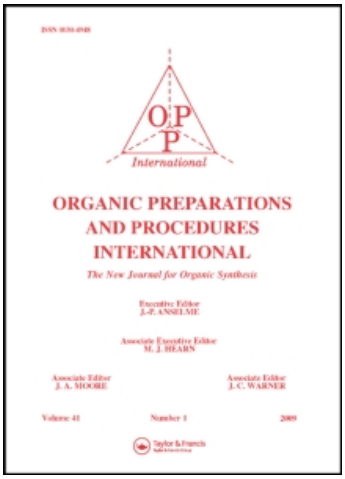

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Fernando Albeiicio[a]; Rafael Chinchilla[b]; David J. Dodsworth[b]; Carmen Nájera[b]
[a] Department of Organic Chemistry, University of Barcelona, Barcelona, SPAIN [b] Department of Organic Chemistry, University of Alicante, Alicante, SPAIN

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NEW TRENDS IN PEPTIDE COUPLING REAGENTS

Fernando Albericio,[†] Rafael Chinchilla,[††] David J. Dodsworth,[††] and Carmen Nájera*,[††]

[†] *Department of Organic Chemistry, University of Barcelona, E-08028 Barcelona, SPAIN*
[††] *Department of Organic Chemistry, University of Alicante, E-03080 Alicante, SPAIN*

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[†] *Department of Organic Chemistry, University of Barcelona, E-08028 Barcelona, SPAIN*

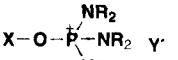
[††] *Department of Organic Chemistry, University of Alicante, E-03080 Alicante, SPAIN*

INTRODUCTION

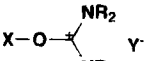
The activation of carboxylic acids for the formation of amides or esters is an important process usually carried out using the so-called peptide coupling reagents.[1] The formation of the amide bond is the main goal in the synthesis of a huge array of organic compounds of biological interest[2] such as peptides, peptoids, oligocarbamates, oligoamides, β-lactams, polyenamides, benzodiazepines, diketopiperazines, and hydantoins. The ester group is another important functionality present in many organic compounds and can also be prepared directly from the carboxylic acid and the corresponding alcohol using peptide coupling reagents.

The coupling techniques can be carried out in solution or in the solid-phase using two different methods: the *in situ* activation of the carboxylic acid or the prior preparation and isolation of an activated species. Whichever method is employed, it has to be very efficient and reliable, for example when long sequences of amino acids are incorporated in solid-phase peptide synthesis.[1,3] Another important consideration is the maintenance of configurational integrity, especially in α-amino acids. Thus, the requirement for a combination of high yields and no racemization represents the main challenge in the development of coupling reagents. In this review, the evolution in the development of coupling reagents from carbodiimides to onium (phosphonium and aminium) salts, as well as other reagents (see Appendix), mainly during the last decade will be presented.

The activation of carboxylic acids using onium salts is a faster process than when using carbodiimides, specially with hindered substrates. These phosphonium and aminium salts are formed from a phosphonium or an iminium cation bonded generally to a XO- group, normally a hydroxylamine derivative. However, carbodiimides in the presence of several additives with an X-OH structure, again usually a hydroxylamine derivative, are still very useful reagents.[4]



phosphonium salts



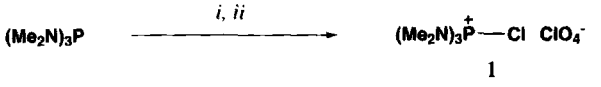
aminium salts

I. PREPARATION OF REAGENTS

1. Phosphonium Salts

The activation of carboxylic acids using phosphonium salts was described in the pioneering works of Kenner,[5] Castro,[6] Hruby,[7] and Yamada.[8] Thus, the treatment of hexamethylphosphoramide

(HMPA) with tosyl chloride, anhydride or thionyl chloride,[5] or the reaction of phosphine or phosphorous amides with tetrahalomethanes[6-8] were amongst the methods proposed for the synthesis of acyloxyphosphonium salts which were then used as acylating reagents. Castro and Dormoy could isolate the chlorotrisdimethylaminophosphonium cation as its perchlorate **1** by reaction of tris(dimethylamino)phosphine with carbon tetrachloride in ether followed by addition of an aqueous solution of ammonium perchlorate[9] (*Scheme 1*).

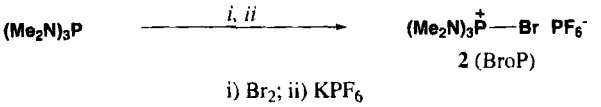


1

i) CCl_4; ii) NH_4ClO_4

Scheme 1

The corresponding bromo derivative **2** (BroP) was prepared in a similar way in 85% yield by using bromine in ether at 0° followed by anion interchange with potassium hexafluorophosphate[10] (*Scheme 2*). The substitution of the tris(dimethylamino) group by the tripyrrolidino moiety, in order to

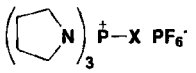


2 (BroP)

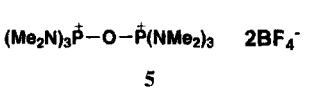
i) Br_2; ii) KPF_6

Scheme 2

avoid the formation of the carcinogenic HMPA as by-product, afforded the new halophosphonium reagents chlorotripyrrolidinophosphonium hexafluorophosphate (PyCloP, **3**) and bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP, **4**),[11] both of which are commercially available. In addition, the Bates reagent (**5**)[12] was one of the first commercially available phosphonium salts.

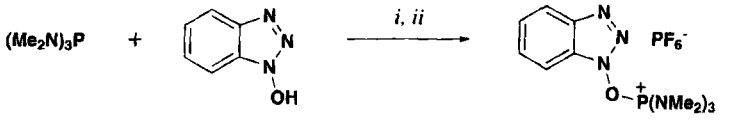


3 (PyCloP); X=Cl
4 (PyBroP); X=Br



5

Benzotriazol-1-yl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP, **6**), which was one of the most used phosphonium salts, was prepared by reaction of tris(dimethylamino)phosphine with carbon tetrachloride in the presence of 1-hydroxybenzotriazole (HOBt) in tetrahydrofuran (THF) at –30° followed by interchange of the chloride anion with the hexafluorophosphate anion[13] (*Scheme 3*). A more economical preparation of this reagent involved the reaction

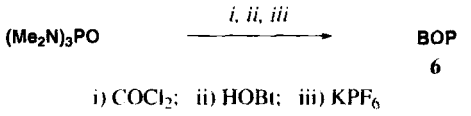


6 (BOP)

i) CCl_4; ii) KPF_6

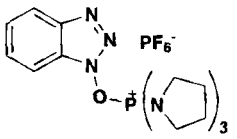
Scheme 3

of HMPA with phosgene in toluene followed by reaction with HOBt in the presence of triethylamine and then finally anion exchange[14a] (*Scheme 4*). Phosphoryl chloride can also be used for the preparation of the chlorophosphonium cation intermediate, which can be isolated as hexafluorophosphate or



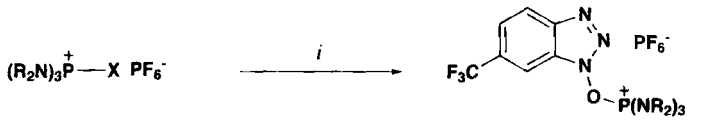
Scheme 4

perchlorate in almost quantitative yield.[14b] In order to avoid the use of HMPA, the pyrrolidine derivative **7** (PyBOP®) has been prepared under similar reaction conditions and it is also commercially available.[15] Both the reagents, BOP (**6**) and PyBOP (**7**), can be prepared by using triphosgene which is less moisture-sensitive and easier to handle than $POCl_3$.[16]

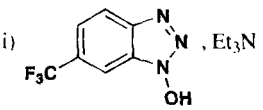


7 (PyBOP)

Related HOBt-substituted reagents such as CF_3-BOP (**8**) and CF_3-PyBOP (**9**) have been prepared[17] following the same protocol as for BOP (**6**) and PyBOP (**7**).[14b] In the first case, 1-hydroxy-6-(trifluoromethyl)benzotriazole[18] was added to a mixture of chlorotris(dimethylamino)phosphonium hexafluorophosphate and triethylamine in acetone, and in the second case the reagent was added directly to PyBrOP (**4**) (*Scheme 5*).



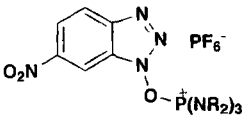
8 (CF_3-BOP); R = Me
9 (CF_3-PyBOP); R-R = $(CH_2)_4$



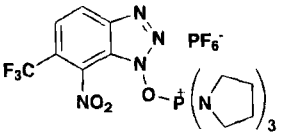
Scheme 5

Several analogues containing electron-withdrawing substituents in the benzotriazole ring such as [(6-nitrobenzotriazol-1-yl)oxy]tris(dimethylamino)phosphonium hexafluorophosphate (**10**, NOP), the pyrrolidino derivative PyNOP (**11**) and the so-called PyFOP (**9**) have been prepared from their respective phosphoramides.[19] In the case of NOP (**10**), HMPA was treated *in situ* with $POCl_3$ in dichloromethane followed by addition of a mixture of trifluoroacetic acid (TFA) and 6-nitro-1-hydroxybenzotriazole and then final anion interchange. For the preparation of PyNOP (**11**) and

PyFOP (**9**), the corresponding 6-nitro- or 6-trifluoromethyl-substituted benzotriazoles were allowed to react with PyCloP (**3**). The chlorophosphonium salt **3** is obtained by treatment of tris(pyrrolidino)phosphine oxide with $POCl_3$ in dichloromethane followed by reaction with TFA and KPF_6 in water. The disubstituted benzotriazole[20] derivative [4-nitro-6-(trifluoromethyl)benzotriazol-1-yl)oxy]tris(pyrrolidino)phosphonium hexafluorophosphate (**12**, CF_3-NO_2-PyBOP)[21] has been prepared in 85% yield by reaction of PyBrOP (**4**) with the corresponding disubstituted hydroxybenzotriazole.

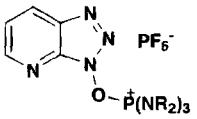


10 (NOP); R = Me
11 (PyNOP); R-R = $(CH_2)_4$

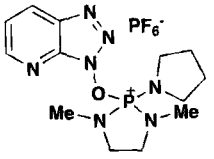


12 (CF_3-NO_2-PyBOP)

1-Hydroxy-7-azabenzotriazole (HOAt),[22] which had been initially used for the preparation of aminium salts (see section I.2), has also been employed in the synthesis of the dimethylamine and pyrrolidine phosphoramide derivatives AOP (**13**) and PyAOP (**14**), respectively[23] as well as for **15** (AOMP; this abbreviation has also been used for compound **62**).[24]

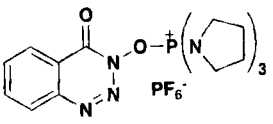


13 (AOP); R = Me
14 (PyAOP); R-R = $(CH_2)_4$

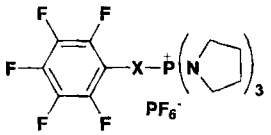


15 (AOMP)

1-Oxo-2-hydroxydihydrobenzotriazine (HOOBt)[25] has been used for the preparation of the phosphonium salt PyDOP (**16**), in 94% yield, by reaction with the phosphonium salt PyCloP (**3**) in the presence of triethylamine.[19] Pentafluorophenol and -thiophenol derivatives of tris(pyrrolidino)phosphine oxide **17** (PyPOP)[19] and **18** (PyPSP)[24] have also been prepared in 92% yield by reaction of the corresponding phenol or thiophenol with PyClOP.

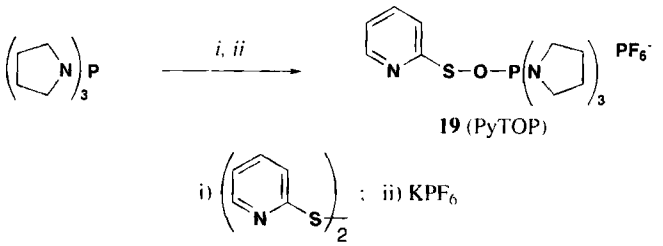


16 (PyDOP)



17 (PyPOP); X = O
18 (PyPSP); X = S

The thiophosphonium salt **19** (PyTOP) has been prepared by treating tris(pyrrolidino)phosphine with 2,2-dipyridyl disulfide followed by precipitation (47%) of the phosphonium salt as its hexafluorophosphate[19] (*Scheme 6*).



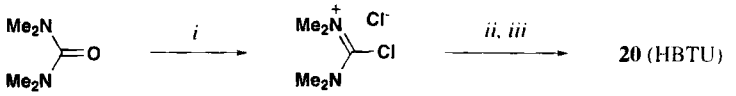
Scheme 6

2. Aminium Salts

Aminium salts bear a positive carbon atom instead of the phosphonium residue and were initially assigned an uronium-type structure by analogy with the corresponding phosphonium salt. However, in some cases it has been demonstrated that they crystallize as aminium salts, as in the case of *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (**20**, HBTU).[26]

20 (HBTU)

The preparation of these commercially available reagents was achieved by transformation of tetramethylurea (TMU) into the corresponding chlorouronium salt (TMU-Cl, **21**), by treatment with phosgene in toluene followed by reaction of **21** with HOBt and interchange with NH_4PF_6.[22] Another route for the preparation of this reagent requires first the anionic interchange and then the reaction of the chlorouronium salt with HOBt in the presence of triethylamine, which then affords HBTU in 86% yield[27] (*Scheme 7*).



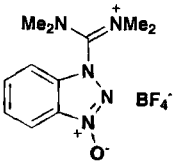
21

i) $COCl_2$; ii) NH_4PF_6; iii) HOBt

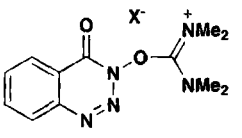
Scheme 7

Chlorotetramethyluronium chloride **21** (TMU-Cl) has also been prepared by replacement of the extremely toxic phosgene by oxalyl chloride.[28] HBTU has been obtained using a one-pot procedure in organic solvents, and also the analogous tetrafluoroborate reagent, (**22**, TBTU), which could

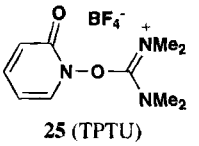
not be prepared by the previous procedure. The two reagents are commercially available. This one-pot method was also applied to the preparation of the HOOBt derivative 2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (**23**, TDBTU), the pyridone derivative 2-(2-oxo-1(2*H*)-pyridyl-1,1,3,3-tetramethyluronium tetrafluoroborate (**25**, TPTU) and the hydroxysuccinimide derivatives 2-succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate (**26**, TSTU) and 2-(5-norbornene-2,3-carboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (**27**, TNTU),[28a] which are also commercially available. The hexafluorophosphate derivative **24**[28b] prepared from HOOBt and TMU has been also prepared following the same strategy.[27b]



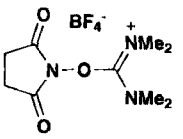
22 (TBTU)



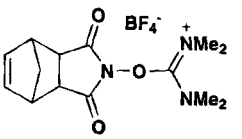
23 (TDBTU); X = BF_4
24 (HDTU); X = PF_6



25 (TPTU)

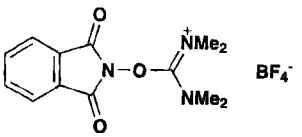


26 (TSTU)

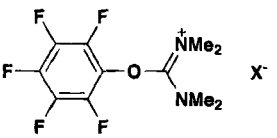


27 (TNTU)

Other XOH derivatives attached to the tetramethyluronium cation include the *N*-hydroxyphtalimide (HOPht) derivative **28**[29] (TPhTU) and the pentafluorophenol derivatives **29**[30] (TPfTU) and **30**[31] (HPfTU).

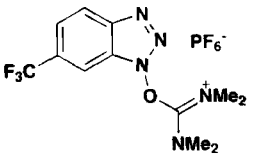


28 (TPhTU)

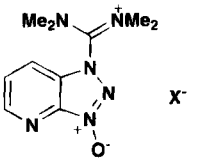


29 (TPfTU); X = BF_4
30 (HPfTU); X = PF_6

In the case of 1-hydroxybenzotriazole derivatives containing electron-withdrawing groups, as mentioned under the phosphonium salts (see above), the 6-trifluoromethyl derivative (**31**, CF_3-HBTU) has been prepared in 78% yield from tetrafluoromethylchloroformamidinium hexafluorophosphate.[17] The corresponding HBTU (**20**) and TBTU (**22**) analogues, containing the HOAt structure instead of the HOBt, have been prepared from the TMU-Cl salts to give the corresponding reagents *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-b]pyridino-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate (**32**, HATU) and tetrafluoroborate (**33**, TATU),[22] which have been shown to be *N*-oxides[26] with aminium structures.

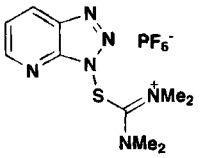


31 (CF_3-HBTU)

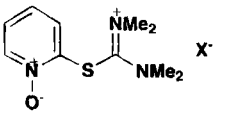


32 (HATU); X = PF_6
33 (TATU); X = BF_4

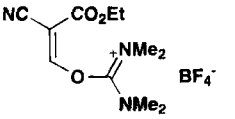
Two tetramethylurea-derived thiouronium reagents have been prepared, the HOAt derivative **34**[24] (HATTU) and the *N*-hydroxy-2-pyridinethione derivatives **35**[32,33] (HOTT) and **36**[33] (TOTT), both following Knorr's strategy.[28,33] The structure of compound **35** was determined by X-ray analysis.[32] *O*-[(Ethoxycarbonyl)cyanomethyleneamino]-*N,N,N',N'*-tetramethyluronium tetrafluoroborate **37** (TOTU) has been developed by a Hoechst group.



34 (HATTU)

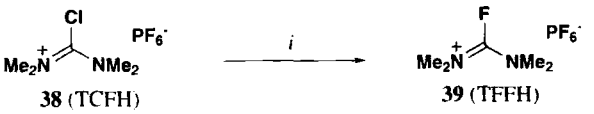


35 (HOTT); X = PF_6
36 (TOTT); X = BF_4



37 (TOTU)

Tetramethylfluoromethylformamidinium hexafluorophosphate (**39**, TFFH)[34] is a stable halouronium reagent which is commercially available and can be prepared by reaction of tetramethylchloroformamidinium hexafluorophosphate (**38**, TCFH) with an excess of anhydrous potassium fluoride in acetonitrile (*Scheme 8*). Reagent **39** has also been prepared using oxalyl chloride[35a] instead of phosgene and **38** has been prepared using $POCl_3$.[35b]

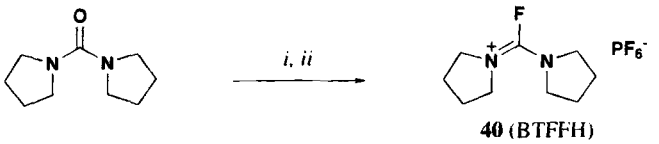


38 (TCFH) → **39** (TFFH)

i) KF, MeCN

Scheme 8

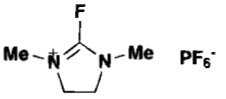
The chlorouronium salts derived from dipyrrolidinourea have been prepared by chlorination with phosgene[34] or oxalyl chloride[36] followed by transformation into bis(tetramethylene)fluoroformamidinium hexafluorophosphate (**40**, BTFFH) in 90% yield, by reaction with KF and KPF_6 in acetonitrile (*Scheme 9*). This fluoride salt **40**, as well as the *N,N'*-dimethylethylenurea (DMI)-derived compound **41** (DFIH), have been described by the same author.[37]



40 (BTFFH)

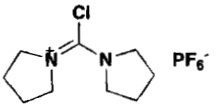
i) $(COCl)_2$, toluene; ii) KF, KPF_6, MeCN

Scheme 9

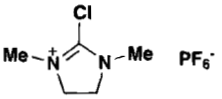


41 (DFIH)

The pyrrolidino chlorouronium salt **42** (PyClU) has been prepared from the corresponding urea by reaction with $POCl_3$[38] or phosgene[39] followed by treatment with aqueous KPF_6. In addition, the chloroimidazolidinium salt **43** (CIP) has been obtained by chlorination of DMI with oxalyl chloride followed by anion interchange with NH_4PF_6.[40] Both reagents are commercially available.

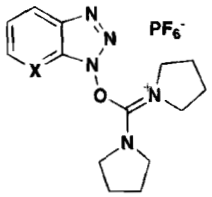


42 (PyClU)

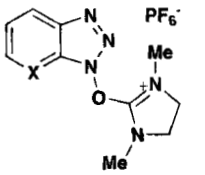


43 (CIP)

1-Hydroxybenzotriazole (HOBt) has been coupled with these chlorouronium reagents **42** and **43** to give the corresponding derivatives **44**[38] (HBPyU) and **45**[40,41] (BOI), respectively. The related 7-aza-1-hydroxybenzotriazole (HOAt) derivatives **46** (HAPyU) and **47** (HAMDU)[23b] have also been prepared.

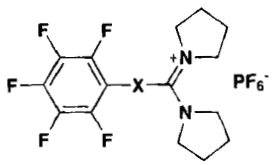


44 (HBPyU); X = CH
46 (HAPyU); X = N

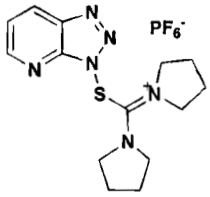


45 (BOI); X = CH
47 (HAMDU); X = N

In the case of the pentafluorophenyluronium salt **48** (HPyOPfp), the preparation has been carried out by treatment of the urea with $POCl_3$ followed by anion interchange and final reaction with potassium pentafluorophenolate.[42] The corresponding thiouronium reagent **49** (HPySPfp) has also been described as well as the reagent **50** (HAPyTU).[43]

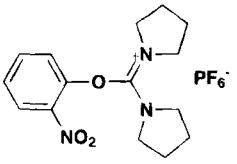


48 (HPyOPfp); X = O
49 (HPySPfp); X = S

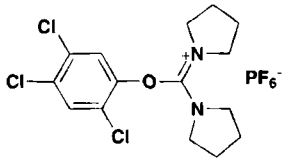


50 (HAPyTU)

2-Nitrophenol and 2,4,5-trichlorophenol have been coupled with the chlorouronium salt **42** (PyClU) to give the two new reagents **51** (HPyONp) and **52** (HPyOTcp) in 90 and 86% yield, respectively.[44]

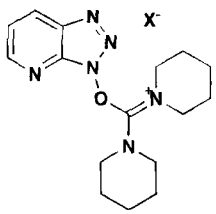


51 (HPyONp)

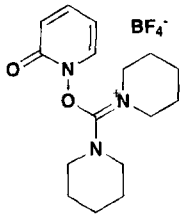


52 (HPyOTcp)

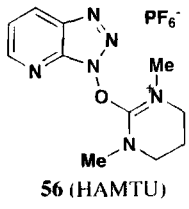
Various other new reagents have been prepared using ureas such as bispiperidineurea and *N,N'*-dimethylpropylenurea (DMPU). Thus, the HOAt-derived **53**[23] (HAPipU) and **54**[23a] (TAPypU), and the *N*-hydroxypyridone-derived **55**[45] (TOPPipU) as well as the HOAt-derived **56**[23b] (HAMTU) have been described.



53 (HAPipU); X = PF_6
54 (TAPipU); X = BF_4

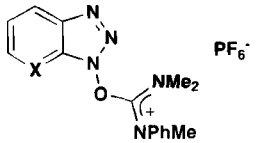


55 (TOPPipU)



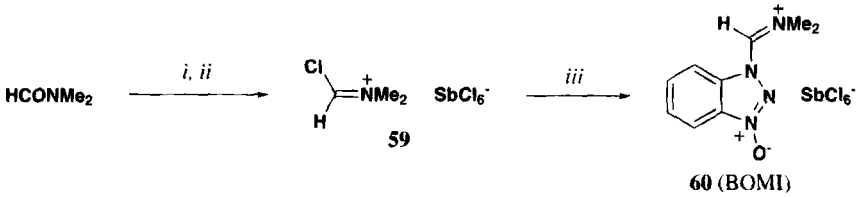
56 (HAMTU)

N,N,N'-Trimethyl-*N'*-phenylurea, prepared from commercially available *N,N*-dimethylcarbamoyl chloride, has been transformed into the corresponding chlorouronium salt in 84% yield by treatment with phosgene followed by anionic interchange. Final reaction with HOBt or HOAt in the presence of triethylamine gave **57** (HBPTU) or **58** (HAPTU), respectively, in 83% yield.[46]



57 (HBPTU); X = CH
58 (HAPTU); X = N

More recently, several iminium salts derived from carboxamides have been prepared. Thus, *N,N*-dimethylformamide (DMF) has been transformed into an iminium chloride **59** by reaction with triphosgene followed by stabilization with $SbCl_5$. Subsequent reaction with HOBt gives benzotriazol-1-yl-oxy-*N,N*-dimethylmethaniminium hexachloroantimoniate **60** (BOMI) in 76% yield[47] (*Scheme 10*). Its structure was determined by X-ray analysis.

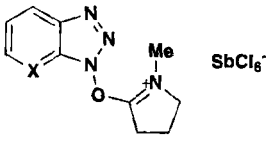


60 (BOMI)

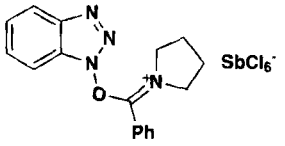
i) $CO(OCCl_3)_2$; ii) $SbCl_5$; iii) HOBt

Scheme 10

The same methodology has been employed for the preparation of the immonium reagent **61** (BDMP) from *N*-methylpyrrolidine (NMP) and HOBt, in 80% overall yield.[48] When HOBt is replaced by HOAt, the related reagent **62** (AOMP; this abbreviation has also been used for compound **15**) is obtained.[49] The HOBt derived reagent **63** (BPMP) has also been prepared from the more highly substituted *N,N*-tetramethylenebenzamide.[49]



61 (BDMP); X = CH
62 (AOMP); X = N

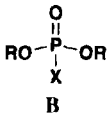


63 (BPMP)

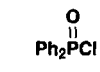
3. Phosphinic and Phosphoric Acid Derivatives

Two types of phosphorous reagents derived from phosphinic (**A**) and phosphoric (**B**) acids have been prepared. Diphenylphosphinic chloride **64**[50] (DppCl) and diphenylphosphinic pivalic acid mixed anhydride **65**[51] were the first phosphinic acid derivatives used in peptide synthesis.

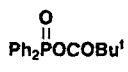
A



B



64 (DppCl)



65

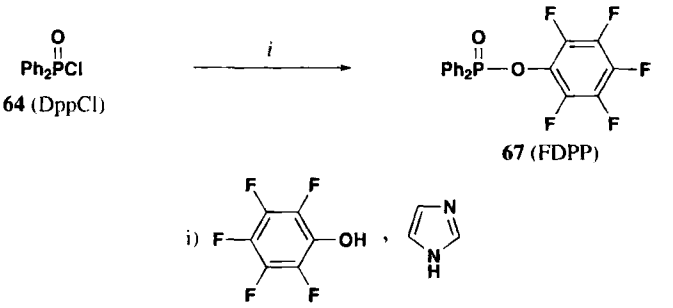
DppCl (**64**) is commercially available and can be prepared by oxidation of diphenylchlorophosphine with oxygen.[50] Apart from the cyclic derivative 1-oxo-1-chlorophospholane **66** (Cpt-Cl),[52] this reagent gives the best results when compared with other dialkylphosphinic chlorides. Reagent **66** is prepared by reacting butadiene with phosphorous trichloride to give 1,1,1-trichlorophospholene, which is then hydrolyzed to 1-oxo-1-hydroxyphospholene and subsequently hydrogenated and chlorinated with thionyl chloride[52] (*Scheme 11*).

66 (Cpt-Cl)

i) PCl_3; ii) ice; iii) H_2, Pd/C; iv) $SOCl_2$

Scheme 11

Diphenylphosphinic carboxylic acid mixed anhydrides are usually prepared *in situ*.[51,53] Pentafluorophenyl diphenylphosphinate **67** (FDPP) is commercially available and can be prepared quantitatively from DppCl (**64**) by treatment with pentafluorophenol and imidazole in dichloromethane at room temperature[54] (*Scheme 12*).



Scheme 12

A wider variety of phosphonic acid derivatives have been prepared. Diphenylphosphoryl azide[55] (**68**, DPPA) and diethylphosphoryl cyanide[56] (**69**, DEPC) were the first phosphonic acid derived reagents used for peptide synthesis, both now being commercially available. Reagent **68** can be prepared in more than 90% yield by allowing diphenylphosphorochloridate to react with sodium azide in acetone at room temperature and is a stable, non-explosive liquid.[55] DEPC (**69**) is easily prepared from triethylphosphite and cyanogen bromide.[56]

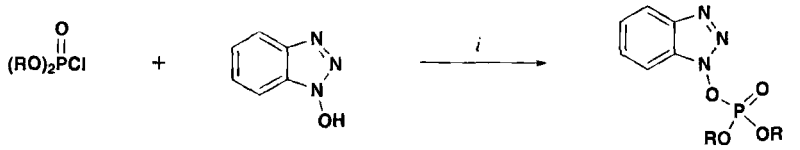
bis(2-Oxo-3-oxazolidinyl)phosphorodiamidic chloride (**70**, BOP-Cl) is the most widely used peptide coupling reagent of this family of phosphorous derivatives.[57] It is commercially available and can be prepared by the reaction of 1,3-oxazolidin-2-one with phosphorous pentachloride in acetonitrile or nitromethane[57] (*Scheme 13*).

70 (BOP-Cl)

i) PCl_5

Scheme 13

Another derivatives of phosphoric acid include benzotriazol-1-yl diethyl (**71**, BDP) and diphenyl (**72**) phosphate, which are prepared in almost quantitative yield by reaction of diethyl and diphenyl chlorophosphate, respectively with HOBt and triethylamine in THF at room temperature[58] (*Scheme 14*). Related organophosphorous compounds derived from benzoxazolone are *N*-diethoxyphosphorylbenzoxazolone **73** (DEPBO)[59] and the cyclic *N*-(2-oxo-1,3,2-dioxaphosphorinanyl)benzoxazolone **74** (DOPBO).[60] With HOOBt as substituent two other reagents 3-[*O*-(2-oxo-1,3,2-dioxaphosphorinanyl)-oxy]-1,2,3-benzotriazin-4(3*H*)-one **75** (DOPBT)[60] and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4-(3*H*)-one **76** (DEPBT)[61] have been described. All these reagents as well as ENDPP (**77**)[62] are obtained following a similar protocol to **71** or **72**.



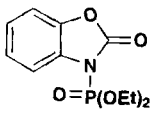
71 (BDP); R = Et

72; R = Ph

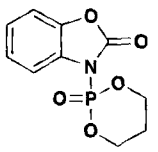
i) Et_3N, THF

Scheme 14

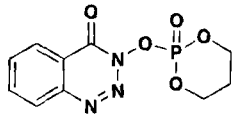
The only phosphonic acid derivative reported is 2-propanephosphonic acid anhydride **78** (PPAA, T3P®) which is a commercially available trimeric reagent prepared by reaction of propanephosphonic acid dichloride with water.[63]



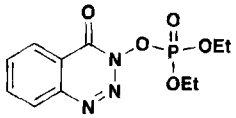
73 (DEPBO)



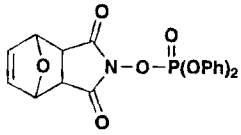
74 (DOPBO)



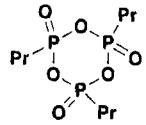
75 (DOPBT)



76 (DEPBT)



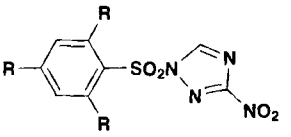
77 (ENDPP)



78 (T3P, PPAA)

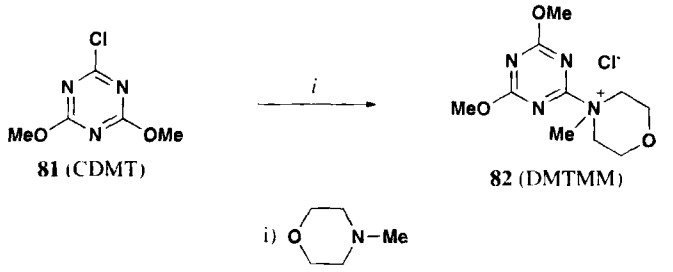
4. Other Coupling Reagents

Arenesulfonyl-1,2,4-triazoles have been used previously as coupling reagents in phosphotriester oligonucleotide synthesis.[64] They can be easily prepared in almost quantitative yield by condensation of the corresponding arenesulfonyl chlorides with the triazole.[64] 1-(Mesitylenesulfonyl)-3-nitro-1,2,4-triazole **79** (MSNT) and 1-(2,4,6-triisopropylbenzenesulfonyl)-3-nitro-1,2,4-triazole **80** (TPSNT) are the usual arenesulfonyltriazolides used for peptide synthesis[65] and are both commercially available.



79 (MSNT): R = Me
80 (TPSNT): R = Pr^i

1,3,5-Triazines have also been used as coupling reagents. Thus, 2-chloro-4,6-dimethoxy-1,3,5-triazine **81** (CDMT) is a stable commercially available crystalline compound readily accessible from cyanuric chloride.[66] The related triazine, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride **82** (DMTMM), has been prepared in 79% yield from CDMT (**81**) by a simple reaction with *N*-methylmorpholine (NMM)[67] (*Scheme 15*).



81 (CDMT)

82 (DMTMM)

Scheme 15

The symmetrically substituted 2,4,6-tris(pentafluorophenyloxy)-1,3,5-triazine **83** (TPfT) has been prepared by reaction of cyanuric chloride with potassium pentafluorophenolate in acetonitrile in 67% yield[31] (*Scheme 16*).

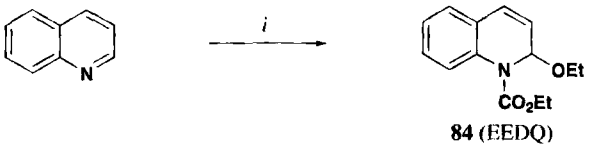
83 (TPfT)

i) C_6F_5OK

Scheme 16

Di-*tert*-butyldicarbonate (Boc_2O), which is an extensively used reagent for the introduction of the acid-labile Boc-protecting group for the amine functionality, has been recently used for the synthesis of dipeptides.[68]

N-Ethoxycarbonyl-2-ethoxy-1,3-dihydroquinoline (**84**, EEDQ)[69] has been commercially available for a long time which can be prepared in 66% yield by reaction of quinoline with ethyl chloroformate in ethanol in the presence of triethylamine (*Scheme 17*).

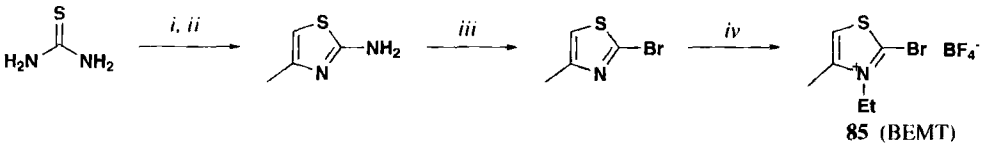


84 (EEDQ)

i) EtOCOCl, Et_3N, EtOH

Scheme 17

2-Bromo-3-ethyl-4-methylthiazolinium tetrafluoroborate (**85**, BEMT) has been recently described as an efficient peptide coupling reagent for hindered amino acids.[70] It has been prepared from thiourea in three steps in 23% overall yield and is a stable crystalline solid (*Scheme 18*).



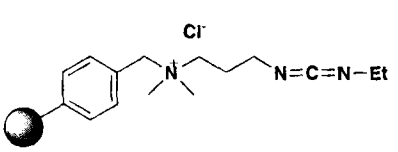
85 (BEMT)

i) $Me_2C{=}O$, I_2; ii) NaOH; iii) $NaNO_2$, NaBr, $CuSO_4$; iv) Et_3OBF_4

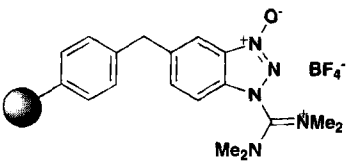
Scheme 18

5. Polymer-Supported Reagents

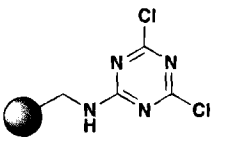
For the synthesis of peptides in solution-phase only a few solid-phase-supported reagents have been described. 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide (**86**, P-EDC) has been obtained by treating Merrifield resins with EDC in DMF at 100° or in refluxing acetonitrile for 15h.[71] Polymer-bound TBTU **87** (P-TBTU)[72] has been prepared by the coupling of chlorotetramethyluronium tetrafluoroborate with polymeric HOBt (P-HOBt).[73] 2,4,6-Trichloro-1,3,5-triazine anchored to different aminated polystyrene resins **88** have recently been prepared by reaction of cyanuric chloride with the corresponding NH_2-functionalized resin.[74]



86 (P-EDC)



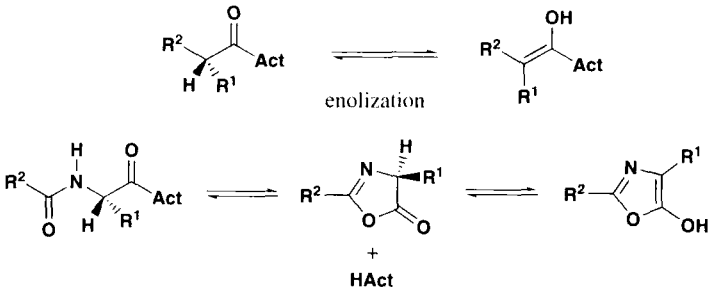
87 (P-TBTU)



88

II. COUPLING MECHANISMS

The formation of an amide and an ester bond occurs through the nucleophilic attack of either the amine or the alcohol on the activated carboxylic acid. Thus, the first step in the formation of these bonds requires the activation of the carboxylic acid. When the carboxylic acid contains a chiral center in the α-position, as is the case with α-amino acids, and is activated[75] then racemization can occur thus representing an important side-reaction that has to be avoided or minimized. The two main mechanisms involved in the racemization of α–amino acids are enolization and, when applicable, formation and posterior enolization of an 5(4*H*)-oxazolone (oxazolonium ion in the case of *N*-alkyl amino acids) (*Scheme 19*).[76]



Scheme 19

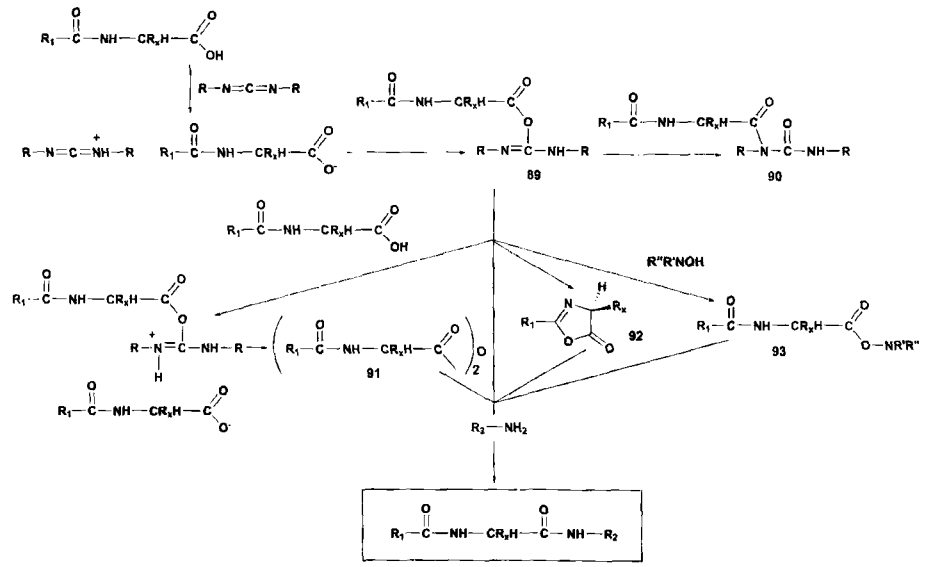
The level of racemization is highly dependent on the method of activation. Thus, those methods which involve a base will be more prone to racemization since the presence of the base will favour the abstraction of the α-proton. Furthermore, if the activating group Act- is a good leaving group then the formation of the 5(4*H*)-oxazolone will be more facile, the α-proton will be more acidic and hence more easily removed by the base. In this respect therefore, it is important to bear in mind that the presence of a base and/or a good leaving group will very often result in a better coupling yield and thus a compromise may have to be reached between the coupling yield and the level of racemization.

1. Carbodiimides

The mechanism of carbodiimide-mediated activation is complex, strongly dependent on the solvent, and still not totally understood (*Scheme 20*).[77-82] The first step involves a proton transfer followed by addition of the carboxylic acid to form the *O*-acylisourea (**89**). This is a very reactive intermediate which attacks the amino component to give the corresponding amide. The *O*-acylisourea can suffer a rearrangement to give the *N*-acylurea (**90**), which is not reactive or attack another carboxylic acid function to give the symmetrical anhydride (**91**), which is also an excellent acylating agent.[83] If the carboxylic acid is an *N*-carboxamide (acetyl, benzoyl, or a peptide chain) or a carbamate α-amino acid (Boc, Fmoc), the *O*-acylisourea can undergo intramolecular cyclization to give a 5(4*H*)-oxazolone (**92**). The formation of the oxazolone occurs more readily in the first case since the carbonyl group of amides is more nucleophilic than that of urethanes.[84] The 5(4*H*)-oxazolones are

also acylating reagents, but no so powerful as the *O*-acylisourea or the symmetrical anhydride and additionally tautomerization to the enol form will provoke racemization (*Scheme 20*). The *O*-acylisourea can be trapped by a nucleophile present in the medium, usually a hydroxylamine derivative (R"R'NOH), to give the corresponding active esters that is usually less reactive but a more stable species (**93**).

Formation of the symmetrical anhydride, the 5(4*H*)-oxazolone (**92**), and the active esters derived from hydroxylamine derivatives (**93**) are not limited to the activation with carbodiimides and they can also be found during activation by other methods.



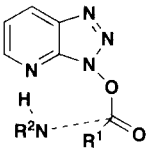
Scheme 20

The first step of the mechanism, the formation of the ion-pair intermediate, explains why the activation of a carboxylic acid is much slower in the presence of a base. DCC for example reacts with acetic acid (HOAc) 30 times slower in the presence of Et_3N.[78] This lower activation rate in the presence of a base [*N,N*-diisopropylethylamine (DIEA)] has also been observed during the activation of Fmoc-amino acids with DIPCDI (**98**) in the presence of HOBt[18] as a trapping agent.[85] Addition of a base however, once the activated species is formed, accelerates the coupling reaction.[85,86] When the activation of carboxylic acids with carbodiimides is carried out in a solvent of low dielectric constant such as $CHCl_3$ or DCM, the supposed formation of an *O*-acylisourea can occur instantaneously.[87a,88] On the other hand, if the activation is performed in a more polar solvent such as DMF, no immediate reaction can be detected and a complex mixture of starting amino acid, symmetrical anhydride, *N*-acylurea, and urea is formed.[88] Thus, activation may be slower in a polar as opposed to a nonpolar solvent. Alternatively, an equilibrium between the carboxylic acid and the *O*-acylisourea may develop. In this case, even in the absence of a second equivalent of the carboxylic acid, the formation

of the symmetrical anhydride can occur since the reaction of the *O*-acylisourea with the unreacted carboxylic acid is much faster than the addition of the acid to the carbodiimide. Furthermore, the rearrangement of the *O*-acylisourea to the *N*-acylisourea occurs rapidily when DMF is used as the solvent which represents a serious limitation to this process.[88] However, the reported existence[87a] of acyclic *O*-acylisoureas has been ruled out.[87b] In fact, to date there is no confirmed evidence for the separated existence of this species. Formation of a 2-alkoxy-5(4*H*)-oxazolone (**92**) from the corresponding alkoxycarbonylamino acids (e.g. Boc, Fmoc derivatives) during carbodiimide activation occurs only in the presence of tertiary base salts. Under these conditions, the racemization of 2-alkoxy-5(4*H*)-oxazolone derivatives does not appear to be problematic.[75,88] However, the alkylcarbonylamino acids (e.g. acetyl, benzoyl, or peptides) are more prone to form the 5(4*H*)-oxazolone, and are thus more sensitive to racemization.[75] Addition of $CuCl_2$ has been shown to suppress the racemization of the 5(4*H*)-oxazolone intermediate.[89]

When the activation step is performed in the presence of an equivalent of a hydroxylamine derivative [usually HOBt[18] or HOAt[22]], the corresponding active esters are obtained cleanly. The main advantage in the use these additives as trapping agents of the *O*-acylisourea lies in their ability to increase the concentration of the active species when DMF is used as a solvent and to reduce racemization of the carboxylic residue. Furthermore, their addition inhibits dehydration of the carboxamide side chains of Asn and Gln to the corresponding nitriles.[90]

HOAt has been described as being superior to HOBt when used as an additive in both solution and solid-phase synthesis. HOAt enhances coupling rates and reduces risk of racemization[23b,91,92] presumably because of the incorporation of a strategically placed nitrogen atom at position 7 of the aromatic system. Incorporation of a nitrogen atom in the benzene ring has two consequences. First, the electron-withdrawing influence of a nitrogen atom (regardless of its position) effects stabilization of the leaving group, leading to greater reactivity. Secondly, incorporation of the nitrogen at the 7-position provides a classic neighboring group effect which can both increase the reactivity and reduce racemization (*Scheme 21*).[91] The corresponding 4-isomer, whilst more acidic than HOAt and HOBt, lacks the ability to participate in a neighboring group effect and has no influence on the extent of racemization during the segment coupling reaction when compared to HOAt.[93]

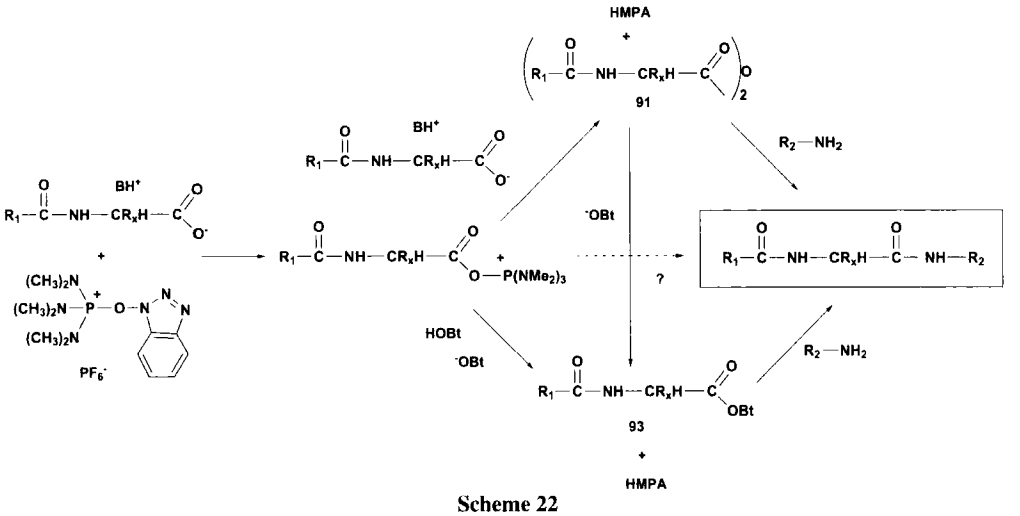


Scheme 21

The addition of a tertiary amine (DIEA) during a carbodiimide/HOXt coupling has been described as being as efficient as the use of onium salts which are amongst the most powerful coupling reagents.[85]

2. Phosphonium Salts

The species that react with phosphonium salts is the carboxylate and therefore the presence of at least one equivalent of base is essential. With regards to the mechanism, several authors[5,7,8,12] have proposed that in the absence of the nucleophile that is incorporated in the reagent, for example HOBt in BOP (**6**), the active species is the acyloxyphosphonium salt. Castro and Dormoy[10a] have suggested that this salt is very reactive and even at low temperatures will react immediately with carboxylate ions present in the medium to give the symmetrical anhydride. This pathway is supported by kinetic studies carried out by Hudson (*Scheme 22*).[94] Several years later, Kim and Patel[95] reported that this intermediate could exist at -20 °C when BOP (**6**) was used as a coupling reagent. However, Coste and Campagne[96] suggested that this species is very unstable and even at low temperatures undergoes conversion to an active ester. In spite of this controversy, it is widely accepted that the active species is an active ester when phosphonium salts containing nucleophilic derivatives are used. These couplings are carried out with an excess of the base, usually 2 equivalents of DIEA, and in the presence of one equivalent of the hydroxylamine derivative, usually HOBt or HOAt.



Scheme 22

The active species detected during couplings with the chloro and bromo derivatives of phosphonium salts, BroP (**2**), PyCloP (**3**), and PyBroP (**4**), in the absence of HOBt are the symmetrical anhydride (**91**), the 5(4*H*)-oxazolone (**92**), and, for Boc-amino acids, the unprotected *N*-carboxyanhydride.[97]

3. Aminium Salts

The mechanism proposed for the activation of carboxylic acids using aminium salts is similar to the one proposed for phosphonium salts. In this case however, the presence of the acyloxyamidinium salt has not been detected. Couplings are typically carried out with 2 equivalents of

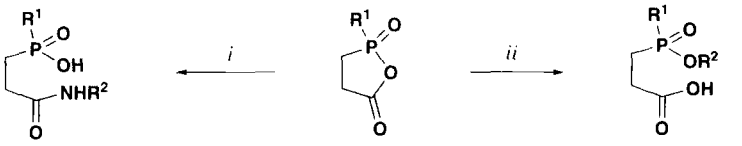
DIEA and 1 equiv of either HOBt or HOAt. The presence of this extra equivalent of the additive usually decreases the level of racemization, although in some cases an increment has been observed. Thus, Carpino and co-workers have demonstrated an enhancenment of the racemization when Fmoc-Phe-Ser(*t*Bu)-OH was coupled onto H-Pro-resin with HATU (**32**) or HBTU (**20**) in the presence of an extra equiv of HOAt or HOBt.[91] On the other hand, it has been shown that racemization is decreased during the coupling of peptide fragments in solution when HOAt or HOBt are added to the aminium-derived coupling reagent.[98,99] For Ser and Cys Fmoc derivatives, which are prone to racemization, the replacement of DIEA by collidine (TMP) also results in a decrease of the racemization.[100-102]

The reaction of carboxylic acids with fluoroamidinium salts such as TFFH (**39**), BTFFH (**40**) and DFIH (**41**) can generate the corresponding acid fluorides *in situ*.[103] It is well known that a potential problem with carbamate protected halides involves their conversion to the corresponding 5(4*H*)-oxazolone (**92**).[103] This transformation was studied in detail in the presence of various solvents and bases using as a model the reaction of Fmoc-dimethylglycine (Fmoc-Aib-OH) with TFFH (**39**).[104] Optimal conditions were obtained using 2 equivalents of DIEA in DMF. With DCM, large amounts of 5(4*H*)-oxazolone accompanied the formation of the acid fluoride. In this solvent, an increase in the concentration of base gave less acid fluoride, and among several pyridine bases which were examined [pyridine, TMP, 2,6-di-*t*-butyl-4-methylpyridine, 2,6-di-*t*-butyl-4-(dimethylamino)pyridine DB(DMAP)], 2,3,5,6-tetramethylpyridine],[99,105] pyridine itself was the most effective although not as efficient as DIEA in DMF.

2-Chloro-1,3-dimethyl-4,5-dihydro-1*H*-imidazolium hexafluorophosphate (**43**, CIP, DCIH)[106] has been found to be effective only in the presence of 1 equivalent of HOAt,[36,37] which may indicate that the coupling proceeds through an oxazolone (**92**) intermediate.

4. Phosphinic and Phosphoric Acid Derivatives

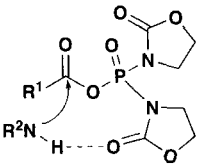
The mechanism of the coupling mediated by phosphinic acids has been postulated to proceed through a carboxylic-phosphinic mixed anhydride.[51] The advantage of these mixed anhydride intermediates as compared to the biscarboxylic derivatives is associated with the regioselectvity. Reactions of biscarboxylic mixed anhydrides are governed by electronic and steric factors,[107] while carboxylic-phosphinic derivatives are dependent on the nature of the incoming nucleophile. Thus, ammonolysis and alcoholysis occur at the carboxylic and phosphinic sites, respectively (*Scheme 23*).[51,53,108]



i) R^2NH_2; ii) R^2OH

Scheme 23

The effectiveness of BOP-Cl (**70**), a phosphoric acid derivative, during the acylation of *N*-methyl amino acid derivatives is attributed to intramolecular base catalysis by the oxazolidinone carbonyl of the mixed anhydride active species (*Scheme 24*).[109]



Scheme 24

A comparative study of the dimethyl derivatives of phosphinic chloride (Me_2POCl) and phosphochloridate [$(MeO)_2POCl$] indicated that the latter was less reactive toward oxygen nucleophiles than dimethylphosphinic chloride, which would suggest that phosphinic chloride derivatives should react with carboxylate anions to form mixed anhydrides more rapidly than phosphorochloridates.[53] Fast formation of mixed anhydrides is an important consideration in coupling reactions. A further advantage of the use of phosphinic carboxylic mixed anhydrides lies in the potential elimination of the substitution of the OR groups.[53]

The active species of the derivatives that contain nucleophiles other than Cl, such as HOBt, HOOBt, or pentafluorophenol, are presumably the corresponding active esters.

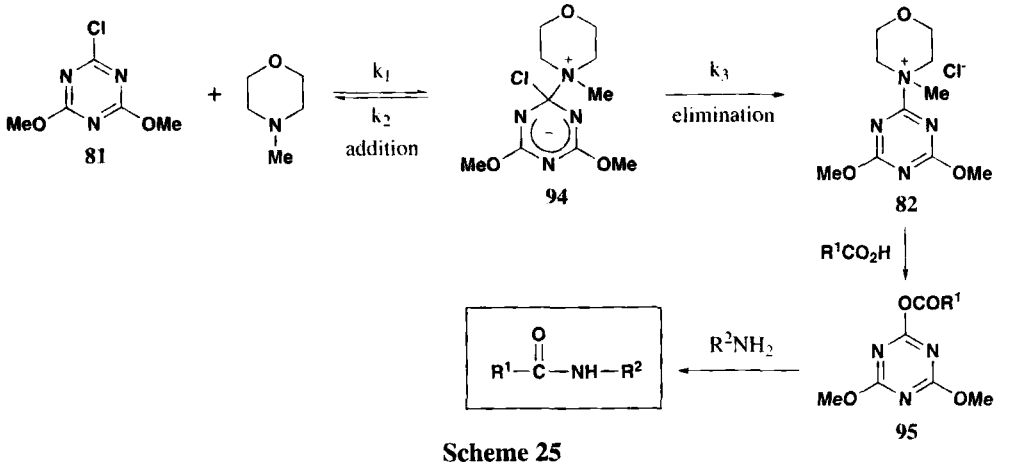
5. Other Coupling Reagents

The activation of carboxylic acids by arenesulfonyl derivatives such as *p*-tolenesulfonyl chloride has been performed.[110a] Moreover, using as reference the activation of 5'-protected nucleosides studied by ^{31}P NMR,[110b-112] it can be concluded that mesitylenesulfonic acid-carboxylate mixed anhydrides, symmetrical anhydrides, and carbonyl azolides may be the active species involved in the coupling step.

The activation of carboxylic acids by 2-chloro-4,6-dimethoxy-1,3,5-triazine (**81**, CDMT) requires the presence of a tertiary amine in the reaction medium. This reaction can be considered as erratic because only a few of these amines are able to react. In addition, the capacity of the amines to participate in the reaction does not correlate with the basicity of the amines in polar solvents. This fact suggests the existence of an intermediate involving the amine as a part of a multistep process.[67,113] The rate of formation of this intermediate, a triazinylammonium salt such as **82**, will strongly depend on the steric hindrance of the amine. Thus, the concourse of hindered amines provokes a loss of reactivity of **81**. Only amines prone to the formation of salts such as **82** when treated with **81** are useful in the activation of carboxylic functions. Et_3N, which does not form a quaternary ammonium salt at low temperature in the reaction with **81**, in not capable of activating benzoic acid.[67]

Thus, the activation of carboxylic acids by **81** is comprised of two subsequent substitution reactions in the triazine ring. The first one involves substitution of the chlorine atom by the amine

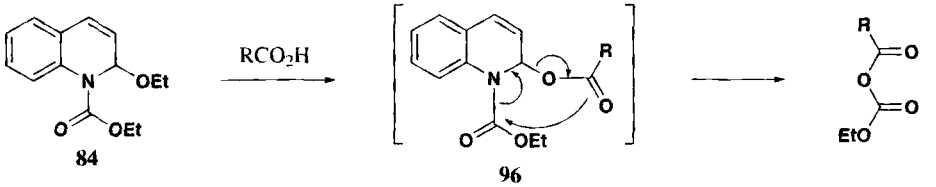
with the formation of a quaternary ammonium salt. This step is extremely sensitive to steric hindrance of amine substituents. The second step, which is exceptionally tolerant to the steric hindrance of the carboxylic acid, involves substitution of the amine leaving group by the carboxylate ion to afford the triazine "superactive esters" **95**. In this regard, the 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride **82** (DMTMM) prepared by reaction of **81** with NMM has been sucessfully applied to the synthesis of amides and esters.[114-115]



Scheme 25

The monitoring of the quaternization of NMM at low temperature evidenced the formation of the zwitterionic addition product **94**, the key intermediate in the classic two step process $A_N + D_N$.[67] Semiempirical modeling of the reaction, as well as measured nitrogen and chlorine kinetic isotope effects also supports this mechanism. A significant chlorine kinetic isotope effect $k_{35}/k_{37} = 1.0058 \pm 0.0005$, and no morpholine nitrogen kinetic isotope effect, $k_{14}/k_{15} = 1.0001 \pm 0.0006$ were observed.[67] Further data confirming this mechanism have been obtained in the process of enantioselective activation of carboxylic acids.[113,116]

The activation of carboxylic acids by EEDQ (**84**) involves the transient formation of a mixed carbonic anhydride.[117] However, the expected intermediate **96** cannot be isolated, even at low temperature, presumably because of a rapid breakdown by way of a six-membered transition state to give quinoline and the anhydride. The same kind of mixed carbonic anhydride is the active species involved when Boc_2O is used as coupling reagent.[68]



Scheme 26

6. Amino Acid Halides

Although acid chlorides have a long history of use,[118,119] there is still controversy on the relative reactivity of the different halides and the mechanism of action. Thus, studies carried out using simple carboxylic halides have revealed different relative orders depending on the nature of the test nucleophile.[102] The fluorides are less reactive than the chlorides towards neutral oxygen nucleophiles such as H_2O or MeOH, but the anion formation reverses the reactivity. With amines, the "normal order" I>Br>Cl>F is followed by the benzoyl halides.[120] These results are expected where C-X bond breaking is important at the transition state for substitution. Presumably in the case of hydroxide or alkoxide ion the increased stabilization of the tetrahedral intermediate due to the enhaced C-F dipole effect is responsible for the increased reactivity of the acid fluoride, an effect which is also commonly seen in the mechanistically related substitution reactions of aryl halides bearing *o*- and/or *p*-electron-withdrawing substituents.[121,122] This discussion about the reactivity of acid becomes more complex when *N*-alkoxycarbonyl protected (Boc, Fmoc) amino acid are involved due to their tendency to convert to 5(4*H*)-oxazolones **92** which are less reactive intermediates. Thus, the benefits to be gained by employing amino acid halides can sometimes be negated.[123,124]

The coupling of acid chlorides requires the presence of a hydrogen chloride acceptor. In the presence of a tertiary amine, such as DIEA or NMM, the corresponding 5(4*H*)-oxazolone **92** is formed when Boc- and Fmoc-amino acid chlorides react.[102] When a hindered base such as 2,6-di-*tert*-butylpyridine is used as a hydrogen chloride scavenger, only a small amount of 5(4*H*)-oxazolone is formed.[124]

Acid chlorides can be coupled in the presence of a 1:1 mixture of an amine and HOBt.[124] In this case OBt esters are formed initially and the advantage of the use of halides can be lost. In addition, KOBt has been added for the coupling of hindered Fmoc-amino acid chlorides,[125] probably acting just as base without role as OBt ester-forming agent.

The utility of acid chlorides as effective activating species has recently been re-established, in conjunction with other protecting groups for the α-amino function. Thus, acid chlorides of 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf),[122,126] *o*-nitrobenzenosulfonyl (*o*NBS),[127,128] and benzothiazole-2-sulfonyl (Bts)[129,130] amino acids have allowed the preparation of hindered peptides. Furthermore, α-azido acids, where the azido function acts as a precursor to the amine, coupled very efficiently without significant racemization.[131]

The advantages offered by fluorides relative to chloro derivatives lies in the lack of conversion to 5(4*H*)-oxazolone **92** in the presence of tertiary amines.[102] Another difference between the chlorides and fluorides is the ability of the latter to effect acylation in the total absence of base, thereby reducing the risk of racemization.[132] The effectiveness of these derivatives can be enhanced in the presence of a silylating agent, such as *bis*(trimethylsilyl)acetamide (BSA), as demonstrated by the coupling of Fmoc-MeAib-F to H-Aib-OMe.[133] BSA may act both as a base and *N*-silylating reagent enhancing the nucleophilicity of the amino function.[133]

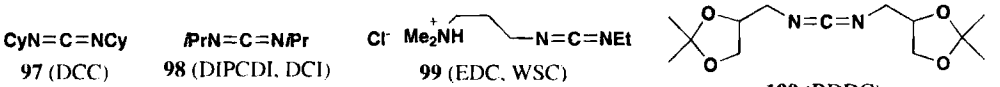
III. PEPTIDE SYNTHESIS

1. Carbodiimides

The use of carbodiimides as peptide coupling reagents was fairly common until the eighties and continues to be a useful synthetic procedure. DCC (**97**) has been mainly used in solid-phase peptide synthesis (SPPS) for the *tert*-butoxycarbonyl (Boc)/benzyl (Bzl) strategy and DIPCDI (**98**, DCI) for the 9-fluorenylmethoxycarbonyl (Fmoc)/*tert*-butyl strategy. For solution-phase couplings 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (**99**, EDC or WSC) has been mainly used.[134a] The newer carbodiimide 1,3-*bis*(2,2-dimethyl-1,3-dioxolan-4-ylmethyl)carbodiimide (**100**, BDDC) is also commercially available and has been used for solution-phase peptide couplings with minimal epimerization.[134b]

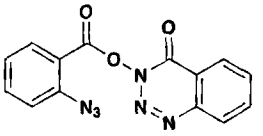
Nowadays, carbodiimides are used with an XOH additive as a trapping agent of the *O*-acylisourea intermediate to form the corresponding active esters, thus decreasing the degree of racemization in numerous cases. HOBt[18] or HOAt[22] and other HOX reagents give the corresponding active esters in the presence of carbodiimides and a tertiary amine (see section III.7). The coupling with the second amino acid takes place faster, and in much better yields, with HOAt esters even with the hindered α-aminoisobutyric acid (Aib).[22] A lower degree of racemization is observed with HOAt than with HOBt in both solution and solid-phase synthesis.[22] HOAt also enhances the coupling rates since the nitrogen located at position 7 in the HOBt structure provides a neighboring group effect thus decreasing the risk of racemization.[23,91,92] The electron-withdrawing effect of the nitrogen also stabilizes the leaving group leading to a greater reactivity.

A recent application of the DIPCDI (**98**)/HOBt mixture involves the coupling of the first two amino acids to [α-(3-nitrobenzamido)benzylpolystyrene] (Nbb)-type resin.[135] Similarly, DCC and HOBt have also been used in the solid-phase synthesis on 2-chlorotrityl chloride resin of the linear receptor-activating myelin basic protein (MBP) peptides.[136] For the solid-phase synthesis of N^{w}-propylarginine-containing dipeptides, EDC (**99**) and HOBt have been used.[137] EDC (**99**) and HOAt have been used for the formation of the amide and ester bonds of the potent antimycobacterial analogues.[92] In the solid-phase synthesis of cyclosporin peptides, both DIPCDI (**98**)/HOAt and HATU (**32**) are effective, especially for consecutive *N*–methyl amino acids.[138,139] The C_2-symmetric cyclic decadepsipeptides luzopeptins and quinoxapeptins have been prepared using EDC-HOAt.[140]



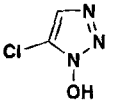
97 (DCC) **98** (DIPCDI, DCI) **99** (EDC, WSC) **100** (BDDC)

1-Oxo-2-hydroxydihydrobenzotriazine (HOOBt)[25] gives very reactive esters (see section III.7) but their formation is accompanied by 3-(2-azidobenzoyloxy)-4-oxo-3,4-dihydro-1,2,3-benzotriazine (**101**) as a by-product, which can then react with the amino group to terminate chain growth.[25]



101

Several coupling additives with triazole and tetrazole structures in the presence of DIPCDI (**98**) have been evaluated in solid-phase Fmoc-based peptide synthesis.[141] 5-Chloro-1-hydroxytriazole (**102**) is comparable with HOAt and HOBt as an acylating agent but shows less supression of racemization. For instance, in the synthesis of Aib-Aib-containing peptides **102** is superior to HOAt. Ethyl 1-hydroxy-1*H*-1,2,3-triazole-4-carboxylate (**103**, HOCt) has been applied in SPPS, and is found to be more efficient than HOBt with DIPCDI (**98**)[142] presenting almost no racemization.[143] These reagents have been introduced because they do not present absorbtion in the UV at 302 nm, thus allowing the monitoring of the coupling process, a feature incompatible with Fmoc-methodology in the case of HOBt or HOAt.



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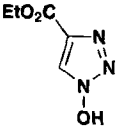
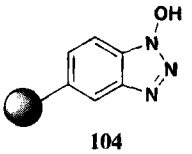


103 (HOCt)

Polymer-bound HOBt[144] (**104**) has been used for the formation of medium ring lactams with DCC (**97**) in the presence of resin-bound esters[145] and also for amides from primary and secondary amines.[146] *N*-Hydroxysuccinimide bound to Merrifield and ArgoPore™ resins (**105**) also give resin-bound active esters, which are transformed into amides when reacted with primary, branched primary and secondary amines.[147]



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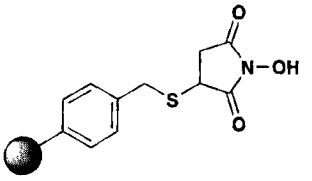
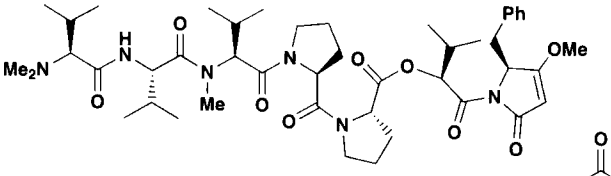


105

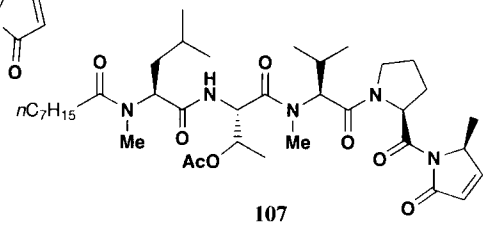
2. Phosphonium Salts

Halophosphonium salts have been used mainly in the liquid-phase for the synthesis of peptides containing *N*-methyl and hindered α-amino acids. Bromotris(dimethy-lamino)phosphonium hexafluorophosphate (**2**, BrOP) is a reagent which was found to exhibit excellent reactivity, when compared with BOP (**6**), in the difficult coupling of *N*-methylated amino acids. When both amino acids were *N*-substituted, BrOP (**2**) still gave good results (70-89% yield) in a short reaction time (1h) without appreciable epimerization.[148] This reagent exhibits better reactivity than other reagents such as BOP (**6**), BOP-Cl (**70**) and Dpp-Cl (**64**). The less toxic pyrrolidine derivatives PyCloP (**3**) and PyBroP (**4**) also gave similar good results during the coupling of Z- or Fmoc-protected *N*-methyl

amino acids.[149] However, in the case of Boc-protected systems, *N*-carboxyanhydrides (see section III.8) are formed when using these reagents and DCC (**97**) and PyBOP (**7**).[149] With reagents **3** and **4**, the intermediates are oxazolone and/or symmetrical anhydrides, which are rapidly aminolyzed.[97] Some examples of the use of PyCloP (**3**) and PyBroP (**4**) include the formation of the pentapeptide part of the antitumorals Dolastatines 15[150a] (**106**), 10[150b] and analogues,[150c] as well as the octanoyl derivative **107** of Microcolin B[151] and the nonapeptide Bradykinin analogues obtained by replacement of the proline residues with *N*-methyl-D- and L-phenylalanine.[152] For the cyclic depsipeptide Aureobasidin A (**108**), which contains four *N*-methyl amino acids, PyBroP (**4**) and DIEA have been used for the synthesis and coupling of the segments as well as for the final lactamization.[153] In the solid-phase (Wang resin) total synthesis of the cyclic ureido-containing hexapeptide Oscillamide Y (**109**) and its analogues, the final cyclization has been carried out with PyBroP (**4**) in DMF/DCM with DIEA as base.[154] For the synthesis of the conformationally restricted analogues **110a** and **110b** of the



Dolastin 15 (**106**)



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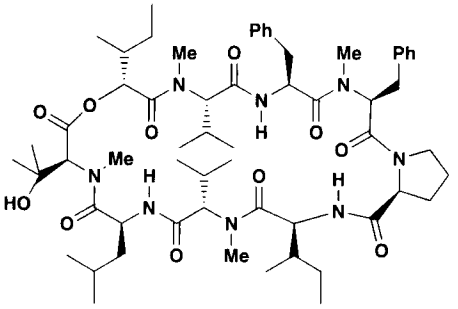
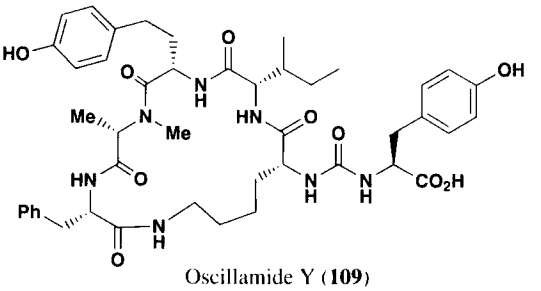
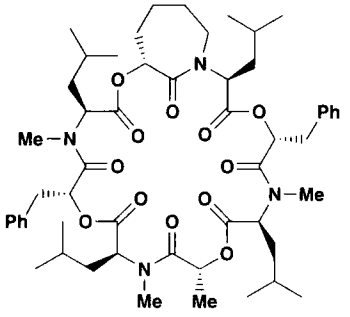


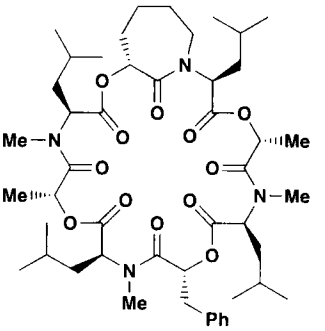
Aureobasidin A (**108**)



Oscillamide Y (**109**)



110a

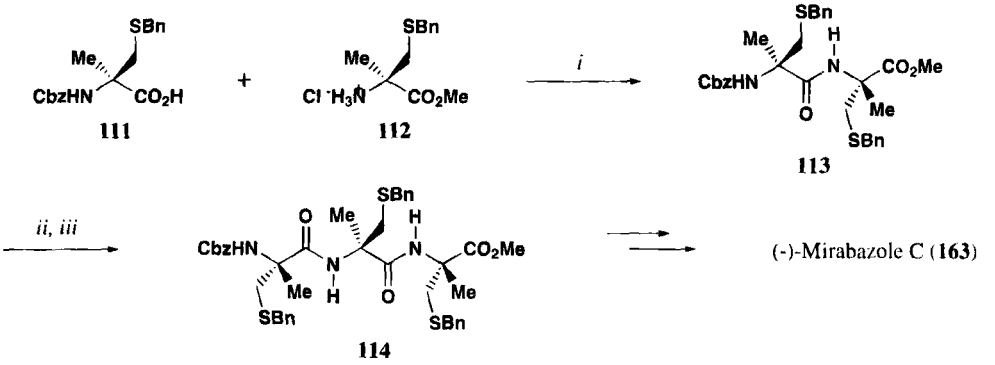


110b

Cyclodepsipeptide PF1022A analogues

anthelmintic cyclodepsipeptide PF1022A, PyBroP (**4**) has been used in the solid-phase synthesis (Kaiser resin) of the linear octadepsipeptide.[155]

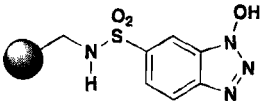
α,α-Dialkyl amino acids, such as α-aminoisobutyric acid (Aib) are difficult to introduce into a peptide. The combination PyBroP (**4**)/DMAP has been found to be very effective for the coupling of two[155] and three[156] Aib residues under solution-phase conditions.[155] (*R*)-*N*-Z-protected α-methylcysteine (**111**) has been coupled with its ester **112** and again with the corresponding dipeptide **113** to give the tripeptide **114**, a precursor of the tetrathiazoline marine alkaloid (-)-Mirabazole C, in 60% yield (*Scheme 27*).[157]



i) PyBroP (**4**), DIEA, DMAP; ii) HBr, AcOH; iii) (*R*)-*N*-*S*-benzyl-2-methylcysteine, PyBroP (**4**)

Scheme 27

For the acylation of amines, the polymer-supported HOBt derivative **115**, bonded by a sulfonamide group to polystyrene, reacted with carboxylic acids in the presence of PyBroP (**4**) to give the corresponding active esters. Subsequent addition of amines afforded the corresponding amides in an automated procedure.[158]



115

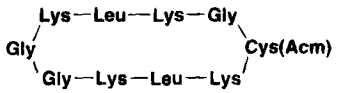
Castro's reagent, BOP (**6**), has been widely used in solid-phase peptide synthesis with or without the addition of an extra equivalent of HOBt.[13,15,94] Fmoc derivatives of Tyr and Thr have been incorporated through a BOP (**6**)-based protocol without additional protection.[159] This strategy avoided the formation of oxazolones and has been applied in solid-phase peptide synthesis.[124] The formation of undesired diketopiperazines (DKPs) has been avoided in the Boc-Bn solid-phase peptide synthesis by using BOP (**6**) with Nbb-resin [α-(3-nitrobenzamido)benzylpolystyrene)] using a neutralization *in situ* protocol.[160]

The synthesis of protected peptides on the Kaiser oxime resin using BOP (**6**)/HOBt/DIEA activation has been achieved with low levels of racemization and applied to the preparation of the 16

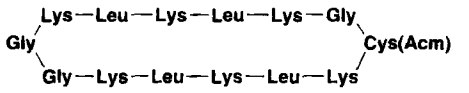
amino acid protected peptide VI derived from the ice nucleation protein.[161] A tricyclic ambiphilic α-helical peptide[162a] and lanthionine peptides have also be prepared using this coupling system.[162b] A series of analogues of the neuropeptide tyrosine (NPY) were prepared with the BOP (**6**) reagent on benzhydrylamine resin[163] as were fragments of a calcitonin gene-related peptide and analogues.[164] In the convergent synthesis of Thymosin β_4, the BOP (**6**)/HOBt methodology proved to be very efficient for the coupling of larger fragments.[165] For the solid-phase synthesis of unsymmetrically functionalized diamides from symmetric diacids, preactivation of the dicarboxylic acid with BOP (**6**) has been shown to be very effective.[166]

Cyclic peptides **116** and **117**, which increase the rate of hydrolysis of oligoribonucleotides have been prepared from acyclic precursors using BOP (**6**) under high dilution conditions in DMF or NMP.[167] The linear precursors were obtained by solid-phase synthesis using a 2-methoxy-4-alkoxybenzyl alcohol-type (Riniker handle) solid-support with DCC (**97**)/HOBt and Fmoc-amino acids. A general method for the synthesis of cyclic peptides containing an Asp residue, linked to a PAM-type resin through the β-carboxylic function by classical Boc/Bn strategy, used BOP (**6**) as the unique coupling reagent. This methodology was applied to the synthesis of the tachykinin peptide antagonist MEN 10207 (**118**)[168] and also to the 18 residue cyclic peptide **119** which corresponds to a loop involved in the curaremimetic action of a toxic snake protein.[169]

Peptide cyclization on oxime resin (PCOR)[162] has been used for the SPPS of the thirty-membered cyclo-decapeptide Tyrocidine A (**120**) using BOP (**6**) as coupling agent for both the chain assembly and subsequent cyclization.[170] Using this solid-phase synthesis and cyclization-cleavage strategy the group of Nishino[171] has prepared a Gramicidin S analog,[171a] cyclic peptides containing α-aminosuberic acid[171b] and cyclic tetrapeptides containing the Arg-Gly-Asp sequence.[171c,d] This "head-to-tail" coupling mode has been used with Fmoc-protection with either BOP (**6**)/HOBt or DIPCDI (**98**)/HOBt followed by final cleavage from the polystyrene resin. BOP (**6**) cyclization was faster than DIPCDI (**98**), but the products were almost identical in purity.[172] Cyclic peptides containing Asp, Asn, Glu and Gln have been prepared by a solid-phase strategy (Fmoc-*t*Bu-allyl) featuring side-chain anchoring to Riniker resin or tris(alkoxy)benzylamide (PAL) linkages and resin-bound cyclization mediated by BOP (**6**)/HOBt/DIEA.[173]



116



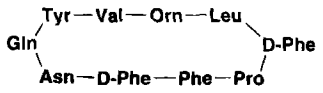
117

Cyclo(Tyr—D-Trp—Val—D-Trp—D-Trp—Arg—Asp)

118

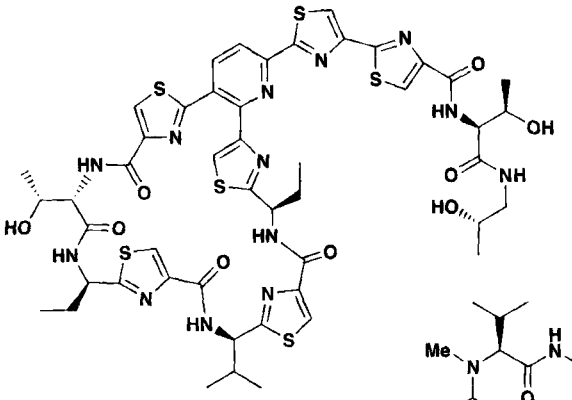
Cyclo(Asn—Tyr—Lys—Lys—Val—Trp—Arg—Asp—His—
—Arg—Gly—Thr—Ile—Ile—Glu—Arg—Gly—Pro)

119

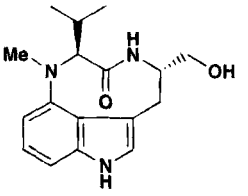


Tyrocidine A (**120**)

In the total synthesis of the antibiotic Micrococcin P (**121**), BOP (**6**) has been used to couple the pyridine skeleton to two other fragments and also in the final intramolecular cyclization, all under solution conditions.[174] For the synthesis of the indolactam core of teolicidin alkaloids, the 9-membered lactam has been formed using BOP (**6**)/HOBt in the case of **122**[175] and **123**[176] in 66 and 83% yield, respectively.



Micrococcin P (**121**)



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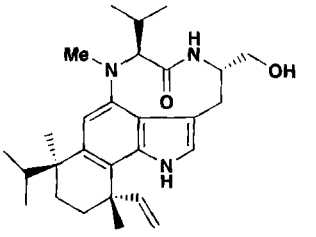
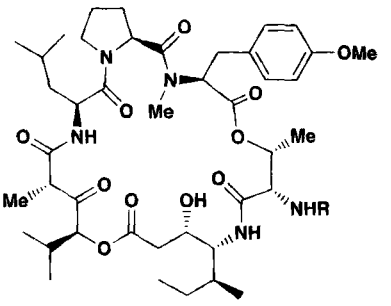
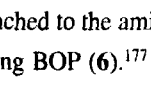


123

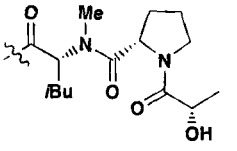
The coupling of *N*-methyl α-amino acids, which is usually effectively performed by PyBroP (**4**), can also be carried out with BOP (**6**). For instance, the substituents attached to the amino group of L-threonine in Didemnins A, B and C (**124**) have been introduced by using BOP (**6**).[177] The core of



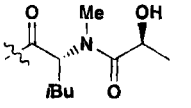
Didemnin A (**124a**), **R** =



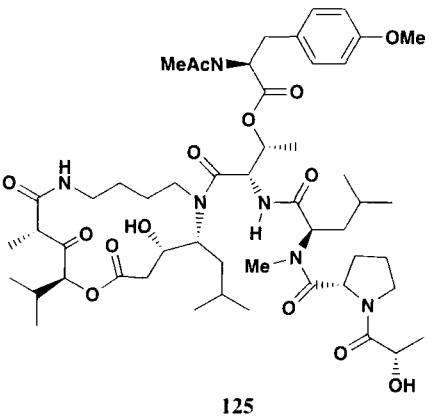
Didemnin B (**124b**), **R** =



Didemnin C (**124c**), **R** =



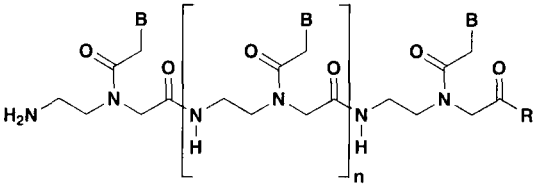
these cyclodepsipeptides, which present a greater cytotoxic activity, has been reduced to an analogue **125** of Didemnin B and the peptide chain has been attached in two steps by means of BOP (**6**).[178] In order to increase the opioid activity of peptide [D-Pro^{10}]-Dynorphin the *N*-methyl group has been introduced in the amino acid components. The solid-phase synthesis was carried out with a (hydroxymethyl)phenoxy acetic acid resin using Fmoc-protected amino acids with DIPCDI (**98**) and HOBt except for the tyrosine derivatives which were incorporated efficiently with BOP (**6**)/HOBt.[179]



125

In the solid-phase synthesis of the C^{α}-substituted corticotropin releasing factor (CRF) antagonists, a 4-methylbenzhydrylamine (MBHA) resin and Boc-amino acids with DIPCDI (**98**) were used. Similarly, for the introduction of Aib and α-Me-Leu in the peptides, BOP (**6**)/HOBt/DIEA were successfully employed.[180] The 11-residue peptaibol from *Trichoderma harzianum* Harzianin HB I contains three Aib residues and its solution-phase synthesis has been carried out with a Boc/OMe strategy using BOP (**6**) for all couplings.[181]

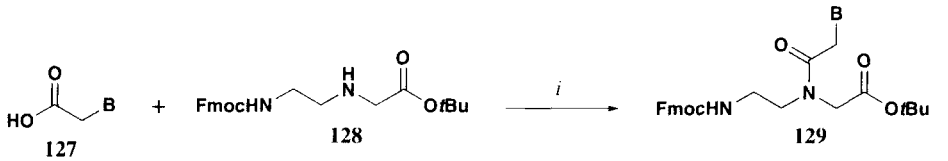
For the synthesis of peptide nucleic acid monomers containing the four natural nucleobases suitable for peptide nucleic acids (PNA) **126** synthesis by oligomerization on solid-phase, several



126

B = T, C(Cbz), A(Cbz), G(Cbz)

coupling reagents have been used.[182] The base acetic acids **127** were coupled to the backbone **128** with either EDC (**99**) or BOP (**6**) as the simplest and most effective reagents and afford products **129** (*Scheme 28*).[183]

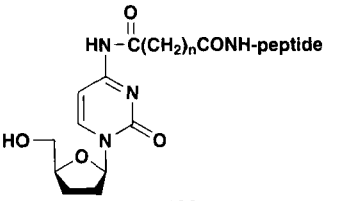


127 **128** **129**

i) EDC (**99**) or BOP (**6**)

Scheme 28

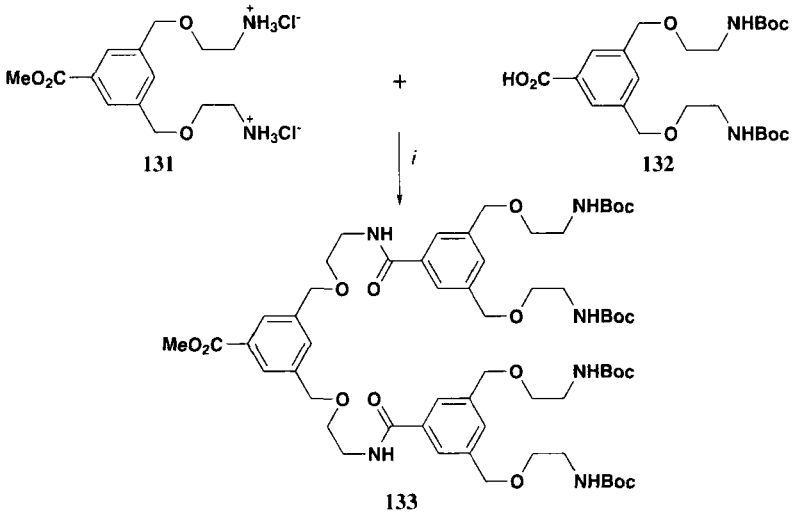
Some peptide-nucleoside conjugates have been prepared to investigate their anti-HIV properties. The synthesis of these new analogues **130** was achieved using BOP (**6**) which was more effective than DCC (**97**)/HOBt.[184]



130

Sugar amino acid conjugates have been prepared in solution by BOP (**6**)-promoted coupling of carboxy-protected amino acids to *N*-acetylneuramic[185] or 2,3-dihydroneuramic acids.[186] The BOP (**6**) coupling of these monomers with the amine group of another neuramic acid derivative affords the corresponding dimers.[185,186] In the preparation of tetracationic metalloporphyrin-spermine conjugates, for attachment to DNA binding molecules, spermine is coupled to a porphyrin monoacid derivative by means of BOP (**6**).[187]

A new fluorigenic substrate for the determination of biotidinase has been prepared using BOP (**6**) reagent for the amidation reaction between D-biotin and 7-amino-4-methylcoumarin.[188] Novel amino acid based dendrimers have been prepared by a convergent method using BOP (**6**) as coupling agent.[189] The preparation of a second generation dendrimer **133** in quantitative yield from the components **131** and **132** is described in Scheme 29.[189]



i) BOP (**6**)

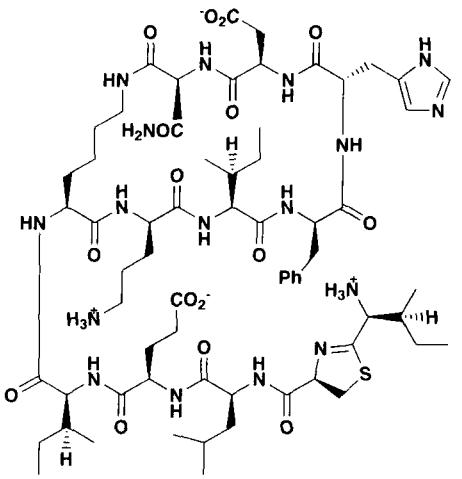
Scheme 29

The pyrrolidino derivative of BOP (**6**), PyBOP (**7**) was prepared in order to avoid use of the carcinogenic hexamethylphosphoric triamide (HMPA) and gives results that are at least as good as

those obtained with BOP.[15] For the solution-phase synthesis of peptides containing α-methyl α-amino acids such as Aib, PyBOP (**7**) was found to be an effective reagent. However, for the coupling of two Aib residues the combination PyBroP (**4**) and DMAP is required.[155] Coupling of Fmoc-protected amino acids can be carried out using PyBOP (**7**) in a rapid continous solution phase method, applicable to the synthesis of large amounts of short peptide fragments such as [leucine]^{5}enkephalin.[190]

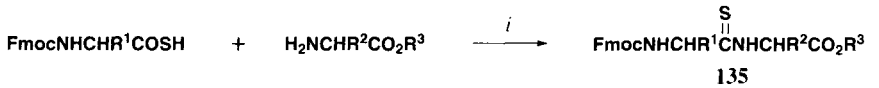
PyBOP (**7**) and BOP (**6**) proved to be convenient reagents for promoting the coupling of lipid moieties to peptides attached to Kieselguhr-supported polyacrylamide resins.[191] The lipopeptides are potential antigenic peptides for hepatitis B virus.

A series of linear photoactive and iodinatable antagonists of the neuropeptidic hormone vasopressin were synthesized by a combination of PyBOP (**7**)-mediated Boc/solid-phase peptide synthesis and solution synthesis approaches.[192] PyBOP (**7**) has been shown to be the most appropriate reagent for the attachment of the first Fmoc-amino acid to a 3-carboxypropanesulfonamide resin.[193] This strategy has been used in the solid-phase synthesis of *C*-terminal peptide thioesters by a Fmoc/*t*Bu method.[194] The PyBOP (**7**)-HOBt combination has been used for the cyclization step on solid support in the total synthesis of Bacitracin A (**134**), a dodecapeptide antibiotic.[195]



Bacitracin A (**134**)

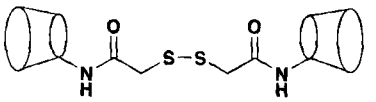
Endothiopeptides **135** have been obtained by using PyBOP (**7**) for the efficient coupling of Fmoc-protected amino monothioacids and amino acid or peptide esters (*Scheme 30*).[196] For the



i) PyBOP (**7**)

Scheme 30

coupling of 6-amino-6-deoxycycloheptaose with dithiodiethanoic acid to β-cyclodextrin dimer **136**, PyBOP (**7**) is a faster coupling reagent than carbodiimides.[197] In the synthesis of oligonucleotide conjugates such as **137**, PyBOP (**7**) has been employed in solution as the activating agent for the carboxylic acid.[198a,b,c] Phosphinic peptides have also been prepared in solution by coupling unprotected aminophosphinic acid with peptides in the presence of BOP (**6**) or PyBOP (**7**).[198d]



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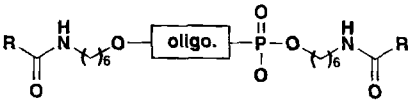
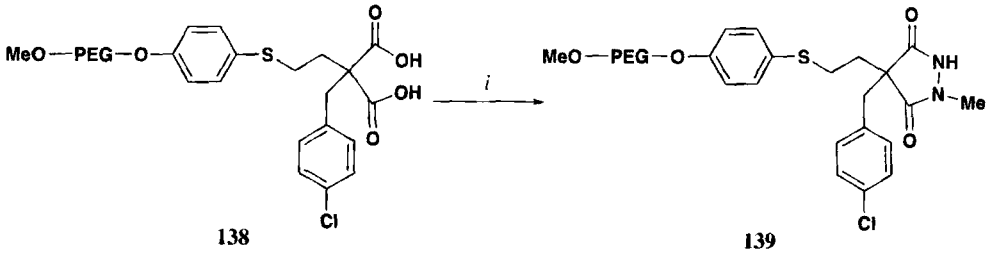


137

Polymer-bound dialkylated malonic acid **138** can be coupled with methylhydrazine in the presence of BOP (**6**) or PyBOP (**7**) to give 3,5-pyrazolidinedione **139** in excellent yield (*Scheme 31*).[199] For the synthesis of (+)-Curacin A, a potent antimytotic with a cyclopropyl substituted thiazoline, (+)-2-methanecyclopropanecarboxylic acid has been coupled with *o*-phenylenediamine in 60% yield using PyBOP (**7**).[200]



138 **139**

i) $MeNHNH_2$, PyBOP (**7**)

Scheme 31

The CF_3-substituted 1-hydroxybenzotriazole phosphinium salt derivatives CF_3-BOP (**8**) and CF_3-PyBOP (**9**) are good coupling reagents for Z- and Fmoc-protected Aib as well as for *N*-methylvaline (MeVal) in solution-phase.[17] The nitro-substituted reagent PyNOP (**11**) and PyFOP (**9**) are better systems than PyBOP (**7**) for the preparation of the dipeptide thioamide Boc-Leu-φ[CSNH]-MetOMe with high stereochemical preservation.[201] The disubstituted CF_3-NO_2-PyBOP (**12**) has proved to be a powerful reagent for the coupling of *N*-methyl amino acids, better than the monosubstituted **8** or **9** and even better than PyBroP (**4**).[21]

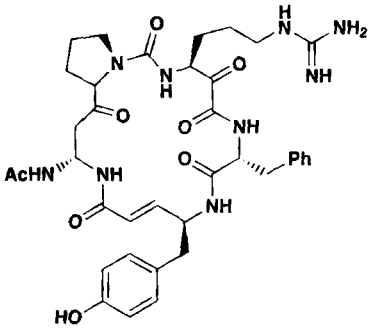
The phosphonium salts derived from HOAt, AOP (**13**) and PyAOP (**14**), for solid-phase peptide synthesis have been shown to be superior to HOBt derivatives.[23b] Thus, PyAOP (**14**) has been used for the coupling of a range of peptides that include those incorporating hindered amino acids, difficult short sequences, and cyclic peptides.[202a] An advantage of this reagent compared to the corresponding uronium salts is that excess PyAOP (**14**) does not participate in chain-terminating side reactions at the amino terminus such as occurs when aminium salts are employed. The use of *N*-tritylamino acids and PyAOP (**14**) is more effective than BOP (**6**)[160] for the suppression of

diketopiperazine formation in Fmoc/*t*Bu solid-phase peptide synthesis using alkoxybenzyl ester resins.[202b] PyAOP (**14**) has been used as coupling agent for the solid-phase synthesis of C-terminal-modified and cyclic peptides by use of a tris(alkoxy)benzylamine-based linker (BAL).[203]

3. Aminium Salts

The onium salts based on HOBt and tetramethylurea (TMU), HBTU (**20**) and TBTU (**22**) have been widely used as peptide coupling reagents in the presence of tertiary amines for optimal efficiency. A recent example of the use of these reagents in Fmoc/solid-phase peptide synthesis is the preparation of the *O*-phosphotyrosyl-containing Ala-Glu-Tyr(P)-Ser-Ala peptide by means of HBTU (**20**).[204] Moreover, endothelial Interleukin-8-[Ala-Il8]$_{77}$ has been prepared on solid-phase by using Boc/Bn protection and TBTU (**22**) activation.[205] In addition, the protected fragments 74-81, 82-99 and 90-90 from HIV 1-protease have been prepared using Fmoc-TBTU (**22**) on Tentagel resin,[206] and Fmoc-protection and HBTU (**20**) coupling on a PAL resin has been used for the synthesis of the side chain of Bacitracin A (**134**).[195]

The addition of HOBt is very effective in limiting the dehydration of C-terminal asparty-lamide peptides to the corresponding nitrile during side-chain to side-chain cyclization either with HBTU (**20**) or PyBOP (**7**).[207] TBTU (**22**)/HOBt has been used for the cyclization of a reduced-size neuropeptide Y analogue under high-dilution conditions of the free peptide.[208] Cyclic hexapeptides containing Asp, Asn or Glx residues were synthesized on a solid support in the presence of TBTU (**22**).[209] For the synthesis of conformationally constrained Dynorphin A analogues with opioid activity, the 14- to 16-membered lactam rings have been prepared using TBTU (**22**).[210] TBTU (**22**) has also been used for the coupling of the two key intermediates and for the ring closure in the convergent synthesis of Cyclotheonamide B (**140**), a cyclic pentapeptide from the marine sponge *Theonella swinhoei*.[211] TBTU (**22**)/HOBt gave faster cyclization than DIC/HOBt in the synthesis of the tyrosine-containing cyclic peptides **141**-**143**.[212]



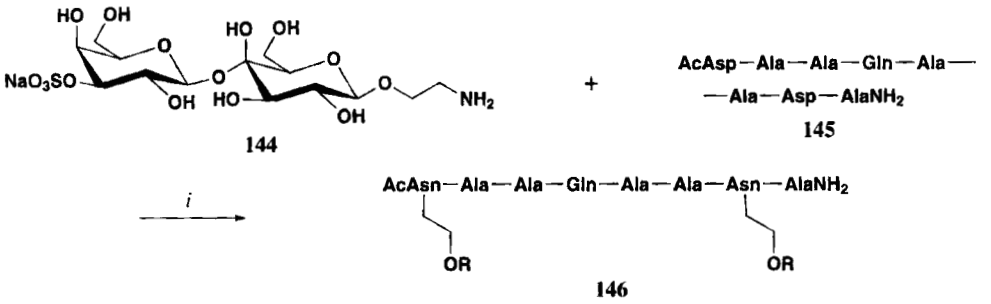
Cyclotheonamide B (**140**)

Cyclo(β-Ala—Tyr—Pro—Ser—Lys—
Lys—β-Ala—Arg—Gln—Arg—Tyr)
141

Cyclo(Ahx—Tyr—Pro—Ser—Lys—
Ahx—Arg—Gln—Arg—Tyr)
142

Cyclo(Ala—Aib—Tyr—Pro—Ser—
Lys—Ala—Aib—Arg—Gln—Arg—Tyr)
143

The coupling of sulfolactoside **144** to the aspartic residues of various peptides such as **145** designed to probe selectin recognition, gave the corresponding glycopeptide **146** in high yield through the use of HBTU (**20**)/HOBt (*Scheme 32*).[213]

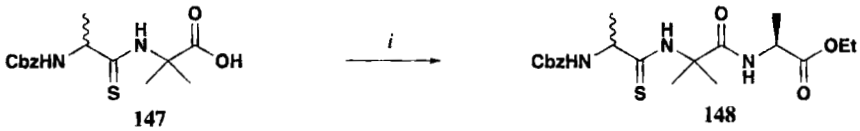


i) HBTU (**20**)/HOBt

Scheme 32

In the solid-phase synthesis of glycopeptides the combination HBTU (**20**)/HOBt/DIEA has been used for the coupling of the peptide and the sugar moiety.[214] Peptide nucleic acid (PNA) oligomers have been prepared by solid-phase peptide synthesis using a Fmoc-BOP strategy.[183] A recent protocol uses the dithiasuccinoyl (DTs) amino protecting group and HBTU (**20**)/DIEA in a 3:1 ratio. The reduction of the amount of the tertiary amine gave better results than with TBTU (**22**), HATU (**32**) or BOP (**6**).[215]

For the synthesis of the Aib-containing thiodipeptide **148**, the endothiodipeptide **147** has been coupled with alanine ethyl ester by means of TBTU (**22**) in 78% yield after 130h (*Scheme 33*).[216]

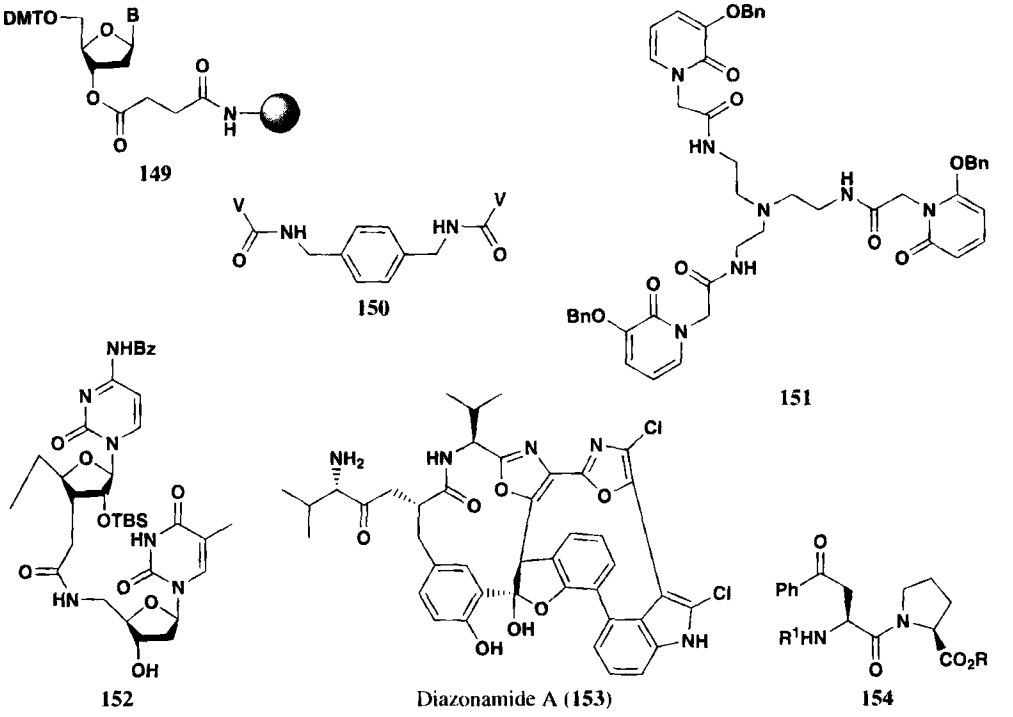


i) TBTU (**22**), HOBt, DIEA, (*S*)-ClH$_3$NCH(Me)CO$_2$Et

Scheme 33

Other applications of TBTU (**22**) and HBTU (**20**) are related to amide formation. A rapid method for the anchoring of nucleoside-3'-*O*-succinates involves the condensation with alkylamine-controlled pore glass (LCAA-CPG) using TBTU (**22**)/TEA to give **149** just in 10 min by solid-phase oligonucleotide synthesis.[217] Polyethylene glycol polyacrylamide (PEGA) resin has been derivatised with *p*-hydroxymethylbenzoic acid linker using TBTU (**22**)/*N*-ethylmorpholine (NEM) and used in solid-phase *C*-glycopeptide synthesis.[218] A dimeric derivative of Vancomycin (V) and *p*-xylyxenediamine **150**, prepared by means of HBTU (**20**), give a tight binding with dimeric L-Lys-D-Ala-D-Ala.[219] Hexadentate ligands of iron(III) such as **151** have been synthesized by reaction of a *N*-substituted 3-hydroxy-2(1*H*)-pyridinone with tris(2-aminoethyl)amine using TBTU (**22**)/NMM in DMF.[220] The nucleoside dimer **152** in which the natural phosphodiester bond is replaced by an isosteric amide

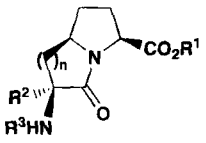
linkage has been prepared by coupling of the acid with the amine by HBTU/HOBt/TEA in moderate yield (57%).[221] In the synthesis of Diazonamide A (**153**) the two amide functions have been prepared by means of TBTU (**22**)/DIPEA.[222]



For the use of the HOOBt derivatives TBDTU (**23**) and HDTU (**24**) as well as other XOH derivatives of the tetramethyluronium cation **25-28**, see section III.1 for a comparison of the efficiency of these reagents. In the case of the pentafluorophenol derivative TPfTU (**29**)[30] it has been used in the solution-phase synthesis of dipeptides **154** which undergo cyclization upon irradiation to give indolizinones, precursors of bicyclic β-turn dipeptides.

Derivatives of HOBt with electron-withdrawing groups include CF_3-HBTU (**31**), which is specially suited for Aib condensations,[17] and the HOAt derivatives HATU (**32**) and TATU (**33**).[22] HATU (**32**) has been widely used in SPPS since it is very reactive in the activation and coupling steps and also reduces the risk of racemization.[22,23] The use of the HATU/HOAt/DIEA combination has been shown to be very efficient for the convergent SPPS of H-(Val-His-Leu-Pro-Pro-Pro)$_2$-OH.[223] Coupling yields over 80% were obtained after 4h using 4 equiv of protected peptide and coupling reagents. The C1 peptides of protein kinase C (PKC) isozymes,[224-226] consisting of ca. 50 amino acids, have been synthesized by a solid-phase Fmoc-strategy with HATU (**32**) as coupling reagent.[224] Peptides containing reverse-turn mimetic bicyclic lactams **155** have been prepared following a

Fmoc/DIPCDI (**98**)/HOAt strategy. The coupling between the peptide and the lactam was performed with HATU/HOAt/2,4,6-collidine.[227] For the solid-phase synthesis of the Cyclosporin A (CsA) 2-7 sequence (H-Abu-Sar-MeLeu-Val-MeLeu-Ala-OH), HATU (**32**) has been shown to be the best reagent.[225] (see section III.10). Conversion of the CsA 2-7 sequence into the linear undecapeptide precursor for the CsA derivatives requires high yield addition of three *N*-methyl amino acids (MeVal, and two MeLeu) which was achieved with either HATU (**32**) or HOAt/DIPCDI.[139] In the total synthesis of the Ser-Thr phosphatase inhibitor Microcystin-LA (**156**), the coupling to an *N*-MeAla moiety and several other difficult amino acid coupling reactions have been performed with HATU (**32**) under solution-phase conditions.[228] For the coupling of MeAla in the SPPS of Oscillamide Y (**109**) and analogues, the combination HATU (**32**)/HOBt proved to be the most successful reagent combination when compared with DIPCDI (**98**)/HOBt and PyBroP (**4**).[154]



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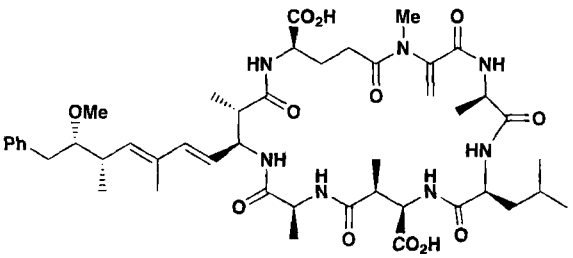
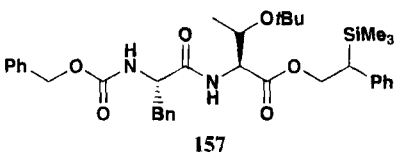


Microcystin-LA (**156**)

(2-Phenyl-2-trimethylsilyl)ethyl (PTMSE) is a novel ester-forming carboxyl-protecting group stable under HATU (**32**)/HOAt coupling conditions. Using this protecting group, dipeptide **157** has been prepared in solution phase in 92% yield.[229] The diketopiperazine **158** derived from L-Asp and (2*S*,3*R*,4*R*)-diaminoproline has been prepared by means of HATU/HOAt/DIEA. This template **158** has been incorporated by standard solid-phase methods with Fmoc-protection into the peptide Ala-Asn-Pro-Asn-Ala-Ala and, after cleavage from the resin, cyclized to the corresponding cyclic β-hairpin mimetic.[230]



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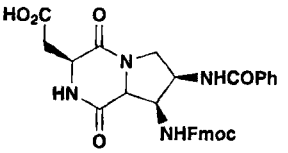
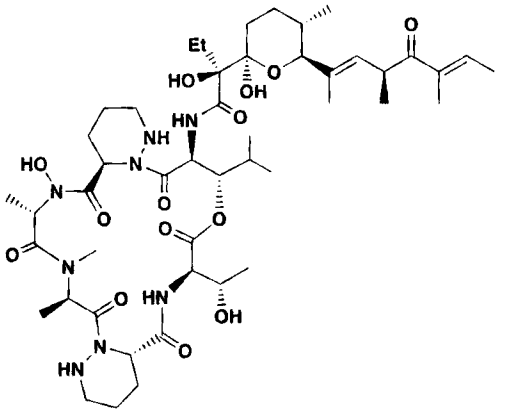


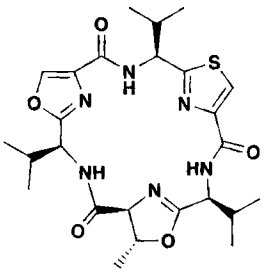
158

In the total synthesis of the antitumor antibiotic A83586C (**159**) the macrolactamization could be achieved only by means of HATU (**32**) although in modest yield.[231] When this cyclization

was attempted with BOP/DMAP complete epimerization occurred in the L-piperazic acid unit, which allowed the synthesis of 4-*epi*-A83586C.[232] The macrocyclic hexapeptide Bistratamide D (**160**) has

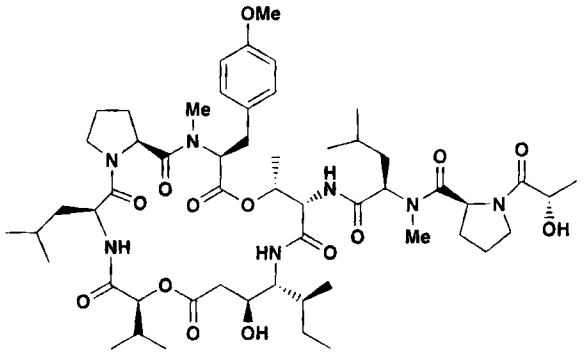


A83586C (**159**)

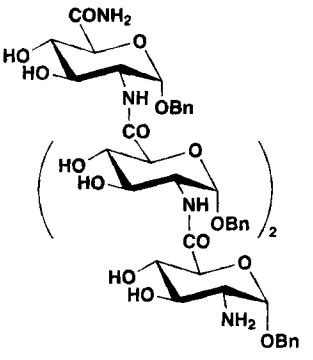


Bistratamide D (**160**)

been prepared in solution-phase by means of EDC/HOBt and the cyclization performed with HATU/DIEA.[233] For the synthesis of antitumor (-)-Tamandarin A (**161**) several coupling reagents have been used (see section 3.10), the macrocyclization being carried out with HATU/DIEA in good yield.[234]



Tamandarin A (**161**)



162

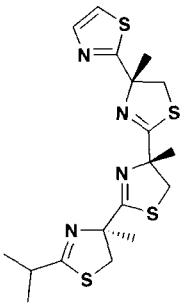
The homologous tetrafluoroborate reagent TATU (**33**) has been used in the attachment of the carbohydrate amino acid to a solid support and in the subsequent steps for the preparation of the amide linked oligosaccharide mimetic **162** without protection of the hydroxy groups.[235]

The 2-mercaptopyridone 1-oxide-based tetramethyluronium salts HOTT (**35**) and TOTT (**36**) are suitable reagents for solution-phase peptide synthesis with low racemization.[33]

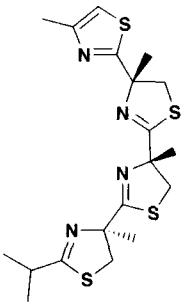
Tetramethylfluoroformamidinium hexafluorophosphate (**39**, TFFH)[34] is a non-hygroscopic salt which allows the formation of Fmoc-amino acid fluorides and thus provides a good alternative to

the corrosive cyanuric fluoride.[236] Cbz- or Fmoc-amino acid fluorides have been tested in the condensation with simple amino acid esters and in SPPS.[237] They show superior efficiency for the introduction of Aib residues even into a model peptide containing four adjacent Aib units, and into the Aib-rich Alamothicin Acid.[238] They also have been used in the solid-phase synthesis of the naturally-occurring peptaibols, peptide alcohols of about 20 units which are rich in hindered amino acids.[239] TFFH (**39**) completes conversion to the corresponding fluoride esters after 8-15 min and after 1-2h for hindered amino acids. This reagent is good for solid-phase synthesis, especially for hindered amino acids, giving shorter reaction times than HATU (**34**) or HBTU (**20**) in, for instance, the synthesis of ACP, Prothrombin and Magainin II amide.[34] The addition of HOAt prevents extensive epimerization and gives similar results to HATU. The massive extent of epimerization observed in the absence of additive is related to the formation of oxazolone intermediates.[34] However, the chloroformamidinium hexafluorophosphate (**38**, TCFH) or the bromo analogue lack the general applicability of **39** as coupling reagents for solid-phase synthesis.[34] Other fluoroformamidinium salts such as the tetramethylurea-derived TFFH (**39**),[240] the pyrrolidinourea-derived BTFFH (**40**) and the *N,N'*-dimethylethyleneurea-derived DFIH (**41**) have been successfully used in SPPS,[36,37] although the addition of HOAt is important to avoid high levels of racemization. Compared with the corresponding chloro derivatives TCFH (**38**), PyClU (**42**) and CIP (**43**), the fluoro analogues gave better results in the preservation of the configuration at the C-terminal carboxylic acid residue, even when HOAt was used as additive with the chloroderivatives.[37] The formation of oxazolones is observed extensively with the chloro derivatives in the absence of additives.[37]

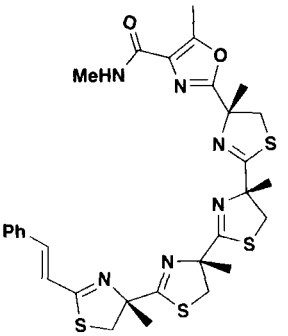
PyClU (**42**) has proved to be as effective as the halophosphonium salts PyCloP (**3**) and PyBroP (**4**) for solution-phase dipeptide synthesis.[38] CIP (**43**) is an efficient coupling agent for Aib-containing dipeptides, the reactivity being enhanced in the order HOAt ≈ HOOBt > DMAP > HOBt by addition of a sub-stoichiometric amount of the additive.[241] This reagent has also been used in the convergent synthesis of (-)-Mirabazole C (**163**), a tetrathiazoline/thiazole alkaloid.[106] The synthesis of the intermediate derived from three 2-methylcysteine residues was achieved by means of CIP (**43**)/HOAt and the same strategy has been followed for the preparation of (-)-Mirabazole B (**164**).[242] The metabolite Thiangazole (**165**), a selective inhibitor of HIV-1, was also prepared by means of CIP (**43**)/HOAt.[243] All these polytiazoline natural products have been isolated from blue-green algae. Two peptaibols, a class of linear antibiotic peptides biosynthesized by soil fungi, with several Aib residues such as Alamethicin F-30 (**166**) and Trichovirin I 4A (**167**), have been prepared with CIP (**43**)/HOAt.[244] For the synthesis of the cytostatic depsipeptide Dolastin 15 (**106**), CIP (**43**)/HOAt was used for the preparation of the peptide fragment in solution and on a solid support, as well as for the preparation of the ester function.[245]



(-)-Mirabazole C (**163**)



(-)-Mirabazole B (**164**)



Thiangazole (**165**)

Ac—Aib—Pro—Aib—Ala—Aib—Ala—Gln—Aib—Val—
Aib—Gly—Leu—Aib—Pro—Val—Aib—Aib—Glu—Gln—Pheol

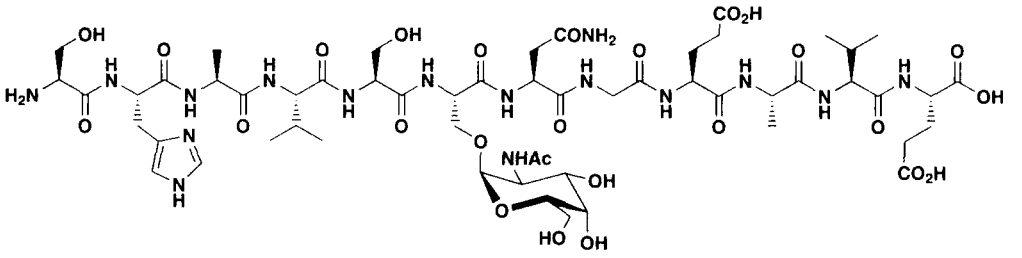
Alamethicin F-30 (**166**)

Ac—Aib—Asn—Leu—Aib—Pro—Ala—Val—
Aib—Pro—Aib—Leu—Aib—Pro—Leuol

Trichovirin I 4A (**167**)

HOBt and HOAt derived reagents of the pyrrolidino chlorouronium salt HBPyU (**44**)[38] and HAPyU (**46**)[23a] have been used for the coupling of *N*-methyl amino acids and for the cyclization of linear peptides, respectively. HAPyU (**46**), HAMDU (**47**), HAPipU (**53**), TAPipU (**54**) and HAMTU (**56**), together with all HOAt-derived reagents have been shown to be very efficient in solid-phase synthesis of peptides containing hindered amino acids.[23b]

The pentafluorophenyl-based reagent HPyOPfp (**48**) has been used in the solid-phase synthesis of a β-turn forming glycopeptide **168** identified as the homophilic recognition domain of mouse epithelial Cadherin 1.[42] The addition of HOAt to reagents HPyOPfp (**48**), HPySPfp (**49**) and HAPyTU (**50**) during the cyclization and segment condensation of model sequences allowed a higher reaction rate and lower extent of epimerization to be obtained.[43] The same effect has been observed in the case of HPyONP (**51**) and HPyOTcp (**52**).[44]



168

The *N*-hydroxypyridone-bispiperidineurea reagent TOPPipU (**55**) has been used for the coupling of sterically hindered amino acids.[45] It has also been used for the coupling of resin-bound Lys with Fmoc-Orn(Boc)-OH in the synthesis of an enantiomerically pure ornithine-based peptide nucleic acid (PNA).[246]

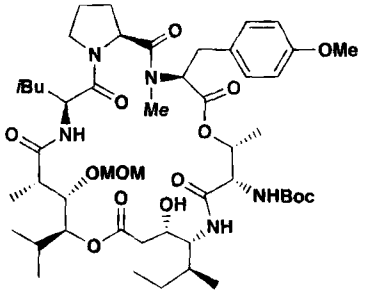
The HOBt and HOAt-derived uronium salts from *N,N,N'*-trimethyl-*N'*-phenylurea HBPTU (**57**) and HAPTU (**58**), respectively, have been efficiently used in solution and solid-phase peptide synthesis.[46] The HOAt derivative **58** shows a higher level of racemization compared to **57**. In addition, four iminium salt reagents stabilized by hexachloroantimoniate **60-63** have recently been prepared from the carboxamides DMF, NMP and *N,N*-tetramethylenebenzamide. BOMI (**60**) is a crystalline solid stable at room temperature which has been used in the synthesis of several oligopeptides in solution and solid-phase conditions and giving excellent results.[47] The four reagents BOMI (**60**), BDMP (**61**), AOMP (**62**) and BPMP (**63**) have been compared with the pyrrolidine uronium derivatives HBPyU (**44**) and HAPyU (**46**). These immonium coupling reagents gave excellent rates and yields and lower racemization than the mentioned uronium salts in the solution-phase synthesis of peptides.[49] They have been employed for the synthesis of active esters such as benzotriazolyl, pentafluorophenyl and succinimidyl esters, useful for the synthesis of lactones and lactams (see Section III.7).

Aminium reagents should be used with caution, since these salts can react with the amino component giving a guanidino derivative, thus terminating the peptide chain.[247] This side reaction is not critical during the coupling of simple protected amino acids because activation is fast and the aminium salt is rapidly consumed or hydrolyzed before exposure to a resin containing an amine terminus. However, during a slower activation process, the aminium salt may react with the amino component. This side reaction is important when very reactive reagents such as HAPyU (**46**), HATU (**32**) and TFFH (**39**) are used. Model experiments carried out with the phosphonium salts PyAOP (**14**) and PyBOP (**7**) have not shown any product correponding to the reaction of the phosphonium salts with the amino component.

4. Phosphinic and Phosphoric Acid Derivatives

Phosphinic chlorides such as diphenylphosphinic chloride (**64**, DppCl) or 1,1,1-trichlorophospholene (**66**, Cpt-Cl) have been used for the *in situ* preparation of amino acids dialkylphosphinic mixed anhydrides.[50-53] In the case of DppCl (**64**) this strategy has been shown to be useful for the solution-phase synthesis of *N*-methylated peptides with very low racemization.[247] Pentafluorophenyl diphenylphosphinate (**67**, FDPP) has been used in solution and solid-phase peptide synthesis and gives good yields with low racemization.[54] Joullié and co-workers. have employed this reagent in selected couplings for dipeptide synthesis and it has been compared mainly with BOP (**6**).[248] For Fmoc-protected amino acids, BOP (**6**) proved to be more efficient than FDPP (**67**) and

MePhe could not be coupled to Z-Leu-Pro. However, for the protected Didemnin macrocycle **169**, FDPP (**67**) gave the best results in the lactamization step (see section III.10).[248] This system (**169**) has been used for the synthesis of Didemnin B (**124b**) analogues for biological testing.[249] For the synthesis of Leualacin (**170**), a cyclopentadepsipeptide calcium blocker, the macrocyclization took place in better yield with FDPP (**67**) than with HATU (**32**).[250]



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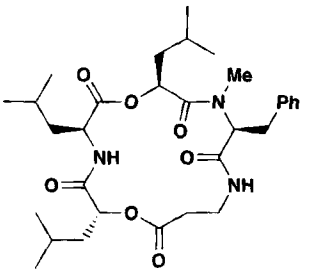
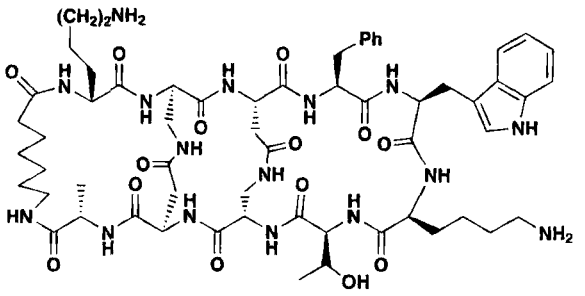
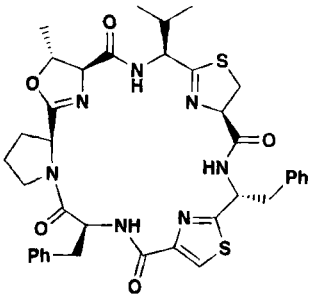


Leualacin (**170**)

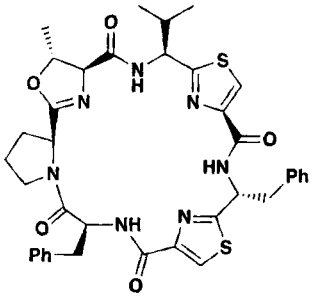
Derivatives of phosphoric acids **68-78** have been widely used in peptide synthesis. Diphenylphosphoryl azide (**68**, DPPA) has been shown to be efficient for cyclizations, for instance in the synthesis of Didemnin A (**124a**).[177] Tricyclic compound **171** is a homodetic peptide in which the amino acid constituents of the ring are joined together solely by amide bonds. The open-chain peptide has been prepared on a solid support using Fmoc-protection and HBTU/DIEA as coupling reagents. The three macrocyclization steps have been performed successfully with DPPA (**68**).[251] Pattenden and co-workers have used DPPA (**68**) extensively for the macrocyclization of heterocyclic-based cyclopeptide natural products mainly of marine origin.[252] Lissoclinamide 4 (**172**) and 5 (**173**) have oxazoline, thiazole and/or thiazoline rings and present a range of biological properties such as immunoregulators, antibiotics, antitumorals and enzyme-inhibitors. They have been prepared by means of DCC (**97**)/HOBt for the acyclic systems, and the macrocyclization has been carried out with DPPA (**68**).[253] The synthesis and assignment of the configuration of Cyclodidemnamide (**174**)[254] has been performed using a similar protocol, as well as Mollamide (**175**)[255] which is a reverse prenyl substituted cytotoxic cyclopeptide.



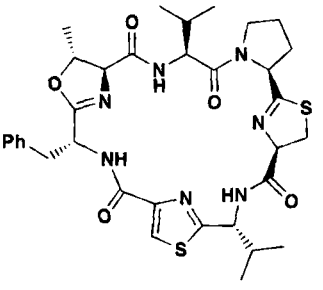
171



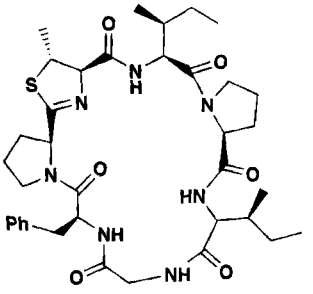
Lissoclinamide 4 (**172**)



Lissoclinamide 5 (**173**)



Cyclodidemnamide (**174**)



Mollamide (**175**)

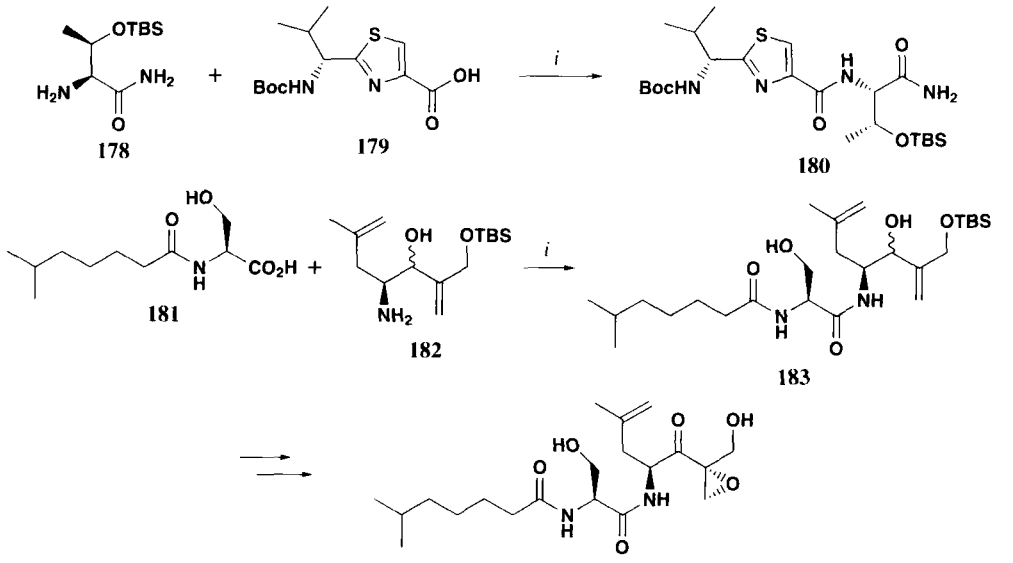
A recent solid-phase synthesis of a 1-substituted pyroglutamate pyrrolidone ring has been achieved by using DPPA (**68**) as activating agent (*Scheme 34*).[256]

176 177

i) TFA; ii) DPPA (**68**)

Scheme 34

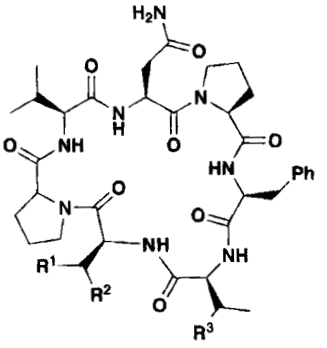
In the synthesis of the fragment A-C of the peptide antibiotic Micrococcin P (**121**)[174] H-Thr(TBS)-NH_2 (**178**) has been coupled with the thiazolecarboxylic acid **179** by means of DPPA (**68**) to give dipeptide **180** (*Scheme 35*).[257] In the synthesis of the antibiotic Eponemycin (**184**), 6-methyl-heptanosylserine (**181**) has been coupled with aminoalcohol **182** with DPPA (**68**)/TEA in DMF to give **183** in 72% yield (*Scheme 35*).[258]



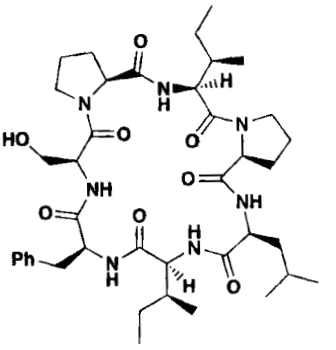
i) DPPA (**68**)

Scheme 35

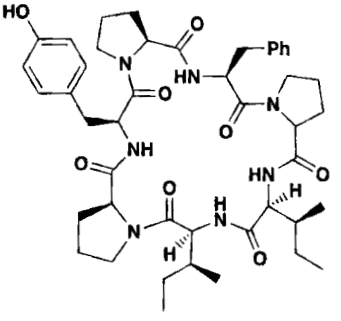
Diethyl phosphorocyanidate (DEPC, **69**) has been used by Pettit and co-workers for the solution-phase synthesis of heptapeptides of marine origin.[259,260] The open chain precursors of Axinastatin 2 (**185**) and 3 (**186**), have been prepared by employing Fmoc/*t*Bu in DCM and K_2CO_3 as base with only one exception, Fmoc-Asn, which was coupled as its *p*-nitrophenyl esters.[259] The use of DEPC (**69**)/DIEA as base, which is frequently used with Fmoc protection gave non-reproducible results. However, in the case of the heptapeptide precursor of the marine sponge Stylopeptide 1 (**187**), the combination DEPC/DIEA was used except for the cyclization step which was performed by means of TBTU (**22**)/DIEA in DCM giving the cycloheptapeptide in 67% yield.[260] The same conditions have been employed for the synthesis of Phakellistatin 2 (**188**)[261] and 5 (**189**).[262] For the cyclization step TBTU (**22**) was used for **188** and PyAOP (**14**) for **189**. In the convergent synthesis of (-)-Dolastin 10 (**190**), a potent antineoplastic and tubulin-inhibitory substance, BrOP (**2**) was used first for the synthesis of dipeptide Val-Dil-O*t*Bu and then DEPC/TEA[263] for the remainder of the peptide bonds.[264]



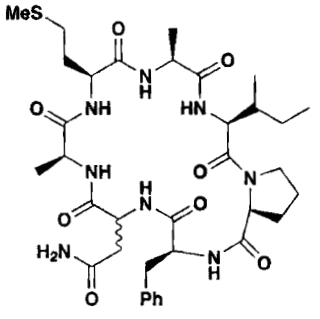
Axinastatin 2 (**185**, R^1 = *i*Pr, R^2 = H, R^3 = Me)
Axinastatin 3 (**186**, R^1 = *i*Pr, R^2 = H, R^3 = Et)



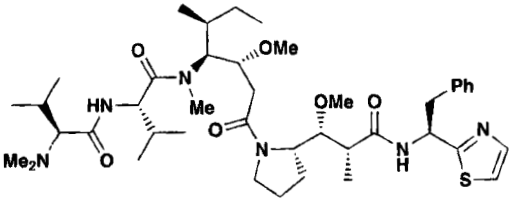
Stylopeptide 1 (**187**)



Phakellistatin 2 (**188**)



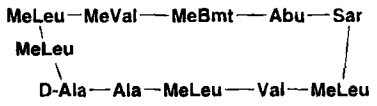
Phakellistatin 5 (**189**)



Dolastatin 10 (**190**)

bis(2-Oxo-3-oxazolidinyl)phosphorodiamidic chloride (70, BOP-Cl)[57] is very effective for the acylation of *N*-methyl amino acids as well as for macrocyclization under high dilution conditions. The solution-phase synthesis of peptides involving *N*-methyl amino acid residues took place more effectively with BOP-Cl (**70**) than with other phosphorous reagents.[109] With regards to epimerization, BOP-Cl is the only coupling reagent useful in the presence of imidazole or HOBt as additives for other type of peptide synthesis.[265] Thus, the 8-11 tetrapeptide fragment of immunosupressor Cyclosporine A (**191**, CsA) has been prepared using both Fmoc- and Z-protection and BOP-Cl (**70**) as coupling reagent in 65 and 73% yields, respectively, with less than 1% of racemization in each stage.[266] The 2-7 fragment has also been prepared by means of BOP-Cl (**70**) although some limitations

have been found for the Boc-Val coupling.[267] D-Lys[8]-Cyclosporine A has been prepared by coupling of both fragments followed by the final cyclization.[267]



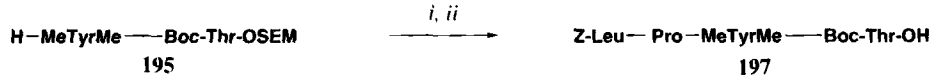
Cyclosporine A (**191**)

Cyclo(—Leu—Sar—Sar—Gly—)
192

Cyclo(—Val—Sar—Sar—Gly—)
193

Cyclo(—MeLeu—Gly—D-Ala—Sar—)
194

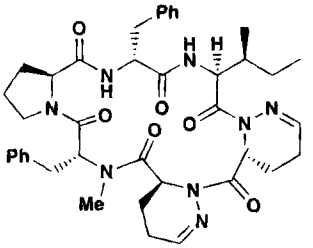
Cyclic tetrapeptides **192-194** containing sarcosine residues have been prepared by a Boc/BOP-Cl (**70**) strategy and the final cyclization step has been achieved using pentafluorophenyl ester activation.[268] In the total synthesis of Didemnins A, B and C (**124**) by Joullié and co-workers,[177] BOP-Cl has been used for the coupling of the secondary amine **195** with Z-leucylproline (**196**) following the preactivation protocol developed by Anteunis and co-workers[265] thus affording the tetrapeptide **197** in 75% yield (*Scheme 36*).



i) Z-Leu-ProOH (**196**), BOP-Cl (**70**), TEA, -15°C; ii) HF

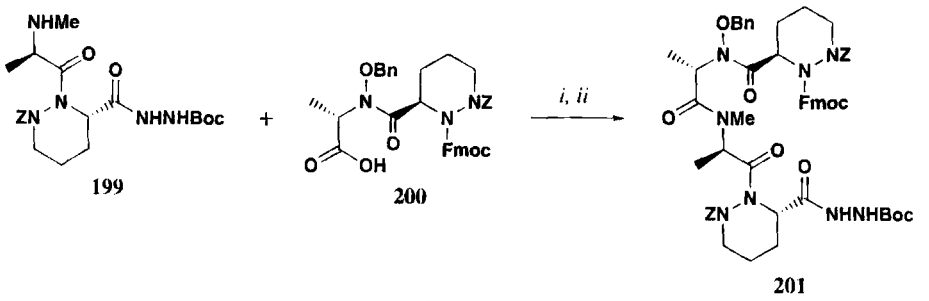
Scheme 36

In the synthesis of cyclic heptapeptide oxytocin antagonists L-365,209 (**198**) and analogs, the linear precursors were prepared by Fmoc/BOP-Cl/DIEA methodology and the final cyclization by



L-365,209 (**198**)

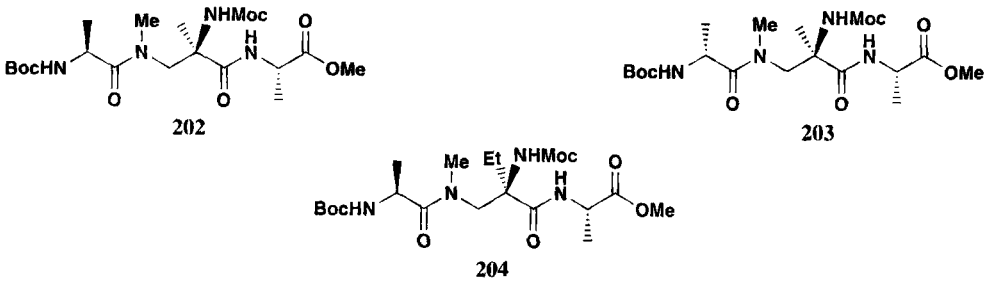
DPPA (**68**).[269] The cyclic depsipeptide Leualacin (**170**) has been prepared using solution methods. Three fragments have been coupled using BOP-Cl (**70**)/NMM in DCM, and the cyclization by DPPA (**68**).[250b] In the total synthesis of antitumour antibiotic A83586C (**159**), compound **199** has been coupled with acid **200** after sequential treatment with TEA and BOP-Cl (**70**) to provide **201** in 75% yield (*Scheme 37*).[231]



i) TEA, -10°C; ii) BOP-Cl (**70**)

Scheme 37

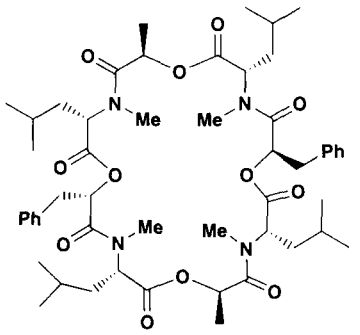
For the synthesis of peptides **202-204,** containing α,α-disubstituted amino acids, BOP-Cl (**70**) has been shown to be efficient using the methoxycarbonyl (Moc) protecting group instead of Boc.[270]



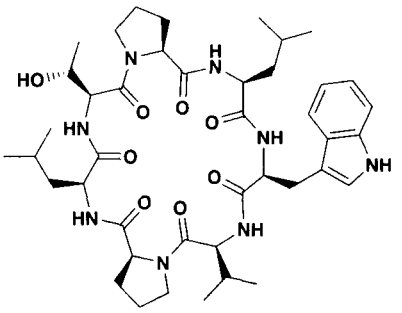
The regioselectivity in the synthesis of lysine dipeptides has been studied recently using isobutyl chloroformate or BOP-Cl (**70**). The dipeptides of Lys and other amino acids **205** have been mainly obtained with BOP-Cl (**70**) in 54-88%, whereas mainly N^{ε}-amidation took place using isobutyl chloroformate thus affording products **206**.[271]

A highly efficient solution-phase synthesis of the antihelmintic cyclooctadepsipeptide PF1022A (**207**) demonstrated that BOP-Cl (**70**) was the reagent of choice for the coupling of the fragments containing MeLeu and also for the final cyclization (85-90% yield).[272] In the synthesis of a PF1022A analog (**207**), PyBroP (**4**) was used as coupling reagent for the solid-phase synthesis. However, for the solution-phase, DCC (**97**) was used for the acyclic precursor whereas BOP-Cl

(**70**)/DIEA at high dilution was used for the macrolactamization.[155]



PF1022A (**207**)



Axinastatin 4 (**208**)

In the previously mentioned synthesis of different cycloheptapeptides from a marine sponge, Axinastatin 2 (**185**) and 3 (**186**), DEPC (**69**) was found especially effective for the final cyclization.[259] In the synthesis of Axinastatin 4 (**208**), solid-phase methods based on Wang resin and Fmoc/DIPCDI (**98**) were used for the acyclic heptapeptide and the final cyclization was carried out by BOP-Cl (**70**) in 94% yield under high dilution conditions.[273]

The rest of the phosphoric acid derivatives **71**-**77** have had limited use as coupling reagents. Benzotriazol-1-yl diethyl (**71**, BDP) and diphenyl (**72**) phosphate gave low racemization degrees in the solution-phase synthesis of peptides.[58b] DEPBO (**73**), DOPBO (**74**), DOPBT (**75**) and DEPBT (**76**) gave also similar results.[61] The latter has recently been compared with several phosphonium and aminium salts in racemization tests and gave excellent results, also being suitable for solid-phase synthesis.[274]

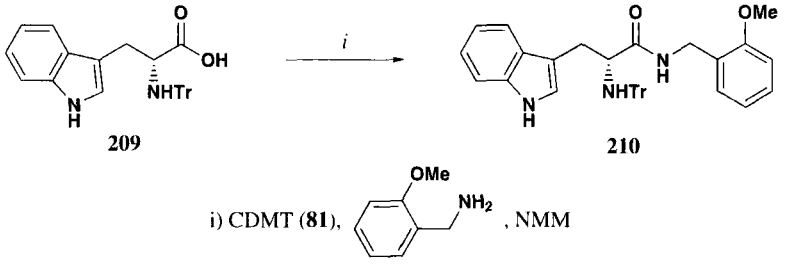
Propanephosphonic anhydride (**78**, PPAA, T3P®) is a good reagent for solution-phase peptide synthesis[63] and cyclization reactions. It gave better results than BOP-Cl (**70**) in the synthesis of D-Lys^8-Cyclosporine A.[267] In the solid-phase synthesis of the undecapeptide of CsA (**191**), DIPCDI (**98**)/HOAt proved to be the more efficient reagent, whereas PPAA (**78**) was used for the cyclization under high dilution conditions.[227] Recently, it has been found that PPAA (**78**) is a superior reagent to HATU (**34**) or HAPyU (**46**) for cyclization reactions, especially for sterically hindered peptides.[275]

5. Other Coupling Reagents

1-Mesitylenesulfonyl-substituted 3-nitro-1,2,4-triazole (**79**, MSNT) has been used as a coupling reagent for anchoring Fmoc-amino acids in high yields to hydroxyl-functionalized solid-supports in the presence of 1-methylimidazole.[65a] This methodology has been used to anchor the first amino acid [Fmoc-Lys(Boc)-OH] to a polyethylene glycol polyacrylamide (PEGA) resin derivatized with *p*-hydroxymethylbenzoic acid linker for the solid-phase synthesis of *C*-glycopeptides.[218] MSNT

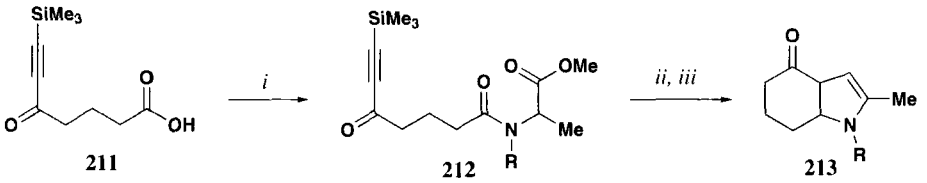
(**79**) and TPSNT (**80**) have been used in the presence of *N*-methylimidazole or 4-morpholinopyridine-1-oxide as reagents for solid-phase synthesis with low racemization.[65b]

2-Chloro-4,6-dimethoxy-1,3,5-triazine (**81**, CDMT) is a cheap reagent which has been used mainly in SPPS. In the presence of *N*-methylmorpholine (NMM) as base the reagent gives low levels of racemization. It has also been used for the coupling of hindered amino acids.[276] The reagent has been employed in the synthesis of *R*-tryptophan amide **210**, a precursor of the NK-1 antagonist LY303870, which was obtained in 93% yield and enantiomerically pure (*Scheme 38*).[277] New anticonvulsant compounds, *N*-substituted amides of α-(4-phenylpiperazino)-GABA, have been prepared by



Scheme 38

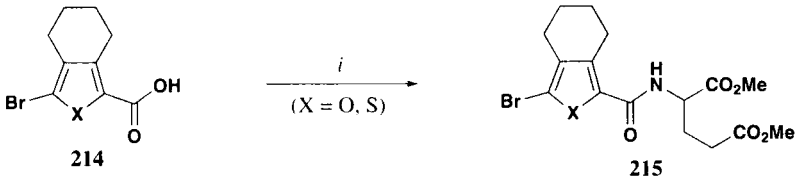
condensation of 2-(4-phenylpiperazino)-4-phtalimidobutyric acid with benzylamine in the presence of CDMT (**81**).[278] Good yields were also obtained in the acylation reaction of *N*-alkyl substituted amino acids to give products **212** which are precursors of oxotetrahydroindoles **213** (*Scheme 39*).[279]



i) RHNCH(Me)CO_2Me, CDMT (**81**), NMM; ii) LiI; iii) Ac_2O

Scheme 39

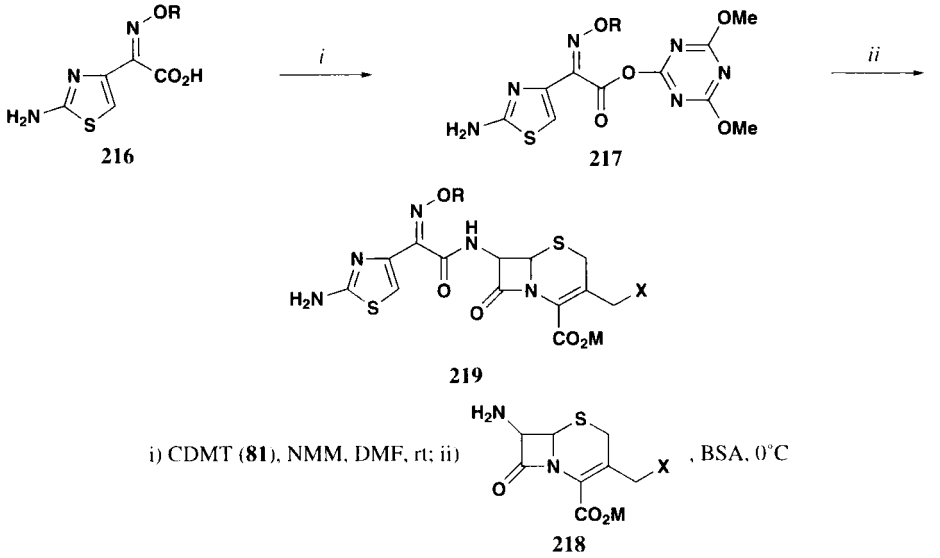
In the preparation of two new analogs of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF) as potential antitumor agents, L-glutamic acid amides **215** have been prepared by CDMT (**81**)-mediated coupling of acid **214** (*Scheme 40*).[280]



i) L-Glutamic acid dimethyl ester, CDMT (**81**), NMM

Scheme 40

The synthesis of cephalosporin derivatives **219** has been carried out in a two-step process. 7-Aminocephalosporamic acid derivatives **218** were acylated with esters **217** derived from acids **216** using CDMT (**81**)/NMM in DMF or MeCN in 60-94% yield (*Scheme 41*).[281]



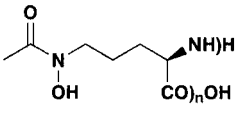
Scheme 41

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (**82**, DMTMM), formed *in situ* by reaction of CDMT (**81**) with NMM has been isolated[67] and used for the synthesis of amides. Reaction rates in THF are faster than with the CDMT/NMM system.[114] The direct coupling of 2-(2-amino-4-thiazolyl)-2-*syn*-methoxymino acetic acid (**216**, R = Me) with *tert*-butyl-7-aminocephalosporanate (**219**, M = *t*Bu, X = OAc) was achieved using DMTMM (**82**) and gave the corresponding product in 73% yield for 1d.[282] This reagent has been compared with PyBOP (**7**) in solid-phase peptide synthesis[283] and yields and purities of the peptides were always comparable to those obtained with PyBOP as coupling agent.

The related derivative 2,4,6-tris(pentafluorophenyloxy)-1,3,5-triazine (**83**, TPfT) was shown to be less reactive than Pfp phosphonium and uronium derivatives.[31]

The old reagent *N*-ethoxycarbonyl-2-ethoxy-1,3-dihydroquinoline (**84**, EEDQ) was initially used for SPPS with Boc-amino acids,[284] but recently it has been mainly used for the solution-phase synthesis of dipeptides by condensation of *N*-protected amino acids (Z, Boc and Aloc) with amino acid heptyl esters. These dipeptides can be hydrolyzed at pH=7 and 37° by a lipase without attack of the urethane group.[285a]

Albomycin-like peptides **220-223** derived from N^5-acetyl-N^5-hydroxy-L-ornithine, the key constituents of several microbial siderophores, iron(III)-transport compounds, have been prepared using EEDQ (**84**).[285] The 3-(3,6-dioxopiperazin-2-yl)propanoic acid was synthesized from L-5-methyl glutamate and ethyl glycinate using EEDQ (**84**).[286] The peptide fragment of the siderophore Pseudobactin (**224**) has been prepared in solution-phase with EEDQ (**84**) without protection of the hydroxyl groups.[287] Solid-phase synthesis on polystyrene or polyethylene glycol grafted polystyrene resins of peptidoglycan monomers **225** and **226** was conducted by coupling lipid-bearing glycocarboxylic acids to resin-bound peptides with different coupling reagents.[288] The efficiency of these reagents was found to be HATU (**34**) > HBTU (**20** > PyBOP (**7**) > EEDQ (**84**). EEDQ (**83**) has also been used as the coupling agent for the synthesis of several hexaglycosyl and nonaglycosyl heptapeptides with phytoalexin elicitor activity.[289]



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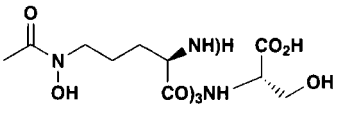

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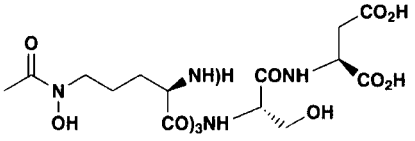

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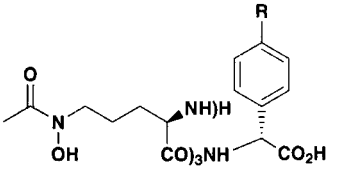
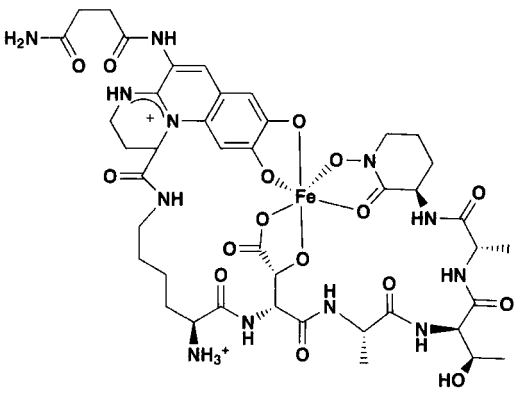
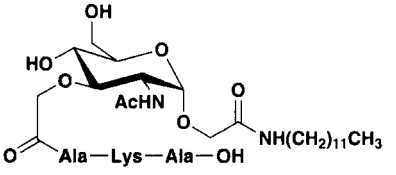


223 (R = H, OH)



Pseudobactin (**224**)



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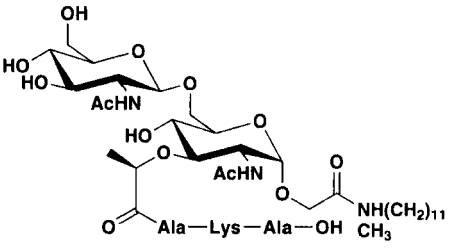
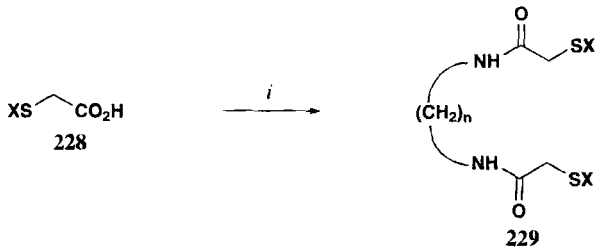


226

Fragment coupling has also been carried out using EEDQ (**84**). The synthesis of galactose clusters that are linked to a steroid by a peptide-like spacer unit such as **227** has been carried out with EEDQ (**84**).[290] Ligands (DADS) **229** for use in ^{99m}Tc radiopharmaceuticals have been prepared from benzoyl or benzyl-protected thiolacetic acid **228** (*Scheme 42*).[291] Pyrimidine nucleosides and their 5'-amino-5'-deoxyanalogs have also been prepared by acylation with 3-(3-indolyl)propionic, nicotinic and 1-nitroanthraquinon-2-carboxylic acids by means of EEDQ (**84**).[292] The synthesis of L-histidine and (-)-spinacine chitooligosylamides has been achieved via coupling of glycosylamines with Boc-His or (-)-spinacine using EEDQ (**84**) and subsequent deprotection.[293] The disaccharide, which corresponds to the terminal of the vibrio cholerae O1 LPS, has been coupled with 2,4-di-*O*-acetyl-3-deoxy-L-glycerotetronic acid in the presence of EEDQ (**84**) to give the corresponding amide.[294] The convergent synthesis of a fluorescence-quenched glycopeptide involves the EEDQ (**83**)-mediated coupling of 2-acetamido-2,3-di-*O*-acetyl-6-(2'-*tert*-butoxycarnonylamino)benzamido-2,6-dideoxy-β-D-glucopyranosylamine with *N*-benzoyl-Asp-Tyr(NO_2)-OMe followed by deprotection.[295]



X = PhCO, Bn

i) $H_2N(CH_2)_nNH_2$, EEDQ (**84**)

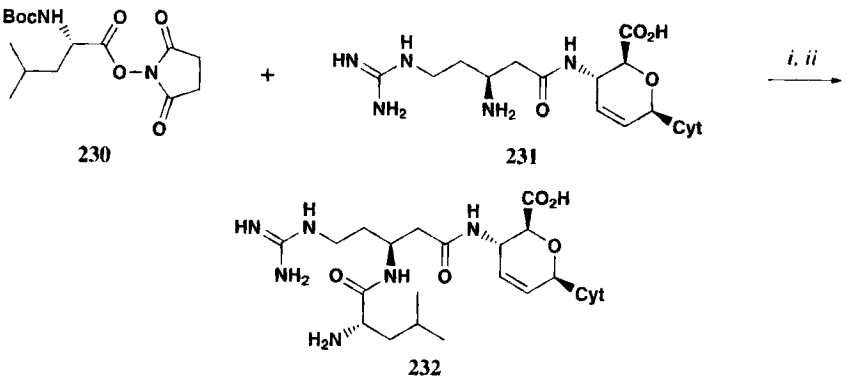
Scheme 42

6. Polymer-Supported Reagents

Polymer-bound EDC (**86**, P-EDC) has been used for the synthesis of amides[71] and more recently for the preparation of acylsulfonamide libraries.[296] P-TBTU (**87**) has been used for peptide synthesis in MeCN as solvent and pyridine as base with results comparable to TBTU.[72] The coupling reactions can also be performed in aqueous MeCN. The solid-supported chloro[1,3,5]triazine **88** was employed for the solution-phase synthesis of different amides and dipeptides.[74]

7. Active Esters

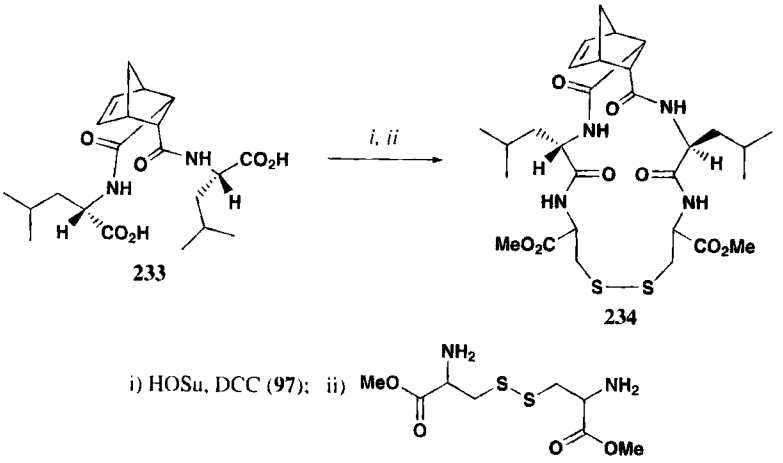
Esters derived from *o*-nitrophenol and *N*-hydroxysuccinimide (HOSu) have been mainly used in solution-phase peptide synthesis.[297] HOSu esters are usually prepared by means of DCC (**97**)[298] or from the acid chloride, and recent applications of these esters are involved mainly with amide formation. For instance, as part of a study of self-resistance mechanisms of *Streptomyces* bacteria, Leucyldemethylblasticidin S (**232**) has been recently prepared in 92% yield by reaction of ester **230** with Domethylblasticidin S (**231**) followed by deprotection (*Scheme 43*).[299] For the



i) $NaHCO_3$; ii) TFA

Scheme 43

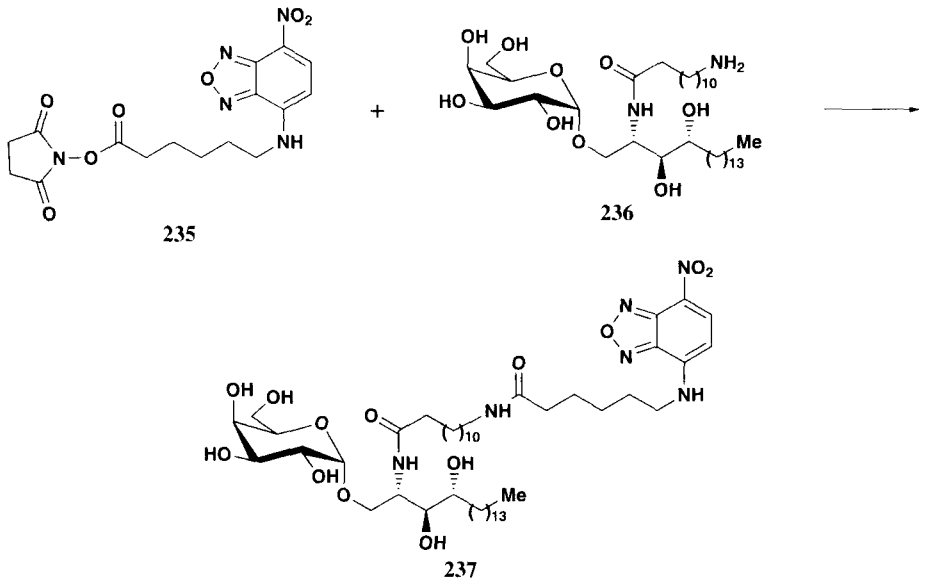
synthesis of a novel family of hairpin[300a] cyclic peptides containing norbornene units as bridging ligands, **234**, the succinimidyl ester has been coupled with cystine diOMe (*Scheme 44*).[300b] In the final



i) HOSu, DCC (**97**); ii)

Scheme 44

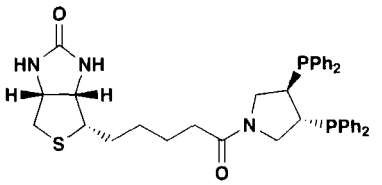
step of the synthesis of the immunomodulator galactosylceramide AGL-597 (**237**), the amide ester (**235**) has been coupled with the galactosylceramide (**236**) in DMF at 25° for 14h (*Scheme 45*).[301]



235 236 237

Scheme 45

The chiral biotinylated 3,4-*bis*(diphenylphosphino)pyrrolidine (biotin-Pyrphos) has been used as a ligand of the corresponding Rh(II) complex in a catalyst embedded in avidin for the asymmetric hydrogenation of itaconic acid. For the preparation of this ligand (**238**) the pyrrolidine unit has been coupled using biotin succinimidyl ester.[302] 3-Hydroxy-2-pyridone derivatives of 4-*tert*-butylcalix[4]arenes are selective extractants of actinide (IV) ions.[303] The tetramine calixarene has been coupled with the succinimidyl ester of the hydroxypyridone[304] to give compound **239** in 92% yield after heating in DMF at 60°.[303]



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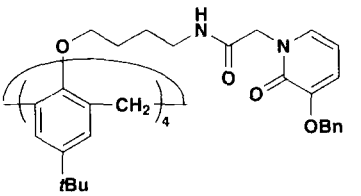
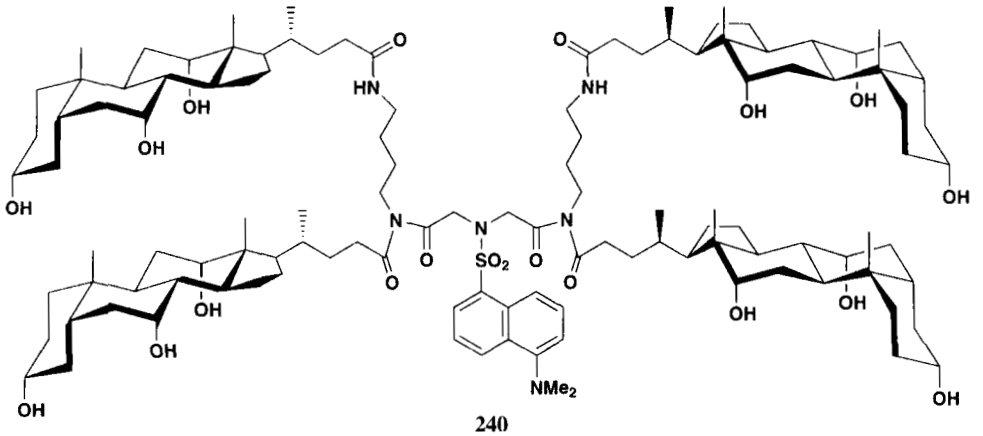


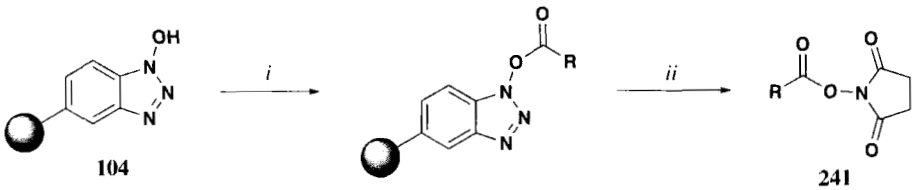
239

Regen and co-workers have described the synthesis of molecular umbrellas such as compound **240** from cholic acid, spermidine, iminodiacetic acid and 5-(dimethylamino)-1-naphthalenesulfonyl (dansyl) chloride. For the coupling of cholic acid and spermidine, the corresponding *N*-hydroxysuccinimide ester has been prepared using HOSu/DCC (**97**).[305] In the final coupling of dansyliminodiacetic acid with spermidine cholic amide, the corresponding succinimidyl ester has been prepared by means of TSTU (**26**).[305b]



240

N-Hydroxysuccinimide esters **241** have been prepared in good yields and purity by reaction of the acid with polymer-bound HOBt (**104**) using DCC (**97**) followed by reaction with HOSu (*Scheme 46*).[306]

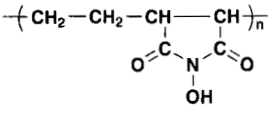


104 241

i) RCO_2H, DCC (**97**); ii) HOSu

Scheme 46

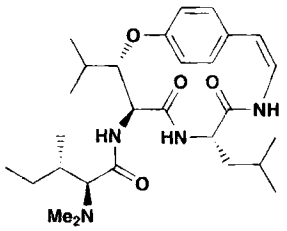
N-Hydroxysuccinimidyl ester resins has been prepared by reaction of cross-linked poly(ethylene-co-*N*-hydroxymaleimide) (**242**, PHMI) with Boc-amino acids in the presence of DCC (**97**). This solid-phase methodology has been used for peptide synthesis, coupling being achieved in



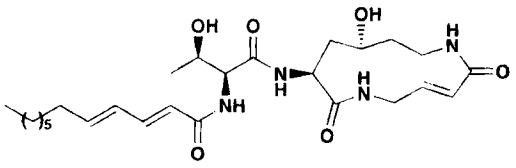
242

DMF at rt. Reaction times can be reduced to 45-60 min by heating to 70°.[307] Polymeric macronet *N*-hydroxysuccinimide esters of Boc-amino acids have been coupled with amino acids in DMSO at rt for 3d.[308] Other *N*-hydroxysuccinimidyl polymers **105** from Merrifield or ArgoPore™ resins, have been used for the preparation of the corresponding esters and give the amides in high yield and purity.[146] Labeling reagents such as fluorescein, coumarin, acridinium and biotin have been supported to this resin **242**. The resulting active esters have been coupled with amines such as striol, thyroxine, phenytoin and desipramine haptens, used in clinically important immunoassays, also in high yield and purity.[309]

Pentafluorophenyl esters (OPfp esters) are more reactive and have been used in solution and solid-phase peptide synthesis. The Fmoc-protected derivatives can be prepared by coupling with PfpOH in the presence of DCC (**97**)[310] or with pentafluorophenyl trifluoroacetate[311] and have been implemented in automated continuous-flow Fmoc/*t*Bu synthesis.[312] In general, no side reaction occurs when Asn and Gln are incorporated without protection[313] and this feature is also observed with the corresponding derivatives of Tyr, Ser and Thr.[314] The addition of HOAt accelerates the reactivity of OPfp esters.[23b,43] The most frequent application of OPfp esters is during the cyclization of linear peptides in solution-phase. Schmidt and co-workers have used OPfp esters for the macrocyclization of Z-protected amino acids during their hydrogenolysis to give ansa peptides.[315] Didemnins A, B, C (**124**) and Prolyldidemnin A has been prepared following this strategy.[316] More recent applications have included the preparation of Frangulanine (**243**) a *p*-ansa compound.[317] Glidobactin A (**244**),[318] a

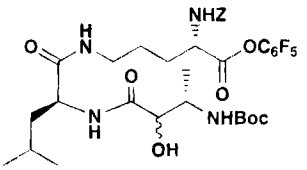


Frangulanine (**243**)



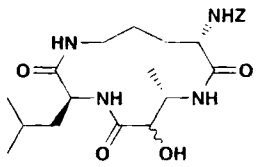
Glidobactin A (**244**)

member of the antibiotic glidobactins and cepafungins families, and Leualacin (**170**), have been synthesized by the same protocol. The prolyl endo-peptidase inhibitor Eurystatin A (**247**) has been prepared by condensation of the OPfp ester **245** with the lactam **246** followed by deprotection of the Z-group and acylation with (*E*)-6-methylhept-2-enoyl chloride (*Scheme 47*).[319] The *p*-ansa cyclopeptide alkaloid (-)-Nummularine F (**250**) has also been prepared by using the Schmidt strategy from



245

i, ii



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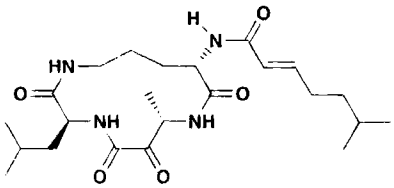
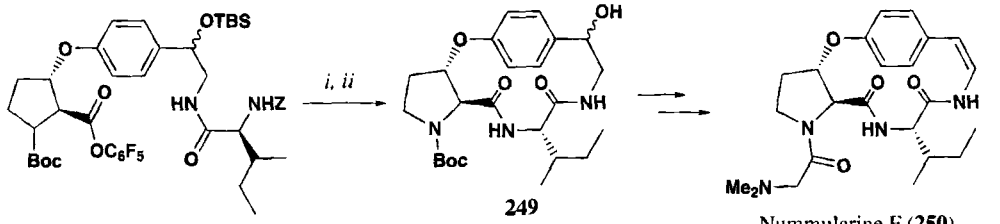


Eurystatin A (**247**)

i) HCl; ii) $NaHCO_3$, rt

Scheme 47

OPfp ester **248**, which has been cyclized in 60-75% yield after transfer hydrogenation at 95° using cyclohexene or cyclohexadiene as the hydrogen source (*Scheme 48*).[320]

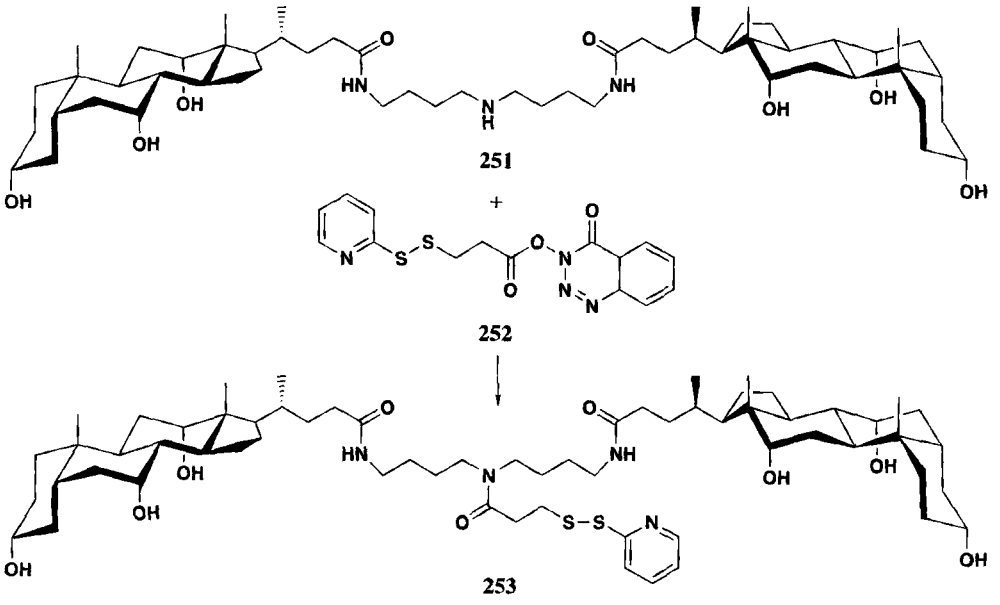


i) 10% Pd/C, cyclohexene; ii) TBAF

Scheme 48

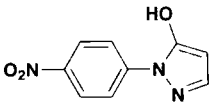
The cyclic tetrapeptides cyclo(-Leu-Sar-Sar-Gly-), cyclo(-Val-Sar-Sar-Gly-) and cyclo(-MeLeu-Gly-D-Ala-Sar-) have been synthesized from the component amino acids by BOP-Cl (**70**) coupling followed by cyclization of the pentafluorophenyl esters in 43, 13 and 30% yield, respectively.[268]

Esters derived from 1-oxo-2-hydroxydihydrobenzotriazine (HOOBt) gave better coupling rates than when used as additive. They have been employed in solid-phase peptide synthesis of the corresponding Fmoc-protected amino acids and they show a good resistance to racemization.[321] The HOOBt liberated from the resin-bound amine provides a useful colour indicator of the progress of the coupling reaction. Regen and co-workers have substituted HOSu esters[305] by HOOBt in the preparation of molecular umbrellas[322,323] such as **253** from 3-(2-pyridyldithio)propionate (**252**, BPDP)[324] and spermidinebis(cholic acid amide) **251** (*Scheme 49*).[322]

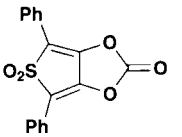


Scheme 49

1-(4'-Nitrophenyl)pyrazolin-5-one (**254**, HOHpp)-derived esters[325] have been used for the attachment of biotin and fluorescein to various biopolymers such as oligonucleotides, peptides and peptide nucleic acids (PNA) because of their higher solubility.[326] 2,3-Dihydro2,5-diphenyl-4-hydroxy-3-oxo-thiophen-1,1-dioxide (**255**, TDO)-derived esters of Fmoc-amino acids have been used for the attachment of the first amino acid to hydroxymethyl resins in the presence of a tertiary base in better yields than the corresponding OPfp esters and without racemization.[327]

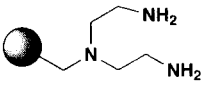


254 (HOHpp)

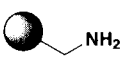


255 (TDO)

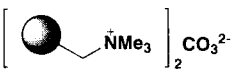
p-Nitrophenyl ester displacements have been recently used for the automated solid-phase extraction of amides in good yield and good to excellent purities.[328] For the sequestration of the HOX by-products formed from acyl-transfer reactants, such as pentafluorophenol, HOSu, *p*-nitrophenol, HOBt, HOAt and imidazol, certain resins **256-260** can be used in the solution-phase synthesis of amides.[329]



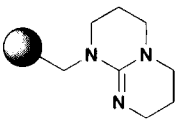
256 (Poliamide resin)



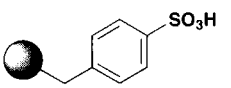
257 (A-21)



258 [A-26 (CO_3^{2-})]

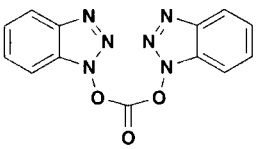


259 (P-TBD)



260 (A-15)

2,2,2-Tribromomethyl esters react with primary and secondary amines using triethylamine and HMPA to afford the corresponding dipeptides and amides. The corresponding esters were formed when alcohols were used as nucleophiles.[330a] Phosphorous(III) reagents such as hexamethylphosphorous triamide or tributylphosphine gave acyloxyphosphonium intermediates, which can also be trapped *in situ* by amine or alcohol nucleophiles, respectively.[330b] The HOBt-derived carbonate 1,1'-(carbonyldioxy)dibenzotriazole (**261**)[331] and more recently benzotriazol-1-yl alkyl derivative **262**,[332]



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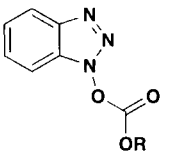


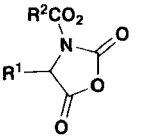
262

have been used for the preparation of unstable HOBt esters which can be used for the synthesis of amides, esters and dipeptides.

8. Amino Acid Anhydrides

Urethane-protected α-amino acids *N*-carboxyanhydrides **263** (UNCAs) are more stable than classical NCAs[295] or Leuch's anhydrides.[333] They are prepared by phosgene treatment of *bis*-trimethylsilyl amino acids followed by protection with Fmoc-Cl or BocON in the presence of NMM or pyridine, respectively.[333,334] UNCAs are stable, crystalline solids in the absence of water and are very soluble in most organic solvents. Upon coupling, carbon dioxide is released, which is an advantage when compared with other methods.[335] They have been used in SPPS with similar rates to BOP (**6**) and HBTU (**20**) activation (see Section III.10) and they are specially useful for sterically hindered peptides.[333,336] For the solution-phase synthesis of the tripeptide Aib-Aib-Aib, the coupling of the third Aib has been achieved in 95% yield by means of Fmoc-Aib-NCA in THF.[156] The esterification of 4-alkoxybenzyl alcohol resin (Wang resin) with Fmoc-histidine(N^{im}-trityl)-NCA has been achieved in high yield and with no detectable racemization.[337]

For the preparation of *N*-trityl and *N*-phenylfluorenyl-*N*-carboxyanhydrides **264,** the protection was carried out before the treatment with triphosgene or phosgene to afford the corresponding TNCAs and PFNCAs, respectively.[338] They have been used in solution-phase of dipeptides by heating with the corresponding amino acid methyl ester in THF at 40° or at reflux with yields in the range 80-90%. Neither racemization nor diketopiperazine formation was detected.



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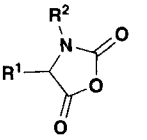


264

A recent route used for the generation of NCAs is *via* the Baeyer-Villiger oxidation of enantiomerically pure azetidine-2,3-diones with MCPBA. The azetidine-2,3-diones are accesible from α-hydroxy β-lactams[339] and by the ozonolysis of α-ethylidene azetidinones[340] (*Scheme 50*). The first method has been successfully applied in the preparation of threonines,[341] α-branched threonines,[342] and azathreonine[343] derived NCAs, as well as for the synthesis of arylalanine- and homoacrylalanine-NCAs.[344] For the Baeyer-Villiger oxidation a combination of bleach and a nitroxide radical, such as 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) has recently been used.[345] The coupling of these NCAs with α-amino acids esters promoted by KCN afforded the corresponding dipeptides in ca. 1d even with hindered amino acids.[345,346]

i) MCPBA; ii) O_3, -78°C

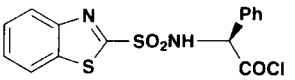
Scheme 50

9. Amino Acid Halides

Protected amino acid chlorides and fluorides have some limitations with respect to their applicability in peptide synthesis. Their instability, the formation of 5(4*H*)-oxazolones and racemization processes are amongst the most common problems encountered (see Section II.6). Nevertheless, there are some benefits to be gained from the use of acyl halides, especially fluorides, which have been recently reviewed.[347]

Fmoc-amino acids chlorides have been successfully used in SPPS.[124] They are prepared by reaction with thionyl chloride and can be stored indefinitely in a dry atmosphere. In order to avoid the base-promoted formation of oxazolones, 1:1 mixtures of base (DIEA, NMM, etc.) and HOBt were used for the rapid solid-phase acylation, possibly *via* the intermediate formation of the corresponding HOBt esters.[124] The potassium salt of HOBt can alternatively be used as base instead of a tertiary amine.[348] The coupling of Fmoc-Aib-Cl with Aib-OBn gave the corresponding dipeptide in 81-85% yield in less than 1h. Parallel studies showed that for the same synthesis of Fmoc-Aib-Aib-OBn, the use of Aib-OPfp/HOBt, Fmoc-Aib-OTcp/HOBt/base, Fmoc-Aib-NCA and $Fmoc(Aib)_2O$ as coupling reagents resulted in 42, 28, 35 and 40% yields, respectively, after long reaction times. These reaction conditions have been applied to the solution-phase synthesis of the Alomethicin 1-4 fragment, Aib-Pro-Aib-Ala, the Emerimicin 2-6 fragment, Aib-Aib-Aib-Val-Gly and the Aib tetramer $Fmoc-(Aib)_4$-OBn in good yield and purity.[348]

Amino acid chlorides derived from phenylglycine **265** and **266**, with the heteroarenesulfonyl groups benzothiazole-2-sulfonyl (betsyl, Bts) and 5-methyl-1,3,4-thiadiazole-2-sulfonyl (thisyl, Ths) as *N*-protection were also prepared by treatment with $SOCl_2$. They have been used in solution-phase synthesis of peptides in the absence of additives. Racemization-free couplings(>99%) in 15 min at 0-5° in DCM have been achieved. Final deprotection can be carried out by means of Zn/HOAc or 50% H_3PO_2.[129] This Bts-protection strategy has been used for the solution-phase synthesis of hindered *N*-methylated tetrapeptides using $PhSH/K_2CO_3$ as the cleavage method for the Bts group.[130] Another strategy for the coupling of α,α-disubstituted amino acids in SPPS is the use of the corresponding α-azido acid chlorides **267**, which are prepared from the α-bromo acids followed by azide substitution and chlorination with $SOCl_2$. These chlorides gave better results than both the corresponding fluorides or *in situ* activation of the α-azido group with TBTU (**22**), the acylation process taking place in 1-2.5h.[131]



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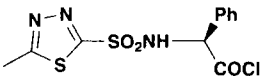

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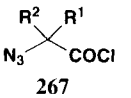


267

In the case of amino acid fluorides, they are compatible with *t*Bu-based protecting groups, present greater stability than chlorides, and are not prone to oxazolone formation in the presence of tertiary amines. They can be stored in DMF for more than 3 days and therefore are suitable for use in multiple peptide synthesizers.[349] The acid fluorides can be easily prepared by treatment of the amino

acid with cyanuric fluoride in the presence of pyridine,[350] (diethylamino)sulfur trifluoride (DAST) in the absence of base,[351] or through use of TFFH (**39**).[34] They are well suited for the coupling of hindered amino acids after prior silylation of the amino acid ester component with *bis*(trimethylsilyl)acetamide (BSA),[132,352] Fmoc-Aib-F has been coupled with Aib-OBn in the presence of DIEA in 69% yield.[348] Hydroxyproline methyl ester linked by the hydroxyl group to the Ellman resin has been acylated with Fmoc-amino acid fluorides to give the corresponding dipeptides, precursors of 2,5-diketopiperazines.[353] They have also been used for the acylation of hydroxymethyl resins in high loading levels and with low racemization.[354] Recent comparative studies of the reactivity of amino acid chlorides and fluorides will be considered in Section III.10.

10. Comparative Studies

Through this chapter the most relevant synthetic applications of the different types of reagents, not only in solid-phase but also in solution-phase synthesis of peptides and related systems has been discussed. The stability of the reagent, the efficiency of the couplings (yield, rate and purity), the racemization problem, the coupling of hindered amino acids and the macrocyclization reaction in the case of cyclic peptides, have been considered. In many cases different peptide coupling reagents have been evaluated to find the best candidate for a particularly problematic coupling. In this section comparative studies of reagents used in different coupling processes will be considered.

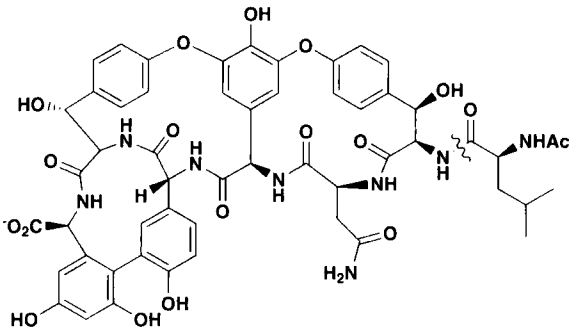
For the anchoring of the first Fmoc-amino acid to the solid support in solid-phase synthesis, specially hydroxy-functionalized resins by an esterification reaction, the carboxyl activation is less important than the reaction solvent.[353] A representative example is given by the successful use of Fmoc-amino acid chlorides by Akaji and co-workers[355] in DCM (containing 40% pyridine). Grandas and co-workers[356] however, failed when using the same method in DMA. Moreover, for DCC (**97**) esterifications catalyzed by DMAP, DCM/DMF (3:1) gives better results than DMF or DMA. However, chlorinated solvents in the presence of TEA can react with HOBt, HOOBt and HOSu to give the *O*-alkylated products.[357] In addition, standard DIPCDI (**98**)/HOBt activation in the presence of pyridine in THF or DCM (containing minimal quantities of DMF or DMA to solubilize the Fmoc-amino acids) can be employed. Amino acid fluorides are effective acylating agents in DCM/pyridine mixtures. These methods are convenient, simple, reliable, high yielding and gave minimal racemization.[353] MSNT (**79**) has also been successfully used for this anchoring process.[65a,218]

Several studies have been carried out on the use of DIPCDI (**98**) and EDC (**99**) with different additives such as HOBt, HOAt, HOOBt, HO(CF_3)Bt and HO(NO_2)Bt, phosphonium BOP (**6**) and ammonium HBTU (**20**) and HATU (**32**) salts in model segment coupling and stepwise assembly by solid-phase techniques. DIPCDI (**98**)/HOAt has been shown to be more effective in preserving the configuration during peptide segment coupling in both DMF and DCM as solvents. In the case of stepwise peptide assembly, the efficiency of DIPCDI/HOAt in DMF can be increased by carrying out the preactivation step in the presence of collidine.[358] The use of collidine leads to lower levels of racemization in the coupling of peptide segments, similar to that observed in the case of *O*-

benzotriazolyluronium salts.[359] SPPS studies with different onium salt-based coupling reagents bearing HOBt and HOAt groups demonstrate that HOAt-derived systems are more reactive than HOBt derivatives during both activation and coupling.[360] The carbon skeleton structure is important for the activation step, pyrrolidino being better than piperidino derivatives or those derived from trialkylamines.[360] Aminium/uronium salts are slightly more reactive than phosphonium salts, but the latter should be used for the activation of hindered species because the former may lead to the formation of guanidino derivatives.[360]

Addition of HOBt and HOAt in several coupling reactions with phenol-based coupling reagents such as HPyOPfp (**48**), HPyONp (**51**) and HPyOTcp (**52**) improves the efficiency of several processes such as a) Fmoc-Ala-Val-OMe, b) (2+1) segment coupling and c) stepwise SPPS assembly of the pentapeptide H-Tyr-Aib-Aib-Phe-Leu-NH_2 and ACP decapeptide (65-74).[44]

Carpino and co-workers have also studied peptide coupling efficiency using carbodiimides and HOAt or HOOBt as additives and the results compared with BOP (**6**), HBTU (**20**), HDTU (**24**) and HATU (**32**).[28b] For the [2+1] couplings Z-Phe-Val-Pro-O*t*Bu, Z-Phe-Val-Ala-OMe, Z-Gly-Phe-Val-OMe, Z-Phe-Val-Pro-NH_2 and Z-Gly-Phe-Pro-NH_2 in the Sakakibara solvents[361] [trifluoroethanol-trichloromethane (TFE/TCM: 1/3)] HOOBt was generally more efficient than HOBt with carbodiimides. However, the use of the onium salt HDTU (**24**) for automated stepwise SPPS is not satisfactory. In the synthesis of a novel derivative **268** of the glycopeptide antibiotic Vancomycin, the coupling between the des-leucylvancomycin aglycone and *N*-acetyl-L-Leu in DMF occurred with racemization in the case of HBTU, whereas TDBTU (**23**) supressed racemization.[362]



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The new DMF-derived formamidinium reagent BOMI (**60**) has been evaluated against other reagents such as DCC (**97**), BOP (**6**), HBTU (**20**) and HBPyU (**44**), and gives the lowest racemization levels during coupling.[47]

Studies on the minimization of cysteine racemization during stepwise SPPS have been carried out with different β-thiol protecting groups such as acetamidomethyl (Acm), triphenylmethyl (Trt), 2,4,6-trimethoxybenzyl (Tmob) and 9*H*-xanthen-9-yl (Xan) and coupling reagents such as BOP (**6**), PyAOP (**14**), HBTU (**20**), HATU (**32**) with HOBt and HOAt as additives and DIEA and NMM as tertiary bases.[361] For the model system H-Gly-Cys-PheNH_2 the racemization level was very high (5-

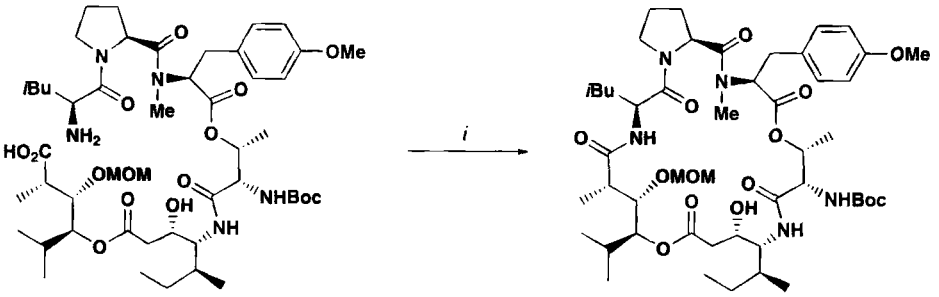
33%). These levels of racemization (<1% per step) were improved by a) avoiding the preactivation step, b) using weaker bases such as 2,4,6-trimethylpyridine or collidine and c) changing the solvent to DCM/DMF (1:1). The use of DIPCDI (**98**)/HOBt or HOAt with 5 min of preactivation or using preformed Pfp esters afforded the same results in both cases in DMC/DMF (1:1).[100]

The coupling of *N*-methyl amino acids, which are present in many natural peptides with important biological properties, for example cyclosporines and pseudopeptides of marine origin such as didemnins and dolastatins, is always a difficult reaction. Several peptide coupling reagents have been used in solution and solid-phase synthesis. Comparative studies have been carried out under SPPS conditions to evaluate several coupling reagents for their utility in preparing peptide sequences related to cyclosporin. Three tripeptides were chosen: H-Val-MeLeu-Ala-NH_2, H-MeLeu-MeLeu-AlaNH_2 and H-MeLeu-MeVal-AlaNH_2 as models. PyBroP (**4**), BOP (**6**), Fmoc-Val-F, HBTU (**20**), BOP-Cl (**70**), DIPCDI (**98**)/HOAt and HATU (**32**) have been compared in the presence of DIEA as base in DMF as solvent, with the latter two HOAt-containing reagents giving the best yields. For the synthesis of the CsA 2-7 sequence (H-Abu-Sar-MeLeu-Val-MeLeu-Ala-OH) using HATU (**32**)/DIEA, less than 4% of D-MeLeu diastereomers were formed.[226] Other studies have been carried out in solution using phosphonium and aminium salts such as PyCloP (**3**), PyBroP (**4**), PyBOP (**7**), PyClU (**42**), HBPyU (**44**), DCC (**97**) and DCC/HOBt with four different dipeptides: Z-MeVal-Val-OMe, Z-Val-MeVal-OMe, Boc-Pro-MeVal-OMe and Z-MeVal-MeVal-OMe.[38] The halogenated reagents **3**, **4**, and **42** proved to be the preferred ones, affording good yields and low racemization levels.[38]

The difficult coupling of α,α-dialkylated amino acids, specially Aib, has been carried out with several reagents including PyBroP (**4**), PyBOP (**7**), DCC (**97**) and DCC/HOBt under solution-phase conditions. Thus, PyBOP (**7**) provides good results and produces epimerization-free peptides. However, the coupling of two Aib residues requires PyBroP/DMAP.[155] For the tripeptide $(Aib)_3$, PyBroP is effective for the synthesis of the dipeptide and Fmoc-Aib-NCA gave excellent results for the tripeptide in THF at rt.[156] Urethane-protected amino acid fluorides are more effective than chlorides for the Aib-to-Aib coupling. However, when the urethane protection is replaced by arenesulfonyl groups the difficult coupling Aib-to-Aib and even MeAib-to-MeAib are easily achieved with acid chlorides but not with fluorides.[122] The new thiazolium-type peptide coupling reagent BEMT (**85**) has been efficiently used for the coupling of *N*-alkyl or α-dialkyl amino acids. It gave better results than PyClU (**42**) and BTFFH (**40**).[70]

Head-to-tail cyclizations are generally the limiting step in the synthesis of cyclic peptides. In these synthesis the degree of success in the macrocyclic coupling depends on the ring size, the type of amino acid residues, the carboxyl-activating reagent and the reaction concentration.[23a] For hexa- and pentapeptides the cyclization efficiency can be enhanced by the presence of turn-inducing amino acids such as Gly, Pro or a D-amino acid. DPPA (**68**) is usually slow in comparison with TBTU (**22**) or BOP (**6**) and also can lead to high levels of racemization such as those observed with DCC (**97**)/HOBt. In the cyclization of the linear GnRH-derived decapeptide H-Nal-D-Cpa-D-Pal-Gln-Tyr-

D-Arg-Leu-Arg-Pro-Lys(Ac)-OH, HAPyU (**46**) and TAPipU (**54**) led to complete reaction within less than 30 min, whereas TBTU (**22**), TOPPipU (**55**) and DPPA (**68**) gave only 60, 10 and 12% yields, repectively. The pyrrolidine urea **46** proved to be more reactive than the piperidine analog **54**. The linear hexapeptide H-Val-Arg-Lys(Ac)-Ala-Val-Tyr-OH was successfully cyclized with HAPyU (**46**) in 55% yield in 30 min and with formation of less than 0.5% of the D-Tyr isomer. In a comparative study, two linear Tyr-containing hexapeptides Tyr(Bn)-Asp(OBn)-Phe-Phe-Ser(*t*Bu)-D-Ala and Tyr-Asp(O*t*Bu)-Phe-Phe-Ser(*t*Bu)-D-Ala, and two analogs containing Thr have been cyclized by means of HBTU (**20**)/HOBt/DIEA, TBTU (**22**)/HOBt/DIEA and DPPA (**68**)/$NaHCO_3$. The best results were obtained with TBTU under high dilution conditions.[363] In the coupling of the amino acid components[300] of the didemnin macrocycle **169**, FDPP (**67**) gave a higher yield (68%) than BOP (**6**) and HBTU (**20**) after 4h at rt (*Scheme 51*).[248] For the synthesis of a cyclopeptide analog of Neuropeptide Y, three methods, DPPA (**68**)/TEA, DPPA (**68**)/K_2HPO_4 and TBTU (**22**)/HOBt/DIEA, have been studied for the cyclization of the linear heptapeptide, the former being the most efficient.[208]



i) FDPP (**67**)

Scheme 51

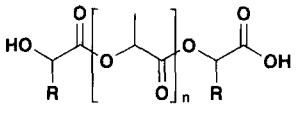
For the macrocyclization of thymopentin-derived pentapeptides, several HOBt and HOAt derivatives such as BOP (**6**), PyBOP (**7**), PyAOP (**14**), TBTU (**22**), HATU (**32**), HAPyU (**46**) as well DPPA (**68**) have been assayed. HOAt-derived coupling reagents significantly improve the head-to-tail cyclization of all-L-penta- and also the hexapeptides. However, these reagents could not fully prevent the formation of cyclodimers or the occurrence of some *C*-terminal epimerization.[364] The addition of HOAt improves the effectiveness of pentafluorophenyl-based coupling reagents in cyclization reactions.[43] Recent studies on cyclization reactions with HAPyU (**46**) and 2-propanephosphonic acid anhydride (78, T3P®) have demonstrated that the latter is a superior reagent for the ring closure of several linear pentapeptides and gives lower racemization levels.[275]

IV. OTHER APPLICATIONS

1. Carbodiimides

The formation of ester bonds is one of the most important applications of carbodiimides.[365] Recent applications of DIPCDI (**98**) are the solid-phase synthesis of depsides and depsipeptides.[366]

Optically active tetrahydropyranyl-protected α-hydroxy acids have been coupled in 97% yield per cycle in the automated preparation of depsides **270** using the same or different acids. For depsipeptides **271**, α-hydroxy and α-amino acids were alternatively introduced in 83% overall yield after 12 coupling steps.



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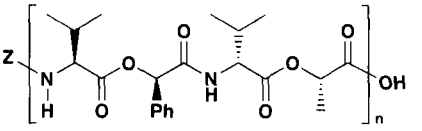
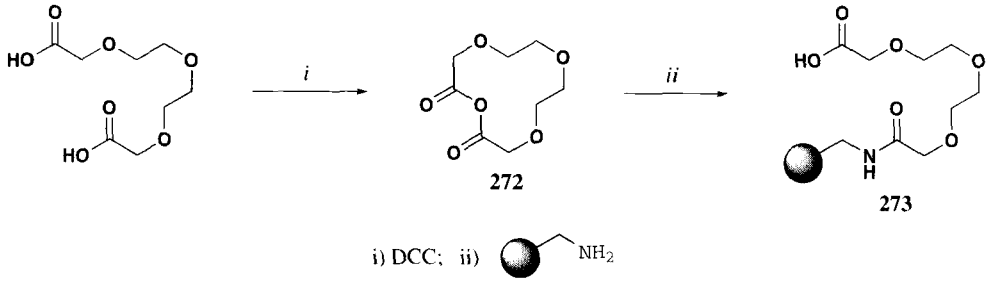


271

Some of these reagents have also been used as dehydrating agents for the synthesis of anhydrides. A recent application in the solid-phase synthesis of tyrosine peptide aldehydes is the preparation by means of DCC (**97**) of the anhydride **272**, which is coupled with the aminomethyl polystyrene resin to give the aminomethyl-PEG-PS-resin **273** (*Scheme 52*).[367] A solid-phase synthesis of 1,3,4-oxadiazoles **274**, usually employed as ester bioisosteres, has also been carried out under very mild

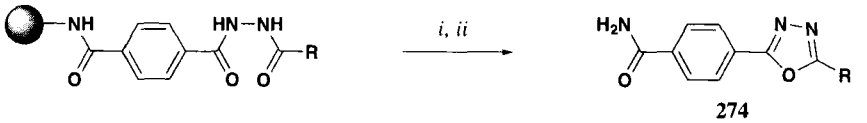


272 **273**

i) DCC; ii) NH_2

Scheme 52

reaction conditions by using DIPCDI (**98**) to induce cyclodehydration in good yields (*Scheme 53*).[368]



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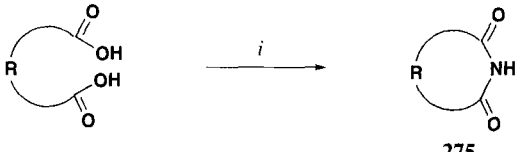
i) DIPCDI (**98**); ii) TFA

Scheme 53

Cyclic imides **275** have been prepared by reaction of diacids with trifluoroacetamide in the presence of EDC (**99**)/HOBt as the best condensing agent (*Scheme 54*).[369]



275

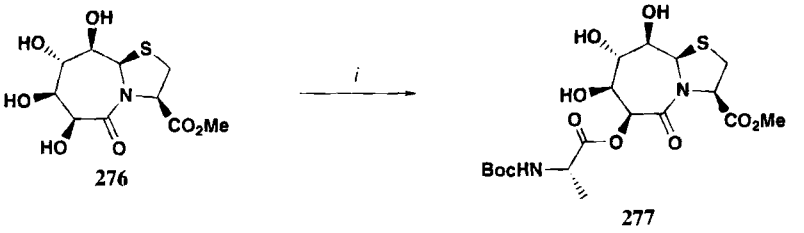
i) CF_3CONH_2, EDC (**99**), HOBt

Scheme 54

DCC (**97**) has been found to affect condensation of arylacetic acids in the presence of DMAP leading to the formation of bisbenzyl ketones.[370] It has also recently been shown that DCC (**97**) promotes olefin epoxidation with aqueous hydrogen peroxide under mild basic or acid catalysis.[371] The presumed reactive species is a peroxyisourea generated *in situ* by the addition of hydrogen peroxide to the carbodiimide.

2. Phosphonium Salts

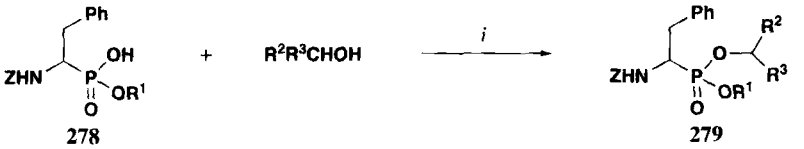
The use of BOP (**6**) or PyBOP (**7**) for the mild and efficient preparation of esters is a well known application of the phosphonium salts.[372,373] Several acid and base labile protecting groups commonly used with amino acids are tolerated under these esterification conditions. Coste and Campagne[96] have demonstrated that the benzotriazolyl ester is formed and then transesterified by the alcohol. The esterification can be carried out at rt in the presence of DIEA in DCM or DMF. A recent example on the use of PyBOP (**7**) as a regioselective esterification reagent is shown in the preparation of the depsipeptide **277** from polyol **276** in DMF at rt in the presence of 1-methylimidazole (*Scheme 55*).[373] The reduction of HOBt esters formed *in situ* from carboxylic acids and BOP (**6**) by means of sodium borohydride in THF takes place in high yields[374] (see Section IV.6).



i) Boc-Ala-OH, PyBOP (**7**), *N*-methylimidazol

Scheme 55

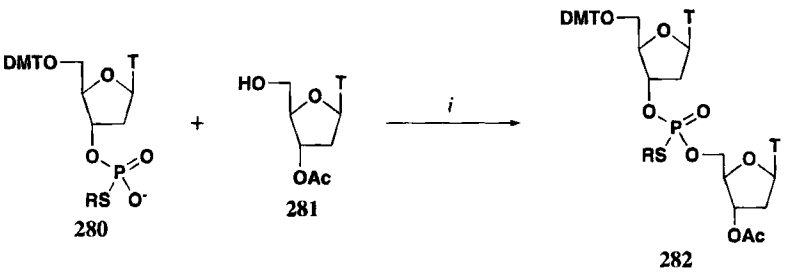
Mixed phosphonate diesters **279** have been prepared from aminophosphate monoesters **278** and various alcohols without racemization using BOP (**6**) or PyBOP (**7**) and TEA in DMF at rt (*Scheme 56*).[375] The solid-phase synthesis of phosphonopeptides has also been carried out by means



i) BOP (**6**) or PyBOP (**7**)

Scheme 56

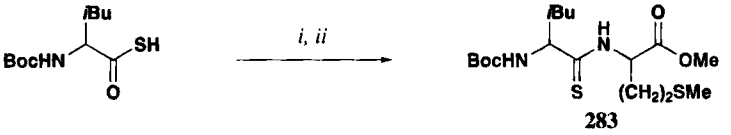
of BOP (**6**)/DIEA.[376] Solution-phase synthesis of dithymidine phosphorodithioacetates **282** has been performed by fast coupling of *O*-thymidin-3'-yl *S*-alkyl dithiophosphate monomers **280** with **281** in the presence of PyNOP (**11**) (*Scheme 57*).[377]



i) PyNOP (**11**)

Scheme 57

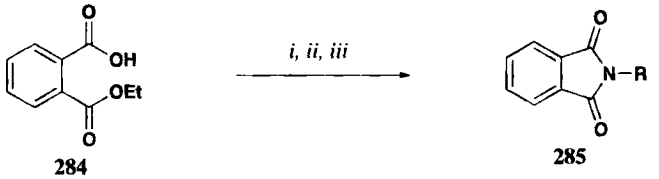
Endothiopeptide **283** was obtained, with low levels of epimerization, with several phosphonium salts such as PyBOP (**7**), PyFOP (**9**), PyNOP (**11**) and PyAOP (**14**). PyNOP (**11**) gave the best results with less than 2% of epimerization (*Scheme 58*).[201]



i) PyXOP; ii) H-Met-OMe.HCl, DIEA

Scheme 58

A new method for the preparation of phthalimides **285** from primary amines is based on the reaction of 2-(ethoxycarbonyl)benzoic acid (**284**) with the amine in the presence of PyBOP (**7**) followed by thermally-induced cyclization using catalytic amounts of TsOH (*Scheme 59*).[378] Primary aliphatic amines are transformed into isothiocyanates by reaction with carbon disulfide in the presence of BOP (**6**) using DMF as solvent.[379] PyBrOP (**4**) has been employed recently for the synthesis of formamidines by reaction of primary amines with DMF in the presence of DIEA at rt for 5h.[380]



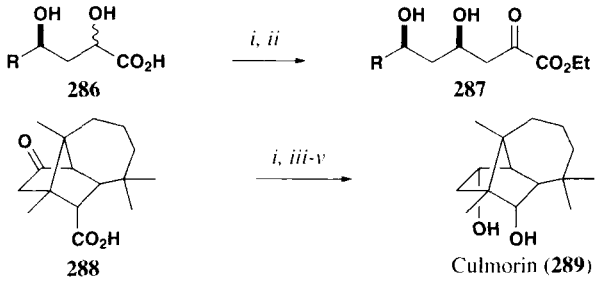
i) PyBOP (**7**), DIEA; ii) RNH_2; iii) D, TsOH

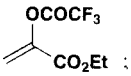
Scheme 59

3. Aminium Salts

These type of reagents have seldom been used in esterification reactions. HOTT (**35**) is an adequate reagent for preparing hindered Barton esters, which are radicals precursors.[32] Recent applications of this methodology are: a) the iterative approach to 1,2,5,...(2n+1) polyols by generation of

chiral hydroxyalkyl radicals from acid **286** followed by radical Michael addition (*Scheme 60*)[381] and b) the stereocontrolled synthesis of (±)-Culmorin (**289**) from acid **288** (*Scheme 60*).[382]





i) HOTT (**35**); ii) hn, ; iii) *t*BuSH, O_2, 80°C; iv) $P(OMe)_3$; v) Li, NH_3, MeOH, -78°C

Scheme 60

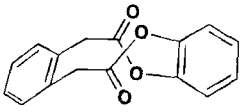
Esterification of Fmoc-protected amino acids or derivatives to 4-alkoxybenzylalcohol resin has been achieved in good yield either with the chlorouronium salt CIP (**43**) or with its HOBt derivative BOI (**45**)[40] (see Section IV.8). CIP (**43**) has also been used in the preparation of esters in the presence of TEA or pyridine at rt in DCM.[383] The latter reagent has been used for the acylation of 2-mercapto-1,3-thiazoline, preparation of anhydrides, *O*- and *C*-acylation of cyclic 1,3-diones, preparation of nitriles from oximes and primary carboxamides, synthesis of isocyanides from formamides, isothiocyanates from dithiocarbamates and carbodiimides from thioureas.[383] Several types of heterocycle can be constructed from appropriate precursors by a CIP (**43**)-promoted dehydration reaction and examples include sydnone from *N*-nitroso-*N*-phenylglycine, azetidin-2-ones from carboxylic acids and imines, γ-imino-a,β-butenolides from maleic acid monoamides, 5-oxazolidinones from *N*-acyl-α-amino acids, 1,3-oxazolidin-2-thiones from 2-amino alcohols and carbon disulfide, 1,3,4-oxadiazoles from diacylhydrazines or from acylhydrazines and carboxylic acids, 1,3,4-oxadiazole-2-(3*H*)-thiones from hydrazides and carbon disulfide, thiadiazoles from thioamides and 4-oxo-3,1-benzoxazines from *N*-acylanthranilic acids.[384] CIP (**43**) can act not only as a powerful dehydrating agent equivalent to DCC (**97**) but it can also be applied to chlorination, oxidation, reduction and rearrangement reactions under neutral conditions.[385] Primary alcohols are converted into chlorides, 1,3-diketones into γ-chloro a,β-unsaturated ketones, secondary alcohols into ketones, primary alcohols are oxidized to aldehydes in the presence of hexamethylenetetramine, sulfoxides reduced to sulfides, hydroxamic acids are rearranged to isocyanates and oximes to carboxamides.[385]

TFFH (**39**) has been shown to be an useful reagent for the preparation of isothiocyanates from primary amines and carbon disulfide, a reaction which is also carried out with BOP (**6**),[379] and for the synthesis of hydrazides from carboxylic acid and hydrazine.[35b]

TBTU (**22**) has recently been used as a new reagent for the cleavage of tetrahydropyranyl, silyl and 4,4'-dimethoxytrityl ethers giving yields higher than 85%.[386]

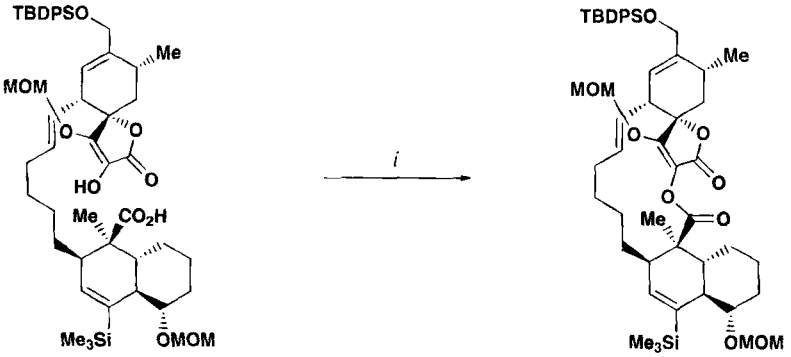
4. Phosphinic Acid and Phosphoric Acid Derivatives

BOP-Cl (**70**) is a useful reagent for esterification reactions[57] and has been shown to be effective for the kinetic resolution of racemic carboxylic acids using optically active alcohols and for the resolution of racemic alcohols with optically active carboxylic acids.[387] BOP-Cl (**70**) is a suitable reagent for the acylation of methyl α-D-glucopyranoside and α-D-mannopyranoside at the primary hydroxy groups.[388] A recent application in lactonization reactions using BOP-Cl (**70**) is the esterification of *o*-phenylenediacetic acid with catechol to give the orthocyclophane **290** in one step.[389] In the



290

synthesis of (-)-Chlorothricolide, the aglycon of Chlorothricin which is an inhibitor of pyruvate carboxylase and is active against Gram-positive bacteria, the macrocyclization of seco-acid **291** to lactone **292** was carried out with BOP-Cl (**70**) in much better yield than with carbodiimides (*Scheme 61*).[390]

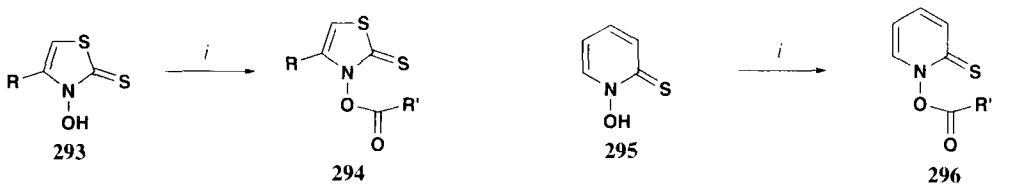


291 **292**

i) BOP-Cl (**70**), TEA, 100°C

Scheme 61

Propanephosphonic acid anhydride (PPAA, **78**) has been shown to be an efficient reagent for the preparation of *N*-acyloxythiazole-2(3*H*)-thiones **294** by the acylation of *N*-hydroxythiazolethiones **293** with carboxylic acids in the presence of DABCO (*Scheme 62*).[391] This methodology can also be applied to the synthesis of Barton esters **296** as previously mentioned with HOTT (**35**).[32] PPAA (**78**), as well as other organophosphorous reagents have been used for the high conversion of alkenes to epoxides by hydrogen peroxide in buffered aqueous THF.[392]



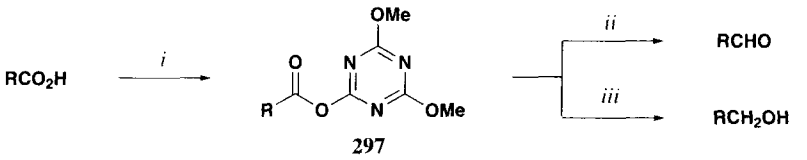
i) $R'CO_2H$, PPAA (**78**), DABCO

Scheme 62

5. Other Coupling Reagents

The thiazol MSTN (**79**) with NMI as base is a good esterification system and has been used to couple carboxylic acids to support-bound alcohols and viceversa.[393] This reagent gave better results than DCC (**97**) or Mitsunobu conditions. Triazolides MSNT (**79**) and TPSNT (**80**) are good condensing agents for the synthesis of polynucleotides in solution-phase.[64, 394]

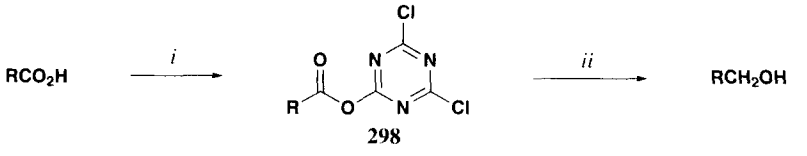
The 1,3,5-triazinylmethylmorpholinium chloride DMTMM (**82**) is an efficient condensing agent which leads to the formation of esters in the presence of NMM.[114,395] The corresponding active esters **297** can be formed and reduced *in situ* to aldehydes or alcohols using Pd/C and hydrogen at ambient or high pressure (*Scheme 63*).[396]



i) DMTMM (**82**), NMM; ii) H_2 (1atm), Pd/C, 0°C; iii) H_2 (5 atm), Pd/C

Scheme 63

Several *N*-Boc-protected amino acids have been reduced to α-amino alcohols without racemization. The same group has reduced active esters **298** prepared *in situ* from cyanuric chloride in the presence of NMM by means of sodium borohydride (see Section IV.6).[397] Several carboxylic acids, including *N*-Boc-, *N*-Z- and *N*-Fmoc-protected α-amino acids, have been reduced to the corresponding amino alcohols in good yields (*Scheme 64*).

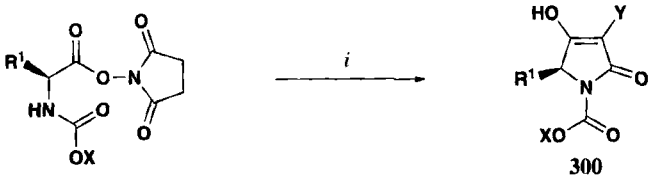


i) , NMM, 3h, rt; ii) $NaBH_4$, H_2O, 0°C

Scheme 64

6. Active Esters

N-hydroxysuccinimide (HOSu) esters **299** have been shown to be more reactive than the *p*-nitrophenyl esters[398] of *N*-alkoxycarbonyl-α-amino acids when reacted with active methylene compounds during the synthesis of 3-substituted tetramic acids **300** (*Scheme 65*).[399] The reaction is carried out in a one-step procedure, the active methylene compound being condensed with the HOSu ester **299** by using NaH as base at rt and affords tetramic acids **300** in optically active form from L-amino acids[399a,c,d] (see Section IV.8).

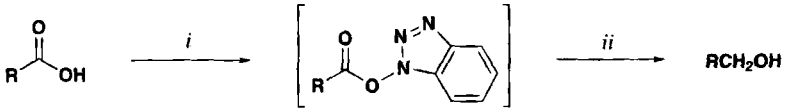


299 **300**

i) $YCH_2CO_2R^2$, NaH, rt

Scheme 65

HOBt esters **301** prepared from carboxylic acids and BOP (**6**) in the presence of DIEA can be reduced with sodium borohydride to give the corresponding alcohols (*Scheme 66*).[373] This methodology is similar to that mentioned in Section IV.5 (*Scheme 64*). These reaction conditions are compatible with the presence of several functional groups such as nitro, halide, cyano, azido and ester. The

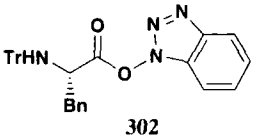


301

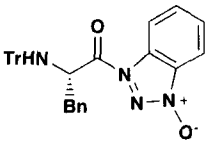
i) BOP (**6**), DIEA; ii) $NaBH_4$

Scheme 66

unique intermediancy of esters **301** is not clear since previous studies by Liskamp and co-workers on the reaction of *N*-trityl amino acids with BOP (**6**) demonstrated that, in the presence of TEA, Tr-Phe-OH gave a ca. 1:1 mixture of the ester **302** and the crystalline compound **303**.[400] It has also been observed that ester **302** completely rearranges to the thermodinamically more estable amide **303** after storage (1-3 weeks). However, Z- or Boc-protected amino acid esters cannot be isolated due to their unstability during work-up.[97] Amide **303** has been reduced to *N*-tritylphenylalaninal in 70% yield together with 30% of the alcohol.[400] Methanolysis of **303** with Tesser's base gave the methyl ester quantitatively and the *t*-butyl ester in 90% yield when KO*t*Bu was used.[400] In the case of *N*-trityl serine and threonine the β-lactones were formed in 95 and 92% yield, respectively.[400]



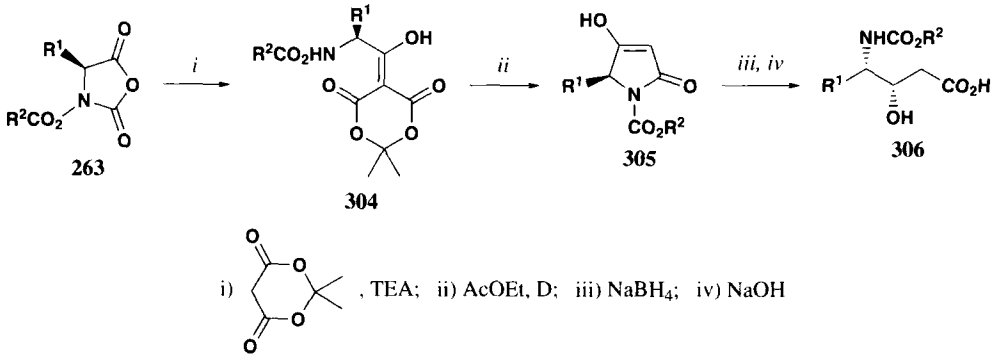
302



303

7. Amino Acid Anhydrides

For the synthesis of optically active *N*-protected tetramic acid derivatives (see also Section IV.8), which are important precursors of β-hydroxy γ-amino acids, UNCAs **263** were allowed to react with Meldrum's acid in the presence of a tertiary amine.[401] This methodology has been previously mentioned for HOSu active esters (see *Scheme 65*). The condensation takes place in the presence of the tertiary amine (TEA, DIEA, NMM, etc.) in a few minutes and the resulting crude adducts **304** were cyclized to enantiomerically pure tetramic acid derivatives **305** in 63-87% yield (*Scheme 67*). Reduction and hydrolysis of compounds **305** gave enantiomerically pure statine derivatives **306**. Base-induced dimerization of *N*-Boc-substituted UNCAs in aprotic media gave 3,5-dialkyl-2,4-dioxo-1-pyrrolidine analogs.[402]



263 304 305 306

i) , TEA; ii) AcOEt, D; iii) $NaBH_4$; iv) NaOH

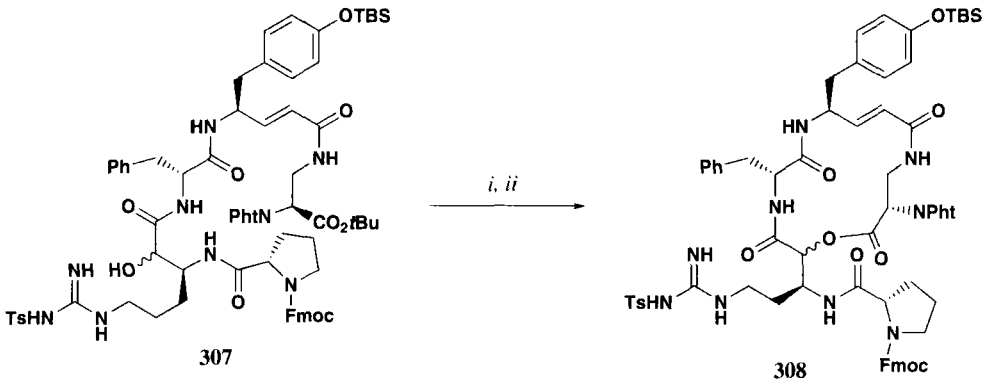
Scheme 67

8. Comparative Studies

In a recent study on the preparation of primary amides from Boc-, Z- and Fmoc-protected amino acids and other carboxylic acids by reaction with ammonium chloride in the presence of tertiary amines, several peptide coupling reagents such as DCC (**97**) EDC (**99**), PyBOP (**7**) and HBTU (**20**) have been tested. The ammonolysis takes place selectively and the reagent of choice depends on the type of amide. PyBOP (**7**) and HBTU (**20**) should be chosen if the product is soluble in organic solvents. Moreover, these reagents give total conversion in 30 min.[403]

Several coupling reagents have been evaluated in depside bond formation. As a model, Fmoc-Ala-OH and a L-phenyllactic acid benzyl ester have been coupled using DCC (**97**)/DMAP, DIPCDI (**98**)/DMAP, PyBroP (**4**), TBTU (**22**)/DIEA or DMAP, TSTU (**26**)/DIEA, TNTU (**27**)/DIEA, UNCA (**263**)/DIEA, acid chloride/DMAP, acid chloride/HOBt, as well as symmetrical and mixed anhydrides.[404] Fmoc-amino acid chloride, UNCA in the presence of a tertiary amine and PyBroP gave the best results, couplings being performed in 6, 4 and 3 h with 61, 80 and 82% yield, respectively. Few side reactions and low epimerization levels were observed.

For the anchoring of Fmoc-amino acids to 4-alkoxybenzylalcohol resin the new reagents CIP (**43**) and BOI (**45**) have been compared with DIPCDI (**98**)/DMAP, PyBroP (**4**) and acid fluoride and the reaction with **43** and **45** takes place faster and with similar degrees of racemization.[40] In the convergent synthesis of cyclotheonamides, macrocyclic peptide inhibitors of serine proteases, the lactonization step has been carried out with different coupling reagents. For the preparation of pentapeptide **307** to give the cyclic peptide **308**, a precursor of Cyclotheonamide A and B, different reagents such as BOP (**6**)/DMAP, DCC (**97**)/HOBt, EDC (**99**)/HOBt, DPPA (**68**)/$NaHCO_3$, HBPyU (**44**) and BOP-Cl (**70**) were compared. The latter reagent gave the best results under high dilution conditions (*Scheme 68*).[363]



i) TFA; ii) BOP-Cl (**70**)

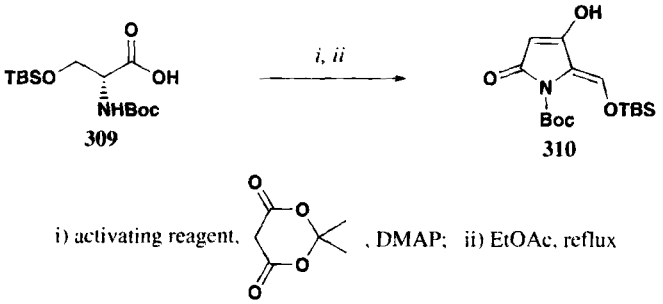
Scheme 68

Several phosphonium salts and phosphonic acid derivatives have been tested for their ability to activate the ambidentate nucleophilic monothio acid group as a thiocarbonyl funstionality suitable for the formation of thioamides. The initial model was the reaction between thioacetic acid and cyclohexylamine and coupling reagents such as PyClOP (**3**), PyBroP (**4**), PyBOP (**7**), PyFOP (**9**), NOP (**10**), PyNOP (**11**), PyPOP (**17**), PyTOP (**19**), BOP-Cl (**70**) and ENDPP (**77**). The best results were obtained with PyFOP (**9**) and PyNOP (**11**).[19]

The solid-phase synthesis of oligonucleotides has been studied using phosphonium and iminium salts as coupling reagents in a phosphotriester mode. Typically, this synthesis is performed

using a carbodiimide reagent in the presence of an amine or HOBt. However, these reactions are too slow (1-16 h) to be automated. With these onium salts the coupling is performed in ca. 10 min and the order of reactivity was HATU (**32**) > PyBOP (**7**) ≈ HBTU (**20**) > BOP (**6**) > BroP (**2**) ≈ HBPyU (**44**) > PyBroP (**5**).[405]

The coupling of carboxylic active species with active methylene compounds has also been studied using different reagents. As a model reaction, protected D-serine **309** has been condensed with Meldrum's acid in DCM and in the presence of DMAP followed by cyclization to compound **310** (*Scheme 69*) using reagents such as isopropenyl chloroformate, FDPP (**67**), BOP (**6**), pentafluorophenol/DCC (**97**), phosgene, DppCl (**64**), DCC (**97**), *N,N*-carbonylimidazole, 2,4,6-trichlorobenzoyl chloride, pentafluorophenyl trifluoroacetate and oxalyl chloride.[406] FDPP (**67**) and BOP-Cl (**70**) were the most successful reagents.



Scheme 69

V. CONCLUSIONS

At the beginning of the last century Emil Fisher proposed the use of acid chlorides for peptide synthesis and at the end of the century, as this review has related, acid halides, both chlorides and fluorides, are again coming into vogue for the same purpose.

From the middle part of the century carbodiimides, azides, active esters, anhydrides and stand-alone reagents such as phosphonium or iminium salts have been, and are still being extensively used. The use of the most effective coupling reagents has allowed for a rapid and flourishing expansion of the field of peptide chemistry and, as a consequence, has promoted an expansion of other areas of organic chemistry in which formation of the amide bond is involved. In this way, not only is the synthesis of small linear peptides containing natural amino acids routinely possible nowadays, but also the laboratory synthesis of large peptides containing 30-50 amino acid residues. In the same way, the synthesis of cyclic peptides containing non-natural and hindered amino acids and the synthesis of peptidomimetic building blocks has also been made possible through the use of routine solid-phase techniques.

Having said this, the reader could think that everything has been accomplished in this field. But no, several challenges still lie ahead such as the stepwise solid-phase synthesis of small proteins

containing up to 100 coded residues or the synthesis of peptides containing extremely hindered building blocks such as α,α-dialkyl amino acids, *N*-alkyl amino acids and the even more challenging *N*-aryl amino acids. It is certain that these challenges will not be overcome through the use of new and more effective coupling methods alone. On the contrary, a proper combination of the coupling reagent, α-amino protecting group, solid support, solvent, temperature and other experimental conditions will be mandatory.

New stand-alone coupling reagents containing better leaving groups which enhance coupling rates and reduce the risk of racemization, in the same way that HOAt does, should be developed. As demonstrated in this review, the use of an acid chloride represent an excellent coupling method but its overall efficiency is not compatible with carbamate-based α-amino groups such as Boc or Fmoc since the method requires the use of a base as hydrogen chloride acceptor and, under these conditions, the corresponding 5(4*H*)-oxazolone is formed. Although the latter can function as an acylating reagent, the oxazolone is much less reactive than the acid chloride. In this respect, the development of new non-carbamate-based α-amino protecting groups such as Pbf, *o*NBS or Bts will be necessary. When the solid-phase approach is used the development and implementation of new solid supports which mimic as closely as possible solution conditions will be more desirable.

With regard to solvents, temperature and other experimental conditions, it may conceivably be said that peptide chemists are more conservative than chemists working in other areas and thus prefer the use of DMF as solvent, reactions at room temperature and stirring methods such as N_2-bubbling, vortex and continuous flow. These conservative reaction conditions however, are due in large part to the technical and engineering restrictions imposed by automatic synthesizers, and their vendors, but the synthesis of challenging peptides also requires a rational and through evaluation of the experimental conditions. The use of other solvents such as DMSO, THF and mixtures of halogenated solvents such as 2,2,2-trifluoroethanol (TFE) or 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in CH_2Cl_2 should be more widely adopted for success in difficult couplings. The use of higher temperatures could have a dual effect. Higher temperatures could weaken and reduce aggregation caused by hydrogen bonding and also coupling rates could be increased. However these advantages could be offset by an increase in undesirable racemization. Apart from the use of high temperatures the aggregation of peptide chains and apolar side-chain protecting groups can also be minimized by the use of denaturants such as urea, detergents or chaotropic agents. Finally, ultrasonic wave and microwave irradiations, which are more accepted for enhancing reaction rates in other fields of organic chemistry should be further investigated in the field of peptide chemistry.

In conclusion, the existing coupling methods together with a new generation of reagents, that will surely be developed in the very near future, in combination with improvements in other reagents and experimental conditions should allow for the facile and routine preparation of any desired peptide. Further improvements in peptide coupling methodologies will help enormously in the introduction of peptides and peptidomimetics as drugs for the cure of a broad range of diseases.

VI. APPENDIX: TABLE OF REAGENTS

Abbreviation	Cmpd. No.	Name
AOMP	**15**	1, 3-Dimethyl-2-(1-pyrrolidinyl)-2-(3*H*-1,2,3-triazolo(4,5-b)pyridin-3-yloxy)-1,3,2-diazaphospholidinium hexafluorophosphate
AOMP	**62**	5-(1*H*-7-azabenzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
AOP	**13**	(7-Azabenzotriazol-1-yl)-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate
Bates reagent	**5**	μ-Oxo-*bis*-[tris(dimethylamino)phosphonium]-*bis*-tetrafluoroborate
BDDC	**100**	1,3-*bis*(2,2-Dimethyl-1,3-dioxolan-4-ylmethyl)carbodiimide
BDMP	**61**	5-(Benzotriazol-1-yloxy)-3,4-dihydro-1-methyl-2*H*-pyrrolium hexachloroantimonate
BDP	**71**	Benzotriazol-1-yl diethyl phosphate
BEMT	**85**	2-Bromo-3-ethyl-4-methylthiazolinium tetrafluoroborate
BPMP	**63**	(Benzotriazol-1-yl)oxy-*N,N*-tetramethylenebenzaminium hexachloroantimoniate
BOI	**45**	*O*-(Benzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate
BOMI	**60**	(Benzotriazol-1-yl)oxy-*N,N*-dimethylmethaniminium hexachloroantimonate
BOP	**6**	Benzotriazol-1-yl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate
BOP-Cl	**70**	*bis*(2-Oxo-3-oxazolidinyl)phosphorodiamidic chloride
BrOP	**2**	Bromotris(dimethylamino)phosphonium hexafluorophosphate
BTFFH	**40**	*bis*(Tetramethylene)fluoroformamidinium hexafluorophosphate
CDMT	**81**	2-Chloro-4,6-dimethoxy-1,3,5-triazine
CF_3-BOP	**8**	[6-(Trifluoromethyl)benzotriazol-1-yl]-*N*-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate
CF_3-HBTU	**31**	2-[6-(Trifluoromethyl)benzotriazol-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate
CF_3-NO_2-PyBOP	**12**	[4-Nitro-6-(trifluoromethyl)benzotriazol-1-yl)oxy]tris(pyrrolidino) phosphonium hexafluorophosphate
CF_3-PyBOP PyFOP	**9**	[6-(Trifluoromethyl)benzotriazol-1-yl]-*N*-oxy-tris(pyrrolidino) phosphonium hexafluorophosphate
CIP	**43**	1,3-Dimethyl-2-chloro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
Cpt-Cl	**66**	1-Oxo-1-chlorophospholane
DCC	**97**	*N,N'*-Dicyclohexylcarbodiimide
DEPBO	**73**	*N*-Diethoxyphosphoryl benzoxazolone
DEPBT	**76**	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4-(3*H*)-one

Table Continued...

Abbreviation	Cmpd. No.	Name
DEPC	**69**	Diethylphosphoryl cyanide
DFIH	**41**	1,3-Dimethyl-2-fluoro-4,5-dihydro-1*H*-imidazolium hexafluorophosphate
DIPCDI (DCI)	**98**	*N,N'*-Diisopropylcarbodiimide
DMTMM	**82**	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
DOPBO	**74**	*N*-(2-Oxo-1,3,2-dioxaphosphorinanyl)benzoxazolone
DOPBT	**75**	3-[*O*-(2-oxo-1,3,2-dioxaphosphorinanyl)-oxy]-1,2,3-benzotriazin-4(3*H*)-one
DPPA	**68**	Diphenylphosphoryl azide
DppCl	**64**	Diphenylphosphinic chloride
EDC	**99**	1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride
EEDQ	**84**	*N*-Ethoxycarbonyl-2-ethoxy-1,3-dihydroquinoline
ENDPP	**77**	1,4-Epoxy-5-norbornene-2,3-dicarboximidodiphenylphosphate
FDPP	**67**	Pentafluorophenyl diphenylphosphinate
HAMDU	**47**	*O*-(7- Azabenzotriazol-1-yl)-1,3-dimethyl-1,3-dimethyleneuronium hexafluorophosphate
HAMTU	**56**	*O*-(7-Azabenzotriazol-1-yl)-1,3-dimethyl-1,3-trimethyleneuronium hexafluorophosphate
HAPipU	**53**	*O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-*bis*(pentamethylene)uronium hexafluorophosphate
HAPTU	**58**	(7-Azabenzotriazol-yl)-1,1,3-trimethyl-1-phenyluronium hexafluorophosphate
HAPyU	**46**	(7-Azabenzotriazol-1-yl)-*N*-oxy-*bis*(pyrrolidino)uronium hexafluorophosphate
HAPyTU	**50**	*S*-(Azabenzotriazol-yl)-1,1,3,3-*bis*(tetramethylene)thiouronium hexafluorophosphate
HATU	**32**	*N*-[(Dimethylamino)-1*H*-1,2,3-triazolo[4,5-b]pyridino-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
HATTU	**34**	*S*-(7-Azabenzotriazol-yl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate
HBPTU	**57**	(7-Benzotriazol-yl)-1,1,3-trimethyl-1-phenyluronium hexafluorophosphate
HBPyU	**44**	(Benzotriazol-1-yl)-*N*-oxy-*bis*(pyrrolidino)uronium hexafluorophosphate
HBTU	**20**	*N*-[(1*H*-Benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide

Table Continued...

Abbreviation	Cmpd. No.	Name
HDTU	**24**	*O*-(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HOCt	**103**	5-Chloro-1-hydroxytriazole
HOTT	**35**	*S*-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPfTU	**30**	2-Pentafluorophenyl-1,1,3,3-tetramethyluronium hexafluorophosphate
HPyONp	**51**	*bis*(Tetramethylene)(2-nitrophenoxy)formamidinium hexafluorophosphate
HPyOPfp	**48**	*bis*(Tetramethylene)pentafluorophenoxyformamidinium hexafluorophosphate
HPyOTcp	**52**	*bis*(Tetramethylene)(2,4,5-trichlorophenoxy)formamidinium hexafluorophosphate
HPySPfp	**49**	*bis*(Tetramethylene)pentafluorothiophenoxyformamidinium hexafluorophosphate
MSNT	**79**	1-(Mesitylenesulfonyl)-3-nitro-1,2,4-triazole
NOP	**10**	[(6-Nitrobenzotriazol-1-yl)oxy]tris(dimethylamino)phosphonium hexafluorophosphate
P-EDC	**86**	Polymeric 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
P-TBTU	**87**	Polymeric *N*-[(1*H*-Benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
PyAOP	**14**	(7-Azabenzotriazol-1-yloxy) tris(pyrrolidino)phosphonium hexafluorophosphate
PyBOP	**7**	Benzotriazol-1-yl-*N*-oxy tris(pyrrolidino)phosphonium hexafluorophosphate
PyBroP	**4**	Bromotris(pyrrolidino)phosphonium hexafluorophosphate
PyCloP	**3**	Chlorotris(pyrrolidino)phosphonium hexafluorophosphate
PyClU	**42**	*bis*(Tetramethylene)chloroformamidinium hexafluorophosphate
PyDOP	**16**	[(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)oxy]tris(pyrrolidino)-phosphonium hexafluorophosphate
PyNOP	**11**	[(6-Nitrobenzotriazol-1-yl)oxy]tris(pyrrolidino)phosphonium hexafluorophosphate
PyPOP	**17**	[(Pentafluorophenyl)oxy]tris(pyrrolidino)phosphonium hexafluorophosphate
PyPSP	**18**	*S*-(Pentafluorophenyl)-1,1,3,3-*bis*(tetramethylene)thiouronium hexafluorophosphate
PyTOP	**19**	(Pyridyl-2-thio)tris(pyrrolidino)phosphonium hexafluorophosphate
TAPipU	**54**	*O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-*bis*(pentamethylene)uronium tetrafluoroborate

Table Continued...

Abbreviation	Cmpd. No.	Name
TATU	**33**	*N*-[(Dimethylamino)-1*H*-1,2,3-triazolo[4,5-b]pyridino-1-ylmethylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide
TBTU	**22**	*N*-[(1*H*-Benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methyl methanaminium tetrafluoroborate *N*-oxide
TCFH	**38**	Tetramethylchloroformamidinium hexafluorophosphate
TDBTU	**23**	*O*-(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TFFH	**39**	Tetramethylfluoroformamidinium hexafluorophosphate
TMU-Cl	**21**	Chlorotetramethyluronium chloride
TNTU	**27**	2-(*endo*-6-Norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate
TOPPipU	**55**	2-[2-Oxo-1(2*H*)-pyridyl]-1,1,3,3-*bis*(pentamethylene)uronium tetrafluoroborate
TOTT	**36**	*S*-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TOTU	**37**	*O*-[(Ethoxycarbonyl)cyanomethyleneamino]-*N,N,N',N'*-tetramethyluronium tetrafluoroborate
TPfT	**83**	2,4,6-Tris(pentafluorophenyloxy)-1,3,5-triazine
TPSNT	**80**	1-(2,4,6-Triisopropyl-benzenesulfonyl)-3-nitro-1,2,4-triazole
TPTU	**25**	2-[2-Oxo-1(2*H*)-pyridyl]-1,1,3,3-tetramethyluronium tetrafluoroborate
TPfTU	**29**	2-Pentafluorophenyl-1,1,3,3-tetramethyluronium tetrafluoroborate
TPhTU	**28**	2-Phthalimido-1,1,3,3-tetramethyluronium tetrafluoroborate
TSTU	**26**	2-Succinimido-1,1,3,3-tetramethyluronium tetrafluoroborate
T3P (PPAA)	**78**	2-Propanephosphonic acid anhydride

REFERENCES

1. (a) F. Albericio and L. A. Carpino, *Methods Enzymol.*, **289**, 104 (1997). (b) F. Albericio and S. A. Kates, in *"Solid-Phase Synthesis, A Practical Guide"*, S. A. Kates, F. Albericio, Eds., pp. 275-330, Marcel Dekker, New York, 2000.

2. (a) P. Wipf, *Chem. Rev.*, **95**, 2115 (1995). (b) F. J. Sardina and H. Rappoport, *Chem. Rev.*, **96**, 1825 (1996). (c) J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, **97**, 2243 (1997). (d) M. D. Fletcher and M. M. Campbell, *Chem. Rev.*, **98**, 763 (1998). (e) M. J. I. Andrews and A. B. Tabor, *Tetrahedron*, **55**, 11711 (1999). (f) C. Nájera and M. Yus, in *"Studies in Natural Products Chemistry"*, Atta-ur-Rahman Ed., Vol. 21, p. 373, Elsevier Science, Amsterdam, 2000.

3. (a) R. B. Merrifield, *Angew. Chem. Int. Ed. Engl.*, **24**, 799 (1985). (b) G. B. Fields, Z. Tian and G. Barany, in *"Synthetic Peptides: A User's Guide"*, G. A. Grant, Ed., pp. 77-183, Freeman,

New York, 1992. (c) G. B. Fields, Ed., *Methods Enzymol., Solid-Phase Peptide Synthesis*, Vol. 289, Academic Press, Orlando, 1997. (d) P. Lloyd-Williams, F. Albericio and E. Giralt, in "*Chemical Approaches to the Synthesis of Peptides and Proteins*", CRC Press, Boca Raton, 1997.

4. A. Williams and I. T. Ibrahim, *Chem. Rev.*, **81**, 589 (1981).

5. G. Gawne, G. W. Kenner and R. C. Sheppard, *J. Am. Chem. Soc.*, **91**, 5670 (1969).

6. B. Castro and J. R. Dormoy, *Bull. Soc. Chim. Fr.*, 3034 (**1971**).

7. L. E. Barstov and V. J. Hruby, *J. Org. Chem.*, **36**, 1305 (1971).

8. S. Yamada and Y. Takeuchi, *Tetrahedron Lett.*, 3595 (**1971**).

9. B. Castro and J. R. Dormoy, *Tetrahedron Lett.*, 4747 (**1972**).

10. (a) B. Castro and J. R. Dormoy, *Tetrahedron Lett.*, 3246 (1973). (b) B. Castro and J. R. Dormoy, *Bull. Soc. Chim. Fr.*, **12**, 3359 (1973).

11. B. Castro and J. Coste, French Patent 8902361, 1989.

12. A. J. Bates, I. J. Galpin, A. Hallet, D. Hudson, G. W. Kenner, R. Ramage, and R. C. Sheppard, *Helv. Chim. Acta*, **58**, 688 (1975)

13. B. Castro, J. R. Dormoy, G. Evin and C. Selve, *Tetrahedron Lett.*, 1219 (**1975**).

14. (a) B. Castro, J. R. Dormoy, B. Dourtoglou, G. Evin, C. Selve and J. C. Ziegler, *Synthesis*, 751 (**1976**). (b) J. R. Dormoy and B. Castro, *Tetrahedron Lett.*, 3321 (**1979**).

15. J. Coste, D. Le-Nguyen and B. Castro, *Tetrahedron Lett.*, **31**, 205 (1990).

16. I. A. Rivero, R. Somanathan and L. H. Hellberg, *Synth. Commun.*, **25**, 2185 (1995).

17. J. C. H. M. Wijkmans, J. A. W. Kruijtzer, G. A. van der Marel, J. H. van Boom and W. Bloemhoff, *Recl. Trav. Chim. Pays-Bas*, **113**, 394 (1994).

18. W. König and R. Geiger, *Chem. Ber.*, **103**, 788 (1970).

19. T. Høeg-Jensen, C. E. Olsen and A. Holm, *J. Org. Chem.*, **59**, 1257 (1994).

20. C. B. Reese and Z. Rei-Zhuo, *J. Chem. Soc., Perkin Trans. 1*, 2291 (**1993**).

21. J. C. H. M. Wijkmans, F. A. A. Block, G. A. van der Marel, J. H. van Boom, and W. Bloemhoff, *Tetrahedron Lett.*, **36**, 4643 (1995).

22. L. A. Carpino, *J. Am. Chem. Soc.*, **115**, 4397 (1993).

23. (a) A. Ehrlich, S. Rothemund, M. Brudel, M. Beyermann, L. A. Carpino and M. Bienert, *Tetrahedron Lett.*, **34**, 4781 (1993). (b) L. A. Carpino, A. El-Faham, C. A. Minor and F. Albericio, *J. Chem. Soc., Chem. Commun.*, 201 (**1994**).

24. J. Klose, P. Henklein, A. El-Faham, L. A. Carpino and M. Bienert, in *Peptides 1998. Proceedings of the 25th European Peptide Symposium*, S. Bajusz, F. Hudecz, Eds., Akadémiai Kiadó, Budapest, p. 204,1999.

25. W. König and R. Geiger, *Chem. Ber.*, **103**, 2030 (1970).

26. I. Abdelmoty, F. Albericio, L. A. Carpino, B. M. Foxman and S. A. Kates, *Lett. Peptide Sci.*, **1**, 57 (1994).

27. (a) V. Dourtoglou, J. C. Ziegler and B. Gross, *Tetrahedron Lett.*, 1269 (**1978**). (b) V. Dourtoglou, B. Gross, V. Lambropoulou and C. Zioudrou, *Synthesis*, 572 (**1984**).

28. (a) K. Knorr, A. Trzeciak, W. Bannwarth and D. Gillessen, *Tetrahedron Lett.*, **30**, 1927 (1989). (b) L. A. Carpino, A. El-Faham and F. Albericio, *J. Org. Chem.*, **50**, 3561 (1995).

29. H. Gausepol, U. Pieles and R. W. Frank, *Peptides Chemistry and Biology: Proceedings of the 12th American Peptide Symposium*, J. A. Smith and J. E. Rivier, Eds., ESCOM, Leiden, p. 523, 1992.

30. P. Wessig, *Tetrahedron Lett.*, **40**, 5987 (1999).

31. J. Habermann and H. Kunz, *J. Prakt. Chem.*, **340**, 233 (1998).

32. P. Garner, J. T. Anderson, S. Dey, W. J. Youngs, K. Gabt, *J. Org. Chem.*, **63**, 5732 (1998).

33. (a) M. A. Bailén, R. Chinchilla, D. J. Dodsworth, C. Nájera, J. M. Soriano and M. Yus, *Peptides 1998. Proceedings of the 25th European Peptide Symposium*, S. Bajusz and F. Hudecz, Eds., Akadémiai Kiadó, Budapest, p. 172, 1999. (b) M. A. Bailén, R. Chinchilla, D. J. Dodsworth and C. Nájera, *J. Org. Chem.*, **64**, 8936 (1999).

34. L. A. Carpino and A. El-Faham, *J. Am. Chem. Soc.*, **117**, 5401 (1995).

35. (a) T. Vojkovsky and B. Drake, *Org. Prep. Proc. Int.*, **29**, 497 (1997). (b) U. Boas, B. Pedersen and J. B. Christensen, *Synth. Commun.*, **28**, 1223 (1998).

36. A. El-Faham, *Chem. Lett.*, 671 (**1998**).

37. A. El-Faham, *Org. Prep. Proc. Int.*, **30**, 477 (1998).

38. J. Coste, E. Frérot, P. Jouin and B. Castro, *Tetrahedron Lett.*, **32**, 1967 (1991).

39. S. Chen and J. Xu, *Tetrahedron Lett.*, **33**, 647 (1992).

40. K. Akaji, N. Kuriyama, T. Kimura, Y. Fujiwara and Y. Kiso, *Tetrahedron Lett.*, **33**, 3177 (1992).

41. Y. Kiso, T. Kimura, Y. Fujiwara, H. Sakikawa and K. Akaji, *Chem. Pharm. Bull.*, **38**, 270 (1990).

42. J. Habermann and H. Kunz, *Tetrahedron Lett.*, **39**, 265 (1998).

43. J. Klose, A. El-Faham, P. Henklein, L. A. Carpino and M. Bienert, *Tetrahedron Lett.*, **40**, 2045 (1999).

44. A. El-Faham, *Lett. Pept. Sci.*, **7**, 113 (2000).

45. P. Henklein, M. Beyermann, M. Bienert and R. Knorr, *Proceedings of the 21st European Peptide Symposium*, E. Giralt and D. Andreu, Eds., Leiden: ESCOM, Science, p. 67, 1991.

46. A. El-Faham, *Bull. Fac. Sci. Alex. Univ.*, **36**, 73 (1996).

47. P. Li and J. C. Xu, *Tetrahedron Lett.*, **40**, 3605 (1999).

48. P. Li and J. C. Xu, *Chem. Lett.*, 1163 (**1999**).

49. P. Li and J. C. Xu, *Tetrahedron Lett.*, **41**, 721 (2000).

50. D. A. Tysse, L. P. Bausher and B. Haake, *J. Am. Chem. Soc.*, **95**, 8066 (1973).

51. A. G. Jackson, G. W. Kenner, G. A. Moore, R. Ramage and W. D. Thorpe, *Tetrahedron Lett.*, 3627 (**1976**).

52. R. Ramage, C. P. Ashton, D. Hopton and M. J. Parrott, *Tetrahedron Lett.*, **25**, 4825 (1984).

53. R. Ramage, D. Hopton, M. J. Parrott, R. S. Richardson, G. W. Kenner and G. A. Moore, *J. Chem. Soc., Perkin Trans.1*, 461 (**1985**).

54. S. Chen and J. Xu, *Tetrahedron Lett.*, **32**, 6711 (1991).

55. T. Shioiri, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972).

56. S. Yamada, Y. Kasai and T. Shioiri, *Tetrahedron Lett.*, 1595 (**1973**).

57. J. Diago-Messeguer, A. L. Palomo-Coll, J. R. Fernández-Lizarbe and A. Zugaza-Bilbao, *Synthesis*, 547 (**1980**).

58. (a) S. Kim, H. Chang and Y. K. Ko, *Tetrahedron Lett.*, **26**, 1341 (1982). (b) S. Kim, H. Chang and Y. K. Ko, *Bull. Korean Chem. Soc.*, **6**, 471 (1987).

59. D. Y. Zhang and Y. H. Ye, *Peptide: Biology and Chemistry, Proceedings of the Chinese Peptide Symposium 1990*, Y. C. Du, Ed., Science Press, Beijing, China, p. 235, 1991.

60. C. X. Fan, X. L. Hao, Y. H. Ye, *Peptide: Biology and Chemistry, Proceedings of the Chinese Peptide Symposium 1992*, Y. C. Du, J. P. Tam and Y. S. Zhang, Eds., ESCOM, The Netherlands, p. 297, 1993.

61. C. X. Fan, X. L. Hao and Y. H. Ye, *Synth. Commun.*, **26**, 1455 (1996).

62. C. Griehl, J. Weigt, H. Jeschkeit and Z. Palacz *Proceedings of the 22nd European Peptide Symposium*, ESCOM, Leiden, p. 459, 1993.

63. H. Wissmann and H. J. Kleiner, *Angew. Chem. Int. Ed. Engl.*, **19**, 133 (1980).

64. N. Natagiri, K. Itakura and S. A. Narang, *J. Chem. Soc., Chem. Commun.*, 325 (**1974**).

65. (a) B. Blankemeyer-Menge, M. Nimtz and R. Frank, *Tetrahedron Lett.*, **31**, 1701 (1990). (b) X. Jorba, F. Albericio, A. Grandas, W. Bannwarth and E. Giralt, *Tetrahedron Lett.*, **31**, 1915 (1990).

66. J. R. Dudley, J. T. Thurston, F. C. Schaefer, D. Holm-Hansen, C. J. Hull and P. Adams, *J. Am. Chem. Soc.*, **73**, 2986 (1951).

67. Z. J. Kaminski, P. Paneth and J. Rudzinski, *J. Org. Chem.*, **63**, 4248 (1998).

68. D. K. Mohapatra and A. Datta, *J. Org. Chem.* **64**, 6879 (1999).

69. B. Belleau, R. Martel, G. Lacasse, M. Ménard, N. L. Weinberg and Y. G. Perron, *J. Am. Chem. Soc.*, **90**, 823 (1968).

70. P. Li and J. C. Xu, *Tetrahedron Lett.*, **40**, 8301 (1999).

71. M. C. Desai and L. M. Stephens Stramiello, *Tetrahedron Lett.*, **34**, 7685 (1993).

72. R. Chinchilla, D. J. Dodsworth, C. Nájera and J. M. Soriano, *Tetrahedron Lett.*, **41**, 2463 (2000).

73. R. Kalir, A. Warshawsky, M. Fridkin and M. Patchornik, *Eur. J.Biochem.*, **59**, 55 (1975).

74. S. Masala and M. Taddei, *Org. Lett.*, **1**, 1355 (1999).

75. D. S. Kemp, in *The Peptides: Analysis, Synthesis, Biology*, Vol 1. E. Gross and J. Meinhofer, Eds., pp. 315-383, Academic Press, New York, 1979.

76. C. Griehl, F. Hoffmann, W. Brandt and M. Plass, in *Peptides 1998. Proecedings of the 25th European Peptide Symposium*, S. Bajusz and F. Hudecz, Eds., pp. 212-213, Akadémiai Kiadó, Budapest, 1999.

77. D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.*, **88**, 1013 (1966).

78. D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.*, **88**, 1020 (1966).

79. A. Arendt and A.M. Kolodziejczyk, *Tetrahedron Lett.*, 3867 (**1978**).

80. J. J. Jones, in *The Peptides: Analysis, Synthesis, Biology*, Vol 1. E. Gross and J. Meinhofer, Eds., pp. 65-104, Academic Press, New York, 1979.

81. G. Barany and R. B. Merrifield, in *The Peptides: Analysis, Synthesis, Biology*, Vol 2. E. Gross and J. Meinhofer, Eds., pp. 1-284, Academic Press, New York, 1979.

82. D. H. Rich and J. Singh, in *The Peptides: Analysis, Synthesis, Biology*, Vol 1. E. Gross and J. Meinhofer, Eds., pp. 241-261, Academic Press, New York, 1979.

83. R. B. Merrifield, L. D. Vizioli and H. G. Boman, *Biochemistry*, **21**, 5020 (1982).

84. F. L. Scott, R. E. Glick and S. Winstein, *Experientia*, **13**, 183 (1957).

85. M. Beyermann, P. Henklein, A. Klose, R. Sohr and M. Bienert, *Int. J. Peptide Protein Res.*, **37**, 252 (1991).

86. C. D. Chang, A. M. Felix, M.H. Jimenez and J. Meinhofer, *Int. J. Peptide Protein Res.*, **15**, 485 (1980).

87. (a) H. S. Bates, J. H. Jones and M. J. Witty, *J. Chem. Soc., Chem. Commun.*, 773 (**1980**). (b) N. L. Benoiton and F. M. F. Chen, *J. Chem. Soc., Chem. Commun.*, 543 (**1981**).

88. H. S. Bates, J.H. Jones, W. I. Ramage and M. J. Witty, in *Peptides 1980. Proceedings of the 16th European Peptide Symposium*, K Brunfeldt, Ed., pp. 185-190, Scriptor, Copenhagen, Denmark, 1981.

89. T. Miyazawa, T. Otomatsu, Y. Fukui, T. Yamada and S. Kuwata, *J. Chem. Soc., Chem. Commun.*, 419 (**1988**).

90. S. Mojsov, A. R. Mitchell and R. B. Merrifield, *J. Am. Chem. Soc.*, **45**, 555 (1980).

91. L. A Carpino, A. El-Faham and F. Albericio, *Tetrahedron Lett.*, **35**, 2279 (1994).

92. Y. P. Xu and M.J. Miller, *J. Org. Chem.*, **63**, 4314 (1998).

93. S. A. Kates, S. A. Triolo, G. W. Griffin, L. W. Herman, G. Tarr, N. A. Solé, E. Diekmann, A. El-Faham, D. Ionescu, F. Albericio and L.A. Carpino, in *Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Chemical Libraries*, R Epton, Ed., pp. 41-50, Mayflower Scientific Ltd., Kingswinford, England, 1997.

94. D. Hudson, *J. Org. Chem.*, **53**, 617 (1988).

95. M. H. Kim and D.V. Patel, *Tetrahedron Lett.*, **35**, 5603 (1994).

96. J. Coste and J.M. Campagne, *Tetrahedron Lett.*, **36**, 4253 (1995).

97. J. Coste, E. Frérot and P. Jouin, *J. Org. Chem.*, **59**, 2437 (1994).

98. A. M. Felix, Z. Zhao, T. Lambros, M. Ahmad, W. Liu, A. Daniewski, J. Michalewsky and E.P. Heimer, *J. Peptide Res.*, **52**, 155 (1998).

99. L. A. Carpino, D. Ionescu and A. El-Faham, *J. Org. Chem.*, **61**, 2460 (1996).

100. A. di Fenza, M. Tancredi, C. Galoppini and P. Rovero, *Tetrahedron Lett.*, **39**, 8529 (1998).

101. Y. Han, F. Albericio and G. Barany, *J. Org. Chem.*, **62**, 4307 (1997).

102. Y. M. Angell, J. Alsina, F. Albericio and G. Barany, *J. Peptide Res.*, in press.

103. L. A. Carpino, M. Beyermann, H. Wenschuh and M. Bienert, *Acc. Chem. Res.*, **29**, 268 (1996).

104. S. A. Triolo, D. Ionescu, H. Wenschuh, N. A. Solé, A. El-Faham, L. A. Carpino and S. A. Kates, in *Peptides 1996. Proceedings of the 24rd European Peptide Symposium*, R. Ramage and R. Epton, Eds., pp. 839-840, Mayflower Scientific Ltd., Kingswinford, England, 1998.

105. L. A. Carpino and A. El-Faham, *J. Org. Chem.*, **59**, 685 (1994).

106. K. Akajii, N. Kuriyama and Y. Kiso, *J. Org. Chem.*, **61**, 3350 (1996).

107. J. Meinhofer, in *The Peptides: Analysis, Synthesis, Biology*, Vol 1. E. Gross and J. Meinhofer, Eds., pp. 263-314, Academic Press, New York, 1979.

109. C. van der Auwera and M.J.O. Anteunis, *Int. J. Peptide Protein Res.*, **29**, 574 (1987).

110. (a) D. Theodoropoulos and J. Gazopoulos, *J. Org. Chem.*, **27**, 2091 (1962). (b) E. M. Ivanova, L. M. Khalimskaya, V. P. Romanenko and V. F. Zarytova, *Tetrahedron Lett.*, **23**, 5447 (1982).

111. S. Chandrasegaran, A. Murakami and L-S. Kan, *J. Org. Chem.*, **49**, 4951 (1984).

112. V. F. Zarytova and D. G. Knorre, *Nucl. Acids Res.*,**12**, 2091 (1984).

113. Z. J. Kaminski, *Biopolymers (Peptide Science)*, **55**, 140 (2000).

114. M. Kunishima, C. Kawachi, F. Iwasaki, K. Terao and S. Tani, *Tetrahedron Lett.*, **40**, 5327 (1999).

115. M. Kunishima, J. Morita, C. Kawachi, F. Iwasaki, K. Terao and S. Tani, *Synlett.*, **8**, 1255 (1999).

116. Z. J. Kaminski and B. Kolesinska, *XV Polish Peptide Symposium*, Olstyn, 1999.

117. B. Belleau and G. Malek, *J. Am. Chem. Soc.*, **90**, 1651 (1968).

118. E. Fischer, *Ber. Deutsch. Chem. Ges.*, **36**, 2094 (1903).

119. E. Fischer and E. Otto, *Ber. Deutsch. Chem. Ges.*, **36**, 2106 (1903).

120. M. L. Bender, J. M. Jones. *J. Org. Chem.*, **27**, 3771 (1962).

121. J. F. Bunnett, E. W. Garbish, K. M. Pruitt, *J. Am. Chem Soc.*, **79**, 385 (1957).

122. L.A. Carpino, D. Ionescu, A. El-Faham, P. Henklein, H. Wenschuh, M. Bienert and M. Beyermann, *Tetrahedron Lett.*, **3**, 241 (1998).

123. N. L. Benoiton, *Biopolymers (Peptide Sci)*, **40**, 245 (1996).

124. L. A. Carpino, H. G. Chao, M. Beyermann and M. Biennert, *J. Org. Chem.*, **56**, 2635 (1991).

125. V. V. S. Babu and H. N. Gopi, *Tetrahedron Lett.*, **39**, 1049 (1998).

126. L. A. Carpino, H. Shroff, S. A. Triolo, E. M. E. Mansour, H. Wenschuh and F. Albericio, *Tetrahedron Lett.*, **34**, 7829 (1993).

127. T. Fukuyama, C. K. Jow and M. Cheung, *Tetrahedron Lett.*, **36**, 6373 (1995).

128. T. Fukuyama, M. Cheung, C.K. Jow, Y. Hidai and K. Toshiyuki, *Tetrahedron Lett.* **38**, 5831 (1997).

129. E. Vedejs, S. Z.Lin, A. Klapars and J. B. Wang, *J. Am. Chem. Soc.*, **118**, 9796 (1996).

130. E. Vedejs and C. Kongkittingam, *J. Org. Chem.*, **65**, 2309 (2000).

131. M. Meldal, M. A Juliano and A. M. Jansson, *Tetrahedron Lett.*, **38**, 2531(1997).

132. H. Wenschuh, M. Beyermann, A. El-Faham, S. Ghassemi, L. A. Carpino, M. Bienert. *J. Chem. Soc., Chem. Comm.*, 669 (**1995**).

133. H. Wenschuh, M. Beyermann, R. Winter, M. Bienert, D. Ionescu and L. A. Carpino, *Tetrahedron Lett.*, **37**, 5483 (1996).

134. (a) A. Williams and I. T. Ibrahim, *Chem. Rev.*, **81**, 589 (1981). (b) F. S. Gibson, M. S. Park and H. Rappoport, *J. Org. Chem.*, **59**, 7503 (1994)

135. E. Nicolás, J. Clemente, T. Ferrer, F. Albericio and E. Giralt, *Tetrahedron*, **53**, 3179 (1997).

136. T. Tselios, L. Probert, I. Daliani, E. Matsoukas, A. Troganis, I. P. Gerothanassis, T. Mavromoustakos, G. J. Moore and J. M. Matsuokas, *J. Med. Chem.*, **42**, 1170 (1999).

137. Y. Lee and R. B. Silverman, *Synthesis*, 1495 (**1999**).

138. Y. M. Angell, C. García-Echevarría and D. M. Rich, *Tetrahedron Lett.*, **35**, 5981 (1994).

139. Y. M. Angell, T. L. Thomas, G. R. Flentke and D. H. Rich, *J. Am. Chem. Soc.*, **117**, 7279 (1995).

140. D. L. Boger, M. W. Ledeboer, M. Kume, M. Searcey and Q. Jin, *J. Am. Chem. Soc.*, **121**, 11375 (1999).

141. J. C. Spetzler, M. Mendal, J. Felding, P. Vedsø and M. Begtrup, *J. Chem. Soc., Perkin Trans. 1*, 1727 (**1998**).

142. L. Jiang, A. Davison, G. Tennant and R. Ramage, *Tetrahedron*, **54**, 14233 (1998).

143. N. Robertson, L. Jiang and R. Ramage, *Tetrahedron*, **55**, 2713 (1999).

144. R. Kalir, A. Warshawsky, M. Fridkin and A. Patchornik, *Eur. J. Biochem.*, **59**, 55 (1975).

145. W. Huang and A. G. Kalivretenos, *Tetrahedron Lett.*, **36**, 9113 (1995).

146. K. Dendrinos, J. Jeong, W. Huang and A. G. Kalivretenos, *Chem. Commun.*, 499 (**1998**).

147. M. Adamczyk, J. R. Fishpaugh and P. G. Mattingly, *Tetrahedron Lett.*, **40**, 463 (1999).

148. J. Coste, M. N. Dufour, A. Pantaloni and B. Castro, *Tetrahedron Lett.*, **31**, 669 (1990).

149. F. Frérot, J. Coste, J. Poncet, P. Jouin and B. Castro, *Tetrahedron Lett.*, **33**, 2815 (1992).

150. (a) N. Patino, E. Frérot, N. Galeotti, J. Poncet, J. Coste, M. N. Dufour and P. Jouin, *Tetrahedron*, **48**, 4115 (1992). (b) F. Roux, I. Maugras, J. Poncet, G. Niel and P. Jouin, *Tetrahedron*, **50**, 5345 (1994). (c) J. Poncet, M. Busquet, F. Roux, A. Pierré, G. Atassi and P. Jouin, *J. Med. Chem.*, **41**, 1524 (1998).

151. R. H. Mattern, S. Gunasekera, O. McConnell, *Tetrahedron*, **52**, 425 (1996).

152. S. Reissmann, C. Schwuchow, L. Seyfarth, L. F. Pineda De Castro, C. Liebmann, I. Paegelow, H. Werner and J. M. Stewart, *J. Med. Chem.*, **39**, 929 (1996).

153. (a) T. Kurome, K. Inami, T. Inoue , K. Ikai, K. Takesako, I. Kato and T. Shiba, *Chem. Lett.*, 1873 (**1993**). (b) T. Kurome, K. Inami, T. Inoue , K. Ikai, T. Takesako, I. Kato and T. Shiba, *Tetrahedron*, **52**, 4327 (1996).

154. I. R. Marsh, M. Bradley, S. J. Teague, *J. Org. Chem.*, **62**, 6199 (1997).

155. E. Frérot, J. Coste, A. Pantaloni, M. N. Dufour and P. Jouin, *Tetrahedron*, **47**, 259 (1991).

156. C. Auvin-Guette, E. Frérot, J. Coste, S. Rebuffat, P. Jouin and B. Bodo, *Tetrahedron Lett.*, **34**, 2481 (1993).

157. M. A. Walker and C. H. Heathcock, *J. Org. Chem.*, **57**, 5566 (1992).

158. I. E. Pop, B. P. Déprez and A. L. Tartar, *J. Org. Chem.*, **62**, 2594 (1997).

159. (a) A. Fournier, C. T. Wang and A. M. Felix, *Int. J. Pept. Protein Res.*, **31**, 86 (1988). (b) A. Fournier, W. Danho and A. M. Felix, *Int. J. Pept. Protein Res.*, **33**, 133 (1989).

160. M. Gairí, P. Lloyd-Williams, F. Albericio and E. Giralt, *Tetrahedron Lett.*, **31**, 7363 (1990).

161. J. T. Jarrett and P. T. Lansbury, Jr., *Tetrahedron Lett.*, **31**, 4561 (1990).

162. (a) G. Ösapay and J. W. Taylor, *J. Am. Chem. Soc.*, **112**, 6046 (1990). (b) G. Ösapay and M. Goodman, *J. Chem. Soc., Chem. Commun.*, 1599 (**1993**).

163. M. Forest, J. C. Martel, S. St-Pierre, R. Quirion and A. Fournier, *J. Med. Chem.*, **33**, 1615 (1990).

164. M. Mimeault, R. Quirion, Y. Dumont, S. St-Pierre and A. Fournier, *J. Med. Chem.*, **35**, 2163 (1992).

165. A. Kapurniotu, P. Link and W. Voelter, *Liebigs Ann. Chem.*, 1161 (**1993**).

166. A. Wahhab and J. Leban, *Tetrahedron Lett.*, **40**, 235 (1999).

167. P. Malon, J. M. Bonmatin and A. Brack, *Tetrahedron Lett.*, **32**, 5337 (1991).

168. P. Rovero, L. Quartara, G. Fabbri, *Tetrahedron Lett.*, **32**, 2639 (1991).

169. A. Tromelin, M. H. Fulachier, G. Mourier and A. Ménez, *Tetrahedron Lett.*, **33**, 5197 (1992).

170. G. Ösapay, A. Profit and J. W. Taylor, *Tetrahedron Lett.*, **31**, 6121 (1990).

171. (a) M. Xu, N. Nishino, H. Mihara, T. Fujimoto and N. Izumiya, *Chem. Lett.*, 191 (**1992**). (b) N. Nishino, M. Xu, H. Mihara, T. Fujimoto, M. Ohba, Y. Ueno and H. Kumagai, *J. Chem. Soc., Chem. Commun.*, 180 (**1992**). (c) N. Nishino, M. Xu, H. Mihara, T. Fujimoto, Y. Ueno and H. Kumagai, *Tetrahedron Lett.*, **33**, 1479 (1992). (d) N. Nishino, J. Hayashida, T. Arai, H. Mihara, Y. Ueno and H. Kumagai, *J. Chem. Soc., Perkin Trans. 1*, 939 (**1996**).

172. J. S. McMurray, *Tetrahedron Lett.*, **32**, 7679 (1991).

173. S. A. Kates, N. A. Solé, C. R. Johnson, D. Hudson, G. Barany and F. Albericio, *Tetrahedron Lett.*, **34**, 1549 (1993).

174. C. Shin, K. Okumura, M. Shigekuni and Y. Nakamura, *Chem. Lett.*, 139 (**1998**).

175. T. P. Kogan, T. C. Somers and M. C. Venutti, *Tetrahedron*, **46**, 6623 (1990).

176. R. R. Webb II, M. C. Venutti and C. Eigenbrot, *J. Org. Chem.*, **56**, 4706 (1991).

177. W.-R. Li, W. R. Ewing, B. D. Harris and M. M. Joullié, *J. Am. Chem. Soc.*, **112**, 7659 (1990).

178. J. M. Ramanjulu, X. Ding and M. M. Joullié, *J. Org. Chem.*, **62**, 4961 (1997).

179. (a) H. Choi, T. F. Murray, G. E. DeLander, V. Caldwell and J. V. Aldrich, *J. Med. Chem.*, **35**, 4638 (1992). (b) H. Choi, T. F. Murray, G. E. DeLander, W. K. Schmidt and J. V. Aldrich, *J. Med. Chem.*, **40**, 2733 (1997).

180. J. F. Hernández, W. Kornreich, C. Rivier, A. Miranda, G. Yamamoto, J. Andrews, Y. Taché, W. Vale and J. Rivier, *J. Med. Chem.*, **36**, 2860 (1993).

181. I. Augeven-Bour, S. Rebuffat, C. Auvin, C. Goulard, Y. Prigent and B. Bodo, *J. Chem. Soc., Perkin Trans. 1*, 1587 (**1997**).

182. (a) M. Egholm, O. Buchardt, P. E. Nielsen and R. H. Berg, *J. Am. Chem. Soc.*, **114**, 1895 (1992). (b) M. Egholm, P. E. Nielsen, O. Buchardt and R. H. Berg, *J. Am. Chem. Soc.*, **114**, 9677 (1992). (c) K. L. Dueholm, M. Egholm, C. Behrens, L. Christensen, H. F. Hansen, T. Vulpius, K. H. Petersen, R. H. Berg, P. E. Nielsen and O. Buchardt, *J. Org. Chem.*, **59**, 5767 (1994).

183. S. A. Thomson, J. A. Josey, R. Cadilla, M. D. Gaul, C. F. Hassman, M. J. Luzzio, A. J. Pipe, K. L. Reed, D. J. Ricca, R. W. Wiethe and S. A. Noble, *Tetrahedron*, **51**, 6179 (1995).

184. N. Mourier, C. Trabaud, J. C. Graciet, V. Simon, V. Niddam, P. Faury, A. S. Charvet, M. Camplo, J. C. Chermann and J. L. Kraus, *Nucleosides & Nucleosides*, **14**, 1393 (1995).

185. P. S. Ramamoorthy and J. Gervay, *J. Org. Chem.*, **62**, 7801 (1997).

186. J. Gervay, T. M. Flaherty and C. Nguyen, *Tetrahedron Lett.*, **38**, 1493 (1997).

187. A. Jakobs, J. Bernadou and B. Meunier, *J. Org. Chem.*, **62**, 3505 (1997).

188. S. Kunugi, N. Nishino, H. Mihara, W. R. Den Tandt and S. Scharpé, *Chem. Lett.*, 391 (**1997**).

189. S. J. E. Mulders, A. J. Brouwer, P. C. J. van der Meer and R. M. J. Liskamp, *Tetrahedron Lett.*, **38**, 631 (1997).

190. T. Høeg-Jensen, M. H. Jakobsen and A. Holm, *Tetrahedron Lett.*, **32**, 6387 (1991).

191. F. Rabanal, I. Haro, F. Reig and J. M. García-Antón, *J. Chem. Soc., Perkin Trans. 1*, 945 (**1991**).

192. E. Carnazzi, A. Aumelas, C. Barberis, G. Guillon and R. Seyer, *J. Med. Chem.*, **37**, 1841 (1994).

193. B. J. Backes and J. A. Ellman, *J. Org. Chem.*, **64**, 2322 (1999).

194. R. Ingenito, E. Bianchi, D. Fattori and A. Pessi, *J. Am. Chem. Soc.*, **121**, 11369 (1999).

195. J. Lee, J. H. Griffin and T. I. Nicas, *J. Org. Chem.*, **61**, 3983 (1996).

196. T. Høeg-Jensen, M. H. Jakobsen, C. E. Olsen and A. Holm, *Tetrahedron Lett.*, **32**, 7617 (1991).

197. H. Yamamura, S. Yamada, K. Kohno, N. Okuda, S. Araki, K. Kobayashi, R. Katakai, K. Kano and M. Kawai, *J. Chem. Soc., Perkin Trans. 1*, 2943 (**1999**).

198. (a) D. L. McMinn and M. M. Greenberg, *J. Am. Chem. Soc.*, **120**, 3289 (1998). (b) J. D. Kahl, D. L. McMinn and M. M. Greenberg, *J. Org. Chem.*, **63**, 4870 (1998). (c) J. D. Kahl and M. M. Greenberg, *J. Am. Chem. Soc.*, **121**, 597 (1999). (d) J. M. Campagne, J. Coste, L. Guillon, A. Heitz and P. Jouin, *Tetrahedron Lett.*, **34**, 4181 (1993).

199. X. Zhao, W. A. Metz, F. Sieber and K. D. Janda, *Tetrahedron Lett.*, **39**, 8433 (1998).

200. J. C. Muir, G. Pattenden and T. Ye, *Tetrahedron Lett.*, **39**, 2861 (1998).

201. T. Høeg-Jensen, A. Holm and H. Sorensen, *Synthesis*, 383 (**1996**).

202. F. Albericio, M. Cases, J. Alsina, S. A. Triolo, L. A. Carpino and S. A. Kates, *Tetrahedron Lett.*, **38**, 4853 (1997). (b) J. Alsina, E. Giralt and F. Albericio, *Tetrahedron Lett.*, **37**, 4195 (1996).

203. K. J. Jensen, J. Alsina, M. F. Songster, J. Vagner, F. Albericio and G. Barany, *J. Am. Chem. Soc.*, **120**, 5441 (1998).

204. J. W. Perich, D. Le Nguyen and E. C. Reynolds, *Tetrahedron Lett.*, **32**, 4033 (1991).

205. J. Sueiras-Díaz and J. Horton, *Tetrahedron Lett.*, **33**, 2721 (1992).

206. B. Henkel, L. Zhang, C. Goldammer and E. Bayer, *Zeit. für Naturf.* 1339 (**1996**).

207. P. Rovero, S. Pegoraro, F. Bonelli and A. Triolo, *Tetrahedron Lett.*, **34**, 2199 (1993).

208. E. Hoffmann, A. G. Beck-Sickinger and G. Jung, *Liebigs Ann. Chem.* 585 (**1991**).

209. A. Trzeciak and W. Bannwarth, *Tetrahedron Lett.*, **33**, 4557 (1992).

210. S. Arttamangkul, T. F. Murray, G. E. DeLander and J. V. Aldrich, *J. Med. Chem.*, **38**, 2410 (1995).

211. H. M. M. Bastiaans, J. L. van der Baan and H. C. J. Ottenheijm, *J. Org. Chem.*, **62**, 3880 (1997).

212. C. Cabrela, M. Langer and A. G. Beck-Sickinger, *J. Org. Chem.*, **64**, 4353 (1999).

213. J. Brüning and L. L. Kiessling, *Tetrahedron Lett.*, **37**, 2907 (1996).

214. K. Nakamura, N. Hanai, M. Kanno, A. Kobayashi, Y. Ohnishi, Y. Ito and Y. Nakahara, *Tetrahedron Lett.*, **40**, 515 (1999).

215. M. Planas, E. Bardají, K. J. Jensen and G. Barany, *J. Org. Chem.*, **64**, 7281 (1999).

216. J. Lehmann, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, **82**, 888 (1999).

217. K. C. Gupta, P. Kumar, D. Bhatia and A. K. Sharma, *Nucleosides & Nucleotides*, **14**, 829 (1995).

218. U. Tedebark, M. Meldal, L. Panza and K. Bock, *Tetrahedron Lett.*, **39**, 1815 (1998).

219. J. Rao and G. M. Whitesides, *J. Am. Chem. Soc.*, **119**, 10286 (1997).

220. B. L. Rai, H. Khord and R. C. Hider, *Tetrahedron*, **55**, 1129 (1999).

221. F. Burlina, A. Favre, J. L. Fourrey and M. Thomas, *Eur. J. Org. Chem.*, 633 (**2000**).

222. X. Chen, L. Esser and P. G. Harran, *Angew. Chem. Int. Ed.*, **39**, 937 (2000).

223. I. Dalcol, F. Rabanal, M. D. Ludevid, F. Albericio and E. Giralt, *J. Org. Chem.*, **60**, 7575 (1995).

224. Y. Yanai, K. Irie, H. Ohigashi, P. A. Wender, *Bioorg, Med. Chem. Lett.*, **7**, 117 (1997).

225. K. Irie, Y. Yanai, H. Onigashi, P. A. Wender, B. L. Miller, *Bioorg, Med. Chem. Lett.*, **6**, 353 (1996).

226. K. Irie, K. Oie, A. Nakahara, Y. Yanai, H. Ohigashi, P. A. Wender, H. Fukuda, H. Konishi and U. Killkawa, *J. Am. Chem. Soc.*, **120**, 9159 (1998).

227. C. Genari, A. Mielgo, D. Potenza, C. Scolastico, U. Piarulli and L. Manzoni, *Eur. J. Org. Chem.*, 379 (**1999**).

228. J. M. Humphrey, J. B. Aggen and A. R. Chamberlin, *J. Am. Chem. Soc.*, **118**, 11759 (1996).

229. M. Wagner and H. Kunz, *Synlett*, 400 (**2000**).

230. M. E. Pfeifer, K. Moehle, A. Linden and J. A. Robinson, *Helv. Chim. Acta*, **83**, 444 (2000).

231. K. J. Hale and J. Cai, *Chem. Commun.*, 2319 (**1997**).

232. K. J. Hale and J. Cai and G. Williams, *Synlett*, 149 (**1998**).

233. S. V. Downing, E. Aguilar and A. I. Meyers, *J. Org. Chem.*, **64**, 826 (1999).

234. B. Liang, P. Portonovo, M. D. Vera, D. Xiao and M. M. Joullié, *Org. Lett.*, **1**, 1319 (1999).

235. C. Müller, E. Kitas and P. H. Wessel, *J. Chem. Soc., Chem. Commun.*, 2425 (**1995**).

236. G. A. Olah, *Synthesis*, 487 (**1973**).

237. (a) L. A. Carpino, D. Sadat-Aalee, H. G. Chao and R. H. DeSelms, *J. Am. Chem. Soc.*, **112**, 9615 (1990). (b) J. N. Bertho, A. Loffet, C. Pinel, F. Reuther and G. Sennyey, *Tetrahedron Lett.*, **32**, 1303 (1991).

238. (a) H. Wenschuh, M. Beyermann, E. Krause, L. A. Carpino and M. Bienert, *Tetrahedron Lett.*, **34**, 3733 (1993). (b) H. Wenschuh, M. Beyermann, E. Krause, M. Brudel, R. Winter, M. Schümann, L. A. Carpino and M. Bienert, *J. Org. Chem.*, **59**, 3275 (1994).

239. H. Wenschuh, M. Beyermann, H. Haber, J. K. Seydel, E. Krause, M. Bienert, L. A. Carpino, A. El-Faham and F. Albericio, *J. Org. Chem.*, **60**, 405 (1995).

240. A. J. Zhang, D. H. Russell, J. Zhu and K. Burgess, *Tetrahedron Lett.*, **39**, 7439 (1998).

241. K. Akaji, N. Kuriyama and Y. Kiso, *Tetrahedron Lett.*, **35**, 3315 (1994).

242. N. Kuriyama, K. Akaji and Y. Kiso, *Tetrahedron*, **53**, 8323 (1997).

243. K. Akaji and Y. Kiso, *Tetrahedron*, **55**, 10685 (1999).

244. K. Akaji, Y. Tamai and Y. Kiso, *Tetrahedron*, **53**, 567 (1997).

245. K. Akaji, Y. Hayashi, Y. Kiso and N. Kuriyama, *J. Org. Chem.*, **64**, 405 (1999).

246. A. C. van der Laan, I. van Amsterdam, G. I. Tesser, J. H. van Boom and E. Kuyl-Yehesldely, *Nucleosides & Nucleotides*, **17**, 219 (1998).

247. I. J. Galpin, A. K. Mohammed and A. Patel, *Tetrahedron*, **44**, 1685 (1988).

248. J. Dudash, Jr., J. Jiang, S. C. Mayer and M. M. Joullié, *Synth. Commun.*, **23**, 349 (1993).

249. S. C. Mayer, J. Ramanjulu, M. D. Vera, A. J. Pfizenmayer and M. M. Jouillé, *J. Org. Chem.*, **59**, 5192 (1994).

250. (a) U. Schmidt and J. Langner, *J. Chem. Soc., Chem. Commun.*, 2381 (**1994**). (b) K. L. McLaren, *J. Org. Chem.*, **60**, 6082 (1995).

251. (a) R. Hirschmann, W. Yao, B. Arison, L. Maechler, A. Rosegay, P. A. Sprengeler and A. B. Smith, III, *Tetrahedron Lett.*, **37**, 5637 (1996). (b) R. Hirschmann, W. Yao, B. Arison, L. Maechler, A. Rosegay, P. A. Sprengeler and A. B. Smith, III, *Tetrahedron*, **54**, 7179 (1998).

252. J. P. Michael and G. Pattenden, *Angew. Chem. Int. Ed. Engl.*, **32**, 112 (1993).

253. (a) C. D. J. Boden and G. Pattenden, *Tetrahedron Lett.*, **35**, 8271 (1994). (b) C. D. J. Boden and G. Pattenden, *Tetrahedron Lett.*, **36**, 6153 (1995). (c) C. D. J. Boden and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 875 (**2000**).

254. (a) C. D. J. Boden, M. C. Norley and G. Pattenden, *Tetrahedron Lett.*, **37**, 9111 (1996). (b) M. C. Norley and G. Pattenden, *Tetrahedron Lett.*, **39**, 3087 (1998). (c) C. D. J. Boden, M. C. Norley and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 883 (**2000**).

255. B. McKeever and G. Pattenden, *Tetrahedron Lett.*, **40**, 9317 (1999).

256. J. M. Alvarez-Gutiérrez, A. Nefzi and R. A. Houghten, *Tetrahedron Lett.*, **41**, 851 (2000).

257. K. Okumura, M. Shigekuni, Y. Nakamura and C. Shin, *Chem. Lett.*, 1025 (**1996**).

258. U. Schmidt and J. Schmidt, *Synthesis*, 300 (**1994**).

259. G. R. Pettit, J. W. Holman and G. M. Boland, *J. Chem. Soc., Perkin Trans. 1*, 2411 (**1996**).

260. G. R. Pettit and S. R. Taylor, *J. Org. Chem.*, **61**, 2322 (1996).

261. G. R. Pettit, M. R. Rhodes and R. Tan, *J. Nat. Prod.* **62**, 409 (1999).

262. G. R. Pettit, B. E. Toki, J. P. Xu and D. C. Brune, *J. Nat. Prod.*, **63**, 22 (2000).

263. Y. Hamada, S. Rishi, T. Shiori and S. Yamada, *Chem. Pharm. Bull.*, **25**, 224 (1977).

264. G. R. Pettit, J. K. Srirangam, S. B. Singh, M. D. Williams, D. L. Herald, J. Barkóczy, D. Kantoci and F. Hogan, *J. Chem. Soc., Perkin Trans. 1*, 859 (**1996**).

265. C. van der Auwera, S. van Damme and M. J. O. Anteunis, *Int. J. Pept. Prot. Res.*, **29**, 464 (1987).

266. (a) R. D. Tung and D. H. Rich, *J. Am. Chem. Soc.*, **107**, 4342 (1985). (b) R. D. Tung, M. K. Dhaon and D. H. Rich, *J. Org. Chem.*, **51**, 3350 (1986).

267. W. J. Colucci, R. G. Tung, J. A. Petri and D. H. Rich, *J. Org. Chem.*, **55**, 2895 (1990).

268. S. A. Miller, S. L. Griffiths and D. Seebach, *Helv. Chim. Acta*, **76**, 563 (1993).

269. (a) R. M. Freidinger, P. D. Williams, R. D. Tung, M. G. Bock, D. J. Pettitbone, B. V. Clineschmidt, R. M. DiPardo, J. M. Erb, V. M. Garsky, N. P. Gould, M. J. Kaufman, C. F. Lundell, D. S. Perlow, W. L. Whitter and D. F. Veber, *J. Med. Chem.*, **33**, 1843 (1999). (b) M. G. Bock, R. M. DiPardo, P. D. Williams, D. J. Pettibone, B. V. Clineschmidt, R. G. Ball, D. F. Veber and R. M. Freidinger, *J. Med. Chem.*, **33**, 2321 (1990). (c) P. D. Williams, M. G. Bock, R. D. Tung, V. M. Garsky, D. S. Perlow, J. M. Erb, G. F. Lundell, N. P. Gould, W. L. Whitter, J. B. Hoffman, M. J. Kaufman, B. V. Clineschmidt, D. J. Pettibone, R. M. Freidinger and D. F. Veber, *J. Med. Chem.*, **35**, 3905 (1992).

270. D. Seebach, A. Studer and E. Pfammatter, *Helv. Chim. Acta*, **77**, 2035 (1994).

271. S. Shatzmiller, P. N. Confalone and A. Abiri, *Synlett*, 963 (**1999**).

272. J. Scherkenbeck, A. Plant, A. Harder and N. Mencke, *Tetrahedron*, **51**, 8459 (1995).

273. R. B. Bates, S. Caldera and M. D. Ruane, *J. Nat. Prod.*, **61**, 405 (1998).

274. H. Li, X. Jiang, Y. Ye, C. Fan, T. Romoff and M. Goodman, *Org. Lett.*, **1**, 91, (1999).

275. J. Klose, M. Bienert, C. Mollenkopf, D. Wehle, C. Zhang, L. A. Carpino and P. Henklein, *Chem. Commun.*, 1847 (**1999**).

276. (a) Z. J. Kaminski, *Synthesis*, 917 (**1987**). (b) Z. J. Kaminski, *Int. J. Pept. Prot. Res.*, **43**, 312 (1994).

277. P. A. Hipskind, J. J. Howbert, S. Cho, J. S. Cronin, S. L. Fort, F. O. Ginah, G. J. Hansen, B. E. Huff, K. L. Lobb, M. J. Martinelli, A. R. Murray, J. A. Nixon, M. A. Staszak and J. D. Copp, *J. Org. Chem.*, **60**, 7033 (1995).

278. B. Malawska and L. Autkiewicz-Michaluk, *Pharmazie*, **54**, 239 (1999).

279. N. K. Nayyar, D. R. Hutchinson and M. J. Martinelli, *J. Org. Chem.*, **62**, 982 (1997).

280. E. C. Taylor and J. E. Dowling, *J. Org. Chem.*, **62**, 1599 (1997).

281. H. W. Lee, T. W. Kang, K. H. Cha, E. N. Kim, N. H. Choi, J. W. Kim and C. I. Hong, *Synth. Commun.*, **28**, 1339 (1998).

282. M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki and S. Tani, *Tetrahedron*, **55**, 13159 (1999).

283. A. Falchi, G. Giacomelli, A. Porcheddu and M. Taddei, *Synlett*, 275 (**2000**).

284. F. Sipos and D. W. Gaston, *Synthesis*, 321 (**1971**).

285. (a) P. Braun, H. Waldmann, W. Vogt and H. Kunz, *Liebigs Ann. Chem.*, 165 (**1991**) (b) E. K. Dolence, C. Lin, M. J. Miller and S. M. Payne, *J. Med. Chem.*, **34**, 956 (1991).

286. S. Jerumanis and J. Lefebvre, *Bull. Soc. Chim. Belg.*, **103**, 127 (1994).

287. J. F. Okonya, T. Kolosa and M. J. Miller, *J. Org. Chem.*, **60**, 1932 (1995).

288. T. Y. Chan, A. Chen, N. Allanson, R. Chen, D. Liu and M. J. Sofia, *Tetrahedron Lett.*, **37**, 8097 (1996).

289. T. Takeda, T. Kanemitsu and Y. Ogihara, *Bioorg. Med. Chem.*, **4**, 1873 (1996).

290. M. G. Peter, P. C. Boldt, Y. Niederstein and J. Peter-Katalinic, *Liebigs Ann. Chem.*, 863 (**1990**).

291. D. Stepniak-Biniakiewicz, B. Chen and E. Deutsch, *J. Med. Chem.*, **35**, 274 (1992).

292. I. L. Plikhtyak, S. V. Makutova, T. P. Ivanova, I. V. Yartseva and S. Y. Mel'nik, *Rus. J. Bioog. Chem. (Engl. Transl.)*, **21**, 396 (1995).

293. J. P. Ley and M. G. Peter, *J. Carbohydr. Chem.*, **15**, 51 (1996).

294. A. Ariosa-Alvarez, A. Arencibia-Mohar, O. Madrazo-Alonso, L. García-Imia, G. Sierra-González, V. Vérez-Bencomo, *J. Carbohydr. Chem.*, **17**, 1307 (1998).

295. V. Ferro, L. Weiler and S. G. Withers, *Carbohydr. Res.* **306**, 531 (1998).

296. C. F. Sturino and M. Laibelle, *Tetrahedron Lett.*, **39**, 5891 (1998).

297. (a) M. Bodanszky, in "*The Peptides: Analysis, Synthesis, Biology*", E. Grass and J. Meinhofer, Eds., Vol. 1, p. 105, Academic Press, New York, 1979. (b) M. Bodanszky, "*Principles of Peptide Synthesis*", Springer-Verlag, Berlin, 1993.

298. "*Enciclopedia of Reagents in Organic Synthesis*", L. A. Paquette, Ed., p. 2780, John Wiley & Sons, Chichester, 1995.

299. Q. Zhang, M. C. Cone, S. J. Gould and T. M. Zabriskie, *Tetrahedron*, **56**, 693 (2000).

300. (a) J. A. Robinson, *Synlett*, 429 (**1999**). (b) D. Ranganathan, V. Haridas, S. Kurur, R. Nagaraj, E. Bikshapathy, A. C. Kunwar, A. V. S. Sarma and M. Vairamani, *J. Org. Chem.*, **65**, 365 (2000).

301. T. Sakai, H. Ehara and Y. Koezuka, *Org. Lett.*, **1**, 359 (1999).

302. C. C. Lin, C. W. Lin and A. S. C. Chan, *Tetrahedron: Asymmetry*, **10**, 1887 (1999).

303. T. N. Lambert, L. Dasaradhi, V. J. Huber and A. S. Gopalan, *J. Org. Chem.*, **64**, 6097 (1999).

304. N. Streater, P. D. Taylor, R. C. Hider and J. Porter, *J. Med. Chem.*, **33**, 1749 (1990).

305. (a) V. Janout, M. Lanier and S. L. Regen, *J. Am. Chem. Soc.*, **118**, 1573 (1996). (b) V. Janout, M. Lanier and S. L. Regen, *J. Am. Chem. Soc.*, **119**, 640 (1997).

306. K. G. Dendrinos and A. G. Kalivretenos, *Tetrahedron Lett.*, **39**, 1321 (1998).

307. M. Fridkin, A. Patchornik and E. Katchalski, *Biochem.*, **11**, 466 (1972).

308. S. M. Andreev, V. A. Tsiryapkin, N. A. Samoilova, N. V. Mironova, Y. A. Davidovich and S. V. Rogozhin, *Synthesis*, 303 (1977).

309. M. Adamczyk, J. R. Fishpaugh and P. G. Mattingly, *Biorg. Med. Chem. Lett.*, **9**, 217 (1999).

310. L. Kisfaludy and I. Schön, *Synthesis*, 325 (**1983**).

311. M. Green and J. Berman, *Tetrahedron Lett.*, **31**, 5851 (1990).

312. E. Atherton, L. R. Cameron and R. C. Sheppard, *Tetrahedron*, **44**, 843 (1988).

313. H. Gausepohl, M.Kraft and R. W. Frank, *Int. J. Pept. Prot. Res.*, **34**, 287 (1989).

314. L. Otvos, I. Elekes and V. M. Y. Lee, *Int. J. Pept. Prot. Res.*, **34**, 129 (1989).

315. (a) U. Schmidt, H. Griesser, A. Lieberknecht and J. Talbiersky, *Angew. Chem. Int. Ed. Engl.*, **20**, 280 (1981). (b) U. Schmidt, A. Lieberknecht, H. Griesser and J. Talbiersky, *J. Org. Chem.*, **47**, 3261 (1982). (c) U. Schmidt, A. Lieberknecht, H. Griesser and J. Häusler, *Angew. Chem. Int. Ed. Engl.*, **20**, 281 (1981). (d) U. Schmidt, A. Lieberknecht, H. Bökens and H. Griesser, *J. Org. Chem.*, **48**, 2680 (1983).

316. U. Schmidt, M. Kroner and H. Griesser, *Tetrahedron Lett.*, **29**, 4407 (1988).

317. U. Schmidt, M. Zäh and A. Lieberknecht, *J. Chem. Soc., Chem. Commun.*, 1002 (**1991**).

318. U. Schmidt, A. Kleefeldt and R. Mangold, *J. Chem. Soc., Chem. Commun.*, 1687 (**1992**).

319. U. Schmidt and S. Weinbrenner, *J. Chem. Soc., Chem. Commun.*, 1003 (**1994**).

320. R. J. Heffner, J. Jiang and M. M. Joullié, *J. Am. Chem. Soc.*, **114**, 10181 (1992).

321. E. Atherton, J. L. Holder, M. Meldal, R. C. Sheppard and R. M. Valerio, *J. Chem. Soc., Perkin Trans. 1*, 2887 (**1988**).

322. S. Shawaphun, V. Janout and S. L. Regen, *J. Am. Chem. Soc.*, **121**, 5860 (1999).

323. V. Janout, C. Di Giorgio and S. L. Regen, *J. Am. Chem. Soc.*, **122**, 2671 (2000).

324. V. Janout, M. Lanier, S. L. Regen, *Tetrahedron Lett.*, **40**, 1107 (1999).

325. D. Hudson, *Peptide Res.*, **3**, 51 (1990).

326. J. Kremsky, M. Pluskal, S. Casey, H. Perry-O'Keefe, S. A. Kates and N. D. Sinha, *Tetrahedron Lett.*, **37**, 4313 (1996).

327. (a) R. Kirstgen, R. C. Sheppard and W. Steglich, *J. Chem. Soc., Chem. Commun.*, 1870 (**1987**). (b) R. Kirstgen, A. Olbrich, H. Rehwinkel and W. Steglich, *Liebigs Ann. Chem.*, 437 (**1988**).

328. R. M. Lawrence, S. A. Biller, O. M. Fryszman and M. A. Poss, *Synthesis*, 553 (**1997**).

329. J. J. Weidner, J. J. Parlow and D. L. Flynn, *Tetrahedron Lett.*, **40**, 239 (1999).

330. (a) J. H. Hans, R. W. Driver and S. D. Burke, *J. Org. Chem.*, **64**, 1430 (1999). (b) J. H. Hans, R. W. Driver and S. D. Burke, *J. Org. Chem.*, **65**, 2114 (2000).

331. M. Ueda, H. Oikawa and T. Teshirogi, *Synthesis*, 908 (**1983**).

332. J. S. Lee, Y. S. Oh, J. K. Lim, W. Y. Yang, I. H. Kim, C. W. Lee, Y. H. Chung, S. J. Yoon, *Synth.Commun.*, **29**, 2547 (1999).

333. W. D. Fuller, M. P. Cohen, M. Shabankareh, R. K. Blair, M. Goodman and F. R. Naider, *J. Am. Chem. Soc.*, **112**, 7414 (1990).

334. W. D. Fuller, M. Goodman, F. Naider and Y. F. Zhu, *Peptide Sci.*, **40**, 183 (1996).

335. J. A. Fehrentz, C. Genu-Dellac, H. Amblard, F. Winternitz, A. Laffet and J. Martínez, *J. Peptide Sci.*, **1**, 124 (1995).

336. (a) C. B. Xue and F. Naider, *J. Org. Chem.*, **58**, 350 (1993). (b) P. A. Swain, B. L. Anderson, M. Goodman and W. D. Fuller, *Peptide Res.*, **6**, 147 (1993).

337. Y. F. Zhu, R. K. Blair and W. D. Fuller, *Tetrahedron Lett.*, **35**, 4673 (1994).

338. T. B. Sim and H. Rappoport, *J. Org. Chem.*, **64**, 2532 (1999).

339. C. Palomo, J. M. Aizpurua, I. Ganboa, F. Carreaux, C. Cuevas, E. Maneiro and J. M. Ontoria, *J. Org. Chem.*, **59**, 3123 (1994).

340. (a) J. M. Bateson, A. C. Kaura and R. Southgate, *Tetrahedron Lett.*, **32**, 2065 (1991). (b) J. H. Bateson, S. C. M. Fell, A. C. Kaura and R. Southgate, *J. Chem. Soc., Perkin Trans. 1*, 1577 (**1992**).

341. C. Palomo, J. M. Aizpurua, F. Cabré, J. M. García and J. M. Odriozola, *Tetrahedron Lett.*, **35**, 2721 (1994).

342. C. Palomo, J. M. Aizpurua, R. Urchegui and J. M. García, *J. Chem. Soc., Chem. Commun.*, 2327 (**1995**).

343. C. Palomo, J. M. Aizpurua, F. Cabré, C. Cuevas, S. Munt and J. M. Odriozola, *Tetrahedron Lett.*, **35**, 2725 (1994).

344. C. Palomo, J. M. Aizpurua, I. Ganboa, E. Maneiro and B. Odriozola, *J. Chem. Soc., Chem. Commun.*, 1505 (**1994**).

345. C. Palomo, J. M. Aizpurua, C. Cuevas, R. Urchegui and A. Linden, *J. Org. Chem.*, **61**, 4400 (1996).

346. (a) C. Palomo, J. M. Aizpurua, R. Urchegui and J. M. García, *J. Chem. Soc., Chem. Commun.*, 2327 (**1995**). (b) C. Palomo, J. M. Aizpurua, I. Ganboa, B. Odriozola, R. Urchegui and G. Görls, *Chem. Commun.*, 1269 (**1996**).

347. L. A. Carpino, M. Beyermann, H. Wenschuh and M. Bienert, *Acc. Chem. Res.*, **29**, 268 (1996).

348. V. C. S. Babu and H. N. Gopi, *Tetrahedron Lett.*, **39**, 1049 (1998).

349. H. Wenschuh, M. Beyermann, S. Rothemund, L. A. Carpino and M. Bienert, *Tetrahedron Lett.*, **36**, 1247 (1995).

350. (a) G. A. Olah, M. Nojima and I. Kerekes, *Synthesis*, 487 (**1973**). (b) J. M. Bertho, A. Loffet, C. Pinel, F. Reuther and G. Sennyey, *Tetrahedron Lett.*, **32**, 1303 (1991). (c) L. A. Carpino, E. M. E. Mansour, D. Sadat-Aalee, *J. Org. Chem.*, **56**, 2611 (1991).

351. C. Kaduk, H. Wenschuh, H. C. Beyermann, K. Forner, L. A. Carpino and M. Bienert, *Lett. Peptide Sci.*, **2**, 285 (1995).

352. H. Wenschuh, M. Beyermann, R. Winter, M. Bienert, D. Ionescu and L. A. Carpino, *Tetrahedron Lett.*, **37**, 5483 (1996).

353. A. Bianco, C. P. Sonken, P. Roepstorff and J. P. Briand, *J. Org. Chem.*, **65**, 2179 (2000).

354. (a) J. Green and K. Bradley, *Tetrahedron*, 49, 414 (1993). (b) D. Granitza, M. Beyermann, H. Wenschuh, H. Haber, L. A. Carpino, G. A. Truran and M. Bienert, *J. Chem. Soc., Chem. Commun.*, 2223 (**1995**).

355. K. Akaji, H. Tanaka, H. Itoh, J. Imai, Y. Fujiwara, T. Kimura and Y. Kiso, *Chem. Pharm. Bull.*, **38**, 3471 (1990).

356. A. Grandas, X. Jorba, E. Giralt and E. Pedroso, *Int. J. Pept. Prot. Res.*, **33**, 386, (1989).

357. J. Ji, D. Zhang, Y. Ye and Q. Xing, *Tetrahedron Lett.*, **39**, 6515 (1998).

358. L. A. Carpino and A. El-Faham, *Tetrahedron*, **55**, 6813 (1999).

359. L. A. Carpino and A. El-Faham, *J. Org. Chem.*, **59**, 695 (1994).

360. F. Albericio, J. M. Bofill, A. El-Faham and S. A. Kates, *J. Org. Chem.*, **63**, 9678 (1998).

361. H. Kurada, Y.-N. Chen, T. Kimura and S. Sakakibara, *Int. J. Pept. Prot. Res.*, **40**, 294 (1992).

362. J. Görlitzer, T. F. Gale and D. H. Williams, *J. Chem. Soc., Perkin Trans. 1*, 3253 (**1999**).

363. (a) S. Zimmer, E. Hoffmann, G. Jung and H. Kessler, *Liebigs Ann. Chem.*, 497 (**1993**). (b) B. E. Maryanoff, M. N. Greco, H. C. Zhang, P. Andrade-Gordon, J. A. Kauffman, K. C. Nicolaou, A. Lin and P. H. Brungs, *J. Am. Chem. Soc.*, **117**, 1225 (1995).

364. A. Ehrlich, H. U. Heyne, R. Winter, M. Beyermann, H. Haber, L. A. Carpino and M. Bienert, *J. Org. Chem.*, **61**, 8831 (1996).

365. "*Encyclopedia of Reagents for Organic Synthesis*", L. A. Paquette, Ed., Vol. 3, p. 1751, John Wiley & Sons, Chichester, 1995.

366. O. Kuisle, E. Quiñoa and R. Riguera, *Tetrahedron Lett.*, **40**, 1203 (1999).

367. P. Page, M. Bradley, I. Walters and S. Teague, *J. Org. Chem.*, **64**, 794 (1999).

368. B. J. Brown, I. R. Clemens and J. K. Neeson, *Synlett*, 131 (**2000**).

369. N. Flaih, C. Pham-Huy and H. Galons, *Tetrahedron Lett.*, **40**, 3697 (1999).

370. S. Bhandari and S. Ray, *Synth. Commun.*, **28**, 765 (1998).

371. G. Majestich, R. Hicks, G. Sun and P. McGill, *J. Org. Chem.*, **63**, 2564 (1998).

372. (a) B. Castro, G. Evin, C. Selve and R. Seyer, *Synthesis*, 413 (**1983**). (b) Y. Chapleaur, B. Castro and R. Toubiana, *J. Chem. Soc., Perkin Trans. 1*, 1940 (**1980**). (c) M. H. Kim and D. V. Patel, *Tetrahedron Lett.*, **35**, 5603 (1994).

373. A. Geyer and F. Moser, *Eur. J. Org. Chem.*, 1113 (**2000**).

374. R. P. McGeary, *Tetrahedron Lett.*, **39**, 3319 (1998).

375. J. M. Campagne, J. Coste and P. Jouin, *Tetrahedron Lett.*, **34**, 6743 (1993).

376. J. M. Campagne, J. Coste and P. Jouin, *Tetrahedron Lett.*, **36**, 2079 (1995).

377. J. Kehler, A. Püschl and O. Dahl, *Nucleosides & Nucleotides*, **16**, 23 (1997).

378. N. Aguilar, A. Moyano, M. A. Pericás and A. Riera, *Synthesis*, 313 (**1998**).

379. U. Boas and M. H. Jakobsen, *J. Chem. Soc., Chem. Commun.*, 1995 (**1995**).

380. S. Delarne and C. Sergheraert, *Tetrahedron Lett.*, **40**, 5487 (1999).

381. P. Garner and J. T. Anderson, *Org. Lett.*, **1**, 1057 (1999).

382. K. Takasu, S. Mizutani, N. Noguchi, K. Makita and M. Ihara, *Org. Lett.*, **1**, 391 (1999).

383. T. Isobe and T. Ishikawa, *J. Org. Chem.*, **64**, 6984 (1999).

384. T. Isobe and T. Ishikawa, *J. Org. Chem.*, **64**, 6989 (1999).

385. T. Isobe and T. Ishikawa, *J. Org. Chem.*, **64**, 5832 (1999).

386. K. S. Ramasamy and D. Averett, *Synlett*, 709 (**1999**).

387. A. Mazón, C. Nájera, M. Yus, A. Heumann, *Tetrahedron: Asymmetry*, **3**, 1455 (1992).

388. A. Liguori, A. Procopio, G. Romeo, G. Sindona and N. Uccella, *J. Chem. Soc., Perkin Trans. 1*, 1783 (**1993**).

389. G. J. Bodwell, T. J. Houghton and D. Miller, *Tetrahedron Lett.*, **38**, 1469 (1997).

390. W. R. Roush and R. J. Sciotti, *J. Am. Chem. Soc.*, **120**, 7411 (1998).

391. J. Hartung and M. Schwarz, *Synlett*, 371 (**2000**).

392. A. S. Kende, P. Delair and B. E. Blass, *Tetrahedron Lett.*, **35**, 8123 (1994).

393. J. Nielsen and L. O. Lyngsø, *Tetrahedron Lett.*, **37**, 8439 (1996).

394. (a) C. B. Reese and Z. Pei-Zhuo, *J. Chem. Soc., Perkin Trans.* 1, 2291 (**1993**). (b) C. B. Reese, Q. Song, M. V. Rao and I. Beckett, *Nucleosides & Nucleotides*, **17**, 451 (1998).

395. M. Kunishima, J. Morita, C. Kawachi, F. Iwasaki, K. Terao and S. Tani, *Synlett*, 1255 (**1999**).

396. M. Farloni, G. Giacomelli, A. Porcheddu and M. Taddei, *J. Org. Chem.*, **64**, 8962 (1999).

397. M. Farloni, A. Porcheddu and M. Taddei, *Tetrahedron Lett.*, **40**, 4395 (1999).

398. J. V. Barkley, J. Markopoulos and O. Markopoulou, *J. Chem. Soc., Perkin Trans. 2*, 1271 (**1994**).

399. (a) A. Detsi, J. Markopoulos and O. Igglessi-Markopoulou, *Chem. Commun.*, 1323 (**1996**). (b) M. Petroliagi and O. Igglessi-Markopoulou, *J. Chem. Soc., Perkin Trans. 1*, 3543 (**1997**). (c) A. Detsi, M. Micha-Screttas and O. Igglessi-Markopoulou, *J. Chem. Soc., Perkin Trans. 1*, 2443 (**1998**). (d) M. Petroliagi and O. Igglessi-Markopoulou, *Tetrahedron: Asymmetry*, **10**, 1873 (1999).

400. K. M. Sliedregt, A. Schouten, J. Kroon and R. M. J. Liskamp, *Tetrahedron Lett.*, **37**, 4237 (1996).

401. J. A. Fehrentz, E. Bourdel, J. C. Califano, O. Chaloin, C. Devin, P. Garrouste, A. C. Lima-Leite, M. Llinares, F. Rieunier, J. Vizavonna, F. Winternitz, A. Loffet and J. Martínez, *Tetrahedron Lett.*, **35**, 1557 (1994).

402. J. J. Leban and K. L. Colson, *J. Org. Chem.*, **61**, 228 (1996).

403. W. Wang and J. S. McMurray, *Tetrahedron Lett.*, **40**, 2501 (1999).

404. J. S. Davies, J. Howe and H. Le Breton, *J. Chem. Soc., Perkin Trans. 2*, 2335 (**1995**).

405. R. T. Pon and S. Yu, *Tetrahedron Lett.*, **38**, 3331 (1997).

406. J. Jiang, W. R. Li, R. M. Przeslawski and M. M. Joullié, *Tetrahedron Lett.*, **34**, 6705 (1993).

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