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ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS FROM CARBOHYDRATES AS CHIRAL TEMPLATES§

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1. INTRODUCTION. THE PROBLEM.

Asymmetric synthesis from carbohydrates has received an explosive interest during the last years, and actually enjoys an increasing renaissance due to the fascinating source of chirality of these compounds[1,2]. Two approaches can be performed to produce chiral molecules. Thus, the sugar is used as an external chiral auxiliary to induce the asymmetry in the target molecule, or as chiral pool in which, the synthesis of a target molecule can be designed so as to incorporate a chiral fragment whose absolute stereochemistry is already known. However, asymmetric synthesis from carbohydrate templates must be regarded under

§Dedicated to the memory of Prof. Toshio Goto.

the following limitations:

a) Several enantiomeric forms of sugars are not easily available. Thus, most L-sugars are unnatural products and they are exclusively obtained by chemical processes.

b) The starting sugar can be more expensive or more inaccessible than the optically active final product. This aspect is particularly important when a multistep synthesis must be planned from the commercially available sugar. In this case, another chiral auxiliary would be a better choice.

c) The suitable carbohydrate skeleton cannot provide all the requisite chiral centers and new asymmetric carbon atoms should be created, or the inherent chirality in any stereogenic center must be inverted. The so-called "off-template" problem can be resolved in some cases by synthetic manipulation[3].

d) The sugar as external chiral auxiliary reagent must be recoverable and recyclable, under ideal conditions.

Despite of these limitations, which are also shared by other chiral auxiliaries, carbohydrates provide the greatest range of homochiral precursors in a variety of acyclic and cyclic forms, chain lengths, desired functionality, and many sugars are cheap and accessible. Probably most target molecules can be constructed totally or in part using carbohydrate templates through careful examination of carbohydrate-type symmetry.

This report deals with the asymmetric synthesis of α-amino acids from carbohydrates as chiral templates. There are relatively few reports concerning the asymmetric synthesis of proteinogenic, natural L-, and unnatural D-amino acids from sugars. Amino acids are low-cost starting materials and commercially available substances of high optical purity. Also, their use as chiral auxiliaries is a common practice by chemists[4], including the synthesis of biologically important aminosugars[5], since carbohydrate-based chiral syntheses of these compounds often involve lengthy multistep sequences from rare and expensive sugars.

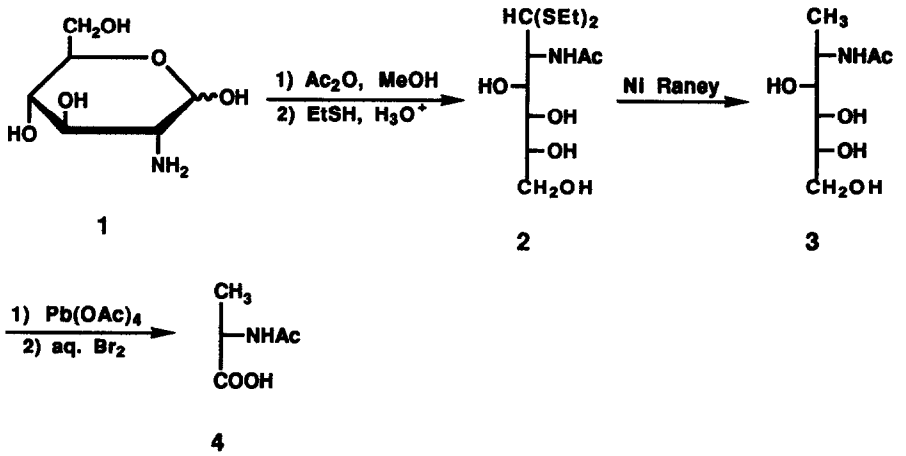
However, the preparation of complex and non-proteinogenic amino acids continues being an important synthetic challenge[6]. Carbohydrates represent an elegant and logical fashion to envisage the chemical solution. Syntheses of these amino acids are especially discussed in this paper. It is not the aim to provide a comprehensive account dealing with this topic. The examples are therefore representative cases, and illustrate the creativity in this field.

On the other hand, resolution of enantiomeric amino acids by means of sugar reagents represents a special topic, beyond the scope of this review, and it will not be discussed here.

2. α-AMINO ACID SYNTHESES.

Carbohydrates have proved to be extremely effective tools for establishing absolute configuration of natural products, including amino acids themselves. Thus, one classical demonstration of the use of sugars as chiral pool was the synthesis of N-acetyl-L-alanine, **4**, a

biological intermediate, from 2-amino-2-deoxy-D-glucose **1**[7]. The sense of chirality at C-2 carbon atom in the amino acid was easily correlated to that in the amino sugar. The acyclic dithioacetal **2**, underwent reductive desulfurization and further oxidative cleavage with lead tetraacetate, but the stereochemical correlation at C-2 was preserved (Scheme 1).



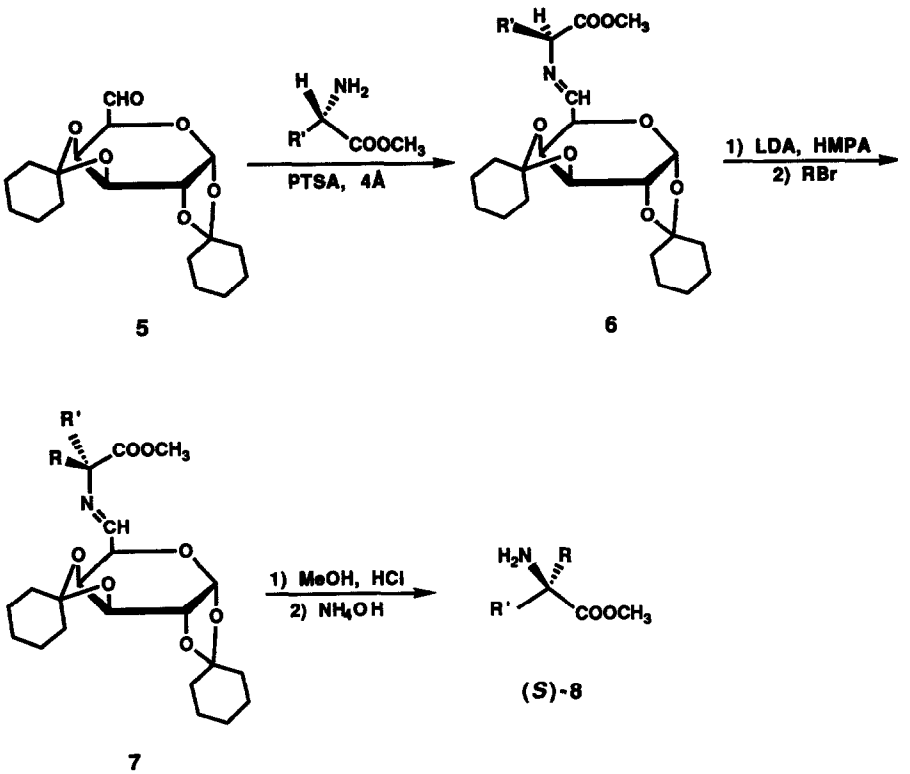
Scheme 1

By chemical interconversions involving especially 2-aminosugars, is possible to relate the stereochemistry of other α-amino acids[8]. The methodology has been also applied to other aminosugars and aminoglycosides[9].

One method particularly effective for inducing asymmetry in amino acid alkylation is to attach a bulky chiral auxiliary to the nitrogen atom, which thus will direct the approach of the alkylating agent from one side of the enolate. The following scheme illustrates such an approach, which has been employed by Schöllkopf[10] (Scheme 2). The Schiff base **6** of the 6-*aldehydo*-D-galactose derivative **5** and L-alanine methyl ester is formed in high yield in the presence of 4Å molecular sieves and a trace of *p*-toluenesulfonic acid. Metallation of **6** occurs smoothly with LDA at -75°C. Subsequent alkylation and further hydrolysis of the alkylated product **7** with hydrochloric acid in methanol furnishes (*S*)-α-methylamino acid methyl ester **8** (Table 1). The use of HMPA is critical for induction of the desired *S*-configuration in the intermediate **7**. In the absence of HMPA, the opposite *R*-configuration is favoured. Other bases such as potassium *tert*-butoxide or sodium hydride can be used in the metallation; however these lead to lower asymmetric induction.

This protocol was also applied to a set of α-alkylated *(S)*-valine, *(S)*-leucine, and *(S)*-isoleucine derivatives (Table 2). The enantiomeric excesses are generally moderate (23-80%) to excellent (90-96%), depending of the alkylating agent. This synthetic route provides access to

racemization-free α,α-disubstituted amino acids, and therefore the %de = %ee in every case.



5 6 7

Scheme 2

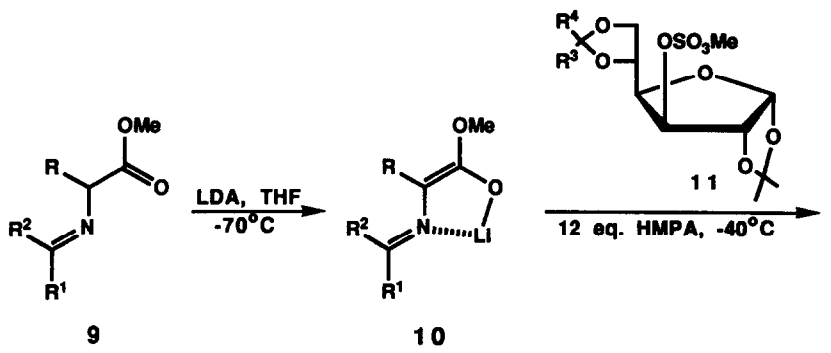
Table 1. α-Methyl-α-Amino Acid Methylesters (8)

R	R'	Yield (%7)	de (%)	Yield (%8)	ee (%)
$C_6H_5CH_2$	CH_3	83	83	72	83
$C_{10}H_7CH_2$	CH_3	78	78	70	78
3,4-dimethoxy benzyl	CH_3	85	85	84	85
$C_6H_5CH{=}CHCH_2$	CH_3	65	60	65	60
$CH_2{=}CH\text{-}CH_2$	CH_3	73	70	73	70
$HC{\equiv}C\text{-}CH_2$	CH_3	69	44	69	44

Table 2. α,α-Disubstituted α-Amino Acid Methylesters (8).

R	R'	Yield (%7)	de (%)	Yield (%8)	ee (%)
$C_6H_5CH_2$	$(CH_3)_2CH$	91	80	57	80
$C_{10}H_7CH_2$		91	>95	62	>95
$C_9H_6NCH_2$		92	74	75	74
4-$BrC_6H_4CH_2$		91	75	63	75
C_6H_5CH=CH		92	76	62	76
CH_2=CH-CH_2		80	76	75	76
CH_3		79	23	61	23
$C_6H_5CH_2$	$(CH_3)_2CHCH_2$	93	75	74	75
CH_2=CH-CH_2		90	57	78	57
HC≡C-CH_2		83	48	68	48
$C_6H_5CH_2$	$CH_3CH_2CH(CH_3)$	94	88	70	88
$C_{10}H_7CH_2$		96	96	68	96
$C_9H_6NCH_2$		92	90	74	90
CH_2=CH-CH_2		87	75	76	75
CH_3		82	29	86	29

With a related methodology, Duhamel and co-workers[11] have studied the asymmetric synthesis of amino acids *via* the electrophilic enantioselective alkylation of the enolates **10** derived from Schiff bases **9** of aminoesters by methyl sulfates derived from sugars **11** (Scheme 3).



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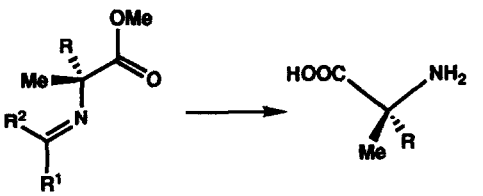


12 13

Scheme 3

Again, the use of HMPA as cosolvent was necessary and both the kinetic and the stereoselectivity were affected. The best enantiomeric excesses were obtained with the sulfates derived from D-(+)-glucose, and the major configuration of the amino acid was always *S*, except for the sulfate derived from β-D-fructopyranose, which was *R*. In the best cases the % ees were only moderate, from 40-76% (Table 3). In order to rationalize the observed stereoselectivity, the authors propose that the chelated lithium enolate coordinates to one of the sugar protective groups, and the preferential attack from one face is then favoured (Fig. 1).

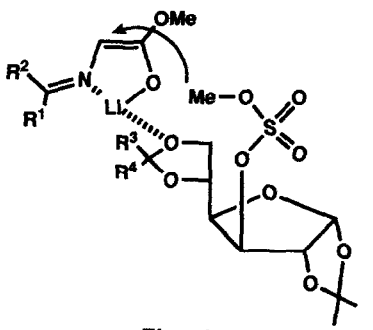
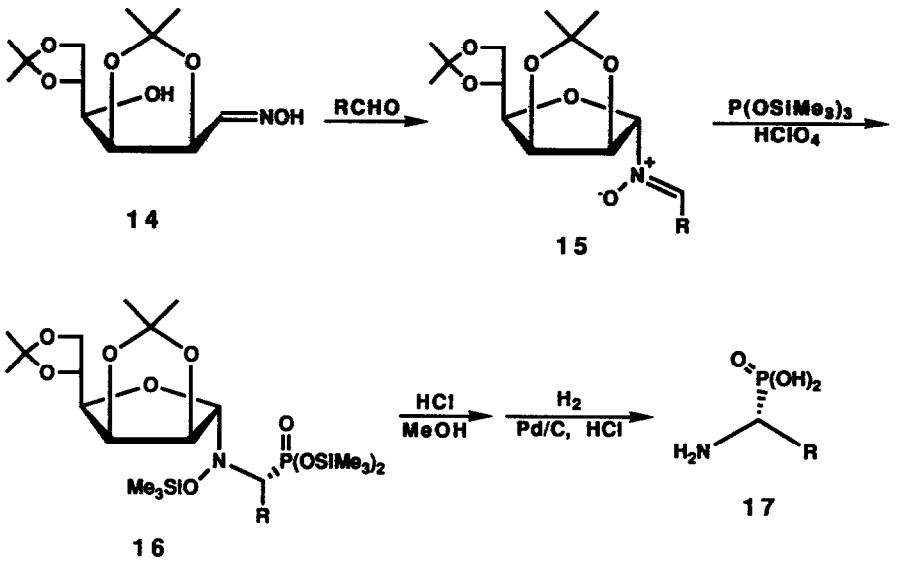


Fig. 1

Table 3. Enantioselective Alkylation of Enolates by Sugar Methyl Sulfates.

R^1	R^2	R^3	R^4	R	% ee (**13**)
C_6H_5	C_6H_5	CH_3	CH_3	H	40
C_6H_5	C_6H_5	CH_3	t-Bu	H	56
$C_6H_5NMe_2$	t-Bu	CH_3	CH_3	H	66
$C_6H_5NMe_2$	t-Bu	CH_3	t-Bu	H	76

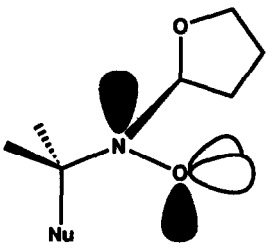
Carbohydrate nitrones and nitroso-sugars have been employed as chiral auxiliaries. Chiral aminophosphonic acids, *e.g. (R)*-**17**, have been obtained[12] in high enantiomeric excess by nucleophilic addition to N-glycosyl nitrones (**15**), as shown in the scheme 4. The C-phenyl-N-glycosylnitrone **15** (R = Ph), did not react with lithium dialkyl phosphites. The reaction with $P(OSiMe_3)_3$ in the presence of catalytic amounts of $HClO_4$ or $ZnCl_2$ gave the diastereomeric silyl esters, which were hydrolyzed with methanol at O°C.



Scheme 4

The conformation of the reacting nitrone has been rationalized on the basis of stereoelectronic and steric effects, which explain the diastereoselectivity observed. The authors propose an orbital interaction between the LUMO of the nitrone and the σ^*-orbital of the C(1)O-bond. NOE experiments indicated a preferred *O*-endo conformer in the ground state of nitrone, and furthermore corroborated by X-ray analysis and theoretical calculations. In this conformer, there is also a favorable effect of the interaction of the lone pairs on N and O atoms (Fig. 2).

Dipolar cycloaddition to related N-glycosyl nitrones has been applied in the synthesis of chiral Acivicin, as it will be outlined in a further scheme.



O-endo conformer

Fig. 2

A recent and conspicuous aymmetric synthesis of α-amino acids has been developed by Kunz and co-workers[13,14]. These authors have estudied the asymmetric Strecker synthesis using 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **18**, as the chiral matrix. Aldehydes react with **18** almost without anomerization to give the Schiff bases **19**, for which the *E*-geometry is proposed. Conditioned by a delocalization of the C=N π-electrons in the σ* orbital of the ring C-O bond, the imines **19** prefer a conformation in which the ring C-O bond is almost perpendicular to the plane of the double bond (Fig. 3).

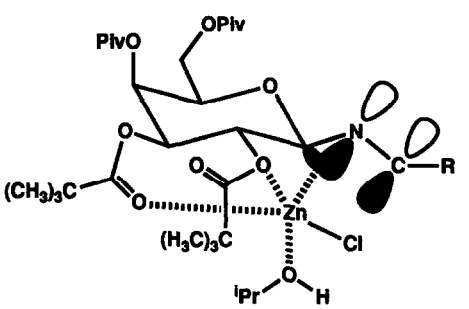
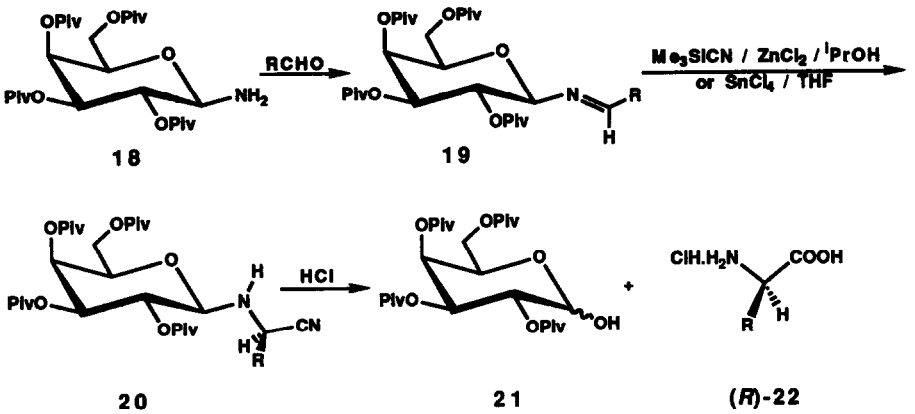


Fig. 3

This conformation is confirmed by a strong NOE effect in the ^{1}H-NMR spectrum between H-1 and the proton introduced by the aldehyde. The observed diastereoselectivity is supported by two hypotheses. Because of the large axial substituent at C-4 of the sugar, the Lewis acids complex the aldimines **19** from the bottom face. Also, the bulky pivaloyl group at C-2 hinders the attack from this side. The cyanide generated from the trimethylsilyl cyanide can approach from the opposite side, which results in the selective formation of the (*R*)-diastereomers.



Scheme 5

The synthetic strategy involves the diastereoselective addition of trimethylsilyl cyanide and a Lewis acid such as zinc chloride or tin tetrachloride, giving the α-amino nitriles **20** in high yields. The diastereomeric ratios lie in the range 6.5-13 : 1. The carbohydrate moiety is easily recovered after acidic hydrolysis, and the corresponding D-amino acid is obtained enantiomerically pure, even in the case of *p*-chlorophenylglycine (Table 4). Optical purity was established by optical rotations, which are in agreement with reported values. The absence of L-enantiomers was also confirmed by thin layer chromatography on chiral plates (Scheme 5).

Table 4. Diastereoselective Strecker Synthesis of N-Galactosyl-α-Aminonitriles (20)

R	Solvent	Catalyst (mol %)	Ratio (**20**) (*R* : *S*)	Yield (%*R*-**20**)
4-$CH_3C_6H_4$	i-PrOH	$ZnCl_2$ (100)	6.5 : 1	78
	THF	$SnCl_4$ (130)	12 : 1	87
4-$NO_2C_6H_4$	i-PrOH	$ZnCl_2$ (5)	7 : 1	80
2-$NO_2C_6H_4$	THF	$SnCl_4$ (130)	1 : 0	91
4-FC_6H_4	i-PrOH	$ZnCl_2$ (5)	6.5 : 1	75
	THF	$SnCl_4$ (130)	10 : 1	84
4-ClC_6H_4	THF	$SnCl_4$ (130)	11 : 1	84
$(CH_3)_2CH$	THF	$SnCl_4$ (130)	8 : 1	74
$(CH_3)_3C$	THF	$SnCl_4$ (130)	13 : 1	86

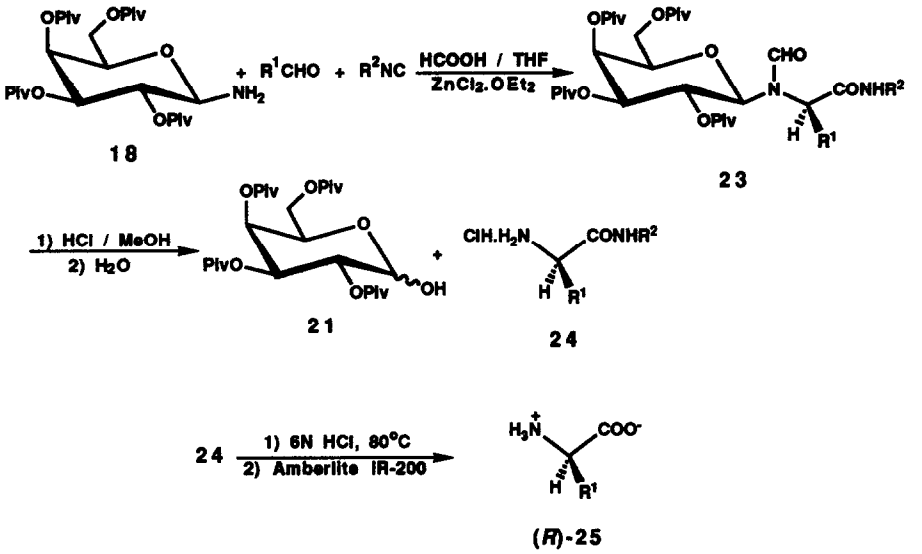
An interesting solvent effect has been observed[14]. When the diastereoselective addition to the Schiff bases is carried out using zinc chloride in isopropanol or tin tetrachloride in THF, the *R*-isomers are formed, but in chloroform solution using zinc chloride as the Lewis acid, a preponderance of the *S*-isomer results (Table 5). The authors demonstrated by ^{1}H-NMR that in both solvents (THF and chloroform) the imine **19** showed the same conformation. The reasons for this behaviour are not yet clear, but in any event this fact is an additional advantage of the synthesis, since the change of solvent allows for access to either D- or L-amino acids.

Table 5. Reverse Diastereoselective Strecker Synthesis of N-Galactosyl-α-Aminonitriles (20).

R	Solvent	$ZnCl_2$ (mol %)	Ratio (**20**) (*R* : *S*)
$(CH_3)_3C$	$CHCl_3$	5	1 : 9
$(CH_3)_2CH$	$CHCl_3$	100	1 : 5
$C_6H_5CH_2CH_2$	$CHCl_3$	100	1 : 3
4-$CH_3C_6H_4$	$CHCl_3$	100	1 : 4.5
4-FC_6H_4	$CHCl_3$	100	1 : 3
4-ClC_6H_4	$CHCl_3$	5	1 : 4
	$CHCl_3$	300	1 : 5
3-ClC_6H_4	$CHCl_3$	5	1 : 6
	$CHCl_3$	100	1 : 5

Kunz and Pfrengle[15,16] have also prepared *(R)*-α-amino acid derivatives stereoselectively by incorporation of the same carbohydrate template into the Ugi four-component reaction. These derivatives are readily converted to the *(R)*-amino acids themselves under acidic hydrolysis (Scheme 6).

In this asymmetric Ugi condensation, the galactopyranosylamine **18** is condensed with an aldehyde, an isonitrile, and zinc chloride (as the etherate) in formic acid to provide the Ugi intermediates **23**. These products are obtained in high yield and with an excellent kinetic ratio of isomers (~ 95 : 5). Also, **23** can be obtained diastereomerically pure by recrystallization (Table 6). Subsequent hydrolysis with methanolic hydrochloric acid affords the amides **24** and the *O*-pivaloyl-D-galactose **21**, which can be recovered and recycled to the chiral auxiliary **18**. Finally, the acidic hydrolysis of the amides **24** followed by ion-exchange provides the free amino acids **25**.



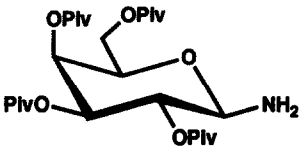
Scheme 6

Table 6. Diastereoselective Ugi Synthesis of N-Galactosylamino Acid Amides, (23).

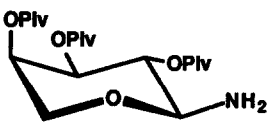
R^1	R^2	Ratio (23) (2*R* : 2*S*)	Yield (% 2*R*-23)	Yield (% 25)
$CH_3CH_2CH_2$	t-Bu	94 : 6	80	
$(CH_3)_2CH$	t-Bu	95 : 5	86	
$(CH_3)_3C$	t-Bu	96 : 4	80	90
$C_6H_5CH_2$	t-Bu	95 : 5	80	82
2-Furyl	t-Bu	95 : 5	90	
C_6H_5	t-Bu	91 : 9	81	85
4-Cl-C_6H_5	t-Bu	97 : 3	92	90
4-O_2N-C_6H_5	t-Bu	94 : 6	91	
$C_6H_5CH{=}CH$	t-Bu	95 : 5	75	
$NC(CH_2)_3$	Ph	93 : 7	80	87

The asymmetric Strecker and Ugi reactions reported by these workers, provide a possibility to prepare unusual *(R)*-amino acids. Although this one is the opposite configuration

of natural amino acids, a growing number of *(R)*-amino acids are being discovered in Nature, as constituents of bacterial cell walls or in peptide and depsipeptide antibiotics. However, a limitation of these protocols is due to the relative expense of the antipodal chiral auxiliary (L-galacto configuration) that would be required for the synthesis of the corresponding *(S)*-amino acids. Again, Kunz *et al.*[17] have solved this problem using 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine (**26**) as the chiral template. Although belongs to the D-series, this sugar is almost a mirror image of the D-galactosylamine **18**, except at C-6 carbon atom, where the functionalization is missing. But the requisite functional groups for the stereodifferentiation are present[13].



18



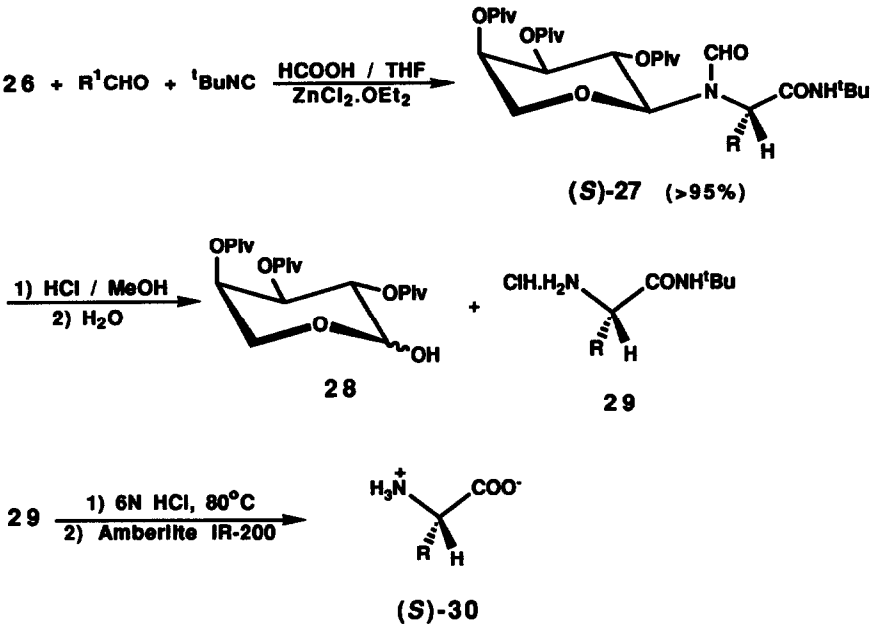
26

This carbohydrate template, **26**, was used in Ugi condensations with aldehydes, *tert*-butyl isonitrile, and formic acid in the presence of zinc choride in THF. The reactions are generally complete after 24 h, even at -25°C. The corresponding amides **27** are formed with an excellent diastereomeric ratio, in the range from 22 to 30 : 1, determined by HPLC analysis of the crude products. These amides **27** are easily converted to the free *(S)*-amino acids **30**, by application of the acidic hydrolysis (Table 7). Again, the chiral template can be recovered almost quantitatively (> 95%) and recycled to the starting auxiliary (Scheme 7).

Recently, Kunz[18-20] has also employed a related route to obtain enantiomerically pure homoallyl amines and β-amino acids, using the diastereoselective Lewis acid induced addition of allylsilanes and allylstannanes to Schiff bases **19**, which illustrates again the versatility of this process.

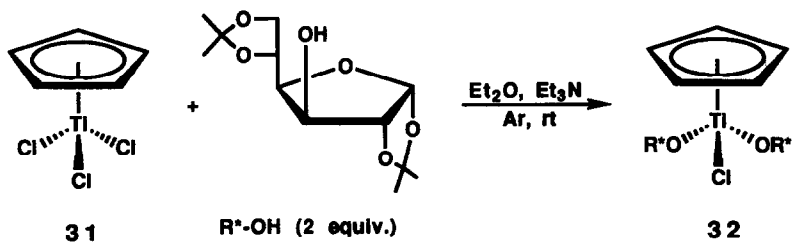
Table 7. Diastereoselective Ugi Synthesis of N-Arabinopyranosylamino Acid Amides, 27.

R	Ratio (**27**, 2*S* : 2*R*)	Yield (% 2*S*-**27**)	Yield (% **30**)
$(CH_3)_3C$	97 : 3	85	70
$C_6H_5CH_2$	97 : 3	87	82
4-ClC_6H_4	98 : 2	91	85
2-Furyl	96 : 4	85	



Scheme 7

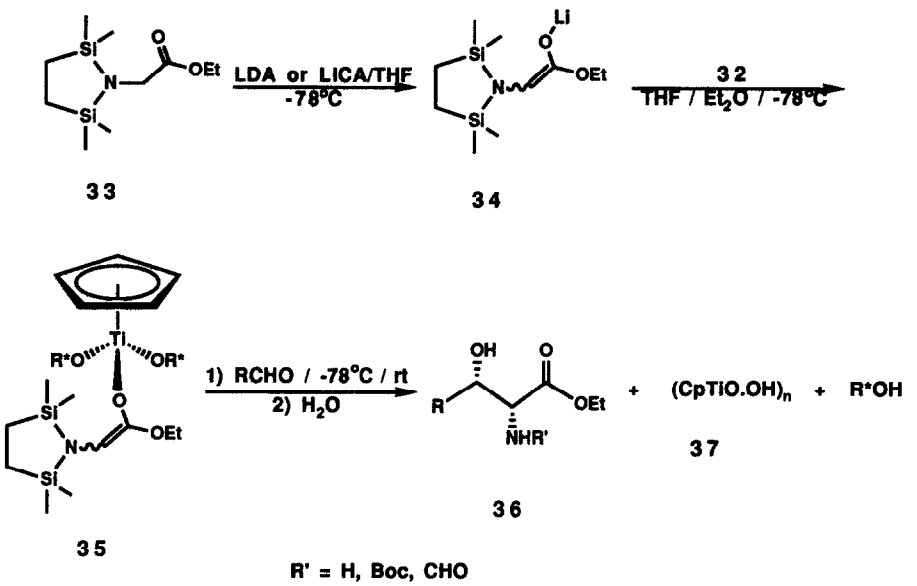
Another outstanding enantioselective synthesis of α-amino acids has been reported by Duthaler, Riediker and co-workers[21,22] utilizing titanium-carbohydrate complexes. A new chiral titanium compound has been developed to promote highly enantioselective allylation of carbonyl compounds[23] and aldol reactions[24]. The compound is a dicarbohydrate chlorocyclopentadienyl titanate **32**, synthesized by reaction of cyclopentadienyl titanium (IV) trichloride, **31**, with the readily available diacetone-glucose (Scheme 8). Reagent **32** is stable under argon in the absence of moisture.



31 R*-OH (2 equiv.) **32**

Scheme 8

The route to enantioselective synthesis of D-*threo*-β-hydroxy-α-amino acids involves the formation of the lithium enolate **34** of the ethyl(aza-disilacyclopent-1-yl)acetate **33**, which can be transmetalated in a slow reaction by the chiral titanate **32**. Subsequent aldol reaction of the titanium enolate **35** yields the corresponding amino acid esters **36**, with high stereoselectivity (Scheme 9).



Scheme 9

The %ees are good to excellent (78-98%). The free amino acid esters **36** can be isolated, but authors recommend to protect the amino function as *tert*-butyl carbamates (R' = Boc group) or as formamides (R' = CHO) (Table 8).

The titanate **37** that precipitates upon hydrolysis can be separated by filtration and converted into the cyclopentadienyltitanium (IV) trichloride **31**, the starting material for the preparation of chiral reagent **32**. By extraction the diacetone-glucose can also be separated from the polar water-soluble amino acids.

The X-ray crystal structure of **32** was determined, showing a monomeric complex. The two alkoxy groups are arranged in an *anti* conformation. The dioxolane ring (with C-5 and C-6 of the glucose) of one sugar ligand is facing towards the cyclopentadienyl ring, whereas in the other ligand, it is situated opposite to the Cp ring. NMR studies indicated that in solution the compound exists in a single conformation[22]. Different sets of signals were observed for the two carbohydrate ligands of complex. The assignment of resonances were established by means of COSY and NOE experiments. Since no NOEs were observed between

protons of different sugar moiety, these two ligands must be spatially separated. The single conformation was also elucidated by NMR measurements at variable temperatures, which gave no information of an inversion at the metal center. Other conformational isomers were not detected, even at -100°C, indicating a rigid conformation in solution.

Table 8. Enantioselective Synthesis of D-*threo*-β-Hydroxy-α-Amino Acid Derivatives From Titanium-Carbohydrate Complexes.

R	R'	Product	Yield (%)	de (%)	ee (%)
CH_3	Boc	36a	53	>98	97
$CH_3CH_2CH_2$	Boc	36b	66	>98	98
$(CH_3)_3C$	Boc	36c	43	>96	96
CH_2=CH	Boc	36d	48	>97	97
$(CH_3)_2C$=CH	Boc	36e	57	99	98
	CHO	36f	61	99	98
	H	36g	45	99	98
C_6H_5	Boc	36h	60	>96	97
CH_3OCO	CHO	36i	70	87	78
$(CH_3)_3COCO$	CHO	36j	66	>96	87

As additional advantages to high stereo- and chemoselectivity, the auxiliaries are relatively inexpensive and available reagents, which can be also recovered. The reagent **32** is *re*-selective, as shown the simple examination of the possible intermediate (Fig. 4).

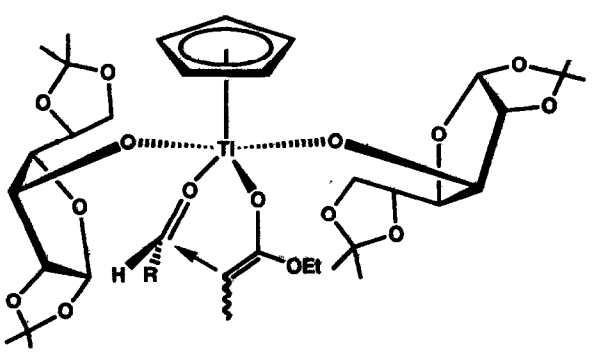
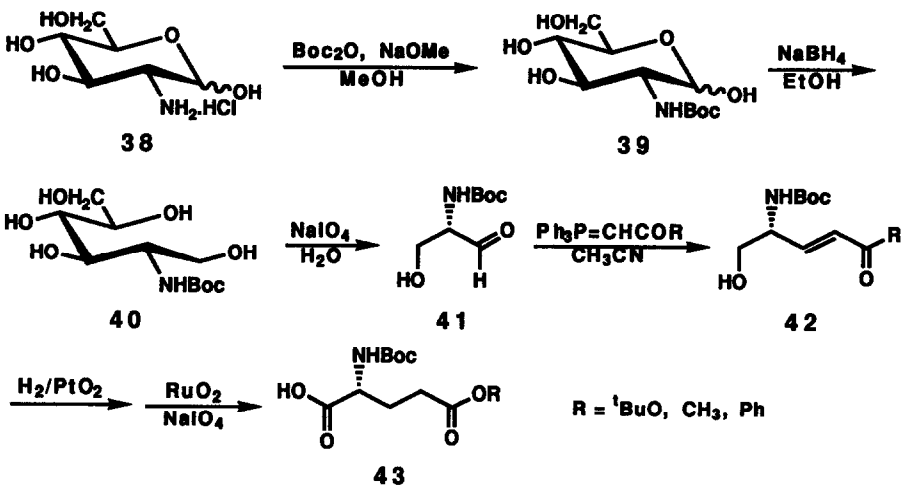


Fig. 4

The *si*-selective diastereomer would be provide the corresponding amino acid isomers, but again the expensive L-glucose is necessary. This Ciba-Geigy group is searching alternative reagents for this purpose.

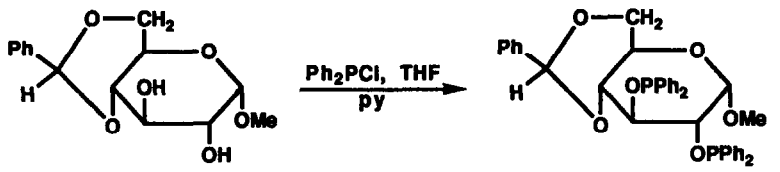
D-Glucosamine has been recently utilized as starting material in a chirospecific synthesis of amino acids, amino aldehydes, and amino alcohols[25]. In three steps, the commercially available D-glucosamine hydrochloride **38** is converted into the crystalline N-*tert*-butyloxycarbonyl-L-serinal **41**. This amino aldehyde was further transformed into amino acid derivatives **43**. Although only three examples are reported, the method demonstrates the suitability of **41** for the synthesis of D-amino acids (Scheme 10).



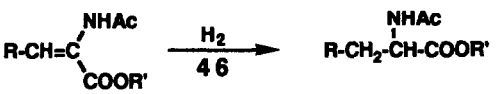
Scheme 10

The previously reported asymmetric syntheses involve a stoichiometric methodology. Chiral sugar organometallic complexes have been also utilized in the synthesis of optically active amino acids, particularly in asymmetric hydrogenations. Thus, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**44**) was converted into methyl 2,3-bis-*O*-diphenylphosphino-4,6-*O*-benzylidene-α-D-glucopyranoside (**45**), by chlorodiphenylphosphine in the presence of pyridine. This compound can be easily purified by reprecipitation and it is stable in air. A cationic complex (**46**), $[(PO\text{-}OP)Rh(NBD)]PF_6$ was prepared by the reaction of **45**, $[(NBD)RhCl]_2$ and $AgPF_6$ in acetone for 24 h (NBD = norbornadiene). This complex was used in the asymmetric hydrogenation[26] of the α-acetamidoacrylic acids and their esters (**47**) (Scheme 11). The reaction is quantitative and rapid at low temperatures (-20 to 30°C). The %ees are moderate to good (Table 9), and the authors noted the high conformational rigidity of the ligand. The amino acid derivatives have the natural *S*-

configuration. However, substrates having no acetamido group are not hydrogenated by this system, which is a limitation of this protocol. Apparently, the acetamido group is essential for hydrogenation due to a strong coordination of both the olefin bond and acetamido group to the rhodium.



44 45

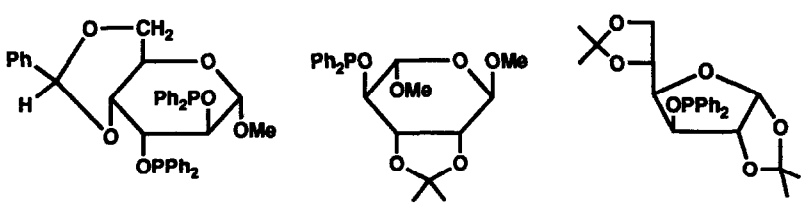


47 48

46 = [(sugar)Rh(NBD)]PF_6

Scheme 11

Other homogeneous asymmetric hydrogenations of dehydroamino acids as well as other prochiral olefins, were carried out using Rh(I) catalysts. These were prepared from chiral phosphinite derivatives of carbohydrates[27-31], such as the compounds (**49**)-(**51**) among others. In the best cases, only moderate %ee were reported.



49 50 51

Table 9. Asymmetric Hydrogenation of α-Acetamidoacrylic Acids and Esters (48).

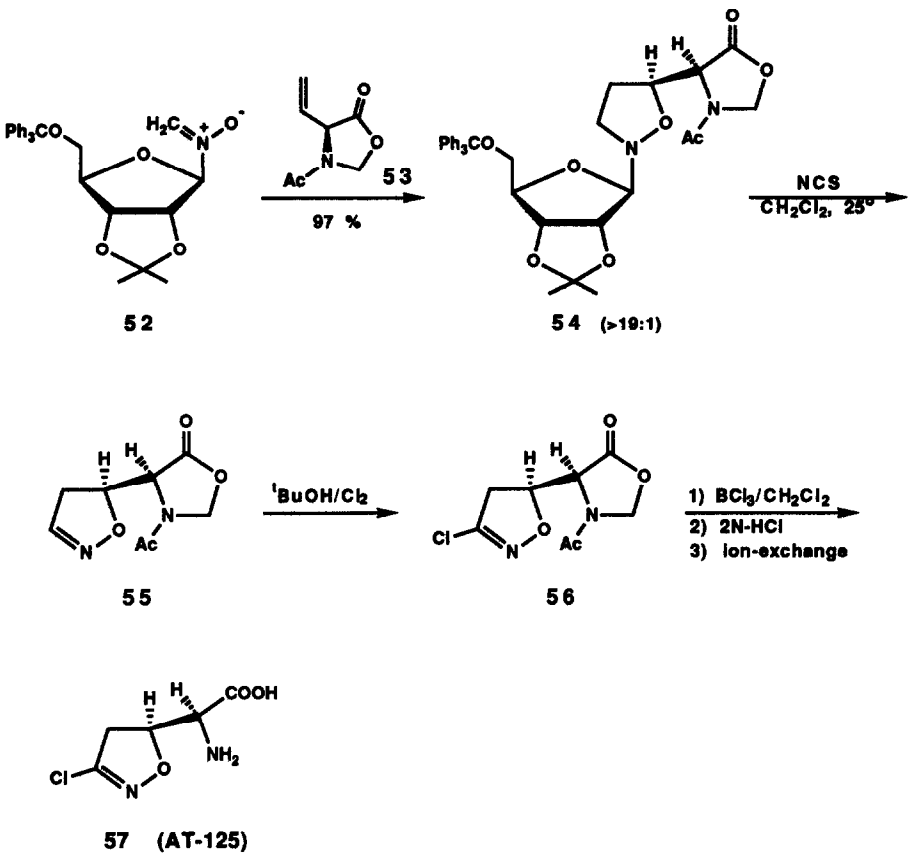
R	R'	Ratio (47 : 46)	Temperature (°C)	Time (min)	ee (% (*S*)-48)
H	H	40	30	20	67
H	H	100	30	20	68
H	H	100	0	30	74
H	H	100	-20	60	80
Ph	H	100	30	60	61
Ph	H	100	0	90	75
H	Me	100	30	10	53
H	Me	100	0	30	78
Ph	Me	100	30	30	60
Ph	Me	100	0	180	65

3. COMPLEX AMINO ACIDS

3.1. Acivicin.

Acivicin (AT-125) is an antitumor amino acid antibiotic isolated at the UpJohn Co. in 1973 from *Streptomyces Sviceus*. The first total synthesis was carried out by Kelly *et al*[32]. Several syntheses have been reported[33] to date with different stereoselectivity of the requisite α*S*,5*S* configurations.

As indicated above, a highly diastereoselective synthesis on a carbohydrate template is the dipolar cycloaddition of the N-glycosyl nitrone **52** with the (2*S*)-vinylglycine derivative[34] **53** (Scheme 12). The key step in this synthesis is the employment of double asymmetric induction, which provides an excellent facial selectivity (> 19 : 1) in high yield. The authors also indicated that the optimum stereoselectivity is kinetically controlled and that variations in reaction conditions may alter this selectivity. Thus, prolonged reaction times for the cycloaddition led to a decrease in diastereoselectivity from > 19 : 1 to 6 : 1. Further oxidation with NCS afforded the desired isoxazoline **55**, which was chlorinated and deprotected to give (+)-Acivicin (**57**). The overall yield is 39% starting from the (2*S*)-vinylglycine derivative.

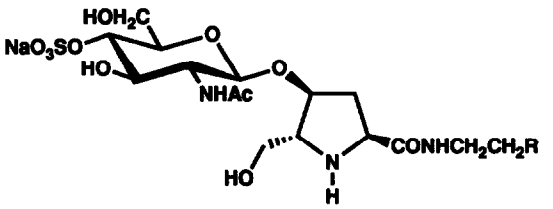


Scheme 12

3.2. Bulgecinine.

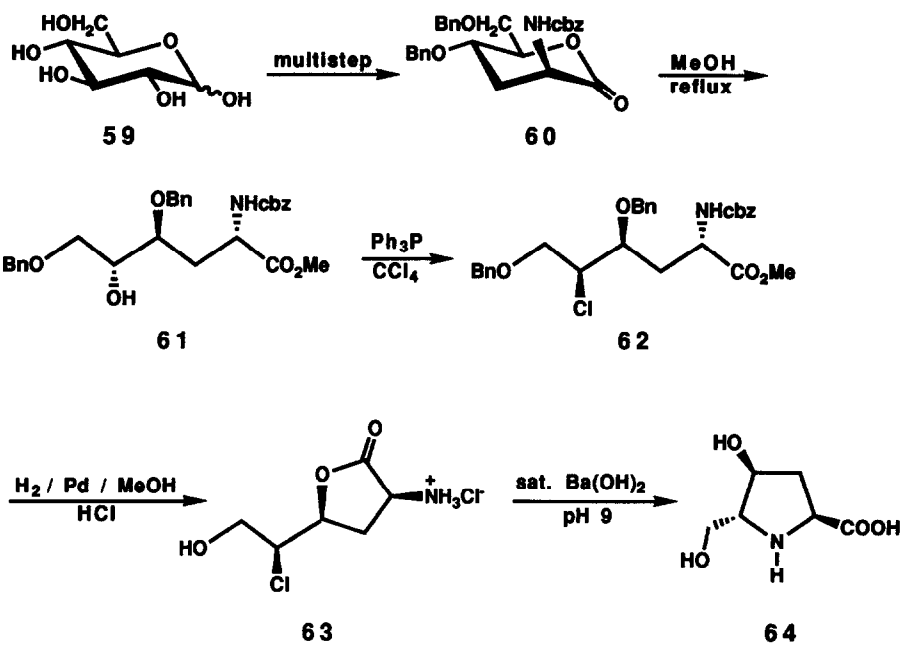
Bulgecin (**58**) is a new class of glycoside antibiotics. They were found in *Pseudomonas acidophila* and *Pseudomonas mesoacidophila* cultures[35]. Although bulgecins themselves show no antibacterial activity, in combination with β-lactam antibiotics, the biological activity is enhanced.

Bulgecins contain a new proline-derived amino acid called bulgecinine (**64**). Several and elegant syntheses from non-carbohydrate precursors have been carried out, especially by Ohfune *et al*[36]. Shiba and co-workers[37] have synthesized bulgecinine from D-glucose (Scheme 13).



58 { A, R=SO3H ; B, R=CO2H }

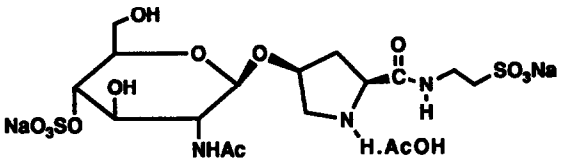
Employing well-established methodology,the starting and inexpensive D-glucose was transformed into the lactone **60**. Ring-opening to the protected amino acid **61**, and conversion into the chloride **62** was achieved with triphenylphosphine in carbon tetrachloride, accompanying an inversion of the configuration on δ-carbon atom. Cyclization gave the lactone **63** and then the desired bulgecinine **64**.



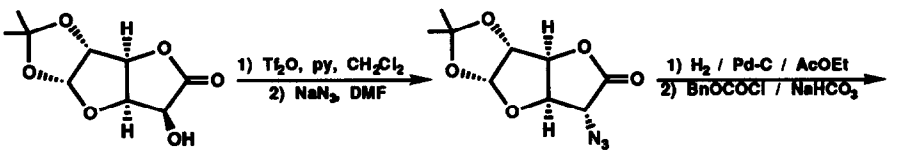
Scheme 13

Shiba[38] has also performed the synthesis of dehydroxymethylbulgecin A (**65**), which was prepared as disodium and monoacetic acid salts, utilizing D-glucosamine hydrochloride as

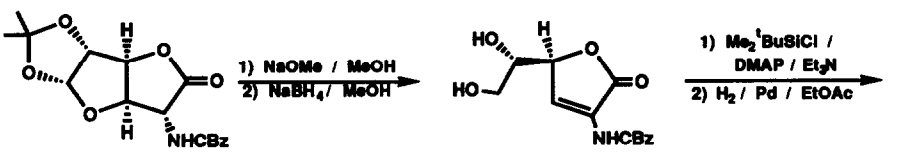
the chiral template.



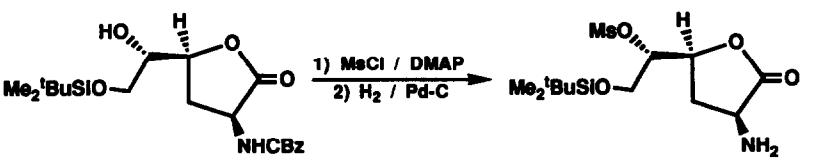
65



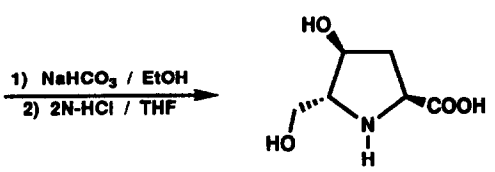
66 67



68 69



70 71

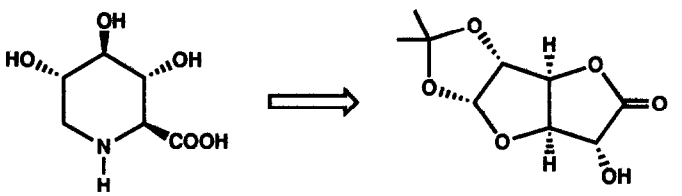


64

Scheme 14

Bulgecinine, as well as other related pyrrolidines, has been also prepared by Fleet *et al*[39] from D-glucuronolactone (Scheme 14). Its isopropylidene derivative **66** was transformed into the azide **67** with inversion through the corresponding triflate. After conventional methods of hydrogenation, acylation, elimination and reduction, the lactone **69** was obtained in high overall yield. The next step involves a stereospecific catalytic hydrogenation, which occurs from the least hindered face to give **70**. Transformation into the mesylate followed by deprotection at the nitrogen atom and cyclization provided bulgecinine (**64**), in 26% overall yield from the precursor **66**.

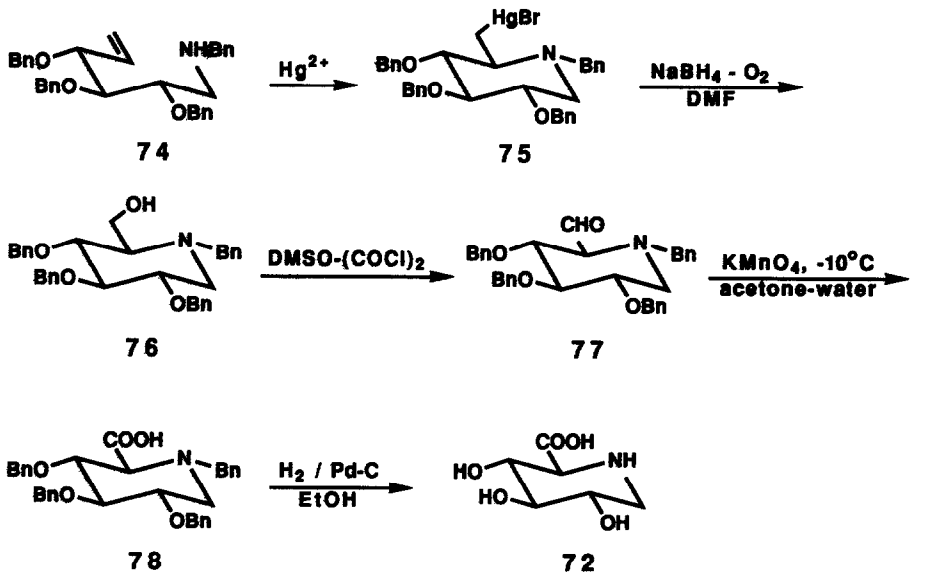
With the same methodology, Fleet and co-workers[39] have also prepared the naturally occurring trihydroxypipecolic acid **72**, a β-D-glucuronidase inhibitor isolated from the seeds of *Baphia racemosa*. The starting sugar precursor was the derivative **73**.



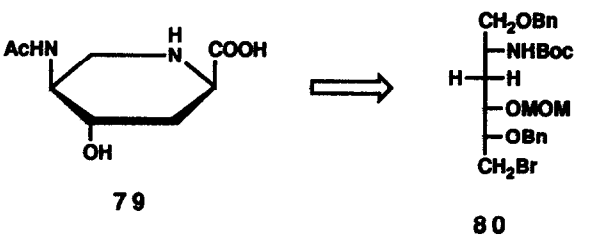
72 **73**

This glucuronidase inhibitor, an acid analog of 1-deoxynojirimycin, has been also prepared[40] using mercuric-ion-induced cyclization of an acyclic precursor (**74**) derived from D-glucose (Scheme 15). The bromomercurial **75** was reductively oxygenated to alcohol **76** in good yield. Oxidation to acid was accomplished in two steps. Swern oxidation provided the sensitive aldehyde **77**, which was immediately oxidized to acid **78** with potassium permanganate in aqueous acetone at -10°C. Debenzylation by hydrogenolysis in ethanol gave the trihydroxypipecolic acid (**72**).

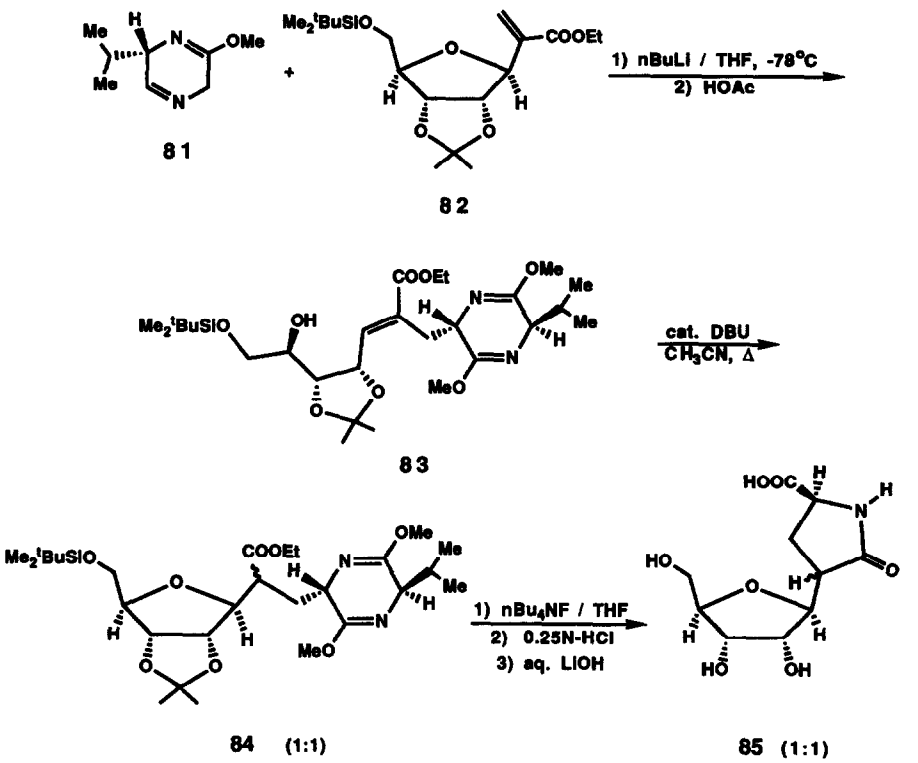
The importance of these substances is shown by the synthesis of analogous compounds. Thus, the pipecolic acid derivative **79**, which is also a nitrogen-containing sugar ring, has been synthesized as a potential sialidase inhibitor[41]. The route proceeded from D-glucosamine *via* intermediate **80**, which was cyclized between N-2 and C-6, and nitrogen introduced at C-5 with inversion of configuration.



Scheme 15



Baldwin *et al*[42] have employed the addition of Schöllkopf's glycine anion equivalent (**81**) to the ribosyl acrylate **82** to give the adduct **83** (53% yield) as a single stereoisomer. Further treatment of **83** with a catalytic amount of DBU afforded **84** as a 1 : 1 diastereomeric mixture. Desilylation, hydrolysis, and base-catalyzed ring closure gave again a 1 : 1 diastereomeric mixture of L-(3*R* and 3*S*)-(β-D-ribofuranosyl)pyroglutamic acids (**85**), in a 23% combined yield from precursor **81**. Spectroscopic data strongly support the assignment of the β-configuration to both products. These compounds have been suggested as intermediates in the biosynthesis of all naturally-occurring C-nucleosides, such as showdomycin or formycin (Scheme 16).



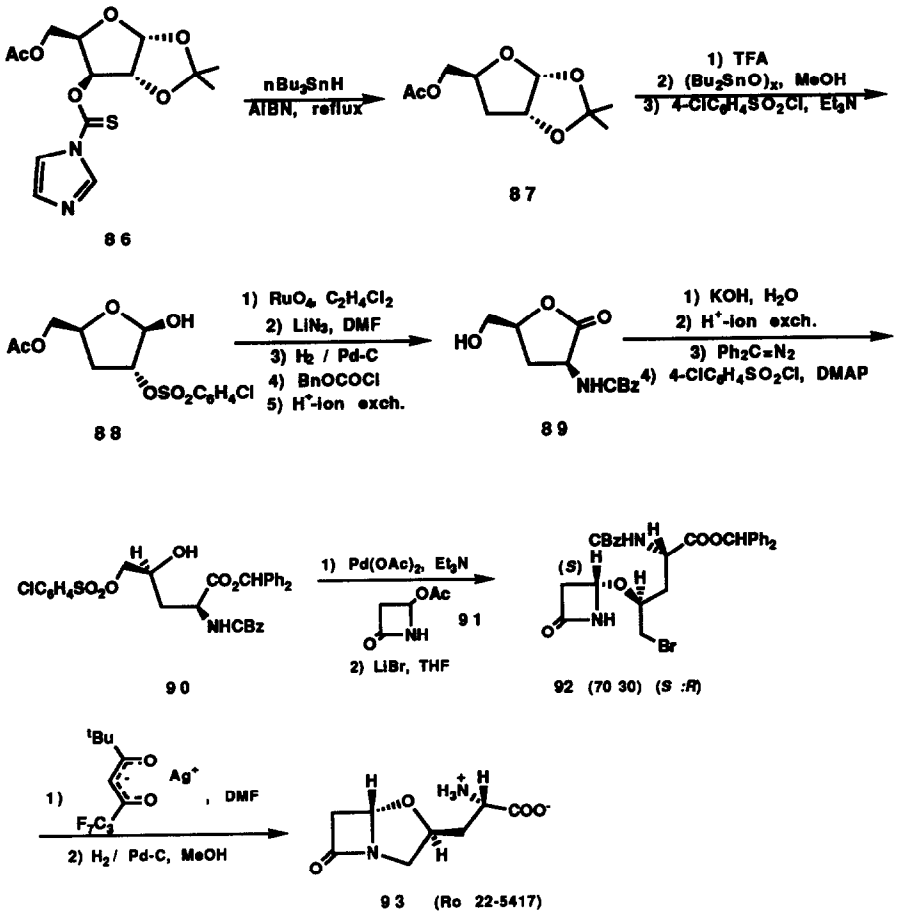
Scheme 16

3.3 Clavalanine.

Clavalanine (Ro 22-5417) (**93**), is an unusual amino acid, which has also a β-lactam structure. It was isolated from *Streptomyces clavuligerus*[43]. The structure and absolute stereochemistry were determined by total synthesis and chiroptical methods. Although clavalanine is structurally related to clavulanic acid, has the unusual (*S*)-stereochemistry at the ring juncture, unlike all the β-lactam antibiotics, which is (*R*). The biological properties are due, in part, to this feature. This compound does not block the peptidoglycan synthesis (common bacterial cell wall), and is neither a substrate of β-lactamase enzymes.

A total synthesis of clavalanine has been performed from D-xylose[44]. Its protected derivative **86** was reduced and then transformed into the sulfonate **88**. Ruthenium-mediated oxidation to the lactone and subsequent S_N2 displacement of the sulfonate, reduction and acylation gave **89**. This versatile intermediate was transformed into the protected amino acid

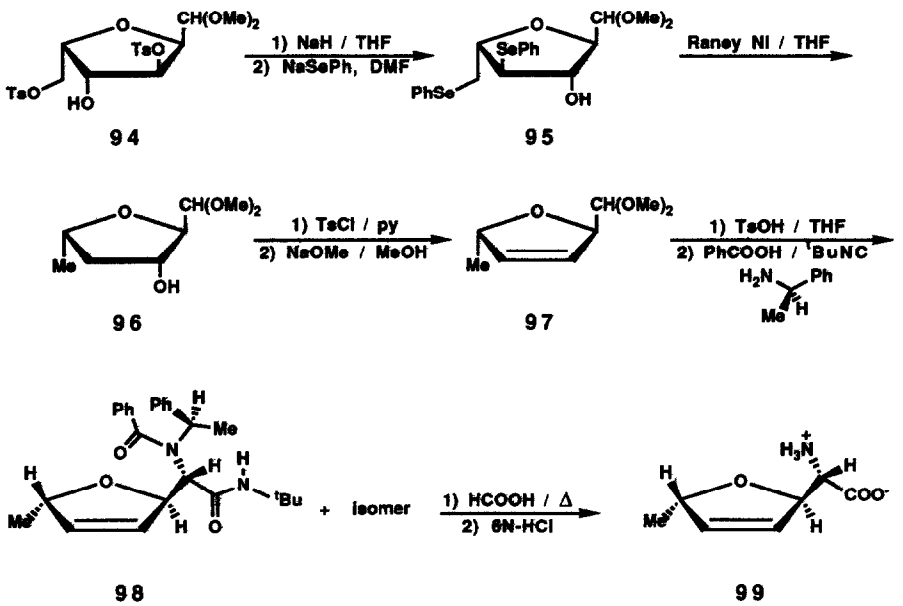
90. This key compound was coupled with acetoxy azetidone, **91**, in the presence of palladium acetate, and the sulfonate was displaced by lithium bromide, which provided **92** as a 70 : 30, (*S*) : (*R*)-mixture. The final and desired cyclization to clavalanine (**93**), was performed with silver 2,2-dimethyl-6,6,7,7,8,8,8,-heptafluoro-3,5-octanedioate, followed by debenzylation (Scheme 17).



Scheme 17

3.4 Furanomycin.

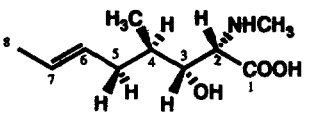
Furanomycin (**99**), is a naturally occurring α-amino acid antibiotic obtained from *Streptomyces threomyceticus*. A total synthesis has been developed by Joullie *et al*[45] from the glucofuranose derivative **94**, correcting also the previously assigned stereochemistry. The compound **94** was converted into the diselenide **95** in quantitative yield, *via* the 2,3-epoxide which is opened regioselectively, due to a preferred steric approach at C-4 atom. Reduction and elimination, under well-established conditions, afforded **97**. It was subjected to the Ugi four component reaction with (+)-α-methylbenzylamine, to give a 1 : 1 diastereomeric mixture (**98**). After separation by chromatography, the desired stereoisomer was deprotected and transformed into the (+)-furanomycin (**99**), the naturally occurring isomer. The overall yield from D-glucose is 6% (Scheme 18).



Scheme 18

3.5 MeBmt.

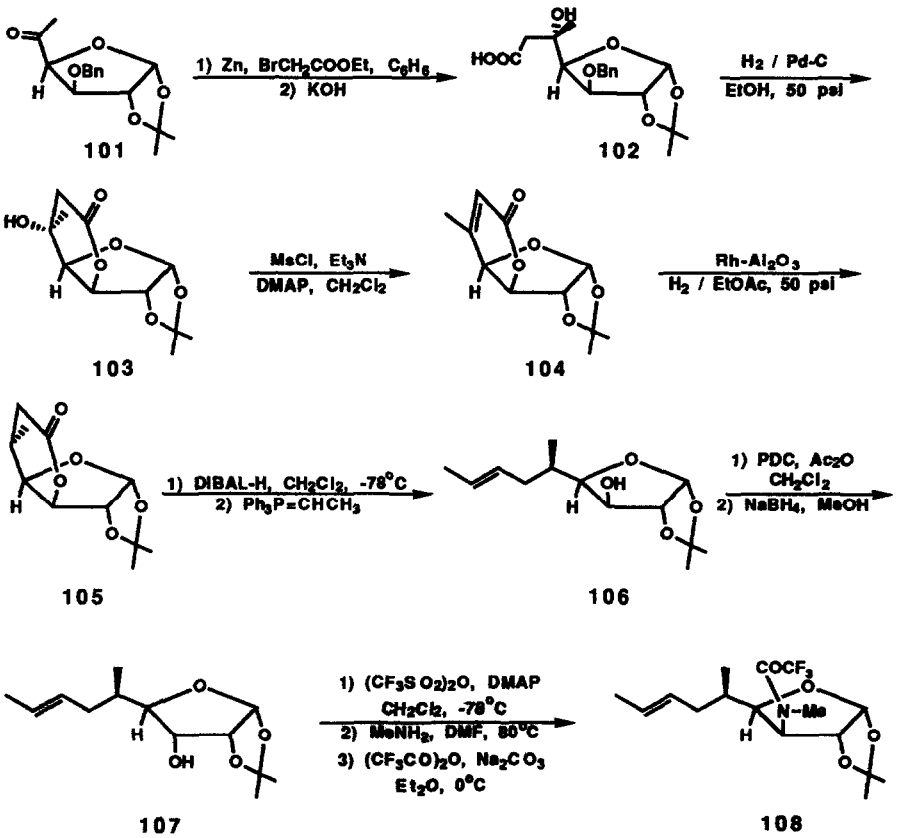
MeBmt, (4*R*)-4-[(*E*)-2-butenyl]-4-N-dimethyl-L-threonine (**100**), is an unusual N-methylated amino acid, which was found for the first time in the immunosuppressive agent Cyclosporine. It has never previously been isolated or known in free form.

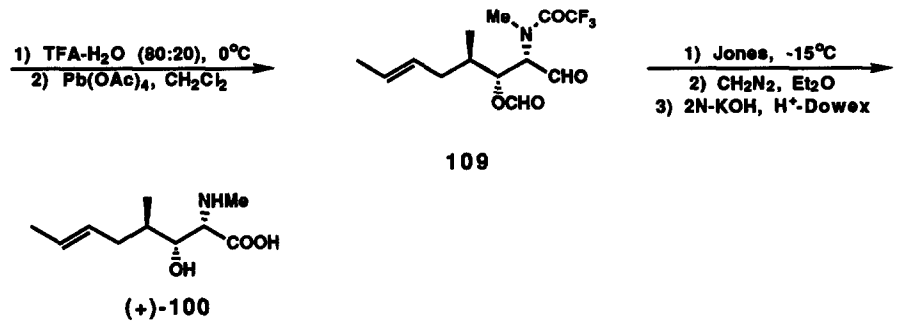


(2*S*, 3*R*, 4*R*, 6*E*)

100 (MeBmt)

The first synthesis of MeBmt was developed by Wenger[46] in 1983 at Sandoz Ltd., from tartaric acid, and then incorporated to the total synthesis of Cyclosporine[47]. This unusual amino acid also occurs as the N-acetyl derivative[48]. Although Wenger demonstrated that MeBmt itself has no immunosuppressive activity, it is of critical importance in the chemotherapeutic action of Cyclosporine[47,49]. Many and elegant syntheses of MeBmt have appeared in the literature[50], and actually is also a synthetic target.





Scheme 19

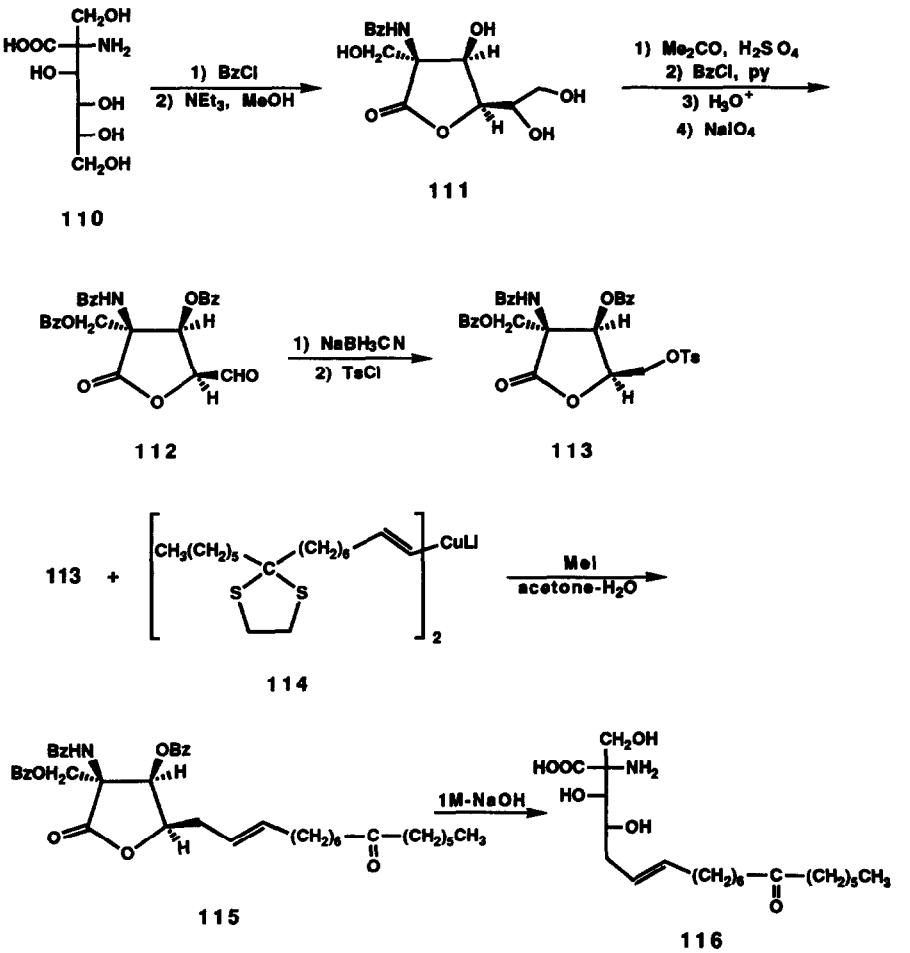
Recently, Rama Rao and co-workers[51] have introduced a highly stereoselective protocol for the synthesis of β-hydroxy-α-amino acids from D-glucose, and then applied in a stereospecific synthesis of MeBmt.

Utilizing an excellent strategy based on the chiron approach, these authors have employed the 1,2-*O*-isopropylidene-D-glucofuranose derivative **101**, as the chiral precursor having desired functionalized chain at C-4 atom (scheme 19). Reformatsky reaction with zinc and ethylbromoacetate gave **102** as a mixture of diastereoisomers, which were used in the next steps, since the new stereogenic center will be destroyed later. Catalytic hydrogenation of the benzyl group afforded the lactone **103** in high yield. Elimination and hydrogenation over Rh-Al_2O_3 at 50 psi furnished the key product **105** as a single isomer, in good yield. The desired chirality of the methyl group in this compound can be rationalized on the basis of a preferred hydrogenation in **104** from its less hindered face. Reduction with DIBAL-H at -78°C and Wittig olefination provided **106**, with the appropriate functionalization at C-4. The introduction of the N-methylamino group at C-3 was achieved by applying double inversion method. Oxidation with PDC and subsequent reduction with sodium borohydride furnished D-allofuranose derivative **107**, which was converted into **108** by displacement of the *O*-triflate by methylamine. The N-methylamino group was conveniently protected as trifluoroacetamide. Sugar deprotection with aqueous TFA and cleavage with lead tetraacetate gave the unstable aldehyde **109**. Jones oxidation to the corresponding acid followed by treatment with diazomethane to its methyl ester, and finally hydrolysis of all protected groups furnished the (+)-MeBmt (**100**).

3.6. Thermozymocidin.

Thermozymocidin (myriocin) (**116**), is an antibiotic isolated from the fungus *Myriococcum albomyces* . Its synthesis has been reported[52] starting from the 2-amino-2-deoxy-2-hydroxymethyl-D-mannonic acid **110**. This substance was of critical importance for success. This compound was converted into the D-manno-1,4-lactone **111**. In several steps it

was transformed into the aldehyde **112**, which is not a very stable compound, and it was therefore necessary to reduce the aldehyde carbonyl group and to transform the corresponding alcohol into the tosylate **113**. Coupling of **113** with the lithium divinylcuprate **114** provided the desired adduct, which gave after hydrolysis of the thioacetal protecting group, benzoylated anhydrothermozymocidin **115**. Finally this was converted into natural (+)-thermozymocidin (scheme 20).



Scheme 20

4. CONCLUSION

A plethora of miscellaneous amino acid antibiotics have been synthesized from carbohydrates and the number is continuously growing. Carbohydrate Chemistry Series, among others, provide a periodical comprehensive account on the synthesis of enantiomerically pure non-carbohydrate compounds. In all cases, symmetry relationships between the target molecule and the starting carbohydrate should be established. In this sense, the chiron approach is becoming an usual tool for synthetic chemists.

The late Karel Wiesner, a father of cardioactive steroid glycosides among other natural products, reactioned to his first successful selective glycosidation : "You know, I only wish I had tackled carbohydrate chemistry earlier in my career. It is a pleasure to have so many functional groups at your disposal!". Obviously, the carbohydrate chemistry is no the panacea for resolving all synthetic problems. In some cases, the idea of replacing other chiral auxiliaries or chiral pools by a carbohydrate-derived process was never a very good one. Rather, they should be considered as an alternative that ensures the desired functionality, as well as the regio- and stereocontrol in bond-forming reactions.

This review illustrates how carbohydrates have become effective in the chiral synthesis of α-amino acids, especially when complex structures have been envisaged. Since amino acids are gaining a great impact as potential enzyme-inhibitors, antimetabolites and pharmaceutical drugs, carbohydrates will doubtless continue as an useful tool in their synthesis.

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