Optically Active N-Protected α-Amino Aldehydes in Organic Synthesis

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Contents

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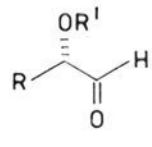
I. Introduction

The synthesis of optically active organic compounds is one of the most important problems of contemporary chemistry. Pure enantiomers attain increasing commercial interest, especially in the field of pharmaceutical products. During recent years, asymmetric synthesis has greatly contributed to progress in highly controlled formation of new chiral centers.[1] These processes still remain the basic problems in the total synthesis of natural products. Preparation of the latter in an optically pure form by application of chiral starting materials is very advantageous, enabling precise programming and efficient realization of synthetic pathways. Many monosaccharides and their readily available derivatives are versatile substrates for the synthesis of optically active target molecules.[2] α-Amino acids are the second important natural source of chiral substrates, useful in stereocontrolled organic synthesis.[2c,3]

Aldehydes are important and versatile compounds, widely used in organic synthesis. In recent years there has been a growing interest in chiral nonracemic aldehydes because of the development of new and effective methods for controlling stereochemistry of several basic organic reactions, such as metalloorganic addition to the carbonyl group,[4] aldol condensation,[5] [4 + 2] cycloaddition with carbonyl heterodienophiles,[6] etc. Protected α-hydroxy (**1**) and α-amino (**2**) aldehydes are of special interest, owing to their ready availability in both enantiomeric forms from natural sources (sugars



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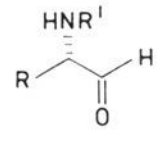

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and α-amino acids, respectively) and to pronounced versatility due to the presence of both the formyl group and suitably protected hydroxy or amino functionality in the molecule.

Recently, several extensive reviews on the application of α-hydroxy aldehydes in organic synthesis have been

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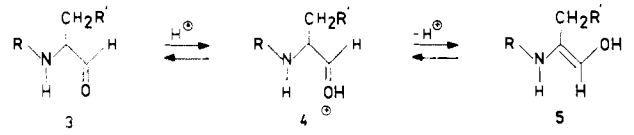

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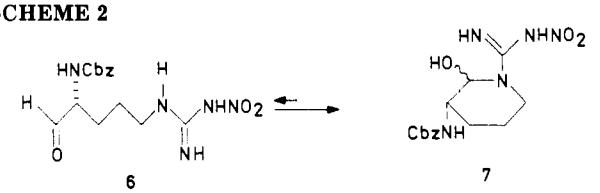


published;[2e,5a,c] but there is no general survey concerning α-amino aldehydes.[7] On account of the increasing interest of chemists in α-amino aldehydes, reflected by an augmenting number of relevant publications, and in view of our belief that their further potential applications may be very important, we resolved to gather and present the actual knowledge concerning the use of optically pure N-protected α-amino aldehydes in stereocontrolled organic synthesis.

In the present review we shall focus attention mainly on the reactions using the carbonyl group of N-protected α-amino aldehydes to form a new chiral center. The main contents of the review are preceded by a presentation of methods for the preparation of N-protected α-amino aldehydes as well as their physical properties and chemical reactivity.

II. Physical and Chemical Properties of N-Protected α-Amino Aldehydes

N-Protected α-amino aldehydes are usually colorless crystals or oils, well soluble in typical organic solvents. They are relatively unstable both chemically and configurationally, particularly in solution. For this reason their elemental analysis and optical rotation measurements should be considered as only approximate. Therefore, it is recommended to use these compounds immediately after preparation; however, if purification is necessary, two methods are available: flash chromatography on silica gel,[8] or formation of much more stable semicarbazone,[9] followed by simple chromatography and subsequent decomposition to return the pure aldehyde.

The optical stability of some N-protected α-amino aldehydes during chromatography on silica gel was first studied by Ito et al.[10] (Table 1, Schemes 1 and 2). As shown in Table 1, the order of the extent of racemization of Cbz-L-α-amino aldehydes on silica gel was as follows: Cbz-*S*-Bzl-L-cysteinal ≫ Cbz-L-phenylalaninal > Cbz-L-leucinal ≫ Cbz-N^G-nitro-L-argininal. The authors[10] proposed a racemization mechanism for compounds **3** involving the protonated form **4** and enol **5** (Scheme 1). Aldehydes **3** with an enol-stabilizing R′ group, e.g., Cbz-*S*-Bzl-cysteinal, racemize extremely quickly during contact with silica gel.

Limited racemization of Cbz-N^G-nitro-L-argininal (**6**) seems to be related to its cyclic carbinolamine structure **7** (Scheme 2), which probably prevents the nitroargininal derivative **6** from racemization due to keto–enol tautomerism.

Further studies on the optical stability of N-protected α-amino aldehydes were carried out by Evans and co-

TABLE 1. Optical Stability of Selected α-Amino Aldehydes on Silica Gel

α-amino aldehyde	deg of racemization, % 0 h[a]	6 h[a]	22 h[a]
Cbz-N^G-nitro-L-argininal	0	5	9
Cbz-L-leucinal	0	32	65
Cbz-L-phenylalaninal	0	53	85
Cbz-*S*-Bzl-L-cysteinal	7	99	100

[a] Exposure time.

TABLE 2. Optical Stability of Boc-L-Leucinal during Storage

storage time, day	storage temp, °C	$[\alpha]^{24}_D$, deg	L/L (HPLC)
0		+18.2	100
1	−30	+17.9	99/1
9	−30	+17.4	99/1
9	+24	+6.9	7/3

workers,[11] who found that the reduction–oxidation procedure (BH_3·THF–CrO_3/Py) generates Boc-α-amino aldehydes with complete retention of chiral integrity (>99.5%). The optical lability of the crude aldehydes depends on their structure. Thus, as expected from previous studies,[10] Boc-L-phenylalaninal appeared to be much less stable than Boc-L-leucinal. Very illustrative results of optical stability investigations of Boc-L-leucinal during storage at various temperatures are shown in Table 2. These studies led to the conclusion that even Boc-L-leucinal subjected to any prolonged treatment regimen, including drying, could no longer be regarded as optically pure unless otherwise verified as such.[11]

Recently, two important reports on configurational stability of N-protected α-amino aldehydes have appeared. The first one by Lubell and Rapoport[12] describes the synthesis of *N*-(9-(9-phenylfluorenyl))-L-alaninal. Exposure to silica gel or to a nonnucleophilic base caused no detectable racemization. The PhFl N-protecting group also maintains the configurational integrity of L-alaninal during C–C bond-forming reactions, affording enantiomerically pure products from Wittig reactions, aldol condensations, and Grignard additions.[12]

The second report by Garner and Park[13] describes the synthesis of N,O-diprotected L-serinal **8** and L-threoninal **9**. These differentially protected β-hydroxy α-

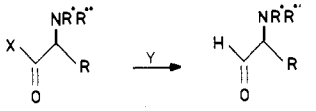
amino aldehydes were shown to be produced in a 93–95% enantiomeric excess. The configurational stability of compounds **8** and **9** during their purification either by vacuum distillation or by flash chromatography was also demonstrated.[13]

III. Preparation Methods of N-Protected α-Amino Aldehydes

A. Reductive Methods

α-Amino aldehydes are mainly obtained from α-amino acids and only on occasion are they obtained from

TABLE 3. Preparation of N-Protected α-Amino Aldehydes by Reductive Methods



X	Y	temp, °C	time	R′	R″	yield, %	ref
OMe, OEt	DIBAL	−50	50 min	H	Cbz	33–68	10
	DIBAL	−78	6 min	H	Boc	85–97	14, 15
	DIBAL	−65	45 min	H	Boc	80	9
	$LiAlH_4$	−20	45 min	H	Cbz	50	16
	DIBAL	−40	30 min	H	Cbz, Boc	52–83	17
	$LiAlH_4$	−20	2 h	H	Cbz, Boc	85–95	18
−N(OMe)Me	$LiAlH_4$	0	20 min	H	Boc	86–96	19, 20
	$LiAlH_4$	0	20 min		PhFl	90	12
−O(O)CoAlk	H_2/Pd–C	5	4–11 h	H	Ac	12–81	21
−Cl	H_2/Pd–C	100	3 h		Pht	60	22

TABLE 4. Preparation of N-Protected α-Amino Aldehydes by Oxidative Methods

(O)	temp, °C	time	R′	R″	yield, %	ref
CrO_3/Py	−10	30 min	H	Boc	56–67	11, 26
	−10	30 min	Pht		35	25
DMSO/SO_3·Py	20	10 min	H	Boc	70–95	25, 27
DMSO/$(COCl)_2$	−63	30 min	H	Boc	90	25, 28
DMSO/TFAA	−78	1 h	H	Boc	88	29
DMSO/DCC	20	48 h	Pht		43	21
	a	*a*	H	Ts	*a*	30
PCC	25	4 h	Bzl	Ts	75	31
PDC	20	24 h	H	Boc	75–95	11, 32, 33

[a] Unspecified.

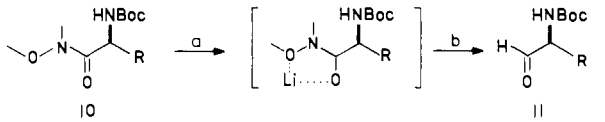
other chiral precursors. Usually the synthetic route proceeds via esters or active amides of α-amino acids, which are finally reduced. A second approach is based on α-amino alcohols obtained from α-amino acids, which are oxidized to afford the desired α-amino aldehydes.

Procedures based on reduction of esters and/or active amides of N-protected α-amino acids are listed in Table 3.

Diisobutylaluminum hydride (DIBAL) reduction of methyl or ethyl esters is often accompanied by some overreduction to the respective alcohols.[9,10,14,15] The same remarks apply to lithium aluminum hydride reduction of imidazolides.[16,17] However, the reduction of 3,5-dimethylpyrazolides is apparently free from overreduction.[18]

Recently, an efficient method without racemization and overreduction was reported by Fehrentz and Castro.[19a] Thus, the preparation of Boc-α-amino aldehydes **11** is based on reduction of *N*-methoxy-*N*-methyl carboxamides **10** with lithium aluminum hydride,[20] which proceeds through a stable lithium-chelated intermediate; further reduction of the lithium salt is precluded by intramolecular complexation, and the aldehyde **11** is obtained upon hydrolysis (Scheme 3).[19a] Similar results were found by Lubell and Rapoport[12] during reduction of the respective isoxazolides. The Fehrentz and Castro method was also successfully applied to the synthesis of tripeptide C-terminal aldehydes.[19b]

SCHEME 3



10 **11**

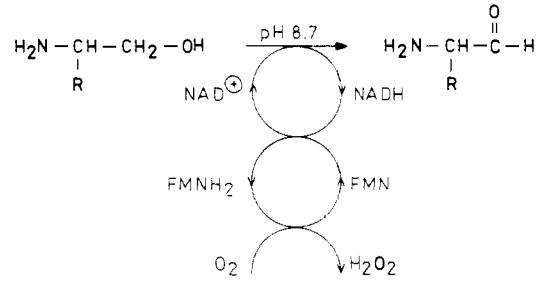
Other reductive methods involving catalytic hydrogenation of mixed carbonic–carboxylic anhydrides[21] and acid chlorides[22] are of limited applicability.

B. Oxidative Methods

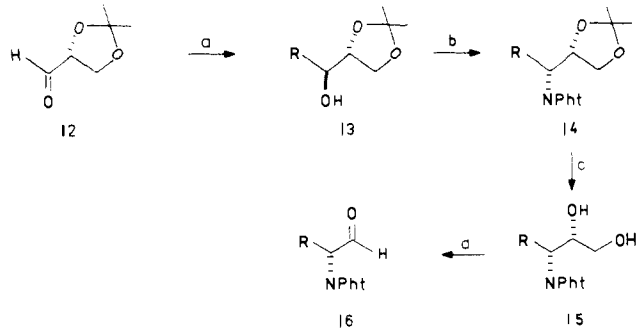
Procedures based on oxidation of N-protected α-amino alcohols are listed in Table 4. The N-protected α-amino alcohols are best obtained by borane–tetrahydrofuran reduction of N-protected α-amino acids[23] or by sodium borohydride–lithium chloride[24] or sodium borohydride–calcium chloride[25] reduction of the corresponding methyl ester.

Collin's reagent was the first oxidizing reagent shown to be efficient, offering a racemization-free procedure for Boc-L-leucinal synthesis.[11] Various activated dimethyl sulfoxide oxidations are of special interest owing to their general nature. These methods are free from racemization and can be applied for oxidation of relatively unstable derivatives of such α-amino acids as tryptophan and methionine.[7] Among these oxidation methods the Parikh–Doering procedure is the best documented[25,27] and is effective not only in the synthesis

SCHEME 4



SCHEME 5[a]



R = Me, Et, Pr^n, CH=CH$_2$, CH$_2$CH=CH$_2$

[a] (a) See ref 4b; (b) PhtNH, Ph_3P, $EtO_2CN{=}NCO_2Et$; (c) TFA; (d) $Pb(OAc)_4$.

of simple N-protected α-amino aldehydes but also in the preparation of peptide C-terminal aldehydes. Oxidation of pentapeptide C-terminal alcohols produced enkephalin aldehydes in 60–70% yield.[27]

Pyridinium dichromate (PDC) oxidation[32] is suspected to cause racemization to various extents, depending on the type of α-amino aldehyde,[11] whereas pyridinium chlorochromate (PCC) was found to be convenient for oxidation of *N*-benzyl-*N*-tosyl α-amino alcohols without racemization.[31]

α-Amino alcohols with nonpolar side chains, such as L-leucinol, L-phenylalaninol, and L-valinol, were found to be good substrates for alcohol dehydrogenase from horse liver, affording the respective α-amino aldehydes (Scheme 4).[34]

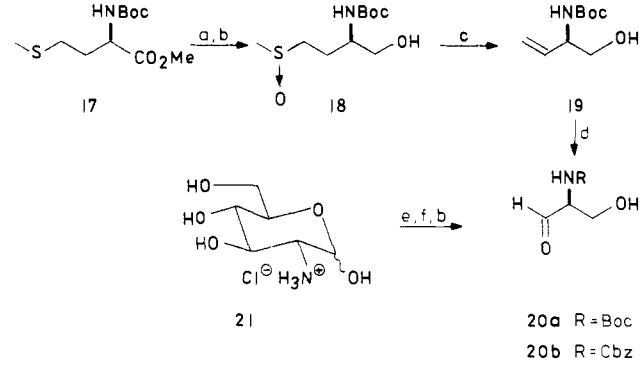
This mild enzymatic method enables preparation of nonprotected α-amino aldehyde semicarbazones, which can be directly used for coupling to certain peptides via the free amino group. To favor complete oxidation of the alcohol, the reaction was carried out in the presence of semicarbazide to trap the aldehyde product, and flavine mononucleotide was used to regenerate the oxidized coenzyme. The resulting α-amino aldehyde semicarbazone was subsequently hydrolyzed at pH 1 in the presence of formaldehyde, regenerating the aldehyde function in good yield.[34]

C. Miscellaneous Methods

A convenient and elegant synthesis of five Pht-L-α-amino aldehydes from 2,3-*O*-isopropylidene-D-glyceraldehyde (**12**) was recently described by Mulzer et al.[35] (Scheme 5).

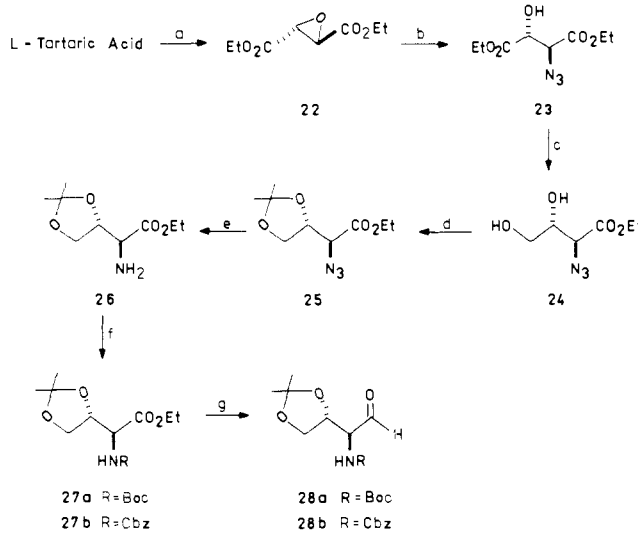
The key steps in the sequence are anti-selective addition of metalloorganic reagent to **12**, Mitsunobu inversion substituting *N*-phthalimide for hydroxyl in compound **13**, and acetonide hydrolysis and glycol

SCHEME 6[a]



[a] (a) $LiAlH_4$; (b) $NaIO_4$; (c) *o*-dichlorobenzene, AcONa, 170 °C; (d) (i) O_3, (ii) DMS; (e) $ClCO_2Bzl$; (f) $NaBH_4$.

SCHEME 7[a]



[a] (a) See ref 39; (b) $TMSN_3$; (c) $BH_3{\cdot}SMe_2$, $NaBH_4$ (cat.); (d) $Me_2C(OMe)_2$, Me_2CO, *p*-TsOH; (e) H_2/Pd–C; (f) $(Boc)_2O$ or $ClCO_2Bzl$; (g) DIBAL.

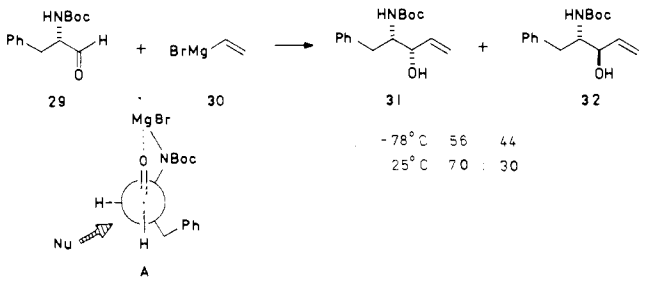
cleavage affording *N*-Pht-D-α-amino aldehyde **16**. The investigated examples testify to the general applicability of this method.

Ohfune and Kurokawa[36] described a practical method for the synthesis of N-protected serinal in both enantiomeric forms from L- or D-methionine (Scheme 6).

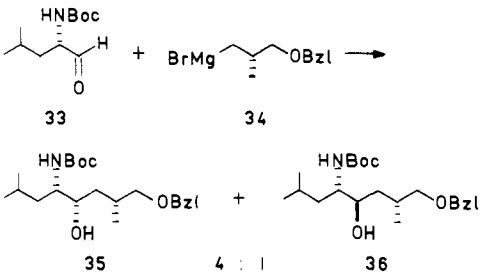
Methionine was used as starting material, since both enantiomers are available and the sulfur functional group is readily convertible to a double bond. Reduction of D-methionine derivative **17**, followed by oxidation of the resulting alcohol, afforded sulfoxide **18**. Thermal elimination provided optically pure unsaturated compound **19**, which was then converted to *N*-Boc-L-serinal (**20a**) by ozonolysis.[36] Recently, a new method for preparation of *N*-Cbz-L-serinal (**20b**) was reported.[37] The synthesis is based on sodium periodate oxidation of suitably protected D-glucosamine **21** (Scheme 6).

Another example of the synthesis of chiral β-hydroxy α-amino aldehydes, starting from L- and D-tartaric acid, was described[38] (Scheme 7). This approach involves a novel oxirane ring opening with hydrozoic acid and selective reduction of α-hydroxy ester as key steps. Transformation of L-tartaric acid into epoxide **22** was performed via a three-step procedure according to Mori and Iwasawa.[39] The opening of the oxirane ring with

SCHEME 8



SCHEME 9



hydrazoic acid, generated in situ from trimethylsilyl azide, afforded compound **23** in a 97% yield. The next crucial step consisted of reduction of the ester group in position α to the hydroxy group. For this regioselective transformation, a reducing system[40] containing borane, dimethyl sulfide, and catalytic amounts of sodium borohydride was applied. The resulting compound **24** was then treated with dimethoxypropane to produce the stable derivative **25**, which was reduced to amine **26**. The final steps involved protection of the amino group and reduction of the ester group with DIBAL to afford the desired N-protected α-amino aldehyde derivatives **28**.

IV. Basic Transformations of N-Protected α-Amino Aldehydes into Useful Synthons

A. Additions of Metalloorganic Reagents

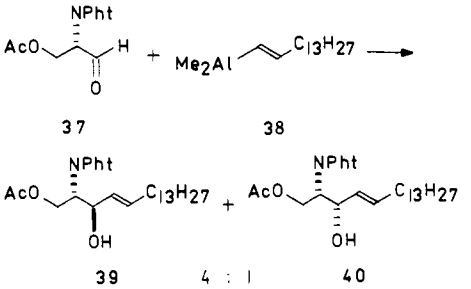
Reactions of metalloorganic reagents with chiral aldehydes are of considerable interest in the context of acyclic stereoselective synthesis.[2e] This type of reaction with N-protected α-amino aldehydes is often used in the synthesis of peptide isosteres.[7]

Simple addition of vinylmagnesium bromide (**30**) to Boc-L-phenylalaninal (**29**), carried out at −78 °C in tetrahydrofuran, afforded a 56:44 mixture of syn (threo) and anti (erythro) allylic alcohols **31** and **32**, respectively (Scheme 8).[41] Similarly, low diastereoselectivity was reported by Thaisrivongs et al.[42] for addition of **30** to *N*-trityl-L-leucinal.

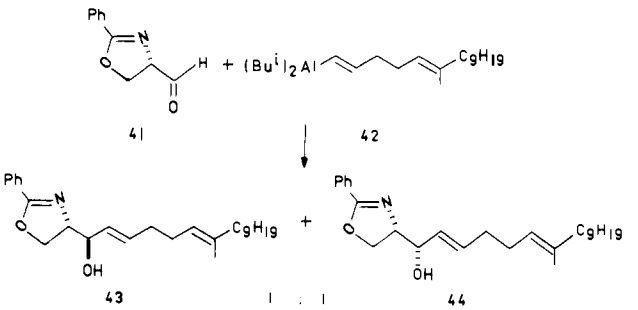
The diastereoselectivity was improved in favor of the chelation-controlled Cram product **31** by carrying out the addition reaction at 25 °C, which gave a 70:30 ratio of **31** to **32**. At higher temperatures a greater proportion of NH protons should be removed to the transition state A prior to addition to the aldehyde carbonyl group, resulting in preferential formation of syn alcohol **31** (Scheme 8).[41]

Addition of the chiral Grignard reagent **34** to Boc-L-leucinal (**33**) was characterized by higher diastereoselectivity.[43] The syn product **35** was formed as the major diastereoisomer (ratio of **35** to **36** was 4:1), presumably

SCHEME 10



SCHEME 11



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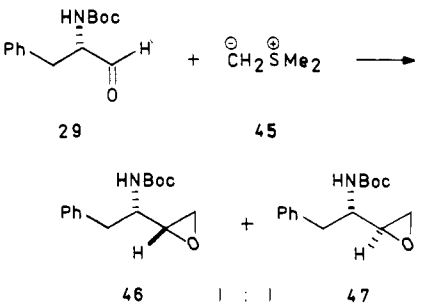


due to double asymmetric induction (Scheme 9).

Addition of the lithium derivative of ethyl propiolate to Boc-L-leucinal (**33**) afforded corresponding hydroxyacetylenic esters as a mixture of diastereoisomers.[44] Further transformations proved that also in this case the syn diastereoisomer was formed predominantly (syn:anti ratio was 4.5:1).

Addition of vinylalane **38** to *O*-Ac-*N*-Pht-L-serinal (**37**), carried out in a 2:1 mixture of benzene and ether at 5–10 °C, afforded the desired alcohols *anti*-**39** and *syn*-**40** in a 4:1 ratio (Scheme 10).[45a]

Addition of ((*Z*)-3-pentadecenyl)magnesium bromide to the aldehyde **37** resulted in a ca. 7:1 mixture of anti to syn products in 18.9% yield.[45b]

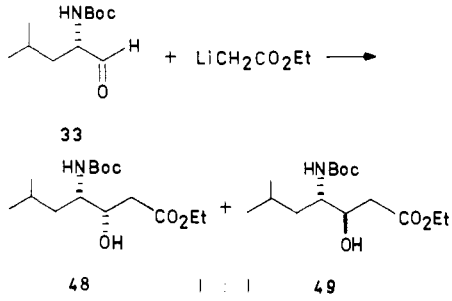
Similar additions of vinylalanes were studied by two other groups.[46,47] In both cases, the oxazolidine form of L-serinal **41** was used. Addition of metalloorganic reagent **42** to aldehyde **41** proceeded without any selectivity, affording an equimolar mixture of alcohols **43** and **44** (Scheme 11).[47]

Similarly, ylides of type **45** reacted with N-protected α-amino aldehydes, e.g., **29**, to afford an equimolar mixture of two diastereoisomeric epoxides **46** and **47** (Scheme 12).[48]

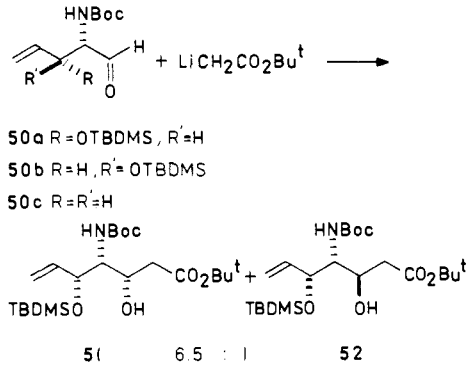
B. Aldol Condensation and Related Reactions

The renaissance of the aldol condensation observed during the past decade resulted from the development

SCHEME 13



SCHEME 14



of new methods of organic synthesis, enabling stereocontrol of the reaction course.[5] A number of syntheses of natural products, starting from N-protected α-amino aldehydes, involves aldol condensation as the key step. Unfortunately, aldol condensation with N-protected α-amino aldehydes is characterized, similarly as in case of metalloorganic addition, by rather low diastereoselectivity. In only one case this reaction with N-protected α-amino aldehydes was found to attain high diastereoselectivity.[18a]

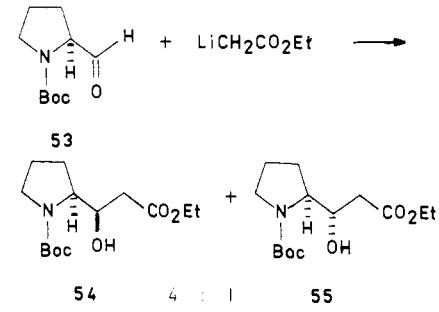
Simple condensation of the lithiated acetic ester with Boc-L-leucinal (**33**) provided a 1:1 mixture of diastereoisomeric alcohols **48** and **49** (Scheme 13).[11,14]

Significant diastereoselectivity was observed for β-substituted N-protected α-amino aldehydes. Condensation of aldehydes **50a** with lithiated *tert*-butyl acetate afforded a 6.5:1 mixture of diastereoisomeric alcohols *syn*-**51** and *anti*-**52** in a 96% yield (Scheme 14).[33] The selectivity of this reaction was obviously dependent upon the configuration of the β-substituent and decreased to a 3:1 ratio of the respective alcohols when the anti aldehyde **50b** was employed under the same reaction conditions. As expected, condensation of aldehyde **50c** with lithiated *tert*-butyl acetate afforded an equimolar mixture of diastereoisomers. The authors[33] proposed for this reaction a model in which both α-chelation and the bulky group in the β-position play an important role in stereocontrol of the reaction course.

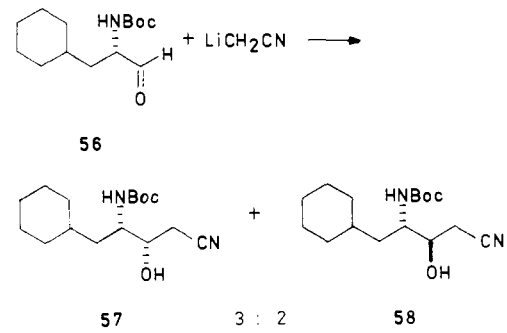
The cyclic structure of N-protected α-amino aldehydes, e.g., Boc-L-prolinal (**53**), seems to play a similar role; the lack of the NH proton in such structure has to be stressed. Aldol condensation of **53** with lithiated ethyl acetate produced a 4:1 mixture of diastereoisomeric alcohols *syn*-**54** and *anti*-**55** (Scheme 15).[49]

This degree of diastereoselectivity is substantial when compared with the results of a similar aldol condensation with the acyclic aldehyde **33** (cf. Scheme 13). Noteworthy is the fact that use of vinylmagnesium bromide instead of lithiated ethyl acetate in the reaction

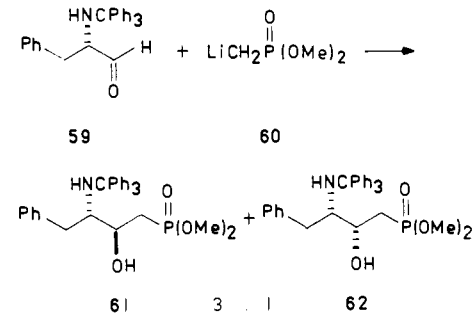
SCHEME 15



SCHEME 16



SCHEME 17



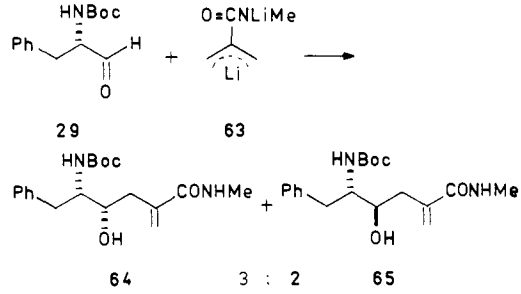
with aldehyde **53**, gave a 1:1 mixture of diastereoisomers. Also in the case of 4-substituted N-protected L-prolinal, reaction with even chiral lithium enolate led to a mixture of diastereoisomers in an only 3:1 syn:anti ratio.[29]

Boc-L-Cyclohexylaninal (**56**) reacted with the lithium enolate of acetonitrile similarly as with Boc-L-leucinal or with Boc-L-phenylalaninal, to afford a 3:2 diastereoisomeric mixture of alcohols *syn*-**57** and *anti*-**58** (Scheme 16).[50] The low diastereoselectivity found for the above aldol condensation can be explained by competition between chelation and steric factor control.

Aldol condensation of *N*-trityl-L-phenylalaninal (**59**) with the lithium enolate of dimethyl phosphonate (**60**) afforded a 3:1 anti:syn ratio of alcohols **61** and **62** (Scheme 17).[51] The same reaction with Boc-L-phenylalaninal gave a 1:1 diastereoisomeric mixture. The above results are consistent with the Cram model for asymmetric induction when the benzyl moiety is assumed to be a large substituent. The trityl protecting group is very bulky and prevents chelating interaction between lithium and the NH proton, whereas the Boc group is not sufficiently bulky.

Titanium-mediated condensation of dilithiated *N*-alkylmethacrylamides with N-protected α-amino aldehydes also resulted in moderate diastereoselectivity. For example, Boc-L-phenylalaninal (**29**) reacted with

SCHEME 18



SCHEME 19

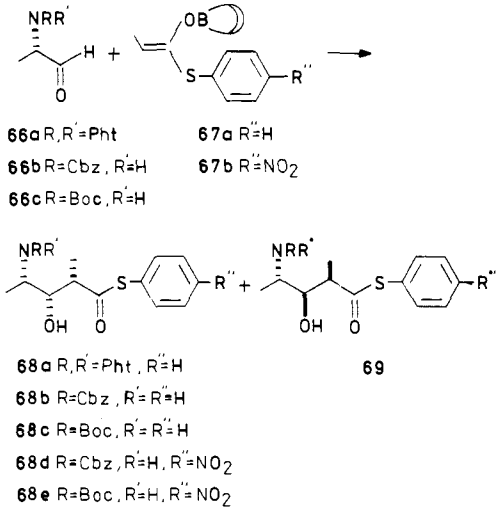


TABLE 5. Aldol Condensation of N-Protected L-Alaninal Derivatives 66a–c with (Vinyloxy)boranes 67a,b

major product	temp, °C	time, min	overall yield, %	diaster ratio 68:69
68a	0	30	70	8:1
68b	0	30	60	35:1
68c	0	30	62	20:1
68d	0	30	60	10:1
68e	0	60	64	8:1

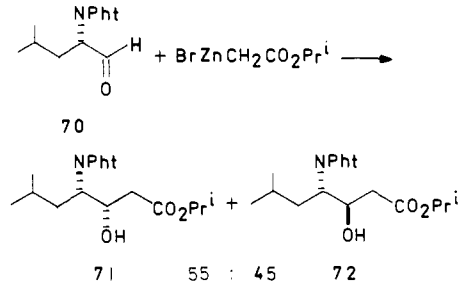
dilithiated *N*-methylmethacrylamide (**63**) in the presence of chlorotitanium triisopropoxide to afford a 3:2 mixture of diastereoisomeric hydroxy amides **64** and **65** (Scheme 18).[52] The same reaction with Boc-L-cyclohexylalaninal or Boc-L-leucinal led to a ca. 1:1 mixture of diastereoisomers.

In light of the above-mentioned examples, the results obtained by Umezawa et al.[18a] seem to be very promising. Aldol condensation of variedly N-protected L-alaninals (**66a–c**) with (vinyloxy)borane derivatives (**67a,b**) was examined under different reaction conditions (Scheme 19). The results are summarized in Table 5.

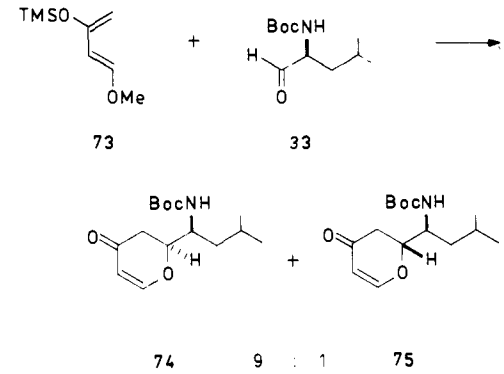
The overall yield of the diastereoisomeric aldol products was generally good. The high diastereoselectivity of this reaction was rationalized by using the commonly accepted six-membered cyclic transition state.[18a]

Only one example of the Reformatsky reaction with N-protected α-amino aldehydes is known.[53] Thus, in the reaction of Pht-L-leucinal (**70**) with the organozinc derivative of isopropyl acetate, a 55:45 mixture of *syn*-**71** and *anti*-**72** alcohols is obtained (Scheme 20). This result is in good agreement with those obtained for simple aldol condensation (cf. Schemes 13 and 16).

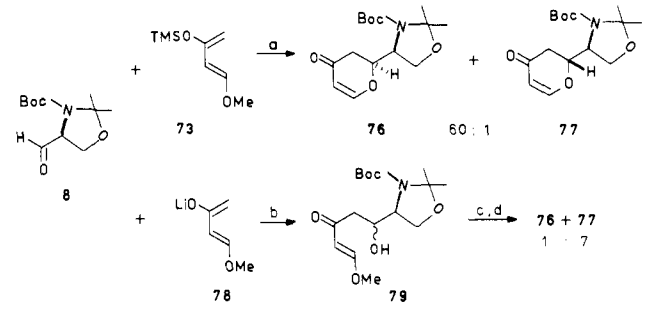
SCHEME 20



SCHEME 21



SCHEME 22[a]



[a] (a) $ZnCl_2$; (b) HMPT–THF, −78 °C; (c) TFA; (d) PPTS.

C. Diels–Alder Cycloaddition and Related Reactions

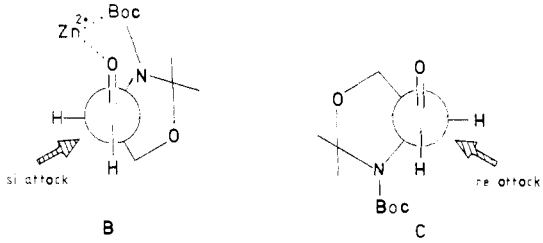
Since the early observations on the ability of activated carbonyl compounds to undergo the Diels–Alder reaction with 1,3-dienes, this field of organic chemistry has been greatly explored.[54]

In basic studies of the cyclocondensation reaction of activated 1,3-dienes with various aldehydes, Danishefsky et al.[55] tested Boc-L-leucinal (**33**) as a dienophile component. The reaction of diene **73** with aldehyde **33** catalyzed by zinc chloride led to a 9:1 diastereoisomeric mixture of pyrones **74** and **75** (Scheme 21). This high syn–anti selectivity can be explained by a strong chelating interaction forming the quasi-cyclic structure of N-protected α-amino aldehyde as well as by the high steric demand of the approaching planar diene conformer.

High diastereoselectivity was also observed for the reaction of the same diene **73** with L-serine derivative **8** (Scheme 22).[56]

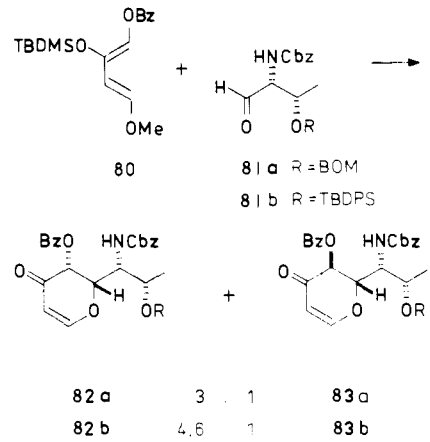
These results are also consistent with chelation-controlled cycloaddition of diene **73** to aldehyde **8** in conformation B from the less hindered si face, to afford a 60:1 mixture of *syn*-**76** and *syn*-**77** pyrones (Scheme 23).

SCHEME 23



B C

SCHEME 24



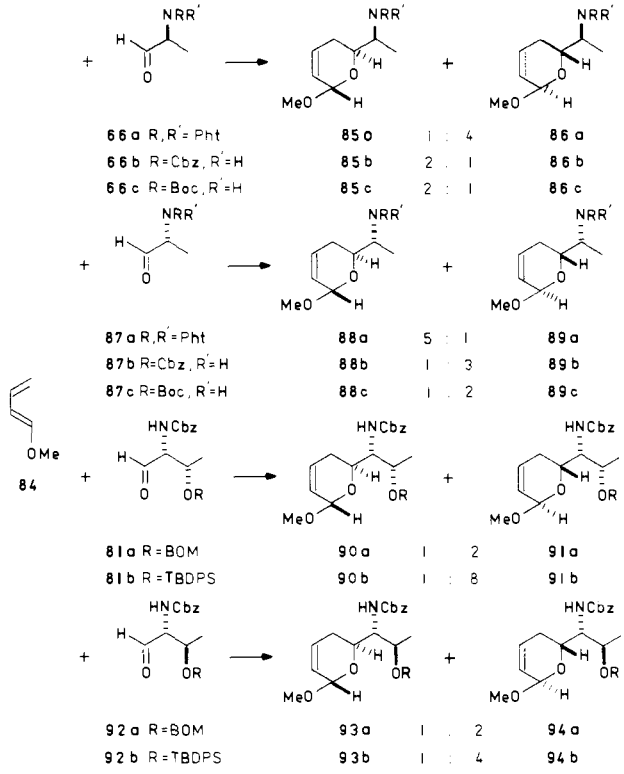
Obviously, obtainment of the opposite (anti) diastereoselectivity in this reaction creates some difficulties. In view of the possibility of two competitive routes for the cyclocondensation reaction of diene **73** with aldehydes,[6a] Garner and Ramakanth[56] proposed an ingenious method for overcoming these difficulties. Addition of lithium enolate **78** to aldehyde **8** afforded epimeric aldol products **79**, which were readily converted to a 1:7 mixture of *syn*-**76** and *anti*-**77** (Scheme 22). This was due to the predominance of the Felkin–Anh[57] conformation C of aldehyde **8** and to the attack of diene **73** from the less hindered *re* face (Scheme 23).

In long-term studies by Jurczak and Golębiowski[58] on N-protected α-amino aldehydes, a search was conducted for a more general anti-selective strategy. Initial investigations involved the reaction of diene **80** with two O-protected *N*-Cbz-L-threoninals **81a** and **81b** in the presence of zinc bromide as catalyst (Scheme 24).

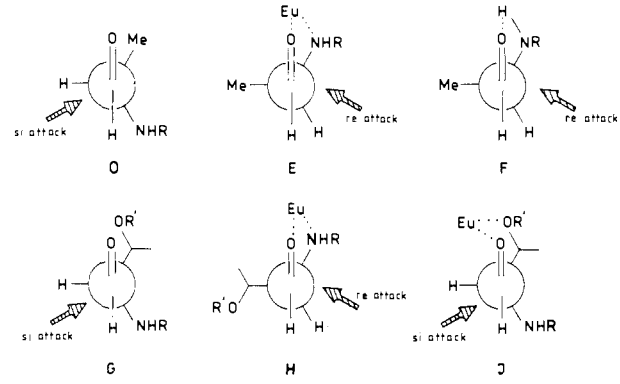
The results pointed out a strong preference of α-chelation interaction leading in both cases to formation of *syn*-**82** pyrones as the major diastereoisomers. For this reason the high-pressure techniques[59] was applied, enabling milder reaction conditions and no need for the strong Lewis acid catalysis used in the previous case. Thus, the high-pressure reactions of diene **84** with variedly N-protected L-alaninal (**66a–c**) and D-alaninal (**87a–c**) catalyzed by 1–5% $Eu(fod)_3$[60] were extensively studied[15,58] (Scheme 25).

The results testified to substantial reversion of stereoselectivity for Pht-L- (**66a**) or -D-alaninal (**87a**) when compared with the Cbz- or Boc-protected analogues (**66b,c** and **87b,c**). This was probably caused by the removal of both NH protons from the amino group paralleled by nitrogen atom deactivation due to the presence of two carbonyl groups in the phthalimide moiety. The necessity of the occurrence of a free NH proton for chelation control was also confirmed by two experiments under very high pressure (25 kbar). The

SCHEME 25



SCHEME 26

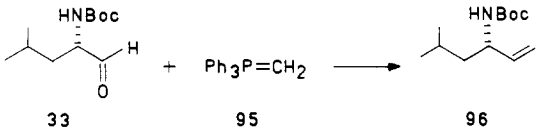


O E F G H J

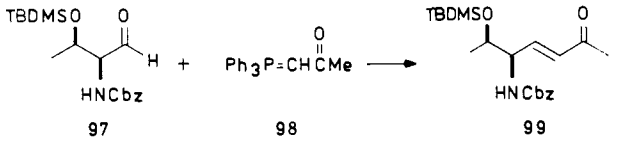
noncatalyzed reaction of Cbz-L-alaninal (**66b**) with diene **84** led to a 2:1 mixture of *syn*-**85b** and *anti*-**86b** adducts (Scheme 25). The same reaction was carried out in the presence of catalytic amounts of $Eu(fod)_3$ to afford a higher yield of the cycloadducts **85b** and **86b**, but the diastereoselectivity was the same as in the previous case. These facts can be interpreted from the three possible conformations of aldehyde **66b**: the Felkin–Anh form D, chelating form E, and hydrogen-bonded form F (Scheme 26). It can be expected that in the catalyzed reaction conformation E will predominate over conformation D. On the other hand, in the noncatalyzed reaction conformation F is preferred over conformation D.[58]

High-pressure [4 + 2] cycloadditions of diene **84** to variedly O-protected *N*-Cbz-D-threoninal (**81a,b**) or *N*-Cbz-D-*allo*-threoninal (**92a,b**) catalyzed by 2–3% $Eu(fod)_3$ were also studied;[58] the results are shown in Scheme 25. Explanation of these results is also based on an analysis of the transition-state stereochemical models G, H, and J (Scheme 26). For aldehydes **81b** and **92b** (R = TBDPS) conformation H should pre-

SCHEME 27



SCHEME 28



dominate over conformation G, leading to diastereoisomers *syn*-**91b** and *syn*-**94b**, respectively, as major products. When the bulky *tert*-butyldiphenylsilyl group was replaced by the strongly chelating (benzyloxy)methyl group (BOM), the population of conformation J substantially increased, giving rise to a higher yield of diastereoisomers *anti*-**90a** and *anti*-**93a** when aldehydes **81a** and **92a**, respectively, were used (Scheme 25).[58]

D. Wittig-Type Reactions

In N-protected α-amino aldehydes, the carbonyl group not only participates in reactions leading to formation of a new chiral center but also may be transformed into other functionalities. This section presents a discussion of the Wittig reaction,[61] permitting introduction of a C=C bond to replace the formyl group of N-protected α-amino aldehydes. The mechanism of the Wittig reaction still remains unclear, and thus the factors governing *Z*-*E* selectivity are not yet well-known.[62] Nevertheless, some conclusions concerning the effect of the type of Wittig reagent and of the reaction conditions on *Z*–*E* selectivity were reached. For example, it is known that application of a stabilized organophosphorus compound in nonpolar solvents yields products predominantly with the *E* configuration, whereas in alcohol-type solvents isomer *Z* predominates. In the case of a nonstabilized Wittig reagent, there is usually a predominance of the *Z* isomer.

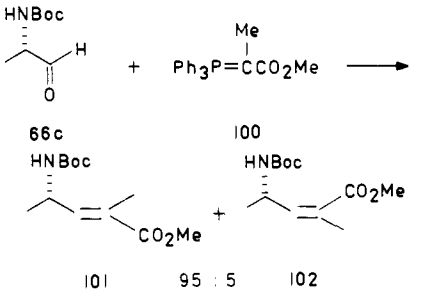
In N-protected α-amino aldehydes, the chiral center seems to play no part in the stereochemistry of the reaction. The *E*/*Z* ratio mainly depends on the nature of the ylide and on the reaction conditions. Recently, Luly et al.[25] took up the problem of racemization during this reaction. In studies of the reaction of ylide **95** with Boc-L-leucinal (**33**), the resulting olefin **96** and starting aldehyde **33** exhibited a similar degree of optical purity (Scheme 27). This result can be rationalized by a racemization mechanism involving enol formation, which is generally accepted for N-protected α-amino aldehydes.[10]

The Wittig reaction of Cbz-L-threoninal derivative **97** with acetonylidenetriphenylphosphorane (**98**) afforded enone **99** without any perceptible epimerization (Scheme 28),[63]

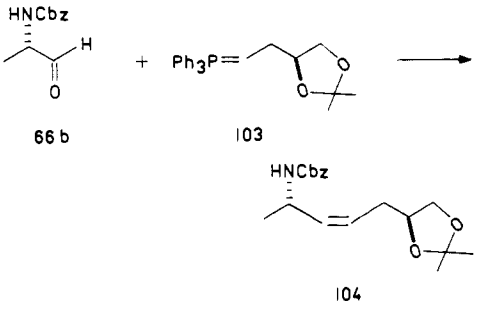
Likewise, the reaction of Boc-L-alaninal (**66c**) with 2-(triphenylphosphoranylidene)propionate (**100**) afforded *E*-olefin **101** as the predominant product (*E*/*Z* ratio was 95:5) (Scheme 29).[64]

In the case of the reaction of Cbz-L-alaninal (**66b**) with chiral ylide **103**, *Z*-olefin **104** was exclusively formed (Scheme 30).[65]

SCHEME 29



SCHEME 30



SCHEME 31

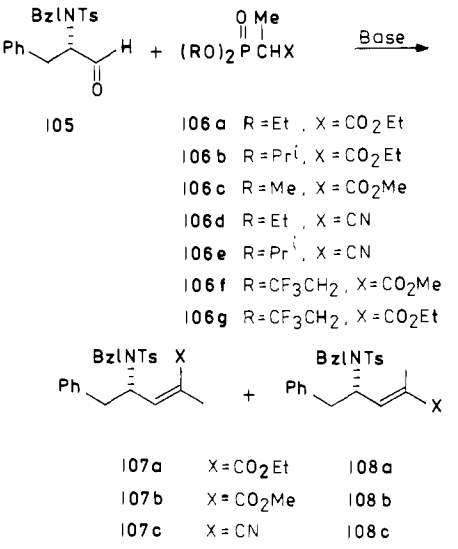
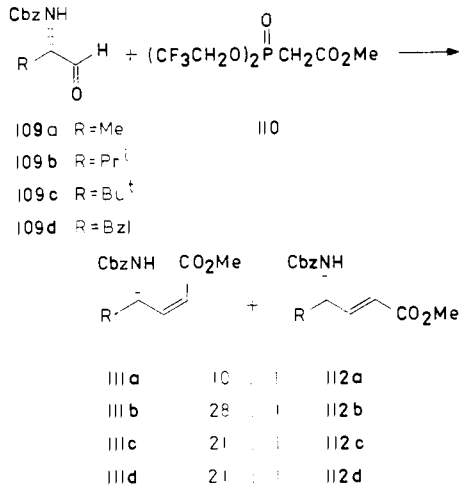


TABLE 6. Olefination of *N*-Benzyl-*N*-tosyl-L-phenylalaninal (105)

phosphonate	products	temp, °C	base	yield, %	*Z*:*E* ratio 107:108
106a	**107a + 108a**	0	NaH	84	1:2
106a	**107a + 108a**	−78	KH	93	1:8.5
106b	**107a + 108a**	0	NaH	100	1:1
106b	**107a + 108a**	−78	KH	80	1:9
106c	**107b + 108b**	0	NaH		1:2
106c	**107b + 108b**	−78	NaH		2:3
106c	**107b + 108b**	−78	KH	41	2:3
106d	**107c + 108c**	0	NaH	98	5:1
106d	**107c + 108c**	−78	NaH	8i	3.3:1
106d	**107c + 108c**	−78	KH	56	3.3:1
106e	**107c + 108c**	0	NaH	91	7:1
106f	**107b + 108b**	−78	KH	79	25:1
106f	**107b + 108b**	0	KH	45	20:1
106g	**107a + 108a**	−78	KH	79	70:1

Very interesting studies on the selectivity of the reaction between *N*-benzyl-*N*-tosyl-L-phenylalaninal (**105**) and a variety of phosphonates and phosphononitriles were recently reported by Hensel and Fuchs[66] (Scheme

SCHEME 32



31). The results are summarized in Table 6.

The best *Z* selectivity was obtained with highly electrophilic β-trifluoroethyl phosphonates **106f** and **106g**. More bulky phosphonate esters (e.g., **106b**) permit equilibration of the β-oxido phosphonate intermediates and a shift of the product distribution toward the thermodynamically preferred *E*-olefin isomers.

Kogen and Nishi[67] carried out similar investigations concerning several Cbz-protected α-amino aldehydes of the type of **109** (Scheme 32). They also obtained a very good *Z* selectivity for the highly electrophilic β-trifluoroethyl phosphonate **110**.

V. Total Synthesis of Natural Products

A. Dipeptide Isosteres

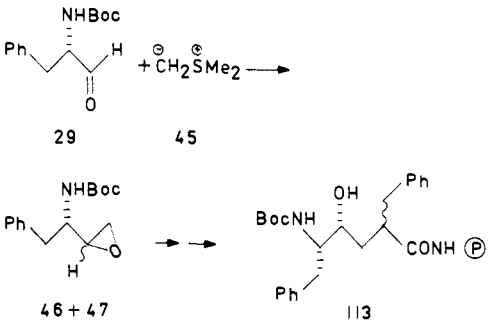
A new branch of synthetic chemistry in the peptide field appeared when chemists started to modify the peptide backbone itself, while maintaining the original side chains. In this way an increased stability toward enzymatic degradation can be obtained, leading to a prolonged or a more selective activity of peptide hormones. Alternatively, nonhydrolyzable peptide analogues can be designed to inhibit a variety of enzymes.[68] A number of such peptide backbone modifications are known, e.g., $-CH_2-$, $-NH-$, or $-O-$ intercalations, α-aza, α-alkyl, and *N*-alkyl peptides, depsipeptides, phosphonamidates, etc.[7]

Dipeptide isosteres, compounds in which the peptide bond is replaced by some approximately isosteric functional groups, e.g., hydroxylmethylene, ketomethylene, thiomethylene, and the carbon–carbon *E* double bond, proved to be valuable for producing enzyme inhibitors and proteolytically stable peptides.[7]

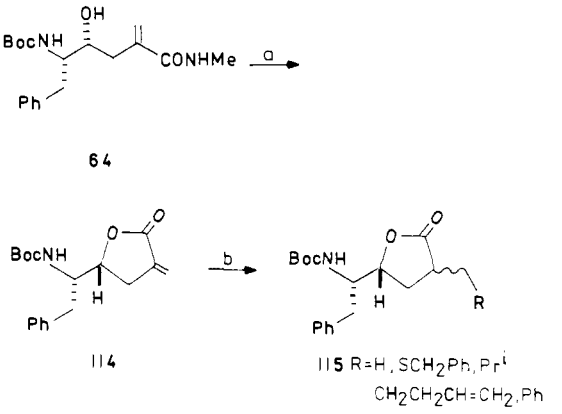
N-Protected α-amino aldehydes are very suitable starting materials for modified peptide synthesis. Moreover, some naturally occurring peptide enzyme inhibitors, such as leupeptin, antipain, chymostatin, and elastinal,[69] have an amino aldehyde function at the *C*-terminal part.

Evans et al.[48] described the stereocontrolled synthesis of the isosteric hydroxymethylene dipeptide **113**. The method is based on the reaction between ylide **45** and Boc-L-phenylalaninal (**29**), leading to a mixture of epoxides **46** and **47**, which was then used for the synthesis of several dipeptide analogues of the type of **113** (Scheme 33).

SCHEME 33

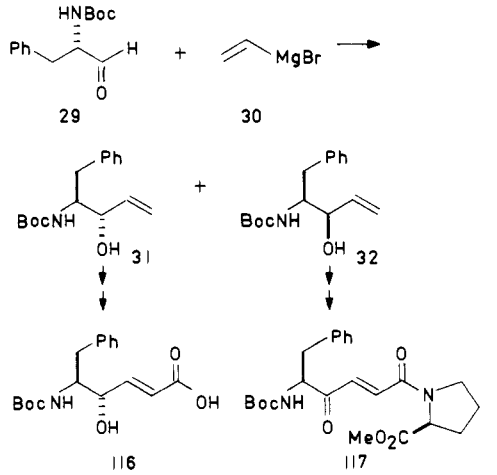


SCHEME 34[a]



[a] (a) Xylene, reflux; (b) +"R".

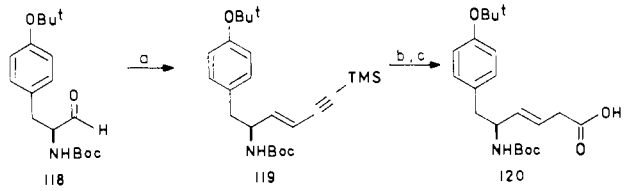
SCHEME 35



A general method for the synthesis of isosteric hydroxymethylene dipeptides was recently reported by Kempf.[52] Pyrolytic cyclization of the compound **64**, obtained from Boc-L-phenylalaninal (**29**) according to Scheme 18, afforded derivative **114**. Addition of nucleophiles to the double bond of **114** led to protected **115** (Scheme 34).

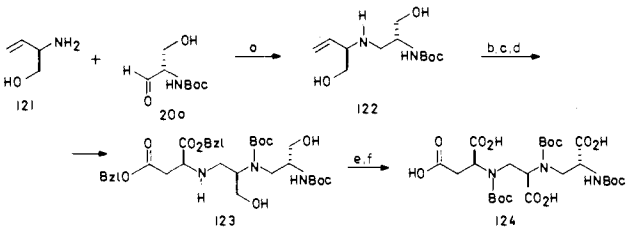
Hanson and Lindberg[41] achieved the synthesis of dipeptide analogues through the reaction of vinylmagnesium bromide (**30**) with Boc-L-phenylalaninal (**29**), affording a mixture of allylic alcohols **31** and **32** (cf. Scheme 8). After chromatographic resolution, pure diastereoisomers **31** and **32** were separately transformed into the respective dipeptide analogues **116** and **117** (Scheme 35). A similar approach to the synthesis of dipeptide analogues was recently reported by Plattner et al.[70]

SCHEME 36[a]



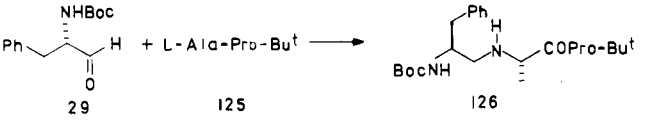
[a] (a) BuLi, $Ph_3P(Br)CH_2C{\equiv}CTMS$; (b) $(Sia)_2BH$; (c) H_2O_2, OH^-.

SCHEME 37[a]



[a] (a) $NaBH_3CN$, pH 6–8; (b) $(Boc)_2O$; (c) (i) O_3, (ii) DMS; (d) L-Asp-OBzl; (e) H_2/Pd–C; (f) PDC.

SCHEME 38



An interesting strategy for the synthesis of an olefinic isostere **120** was applied by Sammes et al.[9,71a] and later by Johnson[71b] (Scheme 36). The Wittig reaction of aldehyde **118** with an ylide generated from $Ph_3P(Br)$-$CH_2C{\equiv}C(TMS)$ afforded acetylene derivative (*E*)-**119**, which was then oxidized by using the Zweifel–Backlund procedure[72] to produce acid **120**. Compound **120** was used as a substrate in several isosteric peptide syntheses.

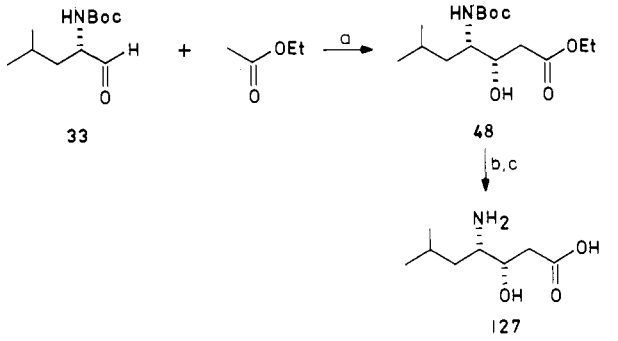
Poly(amino acids) in which the amino acid moieties are linked by the *N*-alkyl bond attracted considerable attention since they possess interesting biological activities.[73] Ohfune and Kurokawa[36] recently reported the synthesis of a typical representative of this class of compounds—aspergillomarasmine A acid (Scheme 37). Amine **121** and *N*-Boc-L-serinal (**20a**), both obtained from D-methionine according to the procedure shown in Scheme 6, were converted to diol **122** by reductive coupling. Protection of the free amino group, followed by ozonolysis and coupling with L-aspartic acid benzyl ester, afforded the acid **123**. Deprotection of the ester group and oxidation of the free hydroxy group should give the required acid **124**, but because of steric hindrance, the central hydroxy group remained unchanged.[36]

Reductive coupling was also used as the key step in the synthesis of simple peptide isostere **126** (Scheme 38).[28,74]

B. Unusual Amino Acids

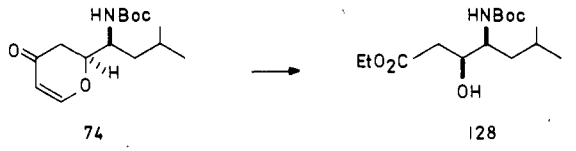
The synthesis of unusual amino acids is of growing interest.[14b,42,75] L-Statine (**127**)[76] is one of the most important members in this class of compounds because of its presence in a number of recently discovered protease inhibitors, such as pepstatine, renin, etc. A simple and efficient synthesis of L-statine was reported by Rich et al.[14a] (Scheme 39).

SCHEME 39[a]

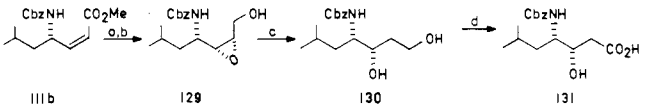


[a] (a) LDA; (b) OH^-; (c) H^+.

SCHEME 40

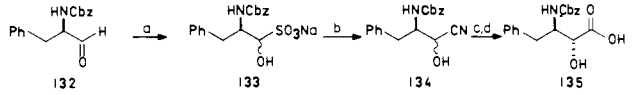


SCHEME 41[a]



[a] (a) DIBAL; (b) *m*-CPBA; (c) Red-Al; (d) O_2, Pt.

SCHEME 42[a]



[a] (a) $NaHSO_3$; (b) KCN; (c) HCl; (d) crystallization.

A similar approach was subsequently used by Evans et al.[11] Aldol condensation of Boc-L-leucinal (**33**) with lithiated ethyl acetate afforded an equimolar syn–anti mixture of the respective esters in 80% yield (cf. Scheme 13). After chromatographic separation, the pure diastereoisomer **48** was hydrolyzed and deprotected to yield optically pure L-statine (**127**).

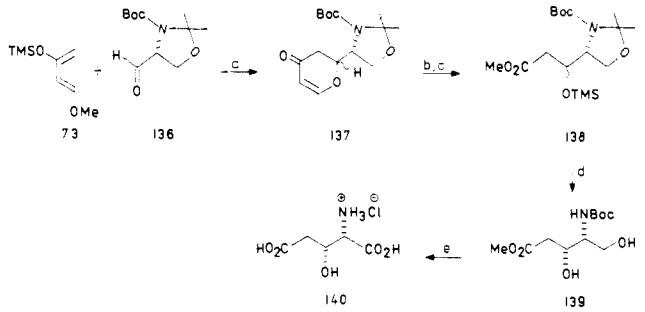
A different approach to the L-statine synthesis was reported by Danishefsky et al.[55] Pyrone **74** obtained from diene **73** and Boc-L-leucinal (**33**) according to the procedure shown in Scheme 21 was subjected to ozonolysis followed by oxidative fragmentation to afford the ethyl ester of *N*-Boc-L-statine (**128**) (Scheme 40).

An efficient synthesis of *N*-Cbz-L-statine (**131**) was recently reported by Kogen and Nishi.[67] Unsaturated ester **111b**, obtained from Cbz-L-leucinal via the Wittig reaction according to the procedure shown in Scheme 32, was reduced and then epoxidized to afford compound **129** as a major product (ratio = 28:1). The epoxide *syn*-**129** was reduced, giving with very high selectivity the desired α-amino alcohol *syn*-**130**. Selective oxidation of the primary hydroxy group provided *N*-Cbz-L-statine (**131**) in 95% yield (Scheme 41).

L-Statine and its analogues were also obtained by Dellaria and Maki[51] as well as by Rich et al.[77]

A nonselective approach to the synthesis of another important unusual amino acid, bestatine,[78] was reported by Umezawa et al.[18b,79] Addition of sodium hydrogen sulfite to Cbz-D-phenylalaninal (**132**) afforded an

SCHEME 43[a]



[a] (a) (i) $ZnCl_2$, (ii) HCl; (b) (i) $NaIO_4$, $RuO_2 \cdot H_2O$ (cat.), (ii) HCl, (iii) CH_2N_2; (c) (i) Et_2NTMS, (ii) flash chromatography; (d) MeOH, *p*-TsOH (cat.); (e) (i) $KMnO_4$, NaOH(aq), (ii) HCl.

equimolar mixture of epimers **133**, which was transformed into a mixture of cyanohydrins **134**. Hydrolysis of **134**, followed by fractional crystallization, provided diastereoisomerically pure *N*-Cbz-D-bestatine (**135**) in 25% overall yield (Scheme 42).

The synthesis of *syn*-β-hydroxy-L-glutamic acid (**140**) was described by Garner.[80] Cyclocondensation of diene **73** with aldehyde **136** led to a >9:1 mixture of pyrones **137**. Subsequent oxidative degradation followed by esterification and protection of the hydroxy group led to compound **138**, which was converted to diol **139** and finally oxidized to afford the desired amino acid **140** (Scheme 43).

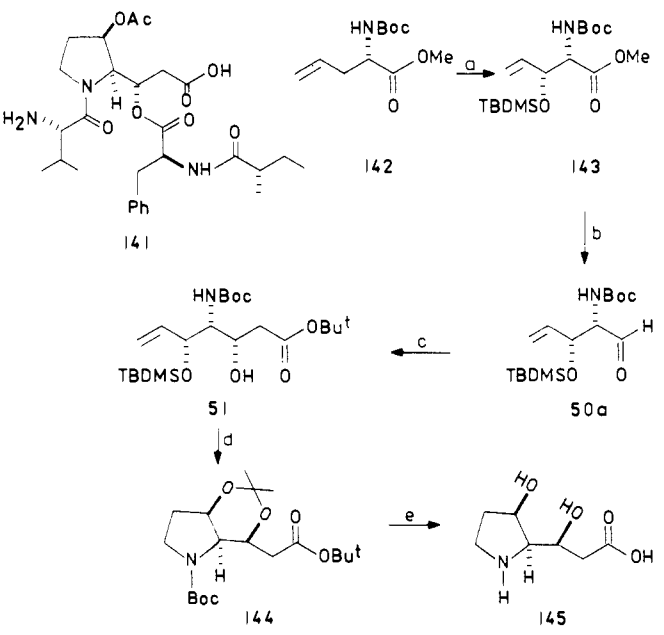
Detoxinine (**145**) is an amino acid component of detoxine (**141**), a selective antagonist of the antibiotic blasticidin S.[81] Recently, Ohfune and Nishio[33] presented a strategy for the synthesis of detoxinine (**145**). The starting material was Boc-L-allylglycine (**142**), which after allylic oxidation, followed by protection of the resulting hydroxy group afforded, after chromatographic separation, diastereoisomerically pure compound **143** in ca. 40% overall yield. Transformation of **143** into aldehyde **50a**, followed by its condensation with the lithium enolate of *tert*-butyl acetate, yielded, after chromatographic separation, the pure aldol product **51**; ozonolysis, Wittig homologation, and subsequent cyclization afforded compound **144**, which was finally deprotected to give the required detoxinine (**145**) (Scheme 44).

Another approach to the synthesis of detoxinine (**145**) was recently reported by Joullie et al.[29] The key step in this synthesis is a stereoselective aldol condensation of N,O-protected 3-hydroxy-L-prolinal with the chiral enolate derived from L-mandelic acid to afford the respective alcohol, which was transformed into detoxinine (**145**).

C. Amino Sugars

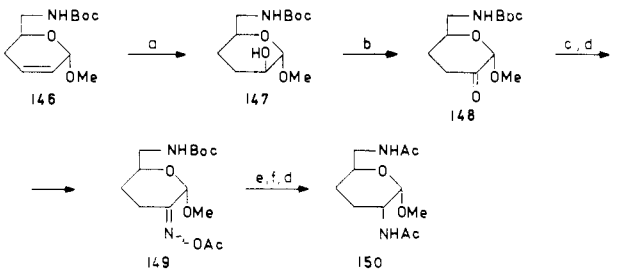
The modern approach to the synthesis of sugars via [4 + 2] cycloaddition[6,82] offers some new applications of N-protected α-amino aldehydes. The simplest nonchiral α-amino aldehyde, Boc-glycinal, was reacted with diene **84** under high-pressure conditions to afford after acidic isomerization the racemic adduct **146** in good yield.[83] Adduct **146** was the starting compound in the synthesis of D,L-purpurosamine C, which is one of the two sugar components of the aminoglycoside antibiotic gentamicin G_{1a}.[84] Hydroboration of adduct **146**, followed by oxidative workup, afforded alcohol **147**, which after oxidation yielded ketone **148**. Transformation of

SCHEME 44[a]



[a] (a) (i) SeO_2, Bu^{t}OH, (ii) TBDMSCl, imidazole; (b) (i) $LiAlH_4$, (ii) PDC; (c) LDA, AcOBu^t; (d) (i) O_3, (ii) DMS, (iii) Am^{t}ONa, $Ph_3P(Cl)CH_2OMe$, (iv) $Hg(OAc)_2$, (v) KI, (vi) $NaBH_4$, (vii) Ph_3P, NBS, (viii) NaH; (e) (i) CSA, (ii) TFA, (iii) 1 N NH_3.

SCHEME 45[a]



[a] (a) (i) $ThxBH_2$·DMS, (ii) H_2O_2, OH^-; (b) PCC, 4A molecular sieves; (c) NH_2OH·HCl; (d) Ac_2O, Et_3N; (e) BH_3·THF; (f) TFA.

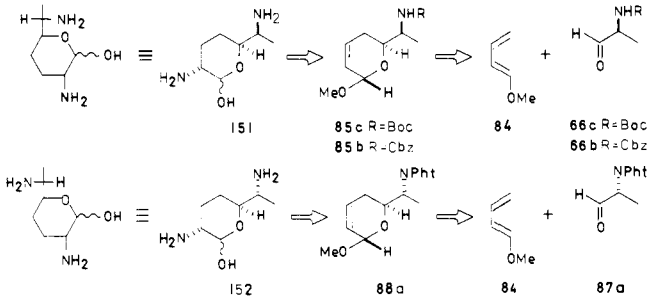
ketone **148** into an oxime, followed by acetylation, provided derivative **149**, which was readily converted to methyl *N*,*N*-diacetyl-D,L-purpurosaminide C (**150**) in 25% overall yield (Scheme 45).[85]

A similar approach was applied to the total synthesis of 6-*epi*-D-purpurosamine B (**151**)[15] and D-purpurosamine B (**152**),[58] the components of the aminoglycoside antibiotics fortimicin A and gentamicin C_2.[86] Starting from either N-protected L-alaninal (**66b,c**) or D-alaninal (**87a**) and controlling diastereoselectivity of the high-pressure [4 + 2] cycloaddition reaction with diene **84**, adducts **85b,c** and **88a** were obtained, respectively (cf. Scheme 25). These adducts were transformed via the above-presented route[85] into the desired derivatives of purpurosamines 6-epi B and B (Scheme 46).[15,58]

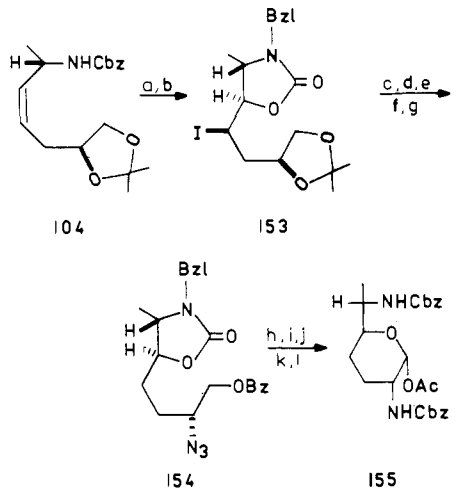
Another stereocontrolled synthesis of 6-epi-D-purpurosamine B derivative **155** was based on iodocyclocarbamation of olefin **104**, obtained from Cbz-L-alaninal (**66b**) via Wittig reaction (cf. Schemes 30 and 47).[65] The C-5, C-6, and C-7 carbon atoms derived from N-protected L-alaninal whereas the remaining part of the carbon skeleton originated from L-malic acid.

Retrosynthetic analysis of lincosamine (**156**), the sugar component of the antibiotic lincomycin[87] (Scheme

SCHEME 46

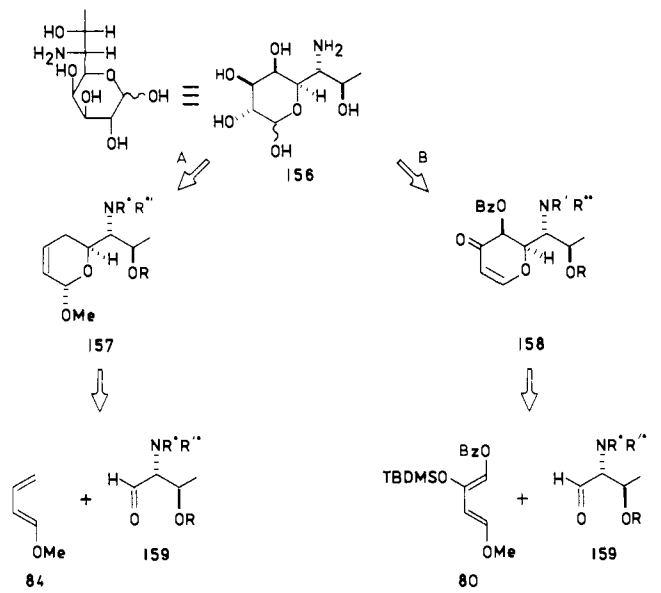


SCHEME 47[a]



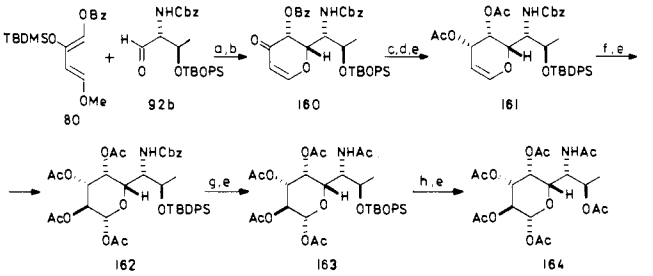
[a] (a) BzlBr, NaH; (b) I_2; (c) Bu_3SnH; (d) 1 N HCl; (e) PhCOCl, Et_3N; (f) MsCl, Et_3N; (g) NaN_3; (h) $Ba(OH)_2$; (i) $H_2/Pd(OH)_2$; (j) $ClCO_2Bzl$; (k) $RuCl_2(PPh_3)_3$; (l) Ac_2O, Py.

SCHEME 48



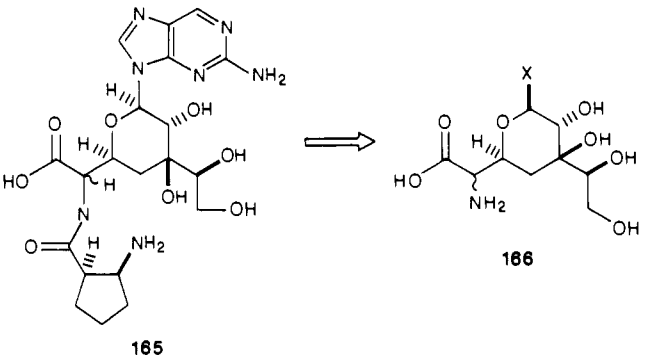
48), offers the possibility of application of a [4 + 2] cycloaddition reaction between dienes **80** or **84** and N,O-protected D-*allo*-threoninal **159** as the key step in the synthetic sequence. Moreover, the use of any one of the four threonine diastereoisomers, combined with stereocontrol of cycloaddition, permits an easy access to each diastereoisomer of lincosamine modified in the C-5, C-6, or C-7 positions.[58] These diastereoisomers of lincosamine, important in biological activity studies, are

SCHEME 49[a]



[a] (a) $ZnCl_2$; (b) TFA; (c) $NaBH_4$, $CeCl_3$; (d) NH_3, MeOH; (e) Ac_2O, Et_3N; (f) *m*-CPBA; (g) H_2/Pd–C; (h) Bu_4NF.

SCHEME 50



difficult to obtain by traditional methods.

Preliminary studies of the above-mentioned systems showed the predominance of the α-chelating interaction in the cyclocondensation step, resulting in high syn selectivity (cf. Scheme 26). Further transformations based on the Danishefsky et al.[88] approach afforded a diastereoisomer **164** of peracetylated lincosamine (Scheme 49).[58]

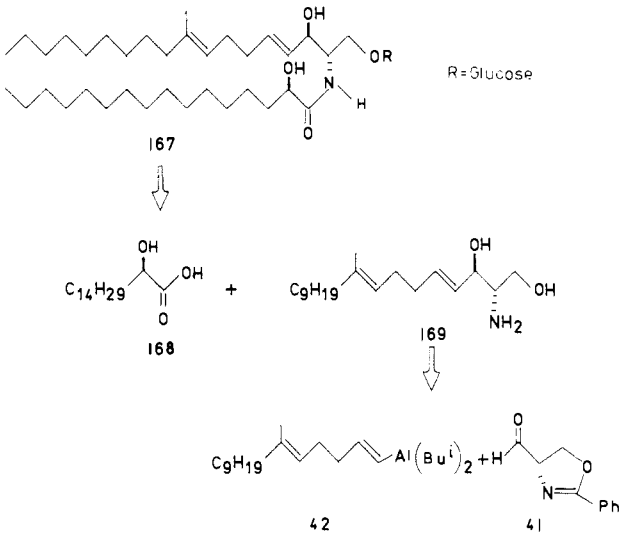
Recently Garner and Ramakanth[56] reported the results of preliminary studies on the total synthesis of the amino sugar related antibiotic amipurimycin (**165**).[89] Retrosynthetic analysis of the sugar part **166** of this antibiotic (Scheme 50) suggested the possibility of applying the cyclocondensation reaction between diene **73** and N,O-protected L-serinal **8** (cf. Scheme 22) as a way for construction of the sugar skeleton. The branching at the C-3 position in **166** can be introduced via a hydroxyl-directed Wittig reaction.[90]

D. Miscellaneous

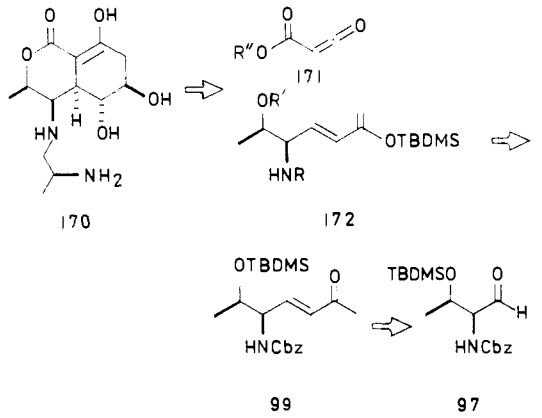
As shown above, N-protected α-amino aldehydes have been used mainly for the synthesis of peptide analogues, unusual amino acids, and amino sugars. Cerebroside (**167**)[91] is an example of a natural compound not belonging to those classes that is obtainable from an N-protected α-amino aldehyde. Retrosynthetic analysis of **167** (Scheme 51)[45-47] showed that amino diol **169**, a crucial intermediate for the synthesis of cerebroside, can be readily prepared by metallorganic addition to aldehyde **41** according to the procedure presented in Scheme 11.

Another application of chiral α-amino aldehydes in the total synthesis of natural products was recently reported by Kozikowski et al.[63] The synthesis of a broad-spectrum antibiotic, actinobolin (**170**),[92] was based on the [4 + 2] cycloaddition reaction of diene **172** with ketone **171** (Scheme 52). Compound **99**, a pre-

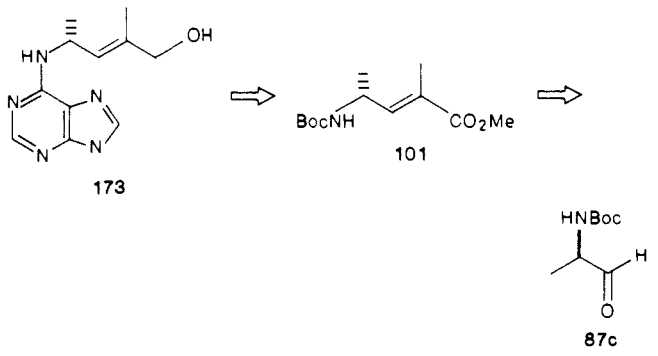
SCHEME 51



SCHEME 52



SCHEME 53

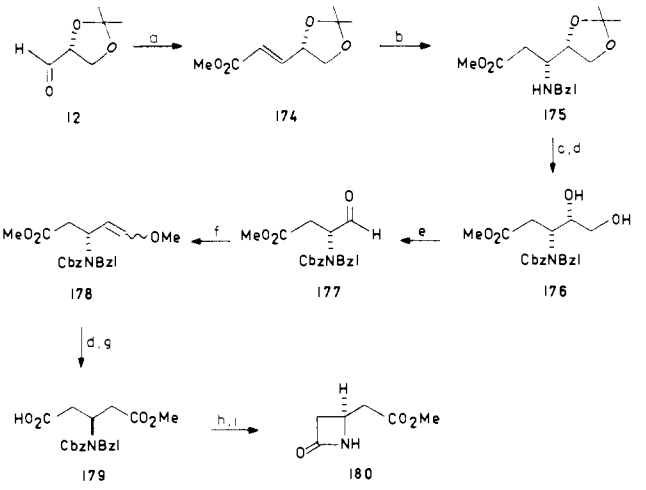


cursor of diene **172**, was obtained from N,O-protected L-threoninal **97** via the Wittig reaction as shown in Scheme 28.

Recently, Fujii et al.[64] described the total synthesis of 1′-methylzeatin (**173**), which is a new representative of cytokinins.[93] Retrosynthetic analysis (Scheme 53) showed that compound **101**, a key intermediate in this synthesis, can be easily obtained from Boc-D-alaninal (**87c**) by the procedure presented in Scheme 29.

(*S*)-4-((Methoxycarbonyl)methyl)-2-azetidinone (**180**), a crucial intermediate in the synthesis of (+)-thienamycin,[94] was obtained by Yamada et al.[95] from 2,3-*O*-isopropylidene-D-glyceraldehyde (**12**) (Scheme 54). In a sequence of five steps, compound **12** was transformed into α-amino aldehyde **177**, which via the Wittig reaction, followed by oxidation, was converted to the chiral monoester of the dicarboxylic acid (**179**). After deprotection of the amino group, compound **179** was cyclized to the desired azetidinone derivative **180**.

SCHEME 54[a]



[a] (a) BuLi, $Ph_3P(Br)CH_2CO_2Me$; (b) $BzlNH_2$; (c) $ClCO_2Bzl$; (d) 75% AcOH; (e) $NaIO_4$; (f) BuLi, $Ph_3P(Br)CH_2OMe$; (g) Jones reagent; (h) H_2/Pd–C; (i) Ph_3P–$(PyS)_2$, MeCN.

Apart from the above examples, some other natural products were synthesized by using N-protected α-amino aldehydes. Bleomycin, an antitumor antibiotic,[96] was obtained by Umezawa et al.[97] using as the key synthon (2*S*,3*S*,4*S*)-4-amino-3-hydroxy-2-methylpentanoic acid, readily obtainable from N-protected D-alaninal via aldol condensation.[18a] *N*-benzyl-*N*-tosyl-L-phenylalaninal (**105**)[66] was used for preparation of chiral diene, which was then applied in the total synthesis of cytochalasin C.[98]

VI. Conclusions

As can be seen from the above-presented literature data, N-protected α-amino aldehydes are versatile chirons, widely recognized, inexpensive, and easily accessible from natural sources. However, the degree of stereoselectivity obtained in some reactions shown is not high enough to meet the present requirements, and thus more work has to be done to elucidate the nature of all factors responsible for asymmetric induction. Higher stereoselectivities will surely extend the utility of these valuable chiral synthons. Finally, we believe that the near future will bring many more examples of synthetic sequences starting from N-protected α-amino aldehydes. The very recent papers published during the past few weeks seem to testify to our optimism.[99,100]

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