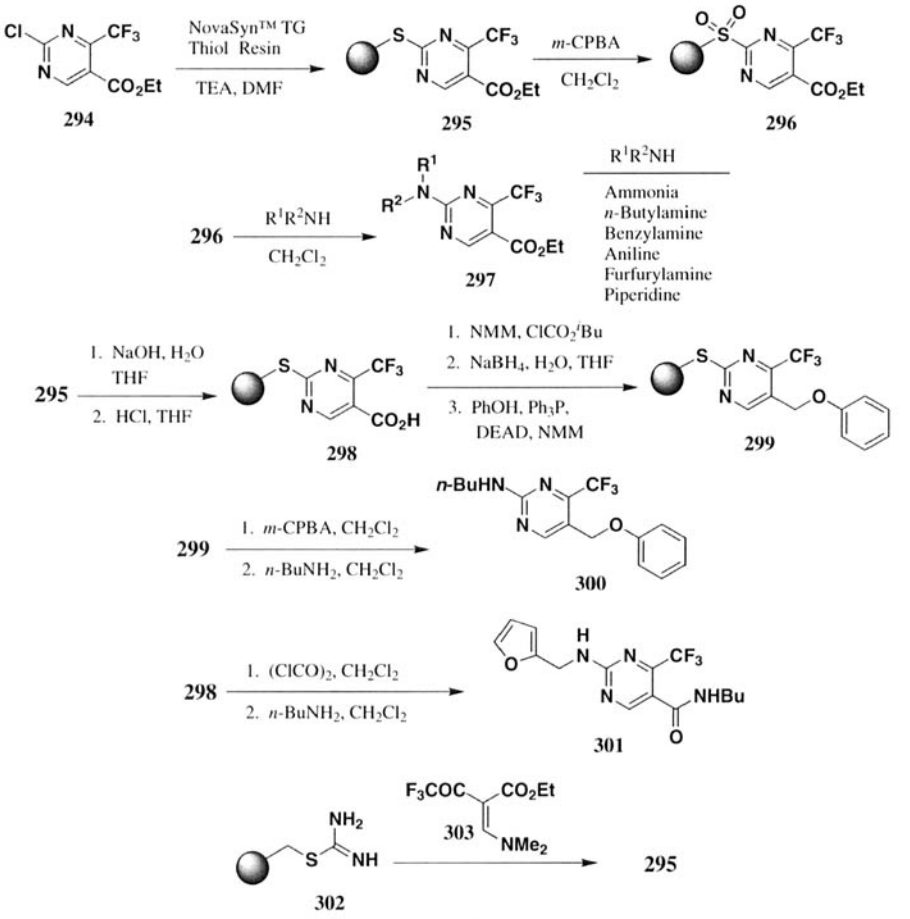
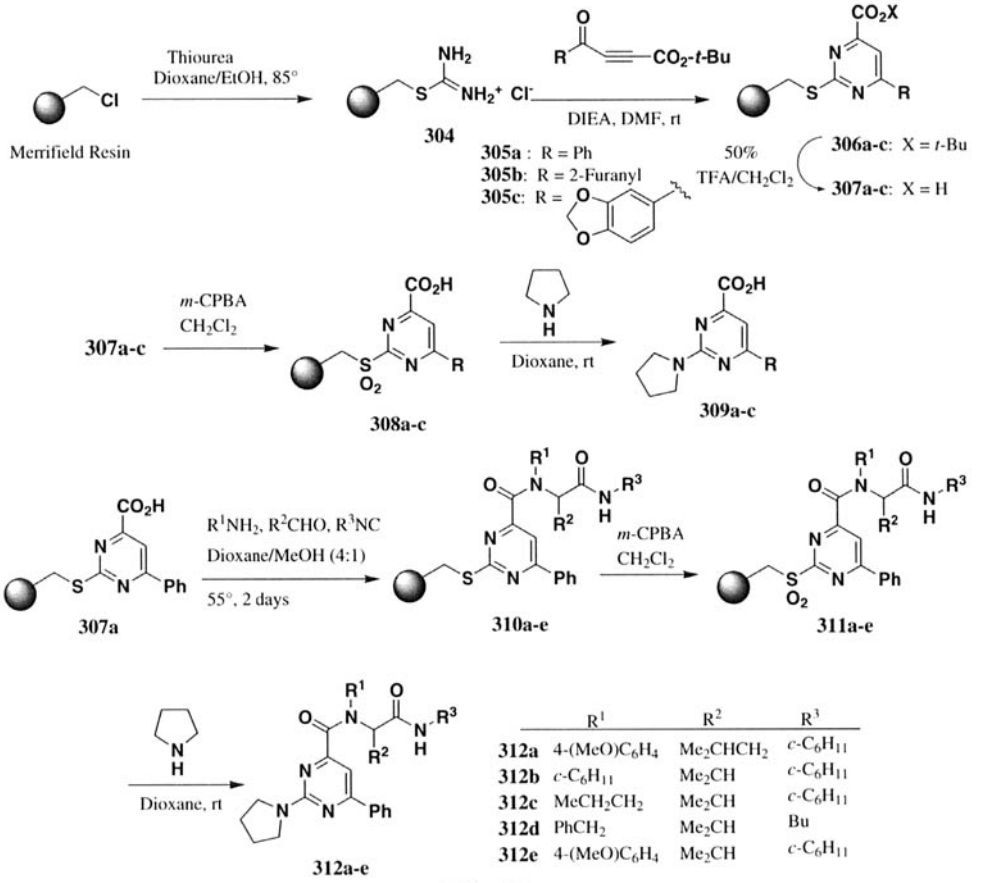


Fig. 50

hydroxide followed by acidification with HCl in THF. Benzyl ether **299** was prepared from **298** by reducing a mixed anhydride with sodium borohydride and using a Mitsunobu reaction to install the phenyl ether. Oxidation of **299** with *m*-CPBA and displacing the sulfone from the resin with *n*-butylamine gave **300**. Conversely, **298** was coupled to *n*-butylamine, oxidized and cleaved from the resin with furfurylamine to give **301**. The authors also show, without any experimental details, that the resin-bound thiourea **302** was coupled to **303** to give pyrimidine **295**, thereby demonstrating that pyrimidines can be synthesized on the solid phase and represents another method of pyrimidine syntheses from that presented in *Fig.* 51.

The solid phase of 2,4,6-trisubstituted pyrimidines has been exemplified by Obrecht and coworkers. The thiouronium salt **304** was prepared by treating high-loaded (3.5 mmol/g) Merrifield resin with thiourea in a 4:1 mixture of dioxane/ethanol at 85° (*Fig.* 51). Condensing one of three different acetylenic ketones **305a-c** in DMF with **304** gave **306a-c** which, after removal of the *t*-butyl esters with trifluoroactic acid, afforded resin-bound 2-alkylthio-4-aryl-6-carboxypyrimidines **307a-c**.

The known solution phase reactions involving ammonolysis and alcoholysis of 2-thiopyrimidines failed to give the desired 2-substituted pyrimidines in acceptable yield and purity when those particularly harsh reaction conditions were applied to the solid phase.[77] It was found that oxidation of



	R^1	R^2	R^3
312a	4-(MeO)C_6H_4	Me_2CHCH_2	*c*-C_6H_{11}
312b	*c*-C_6H_{11}	Me_2CH	*c*-C_6H_{11}
312c	$MeCH_2CH_2$	Me_2CH	*c*-C_6H_{11}
312d	$PhCH_2$	Me_2CH	Bu
312e	4-(MeO)C_6H_4	Me_2CH	*c*-C_6H_{11}

Fig. 51

2-thiopyrimidines **307a-c** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in methylene chloride cleanly afforded the 2-sulfonylpyrimidines **308a-c** which, when exposed to pyrrolidine in dioxane at room temperature, gave 2-pyrrolidinyl-4-aryl-6-carboxypyrimidines **309a-c** in 85-90% yield and 96-99% purity. The potential for the introduction of increased diversity into the pyrimidine synthesis was realized by utilizing an Ugi four-component reaction on resin-bound 2-alkylthio-4-aryl-6-carboxypyrimidines **307**, as exemplified by the use of **307a**. In particular, treating **307a** with a primary amine, aldehyde, and an isocyanide in a dioxane/methanol mixture at 55° gave 2-thio-4-phenyl-6-α-(acylmino)amides **310a-e**. As in the synthesis of **309a-c**, oxidation of **310a-e** with *m*-CPBA gave sulfones **311a-e** which were treated with pyrrolidine to afford 2-pyrrolidinyl-4-phenyl-6-α-(acylmino)amidopyrimidines **312a-e** in 65-87% yield.

Increased diversity was introduced into the 2,4,6-trisubsitututed pyrimidines by using other nucleophiles to displace sulfone **311** from the resin. The use of a diverse set of amines to induce the

nucleophilic removal of pyrimidines was also explored by Gayo and Suto (See *Fig.* 50).[75] Using **311a** as an example, it was found that only one equivalent of a primary or secondary amine or of an azide anion was necessary to cleave material from the resin as demonstrated with the cleavage of **311a** with *N*-methylpiperazine, 3-methylaminopyridine, benzylamine and azide giving **313a-d** in 68%, 53%, 62% and 70% yield, respectively (*Fig.* 52).

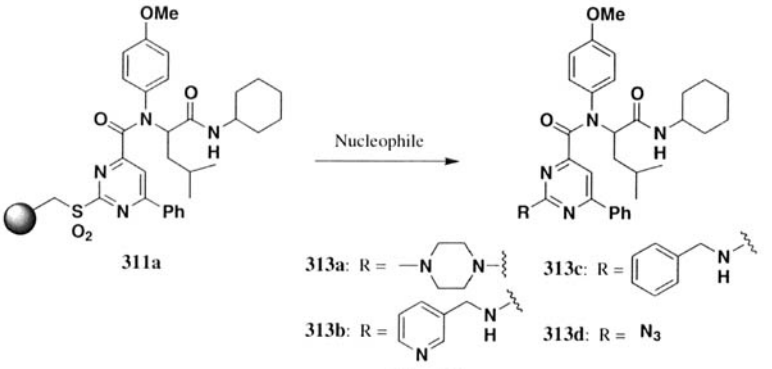


Fig. 52

Resin-bound α,β-unsaturated ketones have been used as intermediates in the synthesis of pyrimidines, dihydropyrimidines, pyridines and pyrazoles.[78] 4-Carboxybenzaldehyde (**314**) was

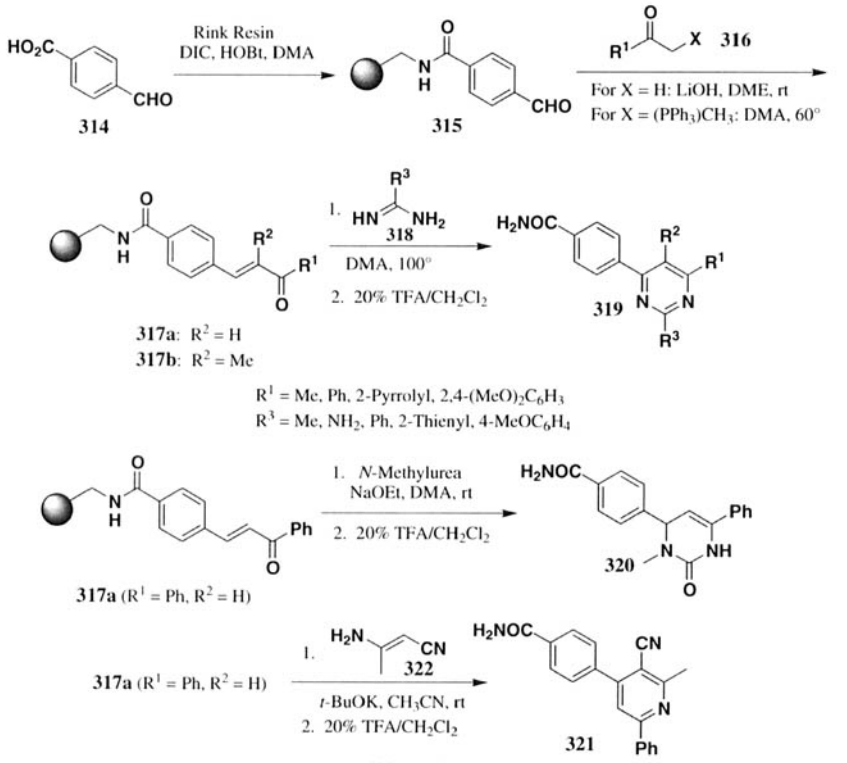


Fig. 53

coupled to polystyrene resin derivatized with a Rink linker to give **315** (*Fig.* 53). The authors claim that aldehydes bearing a furanyl or thiophenyl group can also be used in the following sequence, although this work is not shown. A Claisen-Schmidt condensation between a large excess of methyl ketones **316** and aldehydes **315** afforded the desired α,β-unsaturated ketone **317a**. A Wittig reaction was used when it was necessary to synthesize compound **317b**, where R^2 = Me. This was accomplished upon heating the triphenylphosphonium bromide **316** (X = $(PPh_3)Me$) in dimethylacetamide (DMA) with **315** to give **317b**. Treating **317a,b** at 100° in DMA with amidines **318** and then treating the resin with 20% TFA gave the desired arylpyrimidines **319** in 38-98% yield. Dihydropyrimidine **320** has also been synthesized, in 84% yield, from **317a** (R^1 = Ph, R^2 = H) upon exposure to *N*-methylurea and sodium ethoxide in DMA and cleavage from the resin with 20% TFA. 3-Cyanopyridine **321** was prepared in 46% yield by treating **317a** (R^1 = Ph, R^2 = H) with enamine **322** in acetonitrile containing *t*-butoxide and cleavage with acid.

4. Pyrazolones, Pyrazoles and Biphenyltetrazoles

1,3,4-Trisubstituted pyrazolones have been synthesized by Tietze from resin-bound β-ketoesters (*Fig.* 54). Acyl Meldrum's acid **324** was prepared by condensing five different acid chlorides with Meldrum's acid **323** in the presence of pyridine in methylene chloride. **324** was

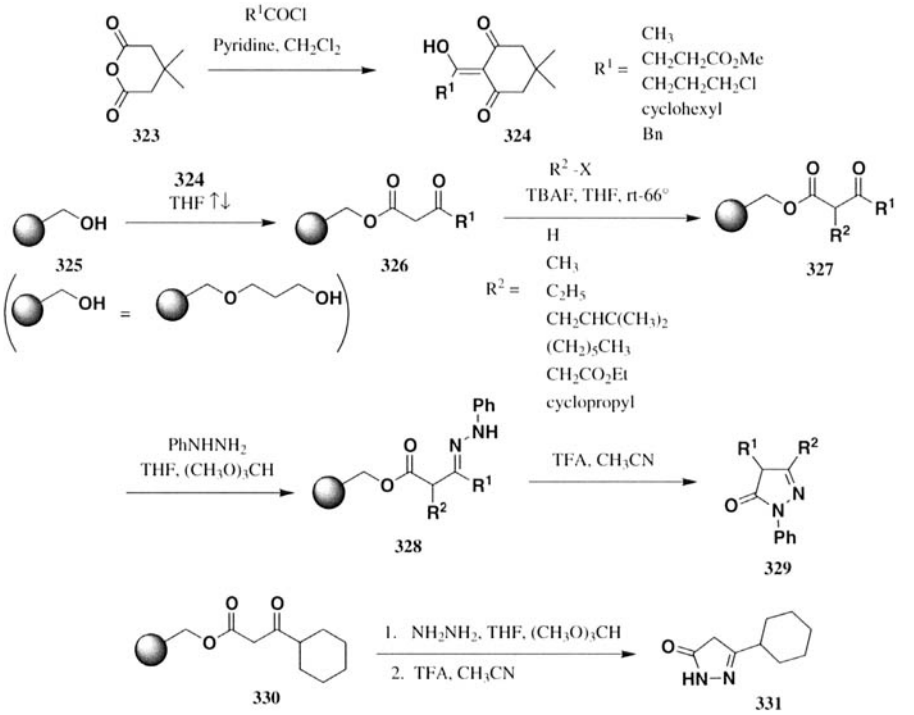


Fig. 54

attached to polystyrene resin **325** in THF at reflux to give resin-bound β-ketoesters **326**, the driving force for the formation of the ester linkage being the release of carbon dioxide and acetone from **324**. Selective mono-C-alkylation of **326** was achieved by using a large excess (36 equivalents) of alkyl

halides in 1 *M* tetrabutylammonium fluoride in THF at 25-66° to give **327**. Phenylhydrazine in trimethylorthoformate/THF was condensed with β-ketoesters **327** to give **328**, which, when treated with 2% TFA in acetonitrile at room temperature, gave the desired 1-phenylhydrazones **329** in 56-95% yield, and 85-95% crude purity. A single example is also given of the synthesis of an *N*-1 unsusbtituted pyrazolone,wherein **330** was treated with hydrazine hydrate, followed by acid to give **331** in 84% yield.

Watson and coworkers describe the synthesis of *N*-acyl- and *N*-sulfonyl-5-amino-3-(4-carboxyphenyl)pyrazoles from a resin-bound β-ketonitrile. Attempts at coupling the *p*-carboxyphenyl-β-ketonitrile **332** to resins under various unspecified conditions failed to yield any of the desired coupled material (*Fig.* 55). It was eventually found necessary to synthesize in solution the linker modified β-ketonitrile **333**. The synthesis of a resin-bound β-ketonitrile was accomplished by first making

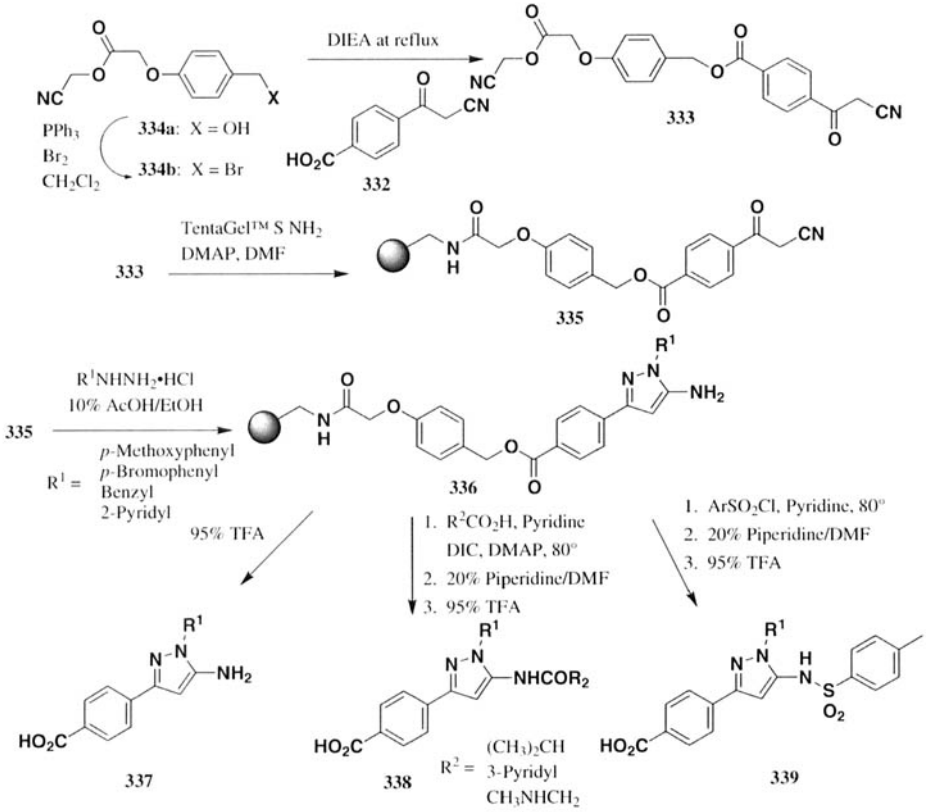


Fig. 55

the benzyl bromide **334b** of the known benzyl alcohol **334a**, coupling *p*-carboxy-β-ketonitrile **332** and displacing the ester of **333** with TentaGel™ S NH_2 resin to give **335**. Treatment of β-ketonitrile **335** with four different monosubstituted hydrazines in ethanol containing 10% acetic acid gave the desired 5-aminopyrazoles **336**. Pyrazoles **336** could be cleaved from the resin with 95% TFA to give pyrazoles **337** with 89-96% purity in unreported yields. It also proved possible to acylate the 5-aminopyra-

zoles **336** with carboxylic acids or sulfonyl chlorides in pyridine at 80°, with DMAP and diisopropylcarbodiimide in the case of the carboxylic acids, to afford, after acidic cleavage, *N*-acyl- and *N*-sulfonyl-5-amino-3-(4-carboxyphenyl)pyrazoles **338** and **339** with purities generally above 90%.

A pyrazole has been synthesized from α,β-unsaturated ketone **317** (R^2 = Ph) (*Fig.* 53).[78] Treating **317** with an excess of 2,3-dimethylphenylhydrazine in DMSO at 100° provided pyrazole **340** in 73% yield as a single diastereomer after cleavage with TFA (*Fig.* 56). A single diastereomer is formed owing to the difference in the nucleophilicity between the hydrazine nitrogens.

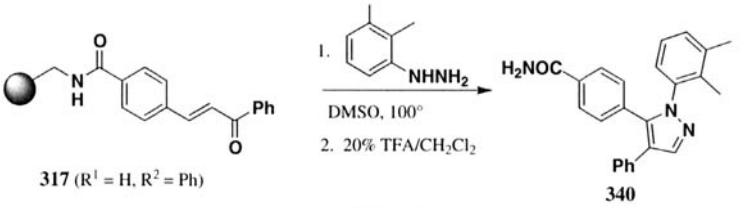


Fig. 56

A dihydropyran, which had been used to prepare Ellman's dihydropyran linker,[74] was used by Yoo and coworkers as a means of linking tetrazoles to a Merrifield resin (*Fig.* 57).[83] The sodium salt of the commercially available carboxylic acid **341** was attached to Merrifield resin in dimethylacetamide (DMA) at room temperature to give dihydropyran **342**. Using tetrazole **343** as a model, the

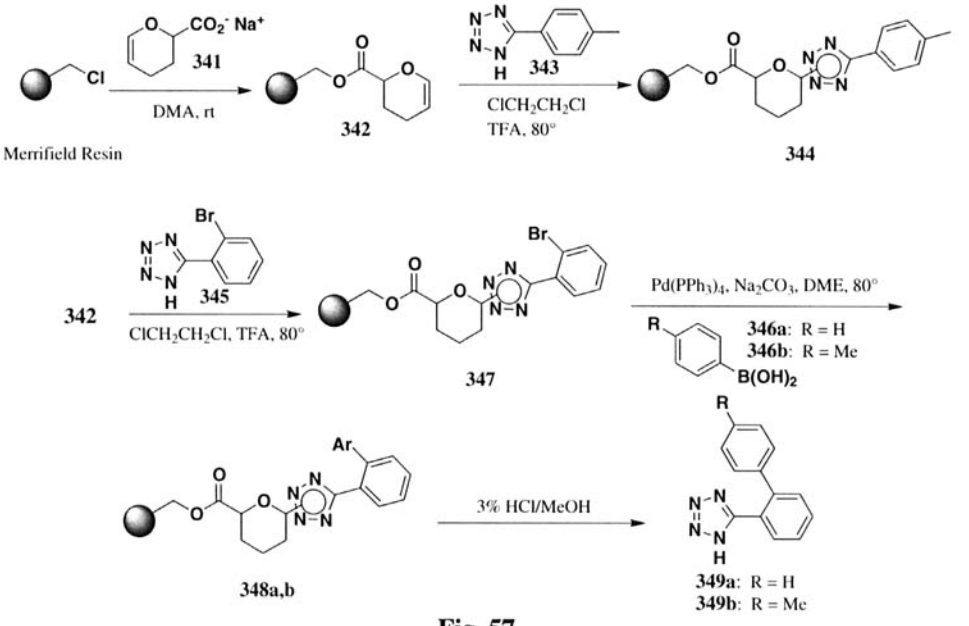


Fig. 57

best conditions found for loading **343** onto resin **342** involved using one equivalent of trfluoroacetic acid to give **344** in 25% yield. The yield was determined by measuring the amount of resin released upon treatment of **344** with 1:1 TFA/water. Even though a TFA/water mixture was used to quantate the yield of **344** loaded onto the resin, the best conditions found for the cleavage of **344** from the resin

was 3% HCl in methanol, and this was used in subsequent cleavages of tetrazoles from the resin. In order to demonstrate the derivatization of tetrazoles, Suzuki couplings were performed on *o*-bromophenyltetrazole **347**. **347** was obtained by coupling bromoterazole **345** to **342**. Two boronic acids **346a,b** were coupled to **347** to give **348a,b**. Following cleavage of **348a,b** from the resin, **349a,b** in 53 and 57% yield, respectively, were obtained.

5. Benzoxazoles, Isoxazolines, Benzimidazoles and Aminothiazoles

Wang and Hauske reported the novel solid phase synthesis of benzoxazoles.[84] The known imidazole functionalized Wang resin **350** was exposed to 1,3-dibenzylamine **351** to give the carbamate derivatized resin **352** (*Fig.* 58).[85] Reacting **352** with anhydride **353a** or **353b** in a 1:1 mixtrure of pyridine/methylene chloride containing DMAP provided carboxylic acids **354a,b**, which were subsequently coupled to substituted 2-aminophenols using PyBOP and NMM in DMF to give **355a-g**.

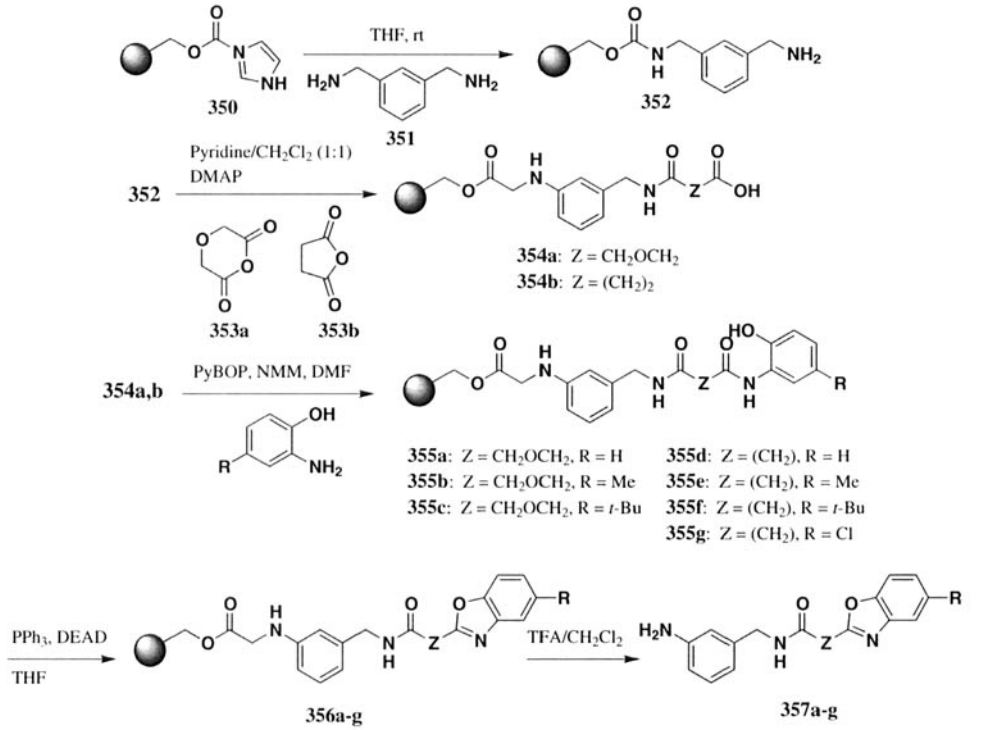


Fig. 58

Cleavage of **355a-g** from the resin with TFA gave the corresponding phenols in 83-97% yield and in 61-95% purity (not shown). The benzoxazole ring was formed upon treatment of phenols **355a-g** with triphenylphosphine and DEAD in THF to deliver **356a-g**. Attempts to form the benzoxazole ring using phosphorus oxychloride or thionyl chloride in toluene at 80° containing one equivalent of pyridine resulted in substantial amounts of uncyclized phenol being cleaved from the resin. Cleavage with TFA gave benzoxazoles **357a-g** in 79-97% yield and 57-94% purity. The lowest purity after the coupling of substituted 2-aminophenols to carboxylic acids **354** was found with compounds containing an electron withdrawing group, such as 2-amino-4-chlorophenol, which gave **355g** in a

purity of 61% following cleavage from the resin. The lower purity of **355g** was translated into the lower purity of benzoxazole **357g**, which was only 57% pure.

Cheng and Mjalli have synthesized Δ^2-isoxazolines through a 1,3-dipolar cycloaddition between nitrile oxides and activated olefins, and they have demonstrated that this chemistry proceeds in high yields and purities when either the aldoxime or the activated olefin is resin-bound (*Fig.* 59).[86] 4-Carboxybenzaldehyde (**314**) was attached to Wang resin to afford benzaldehyde resin **358**. Condensing hydroxylamine hydrochloride with **358** in methanol containing triethylamine gives aldoxime **359**. Oxidation of aldoxime resin **359** with a solution of bleach in THF generates the intermediate nitrile oxide which undergoes a 1,3-diploar cycloaddition with olefins **360a-f** to give, after cleavage from the resin with TFA, Δ^2-isoxazolines **361a-g** in 60-95% overall yield. The use of the internal olefin methyl crotonate (**360f**) produced a 1:1 mixture of the regiomeric isoxazolines **361f,g**. The authors also demonstrated that acrylate resin **362** reacted with nitrile oxides, generated in situ from aldoximes **363a-d**, to afford Δ^2-isoxazolines **364a-d** in 90-98% yield.

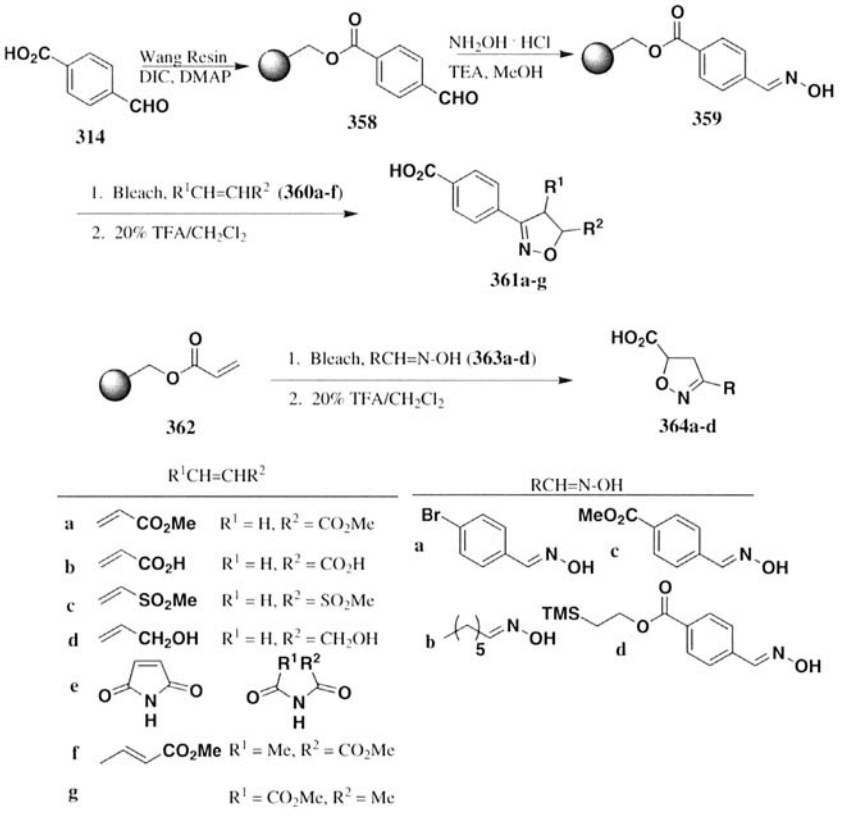


Fig. 59

The condensation of a phenylenediamine with a resin-bound benzaldehyde has been used to prepare benzimidazoles.[87] The solid phase synthesis of a benzimidazole from a resin-bound phenylenediamine and an imidate has already been reported.[88] 4-Carboxybenzaldehyde derivatized

Wang resin **358** was treated with phenylenediamines at 130° in nitrobenzene to afford **365** (*Fig.* 60). The benzimidazoles were removed from the resin with 50% TFA in methylene chloride to afford benzimidazoles **366** in unspecified yield.

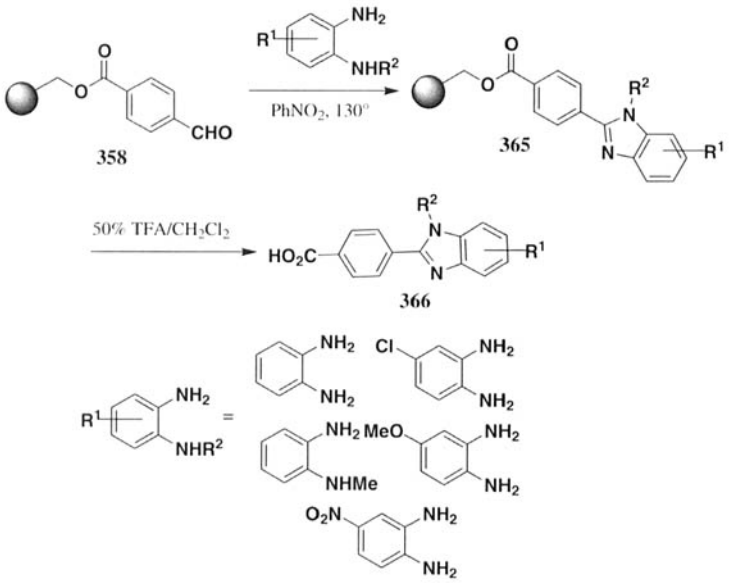


Fig. 60

An *ipso*-fluoro substitution reaction has been applied to the synthesis of benzimidazolones.[89] Resin-bound *o*-fluoronitrobenzoate **190** was treated with primary amines to give nitroaniline **367** (*Fig.* 61). Reduction of the nitro group with stannous chloride dihydrate in DMF and cyclization with disuccinimidocarbonate (DSC) gave benzimidazolone **368**. Alkylation of the remaining N-H proceeded

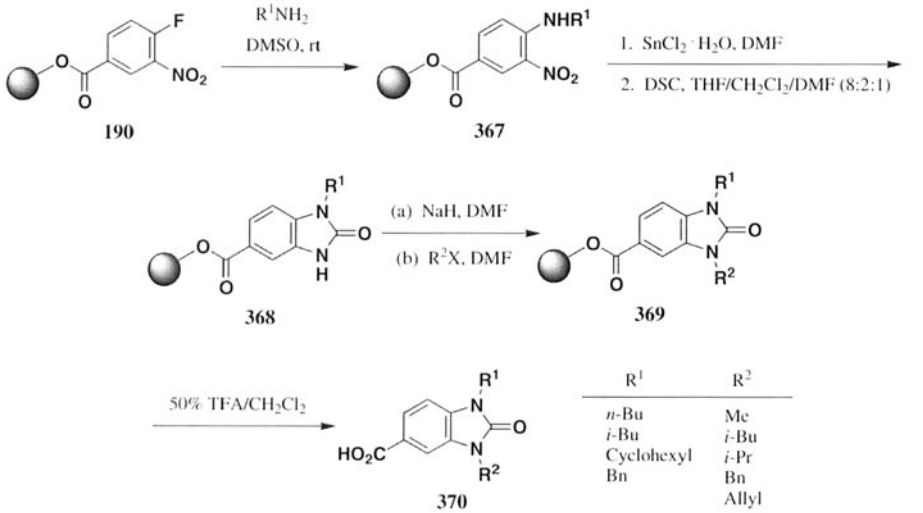
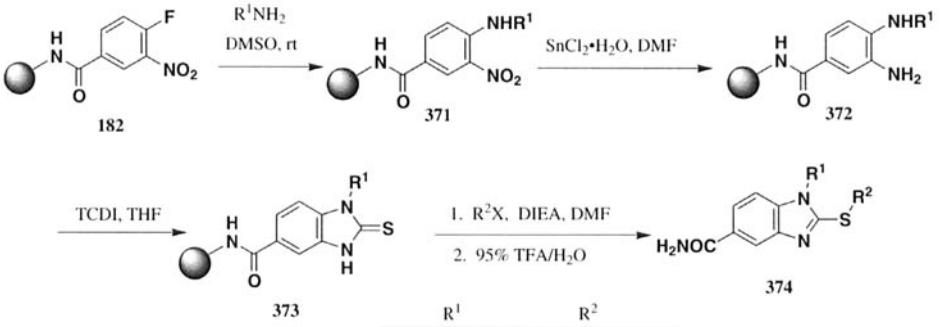


Fig. 61

with sodium hydride followed by addition of alkyl halides to deliver **369**. The 5-carboxybenzimidazolones **370** were obtained from **369** upon treatment with TFA in 90-100% yield.

2-Thiobenzimidazoles have been synthesized from a resin-bound *o*-phenylenediamine intermediate in yet another use of 4-fluoro-3-nitrobenzoic acid (**181**).[90] Using a sequence of reactions similar to that shown in *Fig.* 61, 4-fluoro-3-nitrobenzoate resin **182** was treated with various amines to give nitroaniline **371** (*Fig.* 62). Reduction of **371** to resin-bound *o*-phenylenediamine **372** occurred with stannous chloride hydrate in DMF. Cyclization of **372** to **373** proceeded cleanly only with thiocarbonyldiimidazole (TCDI) in THF. The use of thiophosgene failed to give the desired cyclization product **373** in satisfactory yields. Thiobenzimidazole **373** was alkylated with benzylic bromides in DMF and cleaved from the resin with TFA to give 1-alkyl-2-alkylthio-5-carbamoylbenzimidazoles **374** in 74-99% yield and with purities generally above 90%.

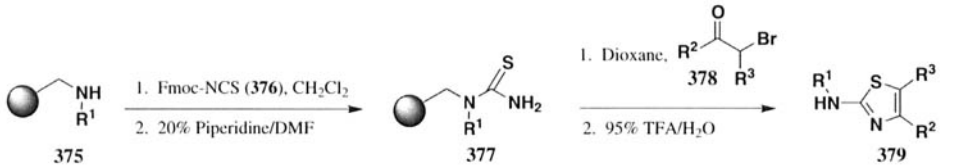


182 371 372 373 374

R^1	R^2
Bn	Ph
$(CH_2)_2CH(CH_3)_2$	2-Naphthyl
p-Fluorophenyl-CH_2	*p*-NO_2-Ph
$CH_2CH_2OCH_3$	*p*-CO_2CH_3-Ph

Fig. 62

The Hantzsch thiazole synthesis has been applied to the solid phase synthesis of 2-aminothiazoles.[91,92] The synthesis of resin-bound thioureas **377** was achieved by treating either Rink amide resin (R^1 = H) or reductively aminated ArgoGel™-MB-CHO resins **375** (R^1 = alkyl) with **376** (*Fig.* 63). **376**



375 377 378 379

Rink Amide Resin (R^1 = H)
or reductively aminated
ArgoGel™-MB-CHO Resin (R^1 = alkyl)

R^1	R^2	R^3
H	Ph	H
$(CH_2)CH_3$	*p*-$Et_2NC_6H_4$	Ph
p-$MeOC_6H_4CH_2CH_2$	*p*-$MeOC_6H_4$	
$MeOCH_2CH_2$	*m*-$NO_2C_6H_4$	
c-C_5H_9	*p*-$NO_2C_6H_4$	
H_2NCOCH_2	*p*-Cl-C_6H_4	
	p-F-C_6H_4	
	Adamantyl	

Fig. 63

was prepared by reacting Fmoc-Cl with potassium thiocyanate in anhydrous ethyl acetate. Thioureas **377** were then treated with an α-bromoketone **378** in dioxane and cleaved from the resin to give the desired 2-aminothiazoles **379** bearing three points of diversity in 69-96% yield and with excellent purities. One example is given where *N*-Fmoc glycine was attached to Rink resin and then the thiazole was synthesized from the amino portion of glycine ($R^1 = H_2NCOCH_2$).

6. Imidazolidones, Hydantoins, Thiohydantoins, Cyclic Ureas and Thioureas

The solid phase preparation of 2-imidazolidones has recently been reported by Goff.[93] A small library was constructed which consisted of treating Rink amide resin-bound allylic bromide **380** with eight primary amines **381a-h** to give **382a-h** and then mixing the amine derivatized resins together in an equimolar ratio (*Fig.* 64). The mixture of resins **382a-h** was treated with 2-bromophenylisocyanate to give a mixture of resin-bound 2-imidazolidones **384a-h**, *via* intermediate **383a-h**. Cleavage of **384a-h** from the resin with TFA gave **385a-h**, as confirmed by mass spectra of the crude product. The limitations associated with this process are that aryl isocyanates bearing a large ortho-substituent and aliphatic isocyanates do not routinely afford clean products. When large ortho-substituted aryl isocyanates were used with Rink amide resin **382**, *O*-cyclized oxazolidinone **386a** was found to occur competitively with the expected *N*-cyclization to give imidazolidone **387a**. Furthermore, the choice of linker profoundly impacted the product distribution when ortho-substituted aryl isocyanates were used. In particular, when using **382b** attached to HMPB-BHA resin, which has an ester linkage to the resin, only imidazolidone **386b** was isolated and no oxazolidinone **387b** was found.

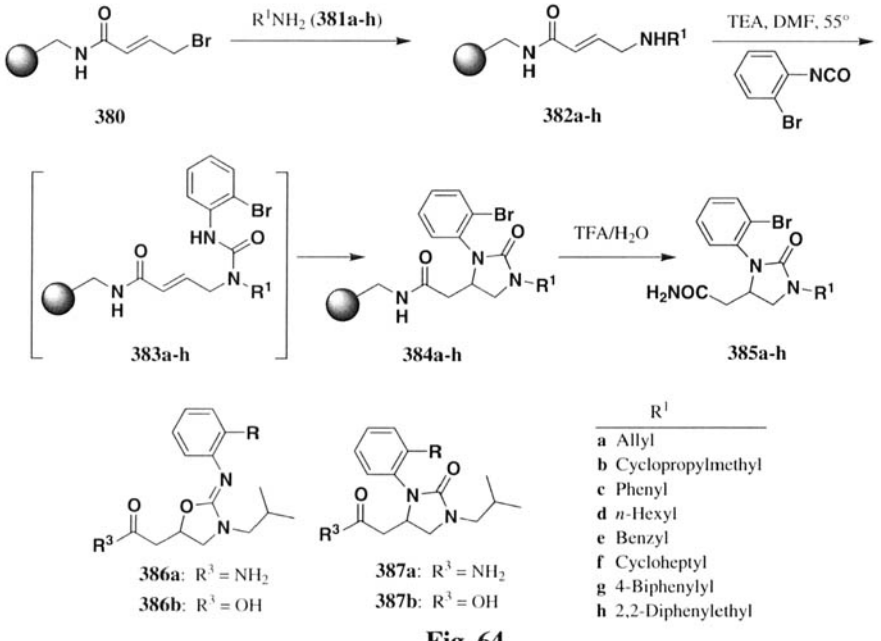


Fig. 64

Kim and coworkers have reported on the solid phase synthesis of eighteen hydantoins which utilized a room temperature base-promoted hydantoin ring forming reaction with concomitant

cleavage of the hydantoin from the resin.[94] Dressman first presented the synthesis of hydantoins *via* a based-promoted cyclization/cleavage step.[95] However, the conditions reported required heating a solution of methanol containing triethylamine at 55-90° for an extended period of time. *N*-Fmoc protected amino acids **388a-e** were coupled to Wang resin and the protecting group removed to give **389a-e** (*Fig.* 65). Condensing aldehydes in dimethylacetamide (DMA) containing 1% acetic acid with **389** gave the intermediate imines **390**, which were then directly reduced with sodium cyanoborohydride to afford **391**. Treating resin-bound amines **391** with 3.5 equivalents of various alkyl and aryl isocyanates in a 1:1 solution of DMF/toluene furnished carbamates **392**. Mixing **392** with neat diisopropylamine at room temperature for between five minutes and one hour cleanly gave the desired

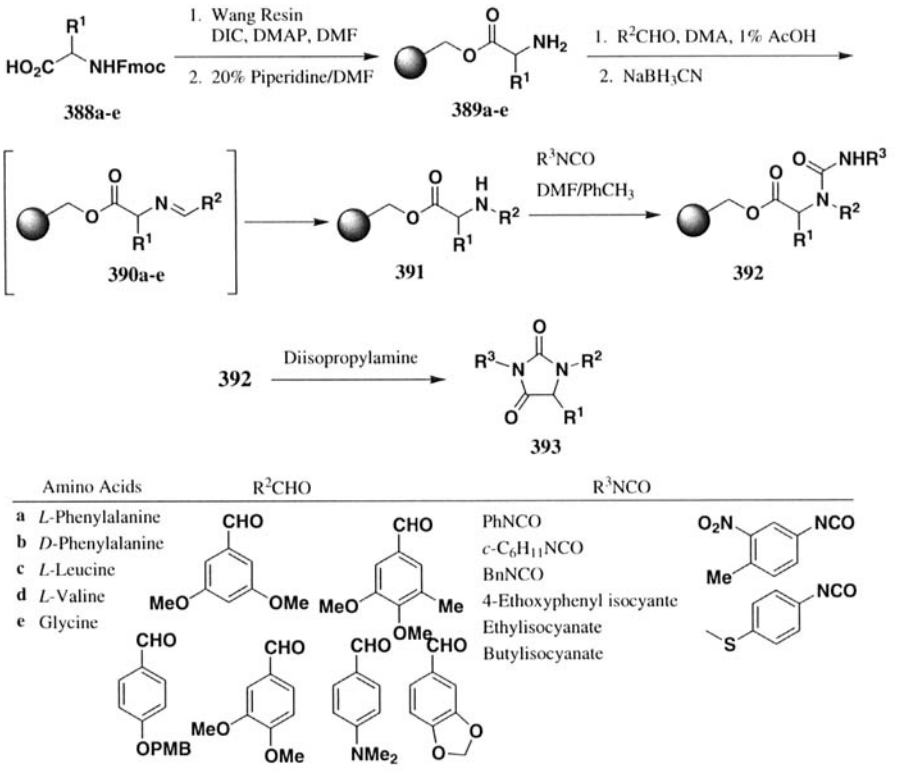


Fig. 65

hydantoins **393** with yields generally above 85%. Other bases which worked in the cyclization reaction were triethylamine, pyrrolidine and piperidine. Diisopropylamine was choosen since it was easier to remove from hydantoins **393**. Another advantage of the mild basic cleavage route is that it avoids strong acids used in the hydantoin route devised by DeWitt.[96]

Matthews and Rivero reported the solid phase base induced hydantoin formation simultaneous with the report by Kim and coworkers.[97,94] Amino acid derivatized Wang resins **394** were reductively alkylated with aldehydes to give secondary amines **395** (*Fig.* 66). Treatment of amines **395** with either isocyanates or thioisocyanates in methylene chloride yielded ureas **396a,b**. Cycliza-

tion and cleavage from the resin to afford hydantoins **397a** and thiohydantoins **397b** was achieved upon treament of resin-bound ureas **396** with triethylamine in chloroform at reflux for 24 hours. Hydantoins **397a** were isolated in 58-91% yield, while the thiohydantoins **397b** were isolated in 92-98% yield. Matthews and Rivero also demonstrated the ability to use resin-bound isocyanates in the synthesis of hydantoins. For instance, resin-bound phenylalanine **398** was converted into its corresponding isocyanate **399** upon exposure to phosgene in methylene chloride containing pyridine. Isocyanate **399** was then treated with amine **400** to give urea **401**, which was cleaved from the resin as previously described to afford hydantoin **402** in 100% yield. The ability to use a resin-bound isocyanate indicates that non-commercially available isocyanates can be used in hydantoin syntheses.

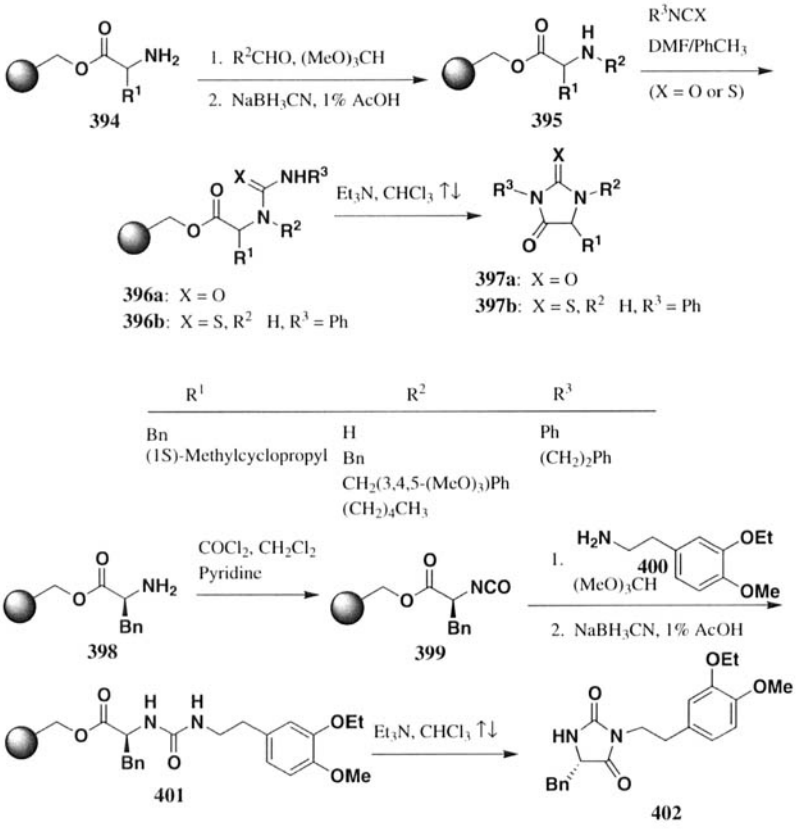


Fig. 66

Xiao and coworkers described the use of a phenyl carbamate to synthesize either unsymmetrical ureas or hydantoins. Dipeptide functionalized TentaGel™ S NH_2 or Wang resins **403a,b** were coupled to phenyl chloroformate in 9:1 dioxane:water containing DIEA to give resin-bound phenyl carbamates **404a,b** (*Fig.* 67). No hydantoin formation occurred under the conditions used to synthesize **404**. It was found that treating **404a,b** with primary or secondary amines in THF containing 0.5 *M* DIEA cleanly gave the unsymmetrical ureas **405a,b** which were cleaved from the resin with TFA to yield **406a,b**. When **404a,b** were treated with DIEA in DMF and cleaved from the resin, hydan-

toins **407a,b** were formed in almost quantitative yields and with high purity. It was found that hydantoin formation was complete on TentaGel™ S NH_2 in 1 hour, whereas up to 24 hour reaction times were necessary for hydantoin formation on Wang resin. It was also found that DBU was a superior base than DIEA for promoting hydantoin formation.

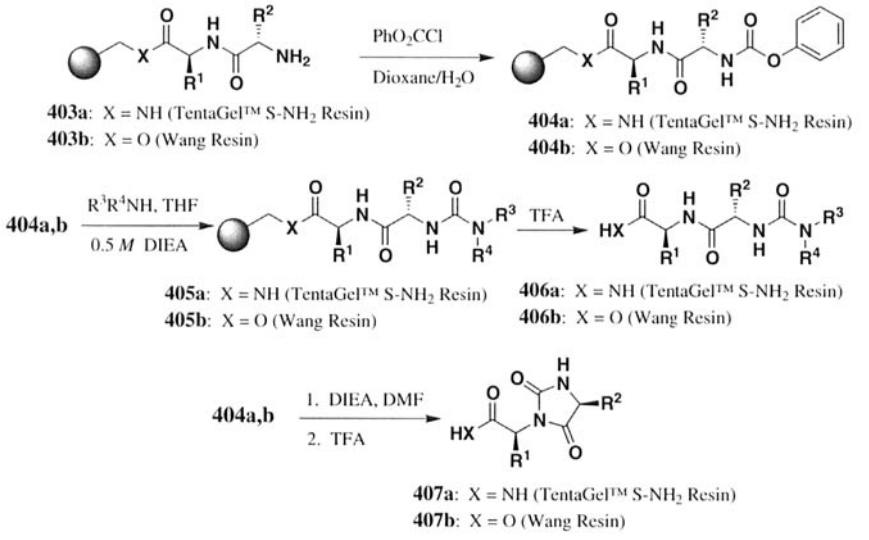


Fig. 67

Houghten and coworkers have used resin-bound peptides to synthesize cyclic ureas and cyclic thioureas.[99] *N*-Fmoc protected amino acids were loaded onto MBHA resin, the Fmoc group removed, and the resulting amine was protected with a trityl group to give **408** (*Fig.* 68). Deprotonation

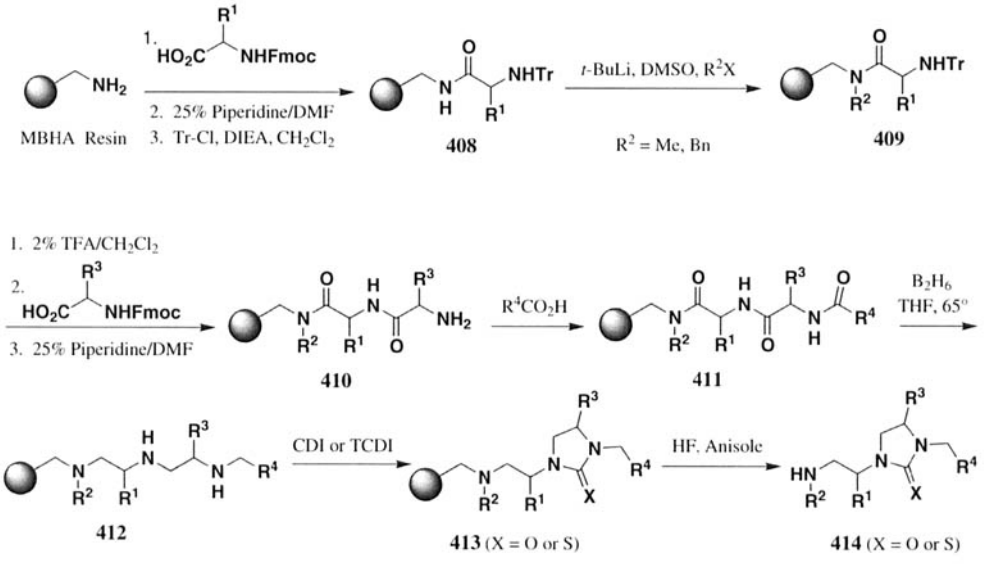


Fig. 68

of **408** with *t*-BuLi in DMSO and addition of either methyl iodide or benzyl bromide gave **409**. Removal of the trityl group, acylation of the resulting amine with another *N*-Fmoc protected amino acid and Fmoc removal produced amines **410**. *N*-Capping **410** with various carboxylic acids then gave the dipeptide **411** bearing four points of diversity. Reduction of the amide bonds was acheived by heating **411** in THF at 65° with diborane to give **412**. Cyclization of triamine **412** was accomplished upon treatment with either carbonyldiimidazole (CDI) or thiocarbonyldiimidazole to give **413**. The cyclic urea/thiourea was removed from the resin with hydrogen fluoride to give **414**. Analysis of the cyclic ureas and thioureas has indicated that less than 1% racemization is observed during the synthesis. This chemistry has been used by Houghten to prepare four combinatorial libraries each containing 118,400 cyclic ureas and thioureas.

7. *Oxopiperazine, Diketopiperazine, Diketomorpholine and 1,4-Diazabicyclo[3.4.0]nonan-2-ones*

A modification of a previously reported solid phase 2-oxopiperazine synthesis has enabled a direct synthesis of 2-oxopiperazines potentially containing five points of diversity, although examples given in the paper contain four points of diversity.[100,101] In the present synthesis, a resin-bound peptoid **415** is acylated with an α,β-unsaturated-γ-aminocarboxylic acid **416** to afford **417**. Acylation of **417** with α-halocarboxylic acids gives **418**, which is then treated with a concentrated solution of amines in dimethylsulfoxide at room temperature to afford resin-bound 2-oxopiperazines **419**. Cleavage from the resin was achieved using a 95% TFA/water mixture to give **420** in 36-93% yield and with purities generally above 80%. Even though there are not any examples of this in the paper, the author states that anilines can be used in the preparation of **416** leading to R^2 = Ph in **420**. This chemistry was also used to synthesize mixtures of 2-oxopiperazines.

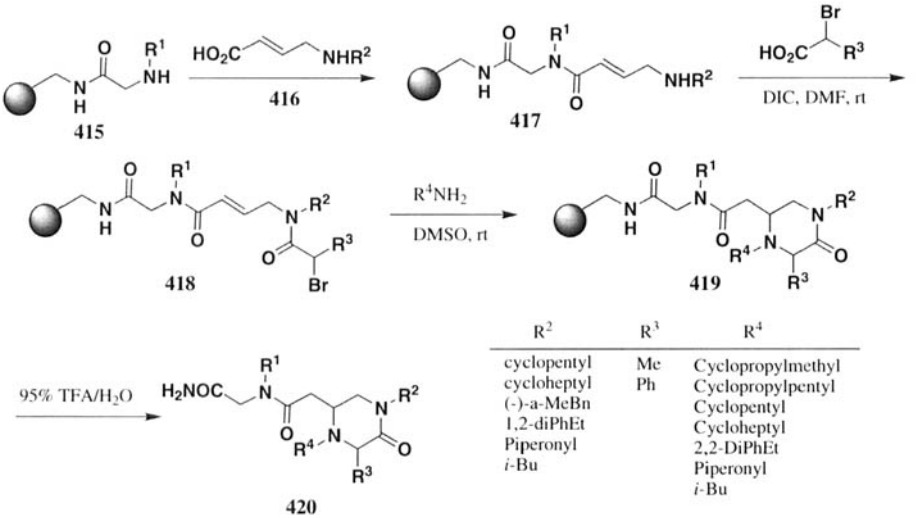


Fig. 69

An intramolecular Mitsunobu reaction has been used by Swayze to construct 3,4,8-trisubstituted 1,4-diazabicyclo[3.4.0]nonan-2-ones (*Fig.* 70).[102] The *N*-triethylsilylethoxycarbonyl (Teoc) protected *L*-prolinol derivative **421** was loaded onto benzaldehyde functionalized ArgoGel-OH resin

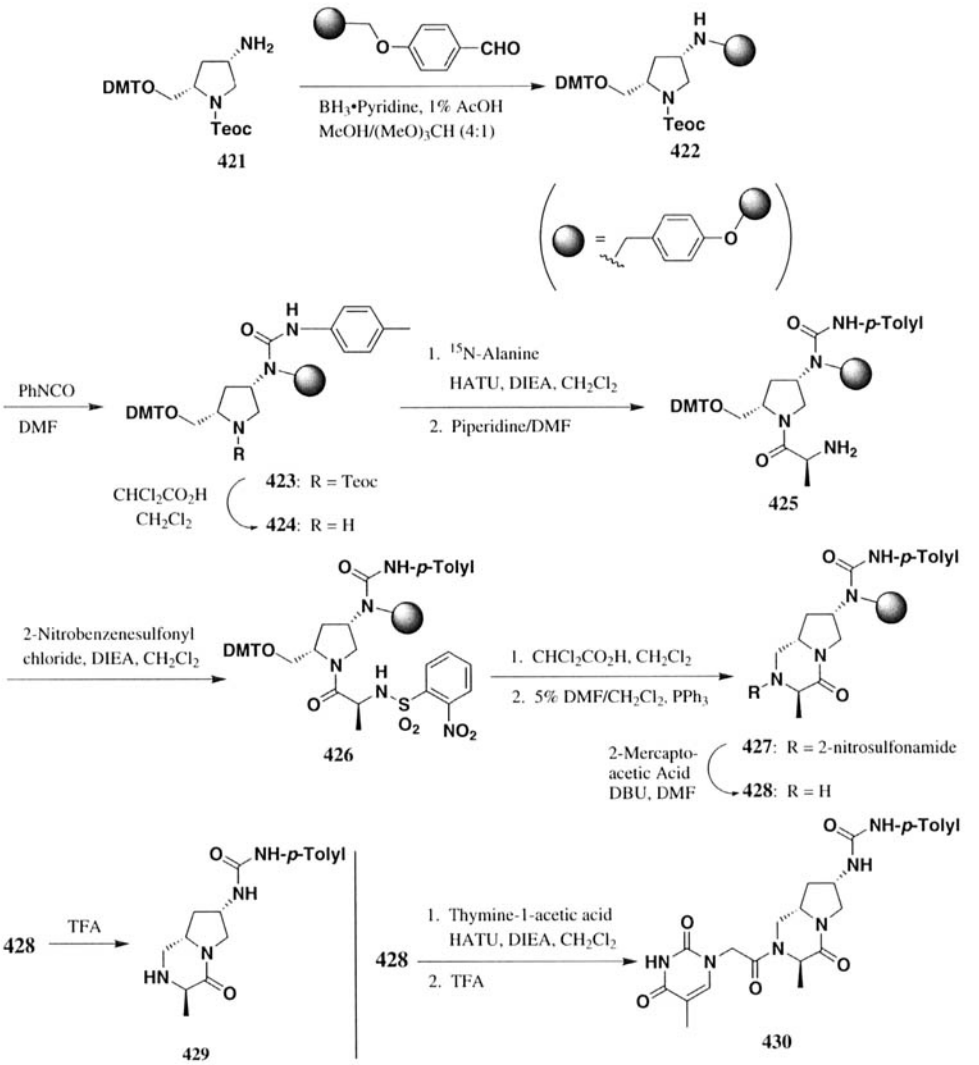


Fig. 70

by a reductive amination to afford **422**. Urea **423** was formed upon treating **422** with *p*-tolyl isocyanate in DMF. In order to follow subsequent reactions more easily, ^{15}N-Alanine was coupled to **424**, obtained after removal of the Teoc group from **423**, to give **425** following removal of the Fmoc group. Sulfonation of amine **425** with 2-nitrobenzenesulfonyl chloride afforded **426**. Removal of the DMT group followed by an intramolecular Mitsunobu reaction produced heterocycle **427**. Cleavage of the sulfonamide from **427** with mercaptoacetic acid/DBU yielded **428**, which was cleaved from the

resin with TFA to give **429** in unspecified yield. Alternately, **428** was acylated with thymine-1-acetic acid to give, after cleavage from the resin, **430** in 64% yield and 50% purity. The overall synthesis of **430** proceeded in twelve steps from commercially available resin.

Two syntheses of diketopiperazines containing either three or four points of diversity and a synthesis of diketomorpholines bearing four points of diversity has been reported.[103] The route to trisubstituted diketopiperazines begins with the esterification of either TentaGel S-OH or PAM resin with *N*-Fmoc or *N*-Boc protected amino acids *via* Mitsunobu conditions or acyl fluorides to give **431** (*Fig.* 71). The acyl fluorides were generated *in situ* using 1,3-dimethyl-2-fluoropyridinium-4-toluenesulfonate (DMFP). Deprotection of the amine protecting group and reductive alkylation with various aliphatic and aromatic aldehydes delivered **432**. It was found that benzaldehyde derivatives required acetic acid during the reduction, whereas aliphatic aldehydes where reduced in methanol. **432** was acylated with a *N*-Boc protected amino acid using DMFP, HATU, DIC/HOAt or a symmetrical anhydride to produce dipeptide **433**. Removal of the Boc group and cyclization in either basic (4% triethylamine) or acidic (1% acetic acid) mixtures of toluene/ethanol furnished trisubstituted diketopiperazines **434**.

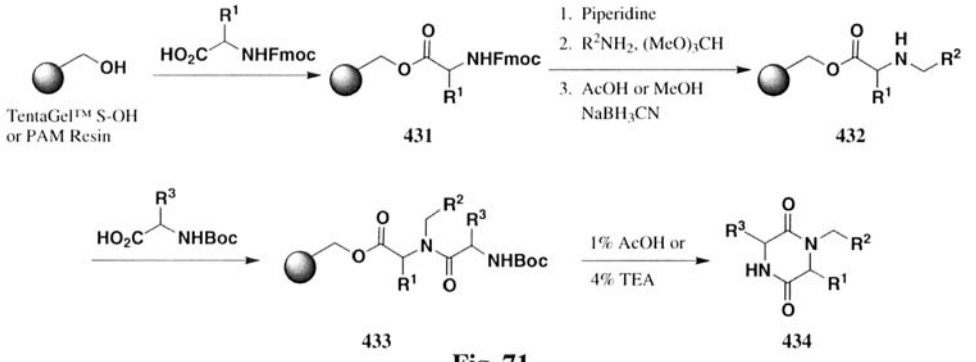


Fig. 71

A multi-component approach to tetra-substituted diketopiperazines is shown in *Fig.* 72. The resin bound amino acid **435** was mixed in a methanol solution with an aldehyde, an *N*-Boc protected

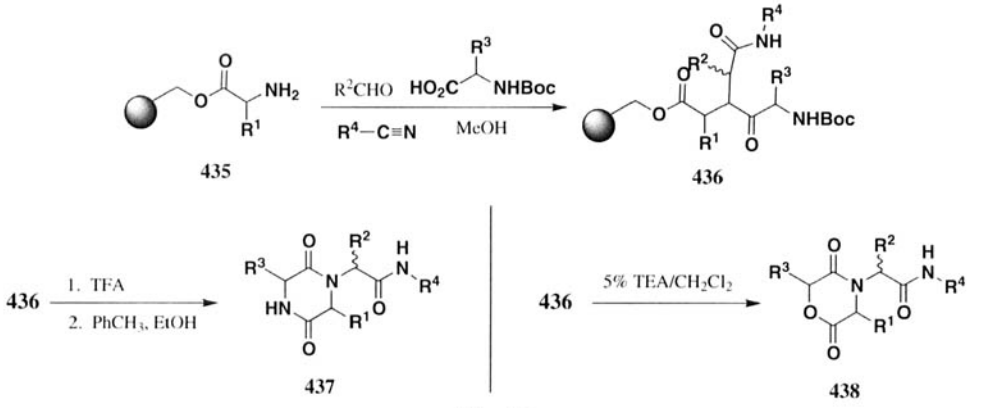


Fig. 72

amino acid, and an isocyanide to give **436**. Removal of the Boc group and cyclization under the conditions mentioned above for *Fig.* 71, afforded diketopiperazines **437**. It was found that Pam resin derived products were obtained in significantly lower yields than those obtained from TentaGel resin. Diketomorpholines were also synthesized using an Ugi reaction. In particular, treating **436** with 5% TEA in methylene chloride gave the trisubstituted diketomorpholines **438**.

III. CONCLUSION

Considerable progress has been made in solid phase heterocyclic synthesis since the end of 1996 as evidenced by the number and breadth of syntheses covered in this review. Advances in the area of tracerless linkages and syntheses which utilize the previous resin linkage site as a crucial component of the anticipated biological activity of a class of heterocycles continues to warrant increased attention, as one of the major limitations of most current syntheses is the vestigial functionality associated with the linkage to the resin. Few syntheses in this review have been demonstrated in actual library development, leading to potential concerns as to the fidelity of the chemistry (See Table 2 for a listing of *Fig.*s which have been used in the preparation of libraries). The paucity of disclosed heterocyclic libraries should change in the near future as more work is presented describing the construction of large heterocycle libraries.

TABLE 2. Listing of Heterocycle Libraries Covered In This Review

Fig.	Reference	Heterocycle Type	# of Compounds Prepared
Fig. 25	46	Tetrahydroquinolines	80
Fig. 29	15	Quinolines	4,140
Fig. 40	63	1,4-Diazepine-2,5-diones	2,720
Fig. 41	65	1,4-Benzodiazepine-2-ones	120
Fig. 45	68	Tetrahydro-β-Carbolines	345
Fig. 46	70	1,4-Benzodiazepine-2,5-diones	2508
Fig. 48	71, 72	Purines	500-1000
Fig. 68	99	Cyclic Ureas and Thioureas	118,400

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(Received May 26, 1998; in final form August 17, 1998)