Stereoselective Approaches to Bioactive Carbohydrates and Alkaloids—With a Focus on Recent Syntheses Drawing from the Chiral Pool

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I. Introduction

Bioactive glycosubstances, over the years, have received great attention in chemical, medicinal, and pharmaceutical research.[1–7] As a consequence, the design and implementation of stereoselective strategies for preparing them by using readily available homochiral precursors constitute prominent issues of a number of laboratories.[8–30] The present article mainly highlights recent approaches to biofunctional carbohydrates and hydroxylated alkaloids, including our own achievements,[13,27,28] which utilize enantiopure or enantioenriched precursors or templates derived from the chiral pool exploiting stereoselective totally chemical homologative techniques.

Here, the chiral pool refers to the domain of chiral nonracemic compounds from the natural realm, including monosaccharides and fragments thereof, amino and hydroxy acids, terpenes, and alkaloids. However, according to a broader definition, this class also includes synthetic entities readily available by resolution of racemates, chemical and enzymatic enantioselective procedures, or straight manipulation of naturally occurring derivatives.[31–41]

Procedures exploiting precursor-to-target interconversions based on functional group manipulations where carbon–carbon bond formation does not constitute a relevant issue are excluded as are those syntheses utilizing auxiliaries or catalysts to introduce chirality into a multistage protocol. Also excluded are methodologies involving chiral or racemic starting materials, where enzyme catalysis governs the installation of the optical activity. These topics have been the subjects of a number of recent accounts.[42–50]

We have chosen to organize our discussion by homogeneous classes of compounds rather than by similarity of the chemical approaches. In the first part, a selection of the most recent diastereoselective syntheses of monosaccharides and modified carbohydrates are discussed. The second section deals with preparation of nitrogenous carbohydrate mimics (azasugars), including monocyclic and bicyclic pyrrolidine- and piperidine-based alkaloids.

The literature cited covers the period from 1992 to Fall 1994. Excellent accounts and book chapters dealing with some of the topics highlighted herein covering the antecedent period are available. Pertinent references are grouped in section V.

II. Synthesis of Carbohydrates and Congeners

The importance of carbohydrates in biochemistry, in medicinal chemistry, and in the various aspects of life processes coupled with the charm and structural diversity of their multichiral architecture have long challenged synthetic chemists toward a multitude of approaches to this rich class of compounds. Among the various means with which a carbohydrate unit can be assembled, methodologies involving as a key operation carbon–carbon bond formation between an enantiopure "short" precursor and a homologative manipulable reactant constitute a leading subject in the modern synthetic chemistry panorama.[14,28–31] This chapter illustrates the design and syntheses of natural and unnatural sugars of biological importance including aminated derivatives and the so-called "higher sugars".[15,16,27] A section is devoted to carbon oligosaccharides where the interglycosidic oxygen atom has been replaced by a carbon–carbon bond.

A. Monosaccharides

The search for novel stereoselective and versatile methodologies to ascend the carbohydrate series represents an important goal of sugar research.[30] Recently, Whitesides, Schmid, and others introduced

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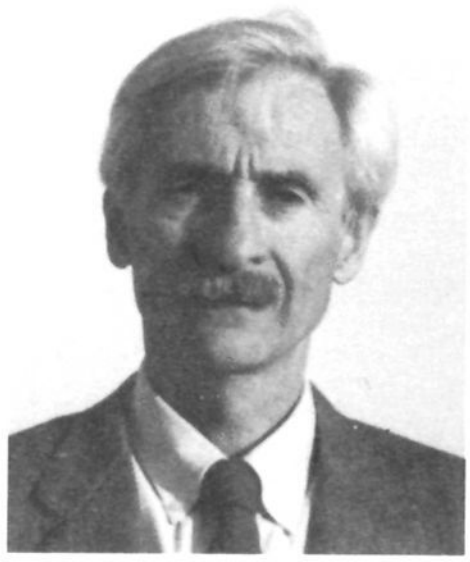


Giovanni Casiraghi was born in Monza, Italy, in 1939 and took his laurea degree in Chemistry in the University of Pavia. After postdoctoral work at the same University with Professor S. Pietra (1965–1968), he joined the Department of Organic Chemistry at University of Parma. In 1971 he became an Assistant Professor and in 1980 an Associate Professor of Organic Chemistry. In 1986 he was promoted to a Professorship in Organic Chemistry and, in the same year, he transferred to the University of Sassari. In 1991 he returned to the University of Parma, joining the Faculty of Pharmacy (Pharmaceutical Department) where he was appointed to the Chair in Organic Chemistry. Topics he is now interested in include asymmetric organic synthesis and the design and implementation of novel synthetic strategies to densely functionalized compounds of biological interest, including carbohydrate mimics, amino acids, modified nucleosides, glyco- and nucleoporphyrins.

Gloria Rassu is a Researcher at the Consiglio Nazionale delle Ricerche, Area della Ricerca di Sassari. She was born in Sassari, Italy, in 1954 and earned her laurea degree in Chemistry at the University of Sassari. After five years of postdoctoral work at the same University, in 1984 she joined the Istituto per l'Applicazione delle Tecniche Chimiche Avanzate del CNR, Sassari, where she assumed her current position. In 1987 she joined the research group of Professor Casiraghi beginning a fruitful scientific cooperation in the carbohydrate chemistry area. In 1991 she began her independent research and now heads a small team of researchers who study the various aspects of the asymmetric organic synthesis. In particular her interests focus on the development of novel stereoselective reactions and the synthesis of natural products and biologically active substances.

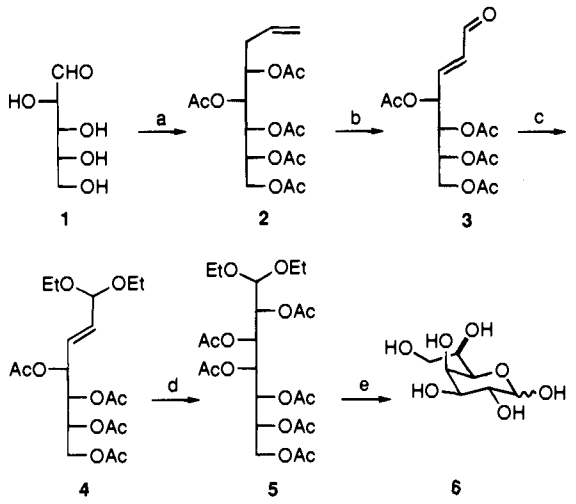
Franca Zanardi was born in S. Secondo, Parma, Italy, in 1968. She studied Chemistry at the University of Parma where she received her laurea degree in 1993. Since 1992 she has been working under the supervision of Professor Casiraghi at the Pharmaceutical Department of University of Parma, where she is currently completing the requirements for her Ph.D. in bioorganic chemistry. Her research interest is in the area of stereocontrolled synthesis of bioactive substances, including modified carbohydrates, nucleosides, amino acids, and porphyrin–sugar conjugates.

Pietro Spanu was born in Sassari, Italy, in 1963. He studied Chemistry at the University of Sassari where he received his laurea degree in 1989. He was introduced to the asymmetric organic synthesis as a postdoc with Professor Casiraghi and, after a three-year stay at the Department of Chemistry of the same University, in 1994 he joined the Instituto per l'Applicazione delle Tecniche Chimiche Avanzate del CNR, Sassari, where he is currently a research associate working under the guidance of G. Rassu.

an extremely efficient technique to assemble various deoxysugars via elongation of unprotected carbohydrates utilizing *in situ*-generated indium reagents in aqueous solvent systems.[51] A convenient route to D-*glycero*-D-*galacto*-heptose (**6**) was devised, utilizing D-arabinose (**1**) as a chiral precursor[52] (Scheme 1). Treatment of **1** in water−ethanol with indium powder and allyl bromide under ultrasound conditions afforded a mixture of epimeric polyols which were converted into their corresponding acetyl derivatives (9:1 *threo*/*erythro* diastereomeric ratio).

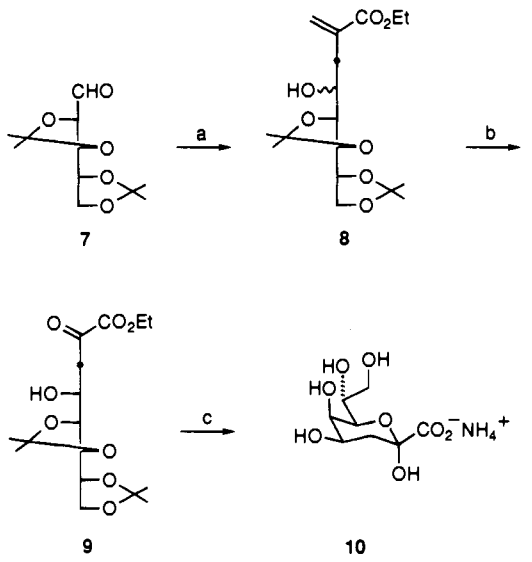
Separation of the diastereoisomers was easily achieved to give octenitol **2** as the major compound. The polyol derivative **2** was further transformed into the α,β-unsaturated aldehyde derivative **3** by combined catalytic osmylation and periodate cleavage, followed by treatment with tetrabutylammonium fluoride. The trans configuration of the double bond in **3** was assigned by proton NMR spectra analyses. Protection of the aldehyde moiety as the diethyl acetal was achieved by treatment of **3** with triethyl orthoformate under acid catalysis conditions giving the acetal **4**. Catalytic osmylation and subsequent acetylation gave a mixture of diastereoisomers (6:1 diastereomeric ratio) which were separated to give **5** as the major product. The final deprotection of derivative **5** was easily attained by transesterification of the acetates with sodium methoxide in methanol followed by acidic cleavage of the diethyl acetal to give D-*glycero*-D-*galacto*-heptose (**6**). By following the same chemistry D-*glycero*-L-*galacto*-heptose was obtained starting from D-xylose.

Scheme 1[a]



[a] Key: (a) In powder, allyl bromide, ultrasonication; then Ac_2O, pyridine, DMAP; (b) OsO_4, KIO_4; then TBAF; (c) H_3O^+, $HC(OEt)_3$; (d) OsO_4, NMO; then Ac_2O, pyridine, DMAP; (e) NaOMe, MeOH; then H_3O^+.

Scheme 2[a]



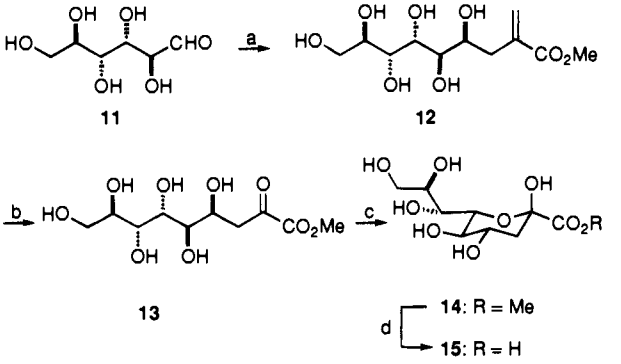
[a] Key: (a) In, ethyl α-(bromomethyl)acrylate, 10% formic acid, aq. MeCN; (b) O_3, MeOH, -78°C; then Me_2S, MeOH, -78°C to rt; (c) aq. TFA; then NH_4OH.

Allylation of 2,3:4,5-di-*O*-isopropylidene-D-arabinose (**7**) with ethyl 2-(bromomethyl)acrylate and indium was the strategy devised by Whitesides in order to obtain 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **10**) an integral component of the lipopolysaccharides of Gram-negative bacteria.[53,54]

So, as illustrated in Scheme 2, treatment of **7** with ethyl 2-(bromomethyl)acrylate, formic acid, and indium metal gave a mixture of diastereoisomers **8** (*erythro*/*threo* ratio = 2:1). After separation, the *erythro* product was ozonized at −78 °C in methanol to provide α-keto ester **9**. Hydrolysis of the protecting groups under acidic conditions followed by neutralization finally yielded KDO **10** in 20% overall yield based on **7**.

Similar chemistry was exploited to access the sialic acid (+)-3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN, **15**) from D-mannose (**11**, Scheme 3).[55] Treatment of **11** with methyl 2-(bromomethyl)acrylate in water in the presence of indium metal gave rise to *syn* adduct **12** along with a minor amount of the *anti* diastereoisomer (6:1 ratio). Direct ozonolysis of **12** in methanol afforded the corresponding keto ester **13** which immediately cyclized to give the (+)-KDN methyl ester **14**. Base-promoted saponification finally afforded pure KDN **15**.

Scheme 3[a]



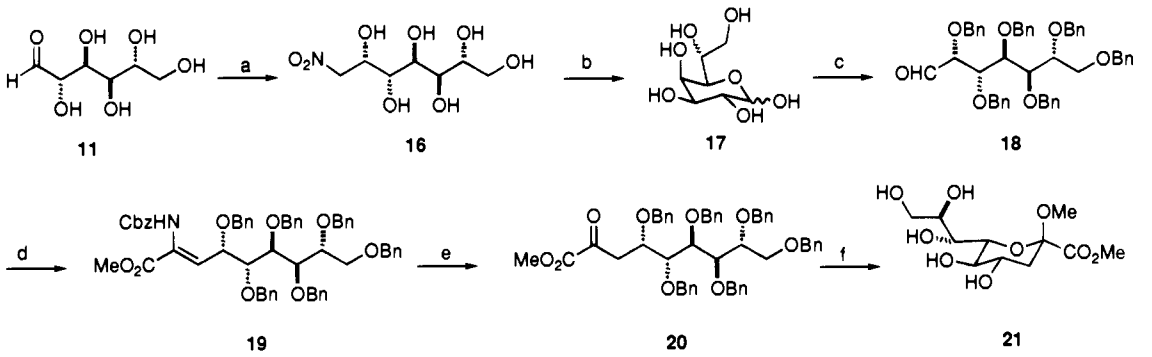
[a] Key: (a) In, methyl 2-(bromomethyl)acrylate, H_2O; (b) O_3, MeOH, -78°C; then Na_2SO_3; (c) spontaneous cyclization; (d) KOH, MeOH.

A convenient synthesis of KDN derivative **21** from D-mannose (**11**) was recently reported by Sato employing as a key reaction a two-carbon Horner–Wittig homologation.[56] The synthesis began with the preparation of D-*glycero*-D-*galacto*-heptose (**17**) which was derived from **11** by nitromethane condensation to give **16** and subsequent Nef oxidation (Scheme 4). Treatment of **17** with ethanethiol in the presence of hydrochloric acid followed by perbenzylation and removal of the aldehyde protecting group resulted in formation of heptose **18** which was subjected to Horner–Wittig condensation with methyl 2-[(benzyloxycarbonyl)amino]-2-(diethoxyphosphoryl)acetate to generate the adduct **19** as a 1:1 mixture of *Z*/*E* isomers. Hydrogenolytic debenzyloxycarbonylation of **19** gave the corresponding methyl α-oxoalkanoate derivative **20** which was transformed to the target compound **21** via reductive debenzylation followed by glycosidation with methanol.

López-Herrera[57] utilized the well known rhodium II-mediated rearrangement of β-acetoxy-α-diazo esters to synthesize KDO **10** and 2-deoxy-KDO **28**, a potent inhibitor of CMP-KDO synthetase. As depicted in Scheme 5, protected aldehydo mannose **22** was condensed with ethyl diazoacetate to obtain a 3.5:1 diastereomeric mixture of β-hydroxy-α-diazo esters **23**. Acetylation and rhodium-catalyzed decomposition afforded the enol acetate **24** which was treated with hydrazine in methanol to afford the protected hydrazone **25**. Desilylation with TBAF in THF provided the corresponding 4-*O*-unprotected hydrazone which was oxidized to diazo ester **26** by activated MnO_2. This diazo compound was treated with *m*-chloroperoxybenzoic acid to give, after complete deprotection, the expected KDO **10**.

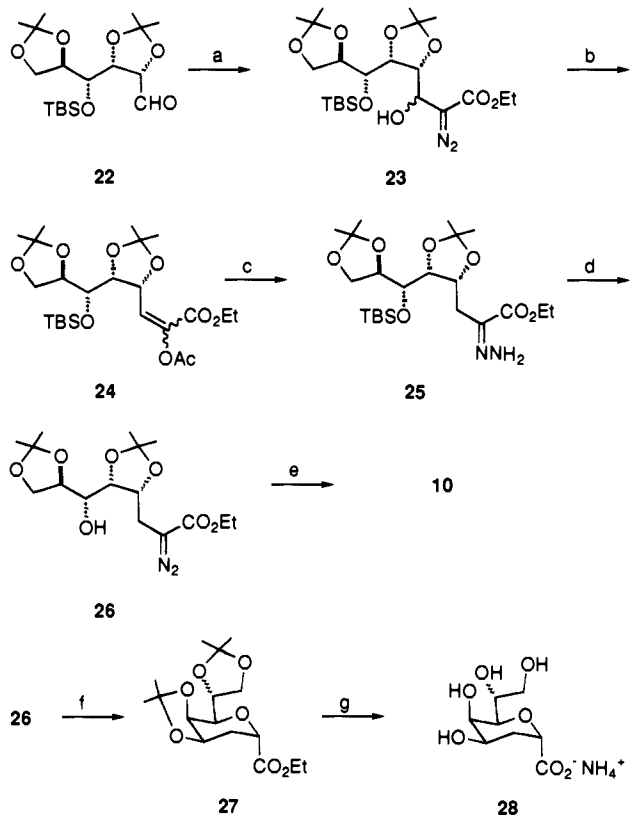
The same intermediate **26** was efficiently exploited by the same author for a short synthesis of 2-deoxy-KDO.[58] Thus treating **26** with a catalytic amount of dirhodium tetraacetate effected its decomposition with nitrogen release and intramolecular OH trapping of the carbenoid species produced from the diazo

Scheme 4[a]



[a] Key: (a) $MeNO_2$, DBU; (b) Nef oxidation; (c) EtSH, HCl; then NaH, BnBr, DMF; then MeI, Na_2CO_3; (d) $(EtO)_2P(O)CH(NHCbz)CO_2Me$, NaH, CH_2Cl_2; (e) H_2, Pd/C; (f) H_2, $Pd(OH)_2$; then Dowex H^+, MeOH.

Scheme 5[a]



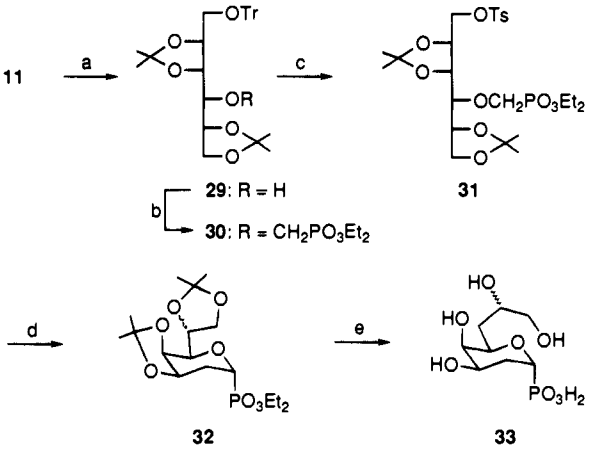
[a] Key: (a) HCN_2CO_2Et; (b) Ac_2O, pyridine; then $Rh_2(AcO)_4$; (c) NH_2NH_2, MeOH; (d) MnO_2, $CHCl_3$; then TBAF, THF; (e) MCPBA, $CHCl_3$; then AcOH; then NH_4OH; (f) $Rh_2(AcO)_4$, C_6H_6; (g) TFA; then NH_4OH.

carbon. As expected, KDO derivative **27** was obtained as a single compound, which was converted to pure 2-deoxy-KDO **28** by removal of the acetonide protecting groups.

In a recent study focused on the design of potent inhibitors for lipopolysaccharide biosynthesis, Baasov synthesized a novel phosphonate analogue of 2-deoxy-KDO **28**, namely the isosteric carbohydrate **33**,[59] utilizing D-mannose (**11**) as a chiral template (Scheme 6).

First, **11** was converted to differentially protected alditol **29** and then phosphonomethylated to phosphonate **30**. A suitable leaving group at C-1 was introduced by conventional exchange of the protective funtionalities to attain the tosylate **31** which was successfully cyclized to single phosphonate **32** by

Scheme 6[a]



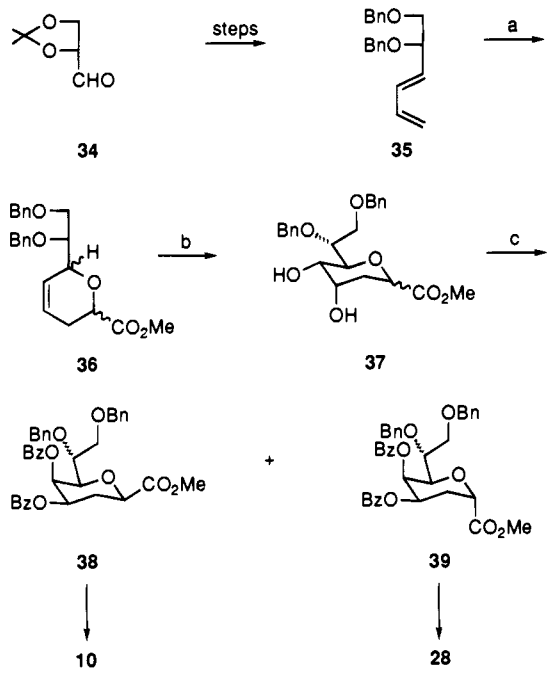
[a] Key: (a) Me_2CO, H_2SO_4; then $NaBH_4$, MeOH; then TrCl, pyridine; (b) $TfOCH_2PO_3Et_2$, NaH; (c) H_2, Pd/C; then TsCl, pyridine, DMAP; (d) LDA, THF, -78°C; (e) Me_3SiBr, CH_2Cl_2; then Dowex H^+.

treatment with LDA, via intramolecular carbon–carbon bond formation. Deprotection of **32** finally provided the target phosphonate **33**, a potential inhibitor of enzymes of KDO biosynthesis.

A novel synthetic strategy to assemble KDO **10** and 2-deoxy-KDO **28** was introduced by Augé[60] based on a hetero Diels–Alder reaction involving a chiral diene derived from D-glyceraldehyde. As shown in Scheme 7, the synthesis started with diene **35** readily prepared in few steps from 2,3-*O*-isopropylidene-D-glyceraldehyde (**34**).

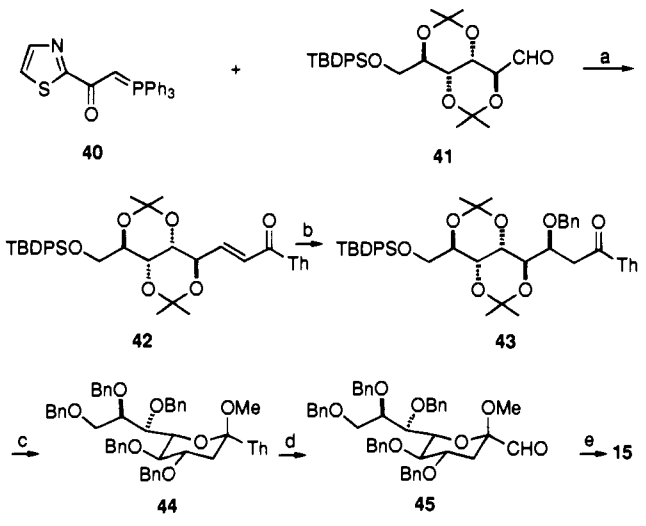
Under optimal conditions, **35** was allowed to react at 130 °C with neat butyl glyoxylate to produce a mixture of four benzylated cycloadducts **36** in the proportion 50:24:16:10. The mixture was hydroxylated with catalytic osmium tetraoxide in the presence of *N*-methylmorpholine oxide to afford an inseparable mixture of diols **37**. To reach the configuration of KDO derivatives, double inversion at C-4 and C-5 was carried out on the mixture **37** by a conventional S_N2 protocol with tetrabutylammonium benzoate. Two diastereomeric compounds were obtained in the ratio 2:1 to which structures **38** (major compound) and **39** were attributed. Compound **38** represents a protected form of 2-deoxy-α-KDO while **39** is a protected derivative of 2-deoxy-β-KDO. The major compound **38** was converted to KDO by a set of reactions involving, as a key operation, diastereoselective hydroxylation at C-2.

Scheme 7[a]



[a] Key: (a) $HCOCO_2Bu$, 130°C; then MeOH, TsOH; (b) OsO_4, NMO; (c) Tf_2O, pyridine; then $PhCO_2NBu_4$.

Scheme 8[a]

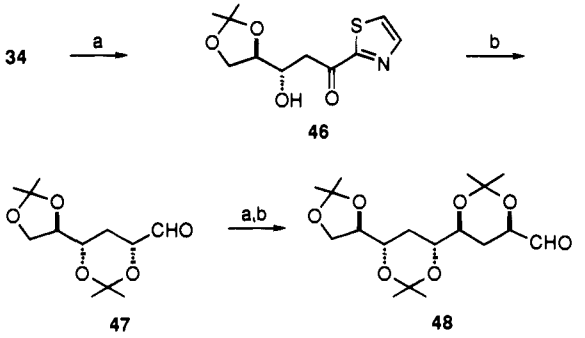


[a] Th = 2-thiazolyl. Key: (a) 4-Å MS, $CHCl_3$, reflux; (b) BnONa; (c) HCl, MeOH; then BnBr, NaH; (d) TfOMe; then $NaBH_4$; then $CuCl_2/CuO$, H_2O; (e) Ag_2O; then H_2, Pd/C; then AcOH.

In a remarkable study aimed at developing the chemistry of 2-[(thiazolylcarbonyl)methylene]triphenylphosphorane (**40**) as a masked pyruvate anion unit, Dondoni[61] successfully opened a versatile route to 3-deoxy-2-ulosonic acids, utilizing simple carbohydrate derivatives as synthons and sources of chirality. As an example, the total synthesis of the biological important sialic acid KDN (**15**) is illustrated in Scheme 8.

Condensation of aldehydo-D-mannose **41**, available from D-mannose by simple functional group protection, with phosphorane **40** proceeded with excellent selectivity to give the (*E*)-enone **42** in good yield. Conjugate addition of sodium benzyl oxide to **42** gave the *syn* adduct **43** selectively, accompanied by only

Scheme 9[a]



[a] Key: (a) 2-acetylthiazole, $LiOBu^t$, THF, -50°C; (b) DIBALH, THF, -78°C; then DMP, CSA; then MeI, MeCN, reflux; then $NaBH_4$, MeOH; then $HgCl_2$, MeCN.

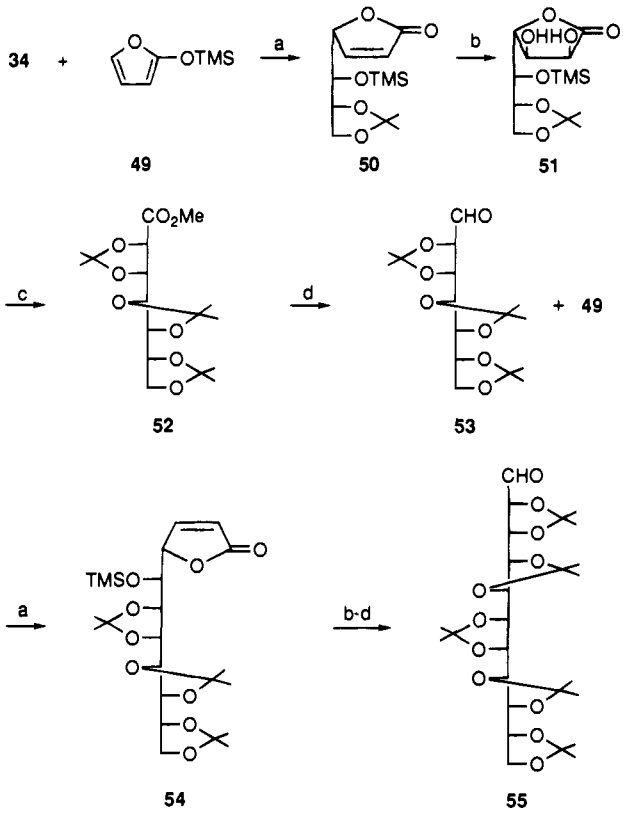
a modest amount of its *anti* diastereoisomer. Two subsequent clean reactions, namely acidic removal of acetonide and silyl protecting groups and perbenzylation, gave rise to methyl pyranoside **44**. Unmasking of the formyl group embodied in the thiazolyl substituent allowed generation of the pyranoside **45** which was finally converted to target KDN **15** by a set of reactions involving oxidation of the aldehyde function to carboxylic group, debenzylation, and hydrolysis of the *O*-methyl glycosidic linkage.

The same author,[62] with the utilization of 2-acetylthiazole as the surrogate of lactaldehyde, designed an effective route to a variety of polyhydroxylated carbon chains. Thus, for example (Scheme 9), condensation of protected glyceraldehyde **34** with the enolate anion of 2-acetylthiazole generated the *anti*-adduct **46** which was transformed to three-carbon homologated hexose **47** by selective reduction of the carbonyl function followed by thiazole unmasking. Reiteration of the same three-carbon homologative reaction generated the polyalkoxy nonanal **48** bearing a sequence of 1,2- and 1,3-diol groups.

A reiterative $C_3 + C_4 + C_4$ homologation strategy was chosen for assembly of D-*glycero*-D-*talo*-L-*talo*-undecose pentaacetonide (**55**).[63] The synthesis started with the popular three-carbon chiron 2,3-*O*-isopropylidene-D-glyceraldehyde (**34**) and required two elongation steps utilizing 2-(trimethylsiloxy)furan (**49**) as a nucleophilic four-carbon homologative reagent. The entire sequence is presented in Scheme 10.

Treatment of **34** with **49** in the presence of BF_3 etherate and protection of the crude product as the TMS ether afforded the seven-carbon butenolide **50** as the major component. *Anti*-selective *cis*-dihydroxylation of the double bond was performed using the $KMnO_4$/dicyclohexano-18-crown-6-ether/CH_2Cl_2 system at ambient temperature. There was obtained D-*glycero*-D-*talo*-heptonolactone (**51**), with no trace of diastereomeric material. Attention was then directed toward elaborating the lactone framework into an open-chain *aldehydo* sugar. Compound **51** was directly transformed into methyl ester **52** by treatment with a large excess of dimethoxypropane in the presence of 3 moles equiv of *p*-toluensulfonic acid at room temperature. Controlled reduction of the methyl ester into subtarget aldehyde **53** was achieved, without any epimerization, by careful addition of DIBALH in CH_2Cl_2 at −90 °C. The first cycle of the

Scheme 10[a]

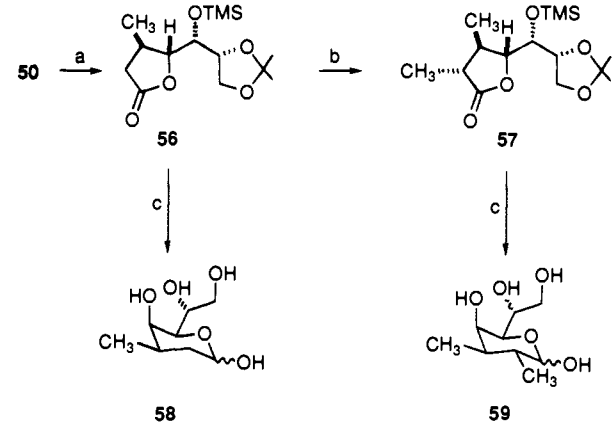


[a] Key: (a) BF_3 etherate, CH_2Cl_2, -90°C; then TMSCl, pyridine; (b) $KMnO_4$, DCH-18-crown-6, CH_2Cl_2; (c) DMP, TsOH; (d) DIBALH, CH_2Cl_2, -90°C.

sequence was thus completed and the setting for proper installation of four additional contiguously oxygenated carbon atoms was at hand. Four-carbon elongation of **53** with **49** generated the 11-carbon unsaturated lactone **54** as the main component. Reiteration of the reaction sequence of the first cycle allowed clean conversion of lactone **54** to undecose pentaacetonide **55** with an overall yield of 5.1% for the entire sequence from **34**.

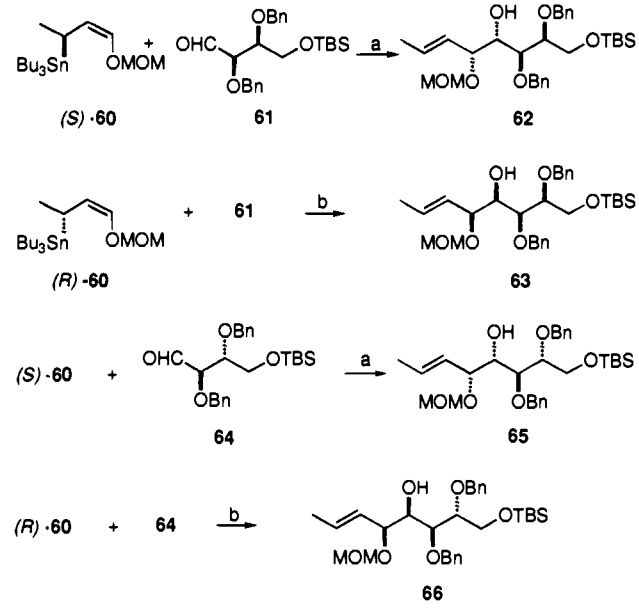
Nonracemic butenolide **50**, obtainable in multigram quantity as previously described, was the template employed in a divergent synthesis of uncommon 2,3-dideoxy-*C*-methylheptose derivatives (Scheme 11).[64] Asymmetric conjugate addition of Me_2CuLi in CH_2Cl_2 at −80 °C introduced a methyl group at C-3 of intermediate **50**. The presence of a bulky substituent on C-4 directed the stereochemical course (*anti*) of this reaction, affording **56** as a single diastereoisomer in 86% yield. Methylation of the enolate (LiHDMS, THF, then MeI) converted **56** into **57**. The diastereoselection was moderate (85:15) due to the presence of the 3β,4α-substituents in the furan ring. Nonetheless, the major crystalline *trans,trans*-diastereoisomer **57** was obtained in 60% yield. At this point, all that remained was to convert the intermediates **56** and **57** into *C*-methylheptoses **58** and **59**, respectively. A common enantioconservative protocol of two sequential reactions ensured clean transformations. Lactone-to-lactol reduction occurred under the usual conditions using DIBALH, while complete cleavage of the silyl and acetonide linkages was accomplished by acidic treatment. In this manner, the expected heptoses **58** and **59** were obtained.

Scheme 11[a]



[a] Key: (a) Me_2CuLi, CH_2Cl_2; (b) LiHDMS, THF; then MeI; (c) DIBALH, CH_2Cl_2; then 3N HCl, THF.

Scheme 12[a]

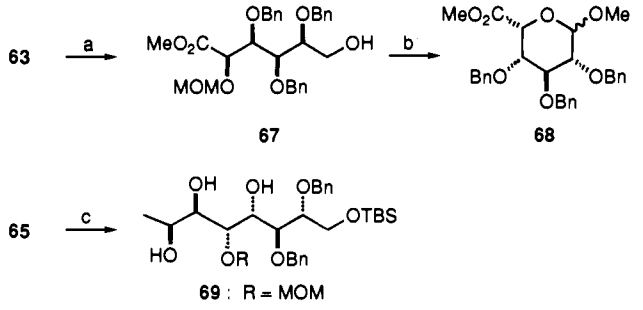


[a] Key: (a) BF_3 etherate; (b) $MgBr_2$ etherate.

The addition of nonracemic or racemic γ-alkoxy allylic stannanes to enantioenriched aldehyde derivatives assisted by Lewis acids was recently employed by Marshall to create a number of polyol fragments endowed with varied chirality.[12] After extensive investigation it was shown[65] that coupling of nonracemic allylic stannane (*S*)-**60** with threose aldehyde **61** afforded the *syn,anti,syn*-adduct **62** in the BF_3-promoted reaction, whereas the enantiomeric stannane (*R*)-**60** gave the *syn,syn,syn*-adduct **63** under $MgBr_2$ catalysis (Scheme 12). On the other hand, (*S*)-**60** and erythrose aldehyde **64** yielded the *syn,anti,anti*-adduct **65** with BF_3, while (*R*)-**60** gave rise to the *syn,syn,anti*-adduct **66** using $MgBr_2$ as a catalyst.

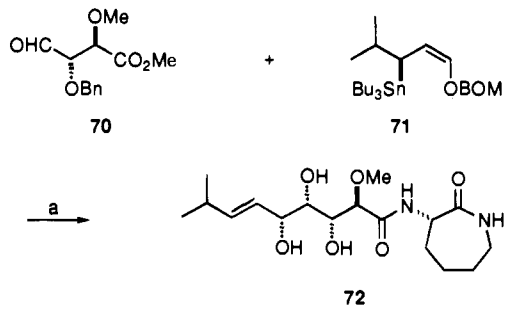
The enantioenriched unsaturated adducts **62**, **63**, **65**, and **66** were exploited during a further investigation to produce a variety of hexose derivatives. Thus, as shown in Scheme 13, by starting with unsaturated polyol **63**, exopyranose derivative **68** was obtained, through intermediate **67**, via ozonolysis and Dess–Martin periodinane oxidation. Furthermore the homoallylic alcohol **65** was directly transformed to

Scheme 13[a]



[a] Key: (a) BnBr, NaH, DMF, 0°C; then O_3, NaOH, MeOH, CH_2Cl_2, -78°C; then TBAF, AcOH,THF; (b) Dess-Martin reagent, CH_2Cl_2; then HCl, MeOH, reflux; (c) OsO_4, NMO.

Scheme 14[a]



[a] Key: (a) $MgBr_2$ etherate, CH_2Cl_2, -20°C to rt; then L-(+)-α-amino-ε-caprolactam, 2.0 M Me_3Al in hexanes; then Li, NH_3, THF, -78°C.

ω-deoxyoctose derivative **69** by dihydroxylation with OsO_4/NMO mixture.

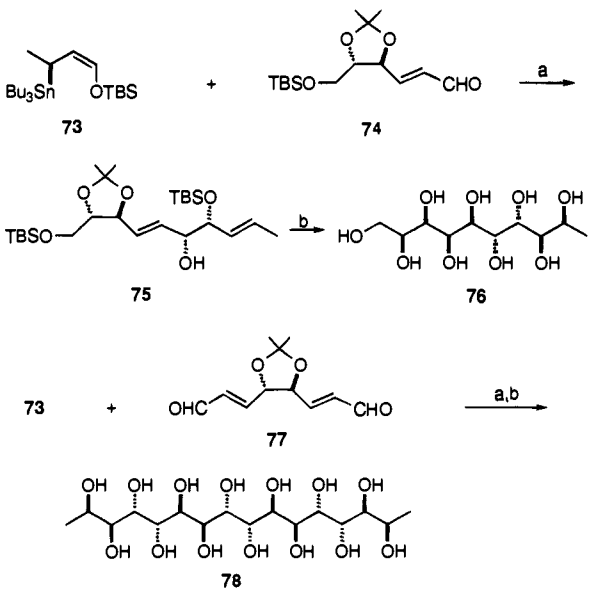
This fine chemistry was also applied to total synthesis of Bengamide E (**72**), an unusual polyhydroxylated amino acid derivative recently isolated from a coral reef sponge[66] (Scheme 14). The synthetic scheme involves, as a pivotal operation, $MgBr_2$-promoted condensation of nonracemic *meso*-tartaric acid derivative **70** with allylic stannane **71** to generate the appropriate polyol fragment in the correct *syn,syn,anti* relative configuration.

This extremely versatile homologative technique was also exploited to synthesize long-chain polyols by sequential addition of enals with chiral nonracemic γ-siloxy allylic stannanes followed by diastereoselective hydroxylation.[67,68] Addition of allylic stannane **73** to enal **74**, derived from (*R,R*)-dimethyl tartrate, produced the adduct **75** as a single isomer, which was converted to nonaol **76** by a three-stage sequence including double diastereospecific dihydroxylation of the two nonconjugated double bonds (Scheme 15).

As a further remarkable extension of this chemistry, bidirectional assemblage of polyol **78** bearing 14 adjacent stereogenic hydroxymethine units was attained, via bis-homologation of the C_2 symmetric dialdehyde **77**, derived from tartrate, with stannane **73**.

From a synthetic perspective, hikizimycin, an anthelmintic agent showing significant activity against a variety of common parasites, constitutes a quite demanding compound by virtue of both the high level of structural complexity and chiral diversity. This

Scheme 15[a]



[a] Key: (a) BF_3 etherate; (b) TBSOTf, 2,6-lutidine; then OsO_4, NMO; then *p*-TsOH.

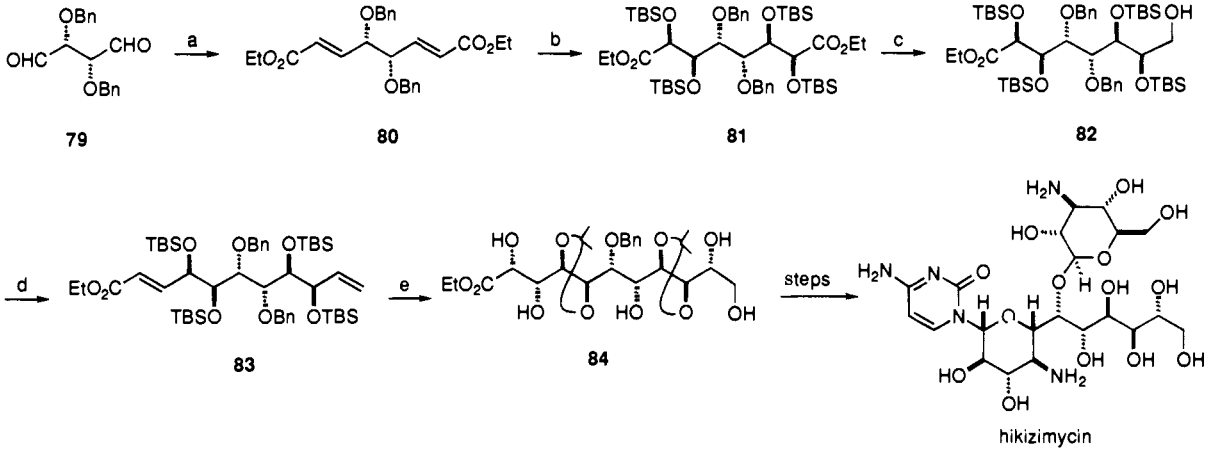
compound is comprised of a cytosine base, an *O*-linked aminohexose, and a core sugar unit of 11 fully oxidized carbons. In his elegant total synthesis of this complex nucleoside disaccharide, Schreiber[69] developed a clever approach to the core undecose moiety **84** by applying a two-directional strategy based on simultaneous two carbon Horner–Emmons homologation of the L-tartrate derived dialdehyde **79**, at both termini (Scheme 16).

Treatment of **79** with triethyl phosphonoacetate and butyllithium afforded the α,β-unsaturated ester **80** via 4 + 2 + 2 simultaneous elongation. Bishydroxylation with catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide followed by silyl ether protection gave fully protected polyol **81**. Careful treatment of C_2-symmetric **81** with DIBALH at −78 °C allowed selective functionalization of one of the two homotopic ester groups giving unsymmetrized alcohol **82**. Swern oxidation of **82** followed by Tebbe olefination established the terminal vinyl group in one direction, whereas the α,β-unsaturated ester moiety at the other end of the chain was fashioned by a reduction, oxidation, and Horner–Emmons olefination sequence to furnish adduct **83**. Replacement of the silyl ether protecting groups with acetonides and subsequent catalytic osmylation in the presence of a dihydroquinine *p*-chlorobenzoate stereoselectively afforded undecose **84**, a key precursor of nucleoside antibiotic hikizimycin.

B. Aminated Compounds

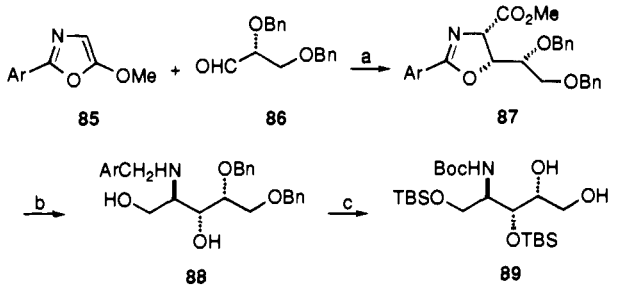
This section discusses salient totally synthetic methodologies to access aminated derivatives of monosaccharides including simple aminosugars, polyhydroxylated cyclic and acyclic amino acids, and sialic acid and congeners. This remarkable class of compounds comprises various bioactive naturally occurring and artificial substances whose chemistry has recently received intense scrutiny resulting in a number of creative synthetic performances.[9,25,70–72] A variety of biologically active compounds incorporate

Scheme 16[a]



[a] Key: (a) triethyl phosphonoacetate, *n*-BuLi, -78°C; (b) OsO_4, NMO, aq. acetone; then TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) DIBALH, CH_2Cl_2, -78°C; (d) Swern oxidation; then Tebbe reagent, toluene, THF, pyridine, -10°C; then DIBALH, CH_2Cl_2, -78°C; then Swern oxidation; then triethyl phosphonoacetate, *n*-BuLi, -78°C; (e) TBAF, THF, 0°C; then acetone, H_2SO_4; then OsO_4, NMO, dihydroquinine *p*-chlorobenzoate, 0°C.

Scheme 17[a]



[a] Key: (a) $SnCl_4$, CH_2Cl_2, -20°C; (b) $LiAlH_4$, THF; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2; then Pd-black, HCO_2NH_4, reflux; then $(Boc)_2O$, Et_3N, THF.

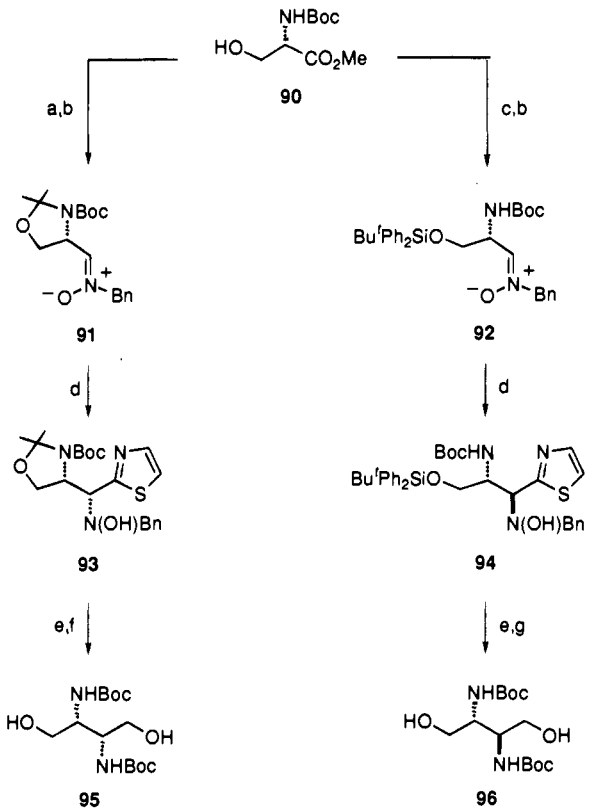
chiral aminopolyol fragments. The chiral *erythro*-2-amino polyol system found, for example, in sphingosine and phytosphingosine was assembled stereoselectively by employing oxazole **85** as a nucleophilic aminoethanol unit.[73]

As illustrated for an *erythro*-2-amino 1,3,4,5-tetrol derivative **89** (Scheme 17), formal [3 + 2] cycloaddition of oxazole **85** to 2,3-di-*O*-benzyl-D-glyceraldehyde (**86**) in the presence of $SnCl_4$ gave rise to *cis*-2-oxazoline-4-carboxylate **87** diastereoselectively along with a small amount (less than 3%) of three other diastereoisomers. Reduction of 2-oxazoline **87** with $LiAlH_4$ gave the expected *erythro*-2-amino 1,3,4,5-tetrol derivative **88** which was finally converted to the amino polyol **89** by a three-step operation including bis-silylation, benzyl and (*p*-methoxyphenyl)-methyl protecting group removal, and protection of the amino function as the *N*-Boc derivative.

With the aim of developing a synthetic route to polyols bearing an adjacent chiral 1,2-diamino unit, Dondoni and Merino[74] exploited enantioenriched nitrones **91** and **92** as convenient bis-aminated synthons (Scheme 18).

According to a divergent protocol, the readily available L-serine derivative **90** was converted to either acetonide-protected nitrone **91** or to the silylated counterpart **92**. Conveniently, the steric course of the coupling with *in situ*-generated 2-lithiothiazole was strictly dependent upon the nature of the nitrone

Scheme 18[a]

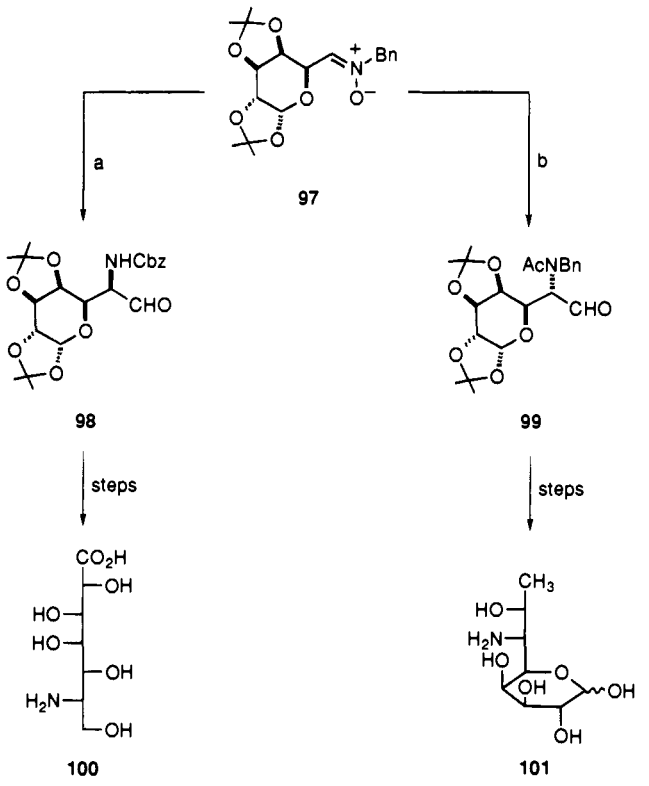


[a] Key: (a) DMP, C_6H_6, TsOH, reflux; (b) DIBALH, toluene, -78°C; then $PhCH_2NHOH$, CH_2Cl_2, $MgSO_4$; (c) Bu^tPh_2SiCl, DMAP, Et_3N, DMF; (d) 2-lithiothiazole, Et_2O, THF, -78°C; (e) $TiCl_3$, MeOH, H_2O; then Boc_2O, dioxane; then TfOMe, MeCN; then $NaBH_4$, MeOH, 0°C; then CuO, $CuCl_2$, MeCN, H_2O; then $NaBH_4$, MeOH, 0°C; (f) TsOH, MeOH, 50°C; (g) TBAF, THF.

protecting groups thus allowing synthesis of either *syn*-adduct **93** or *anti*-adduct **94**. Final deblocking of the masked formyl functionality and successive group manipulation afforded *threo*- and *erythro*-2,3-diaminobutane-1,4-diols **95** and **96**.

Analogously, a formal synthesis of destomic acid (**100**) and lincosamine (**101**) was reported by the same author[75] employing the D-galactose-derived

Scheme 19[a]



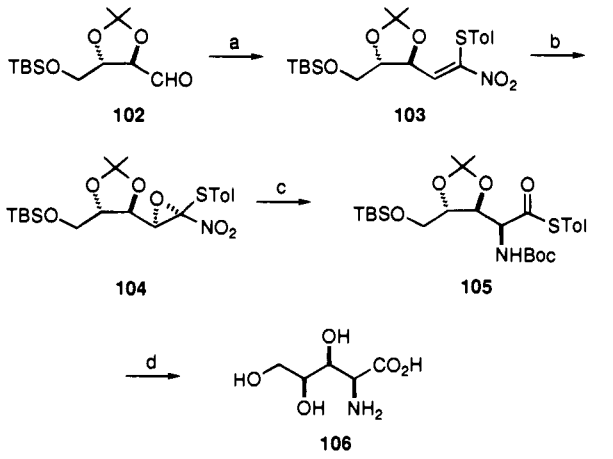
[a] Key: (a) 2-lithiothiazole, $ZnBr_2$, Et_2O, -80°C; then $TiCl_3$, MeOH, H_2O; then BnOCOCl, $NaHCO_3$, dioxane, 0°C; then CF_3SO_3Me, MeCN; then $NaBH_4$, MeOH; then CuO, $CuCl_2$, MeCN, H_2O; (b) 2-lithiothiazole, Et_2ClAl, Et_2O, -10°C; then $TiCl_3$, MeOH, H_2O; then Ac_2O, pyridine, DMAP; then NaH, DMF, BnBr, 0°C; then TfOMe, MeCN; then $NaBH_4$, MeOH; then CuO, $CuCl_2$, MeCN, H_2O.

nitrone **97** as a common chiral precursor. Paralleling the chemistry above for the syntheses of diaminobutane diols **95** and **96**, two key intermediates **98** and **99** were selectively produced, suitable for conversion to amino sugars **100** and **101**, respectively (Scheme 19).

This chemistry also proved fruitful for the synthesis of polyoxamic acid **106**, the acyclic α-amino acid component of polyoxin J, by exploiting the furan ring as a masked carboxyl group.[76] This important polyhydroxylated amino acid was recently prepared[77] from the protected L-threose **102** via the key nitro olefin intermediate **103** (Scheme 20). Nucleophilic epoxidation of **103** gave the *anti*-epoxide **104** with 92% diastereoselectivity. Reaction with ammonia, followed by treatment with *tert*-butyl pyrocarbonate, gave the *syn*-α-amino thioester **105** which was straightforwardly converted to polyoxamic acid **106**.

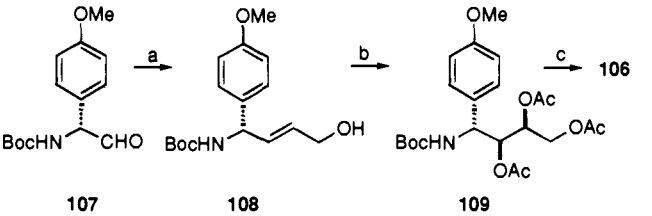
In approaching the same target, Hamada and Shioiri[78] employed the phenylglycinal derivative **107** as the starting chiron, where the aryl moiety was envisioned as a masked carboxyl unit (Scheme 21). Two-carbon Wittig elongation of **107** with 2-(triphenylphosphonylene)acetate followed by reduction of the ester group furnished the allyl alcohol **108** which was converted to the acetylated amino triol **109** by Sharpless asymmetric dihydroxylation and subsequent acetylation with moderate diastereoselectivity. The carboxylic function was created by oxidative degradation of the aryl group affording,

Scheme 20[a]



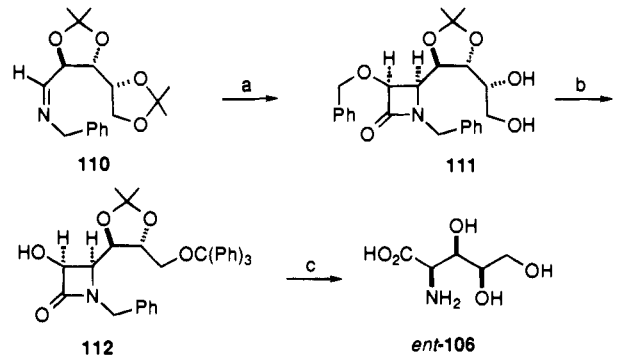
[a] Key: (a) $TolSCH_2NO_2$, $KOBu^t$, Bu^tOH, THF, 0°C; then $MeSO_2Cl$, Pr^i_2NEt, -78°C; (b) $KOOBu^t$, THF, -78°C; (c) NH_3, CH_2Cl_2; then Boc_2O; (d) CF_3CO_2H, H_2O.

Scheme 21[a]



[a] Key: (a) Ph_3PCHCO_2Et, CH_2Cl_2, 0°C; then DIBALH, BF_3 etherate, CH_2Cl_2, -78°C, (b) Sharpless asymmetric dihydroxylation; then Ac_2O, pyridine, (c) $RuCl_3$, $NaIO_4$, EtOAc, MeCN; then *O-tert*-butyl-*N*-*N'*-diisopropylisourea, CH_2Cl_2, 40°C; then aq. HCl, MeOH; then 1N aq. NaOH.

Scheme 22[a]

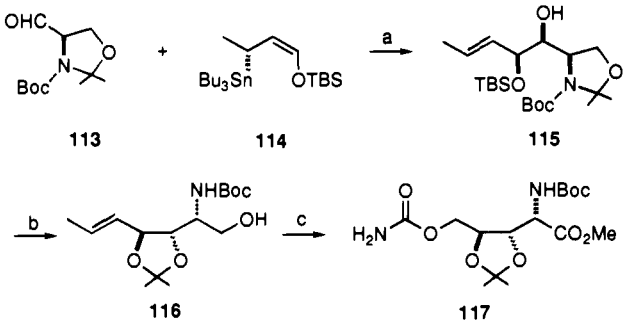


[a] Key: (a) $PhCH_2OCH_2COCl$, Et_3N, CH_2Cl_2; then aq. AcOH; (b) aq. $NaIO_4$, MeCN; then $NaBH_4$, MeOH; then HCO_2NH_4, Pd/C, EtOH; then Ph_3CCl, Et_3N, CH_2Cl_2; (c) $LiAlH_4$, THF; then Pd/C, EtOH, HCO_2NH_4; then NaOH, Boc_2O; then $NaIO_4$, MeCN, CCl_4, $RuCl_3$, H_2O; then TFA, MeOH.

after complete deprotection, polyoxamic acid **106**.

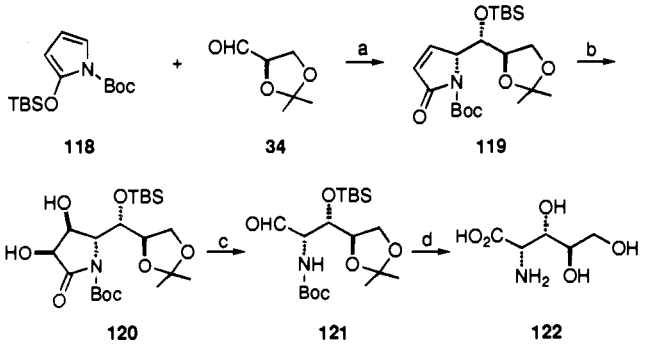
A quite different approach was designed by Bose[79] for an enantiospecific synthesis of the nonnatural enantiomer of polyoxamic acid *ent*-**106** from the protected D-arabinose *N*-benzylimine **110**. As shown in Scheme 22, through a set of several reactions involving β-lactam formation to **111** and oxidative one-carbon excision, the six-carbon lactam **112** was generated. This lactam was elaborated to the target five carbon amino acid *ent*-**106** according to a protocol entailing a series of enantioconservative reactions and further shortening of the chain.

Scheme 23[a]



[a] Key: (a) $MgBr_2$ etherate, CH_2Cl_2, -20°C; (b) TBAF; then *p*-TsOH; (c) PDC; then CH_2N_2; then O_3, MeOH; then $NaBH_4$; then $ClCO_2C_6H_4NO_2$; then NH_3, MeOH.

Scheme 24[a]

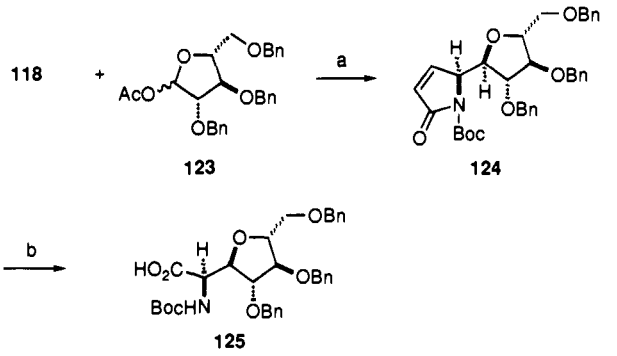


[a] Key: (a) $SnCl_4$, Et_2O, -80°C; then TBSCl, DMF, imidazole; (b) $KMnO_4$, DCH-18-crown-6, CH_2Cl_2; (c) LiOH, THF, 0°C, then Na IO_4, SiO_2, CH_2Cl_2; (d) $NaIO_4$, $RuO_2 \cdot H_2O$ cat., then CF_3CO_2H, MeOH; then SiO_2, NH_4OH.

The continuous synthetic efforts by the group of Marshall[12] in the development of γ-oxygenated allylic stannanes for asymmetric syntheses of complex polyhydroxylated derivatives led to an elegant highly stereoselective entry to the polyoxamic acid derivative **117** from the (*R*)-serine aldehyde **113**.[80] As briefly depicted in Scheme 23, four-carbon homologation of **113** with nonracemic stannane **114** in a matched sense allowed production of a single *syn,syn*-allyl alcohol derivative **115** in high yield. Treatment of **115** with TBAF followed by acid afforded the desilylated rearranged acetonide **116** which was transformed to the polyoxamic acid derivative **117** by oxidation of the primary alcohol followed by oxidative cleavage of the double bond.

Extensive work from our laboratory has demonstrated the viability and excellent versatility of the homologative approach based on furan-, pyrrole-, and thiophene-based siloxydienes for syntheses of densely functionalized enantioenriched compounds.[28] Aimed at exploring the potential of *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (**118**) and 2-(trimethylsiloxy)furan (**49**) for the synthesis of biologically important acyclic and cyclic aminated derivatives, we embarked on a program directed to synthesize polyhydroxylated amino acids. Successful implementation of this strategy to chiral syntheses of polyhydroxy-α-amino acids was achieved starting from enantiopure sugar aldehydes. As an example, the synthesis of 4-epi-polyoxamic acid **122** is illustrated in Scheme 24.[81]

Scheme 25[a]



[a] Key: $TrClO_4$, Et_2O, 0°C; (b) $KMnO_4$, DCH-18-crown-6, CH_2Cl_2; then LiOH, THF, 0°C; then $NaIO_4$, SiO_2, CH_2Cl_2; then $NaIO_4$, $RuO_2 \cdot H_2O$.

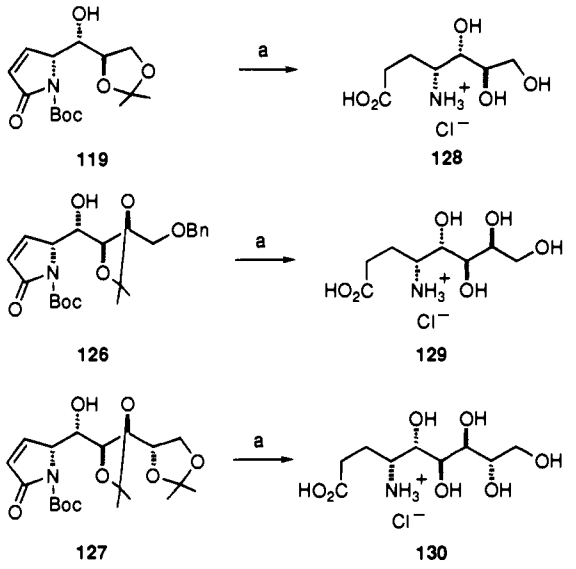
According to an optimal protocol, crystalline lactam **119**, easily available from **34** and silyl ether **118** (95:5 dr), was first subjected to double-bond dihydroxylation with $KMnO_4$/18-crown-6 ether/CH_2Cl_2. This gave saturated lactam **120** as the sole stereoisomer. Hydrolytic lactam opening (LiOH, THF) and subsequent oxidative diol fission at the C2–C3 linkage ($NaIO_4$) provided protected 2-amino-2-deoxy-D-arabinose **121**. Exposure of **121** to $NaIO_4$/catalytic RuO_2 in CH_3CN/CCl_4/water/acetone solvent mixture furnished the protected amino acid almost quantitatively which was fully deprotected by 1:1 trifluoroacetic acid/methanol treatment to amino acid **122**. The same reaction protocol was successfully extended to other aldehydosugar derivatives easily obtainable from common precursors. Regardless of the aldehyde chirality and substitution, a wide variety of hydroxylated amino acids were obtained, via the corresponding amino sugar intermediates, in preparatively useful yields.

As a further extension of this technique,[82] arabinofuranosylglycine **125** was synthesized, in a straightforward fashion, from benzylated *O*-acylarabinofuranose **123**, utilizing **118** as a masked glycine anion equivalent (Scheme 25). Thus, reaction of **118** with **123** in Et_2O in the presence of $TrClO_4$ (0.5 equiv) at 0 °C, afforded unsaturated lactam **124** almost exclusively, which was directly transformed to the protected amino acid **125**, by following the reaction sequence outlined for the acyclic amino acid **122**.

A variety of protected lactam templates, *e.g.* **119**, **126**, and **127** readily obtainable through diastereocontrolled coupling of **118** with suitable aldehyde precursors, were also exploited to prepare diversely substituted 4-amino-2,3,4-trideoxyaldonic acids, *e.g.* **128–130**, representatives of a novel class of GABA *C*-glycoconjugates (Scheme 26).[83] Noticeably, this reaction scheme utilized pyrrole-based silyl enol ether **118** as the γ-anion equivalent of GABA.

Hybrid structures with carbon–carbon-joined amino acid and carbohydrate moieties are often encountered in nature as individual molecules or as the core components of complex nucleoside antibiotics.[84] Cyclic arrays comprise both furanose and pyranose derivatives, bearing either anomeric or terminal substitutions. Furan-based siloxydiene **49** was utilized for preparation of some pyranosidic representatives of this progeny.[85] A versatile synthetic plan (Scheme 27) called for *C*-glycopyranosyl glycine de-

Scheme 26[a]



[a] Key: (a) H_2, Pd/C, THF, NaOAc; then aq. HCl, reflux.

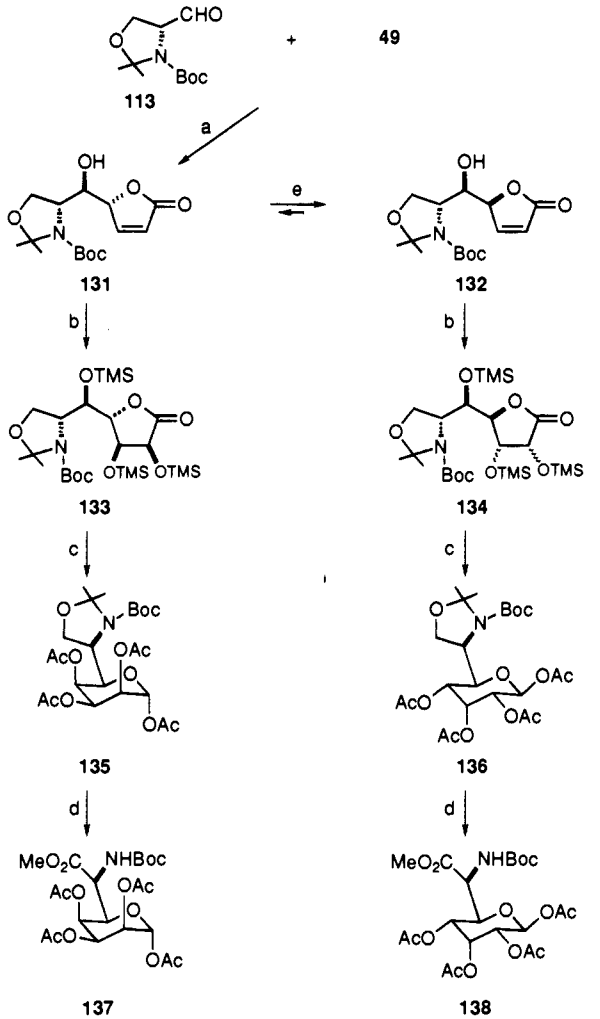
rivatives **137** and **138** to be generated from the *arabino*- and *ribo*-configurated butenolides **131** and **132**, respectively.

The opening move was the preparation of the enantiomerically pure butenolides **131** and **132**, and this was achieved via four-carbon elongation of D-serinal **113** using 2-(trimethylsiloxy)furan (**49**). This reacted with **113** in CH_2Cl_2 in the presence of BF_3 etherate providing seven-carbon *arabino*-configurated butenolide **131** selectively along with only trace amounts of the *ribo*-counterpart **132**. Base-catalyzed C-4 epimerization of the *arabino*-butenolide using Et_3N provided equilibrium mixtures of *ribo* and *arabino* epimers in a ratio of ca. 65:35 from which the more abundant component **132** was obtained in a pure state. The lactone fragments in **131** and **132** were first elaborated according to a highly stereoselective three-step sequence consisting of protection of the free OH at C-5 as the TMS ether, anti-*cis* dihydroxylation of the butenolide double bond using $KMnO_4$, and persilylation. This provided heptonolactones **133** and **134** in high overall yields.

The ring expansion to pyranoses **135** and **136** required three further operations. DIBALH reduction generated γ-lactol intermediates, which, by citric acid–methanol treatment and subsequent peracetylation, were converted to pyranoses **135** and **136**. In the final stages of the synthesis, the remaining carbon to be elaborated was the terminal hydroxymethylene group. Treatment of **135** and **136** with 70% aqueous acetic acid at 60 °C resulted in selective removal of the acetonide groups, giving compounds with unprotected terminal CH_2OH functions. The crude primary alcohols were subjected to oxidation using $NaIO_4$ and catalytic RuO_2, resulting in formation of the expected carboxylic acids, which were finally transformed into the corresponding methyl esters **137** and **138** by CH_2N_2 treatment.

The potential of peptide *O*-glycoconjugates as therapeutic agents has attracted great attention by virtue of the improved activity and bioavailability of peptidyl drugs. To combine these features with an

Scheme 27[a]



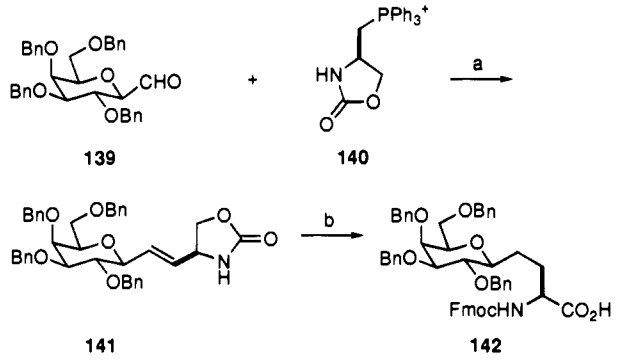
[a] Key: (a) BF_3 etherate, CH_2Cl_2, -80°C; (b) TMSCl, pyridine; then $KMnO_4$, DCH-18-crown-6, CH_2Cl_2; then TMSCl, pyridine; (c) DIBALH, CH_2Cl_2, -80°C; then MeOH, citric acid; then Ac_2O, pyridine, DMAP; (d) aq. AcOH, 60°C; then $NaIO_4$, $RuO_2 \cdot H_2O$; then CH_2N_2, Et_2O; (e) Et_3N, DMAP, CH_2Cl_2.

increased metabolic stability, it was planned to replace the labile *O*-glycosidic linkage in the conjugates with more resistant carbon–carbon junctions. The problem has been addressed by the development of synthetically useful strategies for the synthesis of *C*-glycosylated α-amino acid subunits to be incorporated into pharmacologically active peptides. Thus, for example, β-Gal-*CH*$_2$-Ser **142** was recently synthesized by Bednarski as outlined in Scheme 28.[86]

The key reaction was the coupling of the D-galactose-based aldehydo sugar template **139** with the Wittig reagent **140**, a β-alanyl anion equivalent, to furnish the trans olefin **141** with a high level of stereoselectivity (15:1 *trans*/*cis* ratio). Subsequent reduction of the olefin, protecting group manipulation, and oxidation of the terminal hydroxymethyl to CO_2H furnished a suitably protected *C*-glycosyl-α-amino acid **142** in excellent yield. It was found that incorporation of this unit into a 17-amino acid α-helical peptide had a strong destabilizing effect on the helix.

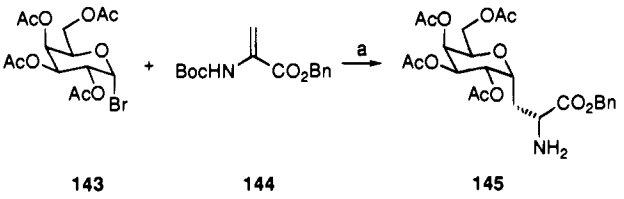
Aimed at increasing the metabolic stability of the gonadodropin-releasing hormone against Buserelin,

Scheme 28[a]



[a] Key: (a) BuLi, THF; (b) $TsNHNH_2$, NaOAc, DME, H_2O; then Boc_2O, Et_3N, DMAP; then $CsCO_3$, MeOH; then TFA, PhSH, CH_2Cl_2; then Fmoc-OSuc, CH_2Cl_2; then Jones.

Scheme 29[a]



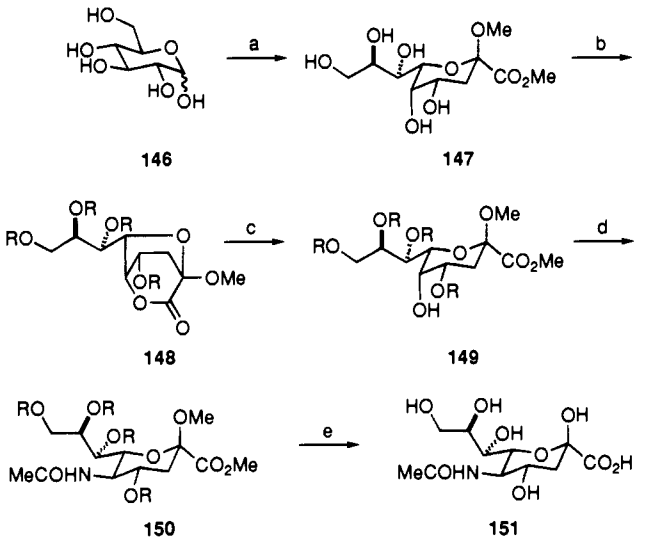
[a] Key: (a) Bu_3SnH, AIBN, toluene, 60°C; then TFA, $NaHCO_3$.

a nonapeptide developed by Hoechst, Kessler and his colleagues[87] prepared the *C*-α-D-galactosylated alanine derivative **145** via free radical addition of peracetyl galactosyl bromide **143** to a dehydroalanine derivative **144** (Scheme 29). The *C*-glycosylated GnRH agonist **145** showed a strongly increased water solubility and proved to be more active than the natural GnRH. The analogous 1-*C*-(α-D-glucopyranosyl)-D-alanine was prepared by Gurjar[88] according to a three-carbon stereoselective homologation of peracetyl glucose at the anomeric center.

Sialic acid (**151**) is an essential component of gangliosides which are involved in cellular interactions, differentiation, and growth. In addition, sialic acid and other related compounds could play an important role in cell–virion recognition. Exploiting his chemistry based on indium-mediated allylation of carbohydrates in aqueous media (*vide supra*), Whitesides[89] succeeded in synthesizing Neu5Ac (**151**) by starting with *N*-acetyl-β-D-mannosamine and ethyl α-(bromomethyl)acrylate.

Using a biomimetic analysis, Shiba[90] envisioned the nine-carbon skeleton of sialic acid (**151**) to be derived from inexpensive D-glucose (**146**) and oxaloacetic acid (Scheme 30). Thus, **146** was coupled with oxaloacetic acid in alkaline solution. The product was then decarboxylated under acidic conditions and treated with HCl in methanol. Five pyranose and furanose isomers, including pyranose compound **147** were obtained in 20% yield and separated from each other. Attention was now directed to introduction of the amino functionality at C-5 in compound **147** with configurational inversion, in the presence of several unprotected hydroxyls. To differentiate the hydroxyl at C-5 from the other ones, formation of bicyclic lactone intermediate **148** was effected by intramolecular lactonization. This resulted in temporary

Scheme 30[a]



[a] R = PhNHCO. Key: (a) oxalacetic acid, OH^-; then HCl, MeOH; (b) $Ba(OH)_2$; then DCC, pyridine; then PhNCO, pyridine; (c) HCl, MeOH; (d) Tf_2O, pyridine, CH_2Cl_2; then $Bu_4N{\cdot}N_3$; then H_2, Pd/C; then Ac_2O, DMAP; (e) NaOH; then Amberlyst 15.

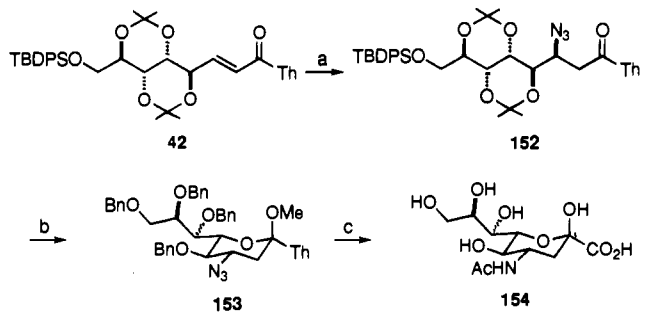
protection of the C-5 OH. The remaining four hydroxyls were then phenylcarbamoylated and the lactone cleaved. This allowed synthesis of the advanced intermediate **149** bearing a free hydroxy function at C-5. The amino group was thus easily installed via the azide by conventional S_N2 displacement. The protected sialic acid **150** so obtained was finally liberated of all the protecting groups by successive alkaline and acidic hydrolyses to give **151**. Despite the low yield of the condensation stage, the low price of the starting sugar and the reagents makes this scheme one of the most valuable from a preparative point of view. Remarkably, the furanose counterparts obtained from the above-mentioned condensation proved useful for syntheses of sialic acid isomers to be evaluated as inhibitors of influenza virus neuramidases.[91]

Unnatural sialic acid *iso*-Neu4Ac (**154**) was recently obtained by Dondoni[92] starting from the same intermediate **42** [ex D-mannose (**11**)] as that used for the synthesis of KDN **15** (*vide supra*). Conjugate azidation of **42** with trimethylsilyl azide in the presence of fluoride anion gave rise to *syn* adduct **152** preferentially (3:1 diastereomeric ratio) which was first cyclized to **153** and then transformed to *iso*-Neu4Ac (**154**) by a simple protocol consisting of unmasking of the formyl moiety embodied in the thiazole fragment, oxidation, reductive removal of the benzyl protecting groups, and *N*-acetylation (Scheme 31).

C. Carbon–Carbon-Linked Oligosaccharides

Carbon oligosaccharides are a class of nonnatural analogues of oligosaccharides wherein the interglycosidic oxygen bridge is replaced by a methylene linker. In a broader context this subclass also includes examples in which the monosaccharide units are connected either directly or by way of more extended carbon linkers. This novel class of pseudocarbohydrates—the first example was reported in

Scheme 31[a]



[a] Th = 2-thiazolyl. Key: (a) $TMSN_3$, F^-, CH_2Cl_2, -20°C; (b) HCl, MeOH; then NaH, BnBr; (c) CHO deblocking; then oxidation; then Li/NH_3; then Ac_2O; then AcOH, H_2O.

1983 by Sinaÿ[93]—is of considerable interest and has attracted wide attention as a result of its biological and structural significance. Among the various approaches culminating in the syntheses of well-defined *C*-oligosaccharides, strategies based on stereocontrolled connection of suitably preformed monosaccharides constitute the avenue of choice for a number of research groups.[94] While, certainly, this technique allows construction of the oligomeric target in an expeditious fashion it, conversely, lacks versatility as construction of the resulting oligomer is strictly biased by the inherent nature of the monomeric carbohydrate blocks. To overcome this intrinsic limitation, novel flexible strategies to access *C*-disaccharides or higher order oligomers have been envisioned and executed (*vide infra*), on the basis of *de novo* implementation of the carbohydrate frame(s) during the homologative process.

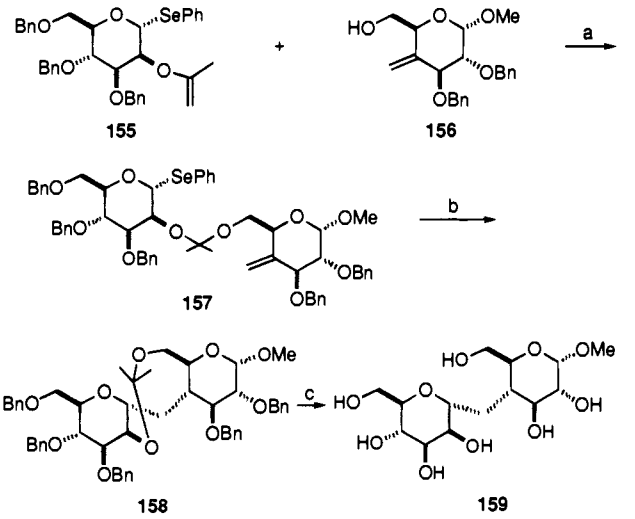
According to Sinaÿ,[95] the intermolecular regio- and stereocontrolled condensation of a nucleophilic, anomeric radical donor with an exomethylene sugar would constitute a potentially general and expeditious strategy for *C*-disaccharide construction. Temporary covalent connection between the donor and acceptor counterparts by means of easily cleavable ketal or silaketal tethers strongly facilitated C–C bond formation between the reacting vicinal centers. Indeed, condensation of enol ether **155** with carbinol **156** generated the ketal intermediate **157** which was selectively cyclized to α-*C*-mannoside **158** with promotion by Bu_3SnH–AIBN (Scheme 32).

Removal of the temporary ketal connection then allowed synthesis of the *C*-disaccharide **159**. According to a similar expedient, methyl α-*C*-maltoside (**161**) was straightforwardly prepared from the silaketal connected precursor **160**, by a regioselective 9-*endo-trig* radical cyclization process.[96] The protected maltoside **163** likewise could be prepared from the silyl-connected intermediate **162** (Scheme 33).[97]

By employing a conceptually related stratagem, a direct and efficient stereoselective synthesis of methyl α-*C*-isomaltoside **167** was devised by Beau and Skrydstrup,[98] as shown in Scheme 34. Coupling of the two subunits **164** and **165** proceeded well providing intermediate **166** which was cyclized in the presence of SmI_2 and further transformed to the ethylidene-linked maltose homologue **167**.

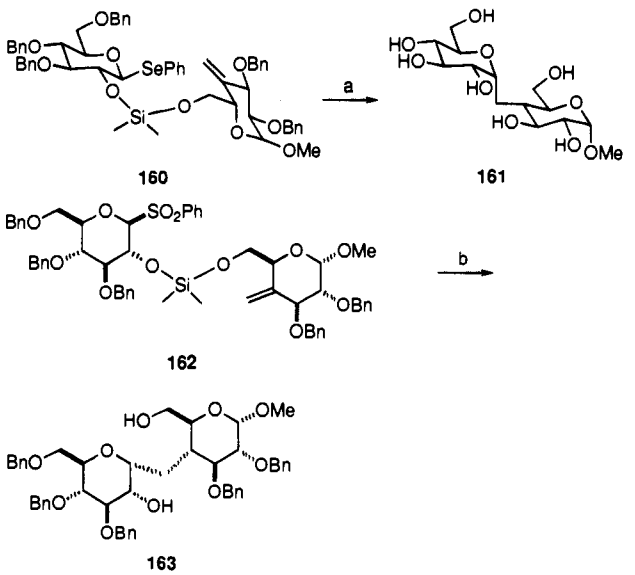
In recent endeavors to synthesize methylene-linked *C*-disaccharides, two complementary approaches,

Scheme 32[a]



[a] Key: (a) camphorsulfonic acid, 4Å MS, MeCN, -40°C; (b) Bu_3SnH, AIBN, toluene, reflux; (c) CF_3CO_2H, CH_2Cl_2, H_2O; then Ac_2O, pyridine; then MeONa, MeOH; then H_2, Pd/C, MeOH, AcOH.

Scheme 33[a]

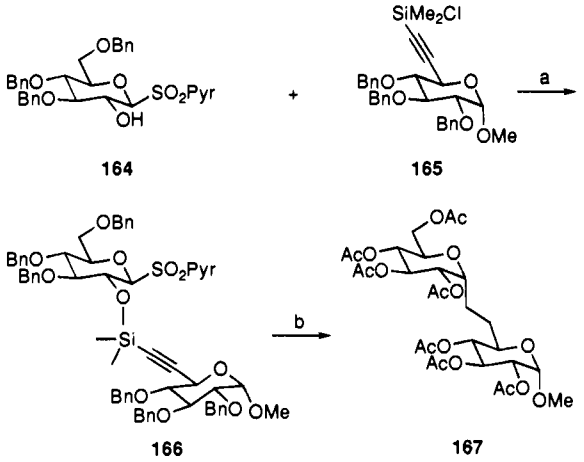


[a] Key: (a) Bu_3SnH, AIBN, benzene, 60°C; then HF, THF; then H_2,Pd/C, MeOH, AcOEt; (b) SmI_2, benzene, HMPA, 60°C; then aq. HF.

namely the coupling of a C_6 electrophile with a C_7 nucleophile and the coupling of a C_6 nucleophile with a C_7 electrophile have been exploited by Schmidt and co-workers.[99–101] For example, C–C bond formation between the lithiated species **168** and gluconolactone **169** furnished the β(1,4)-connected branched undeculose **170**, while condensation of 1-*C*-lithiated 2-(phenylsulfinyl)-D-galactal **171** with 4-*C*-formylglucopyranoside **172** provided a direct entry to hydroxymethine-bridged β(1,4)-disaccharide **173** (Scheme 35). Extending this procedure, β(1,3)-connected *C*-disaccharide **175** was also prepared, by starting with homochiral sulfoxide **171** and the C_7 aldehyde **174**.

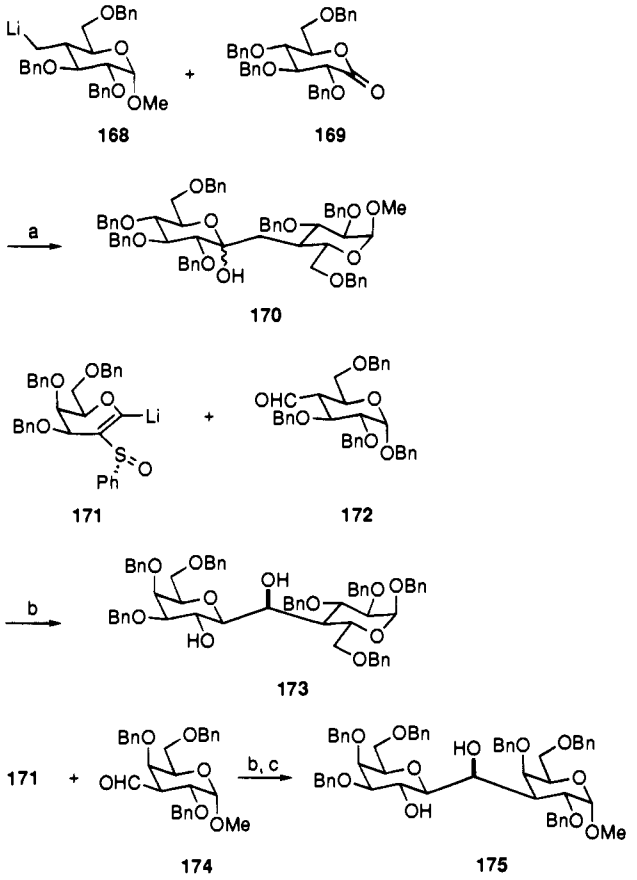
The photolytically induced cross-coupling of α- and β-glycosylmethyl radicals, generated from the corresponding cobaloximes, with nitronate ions derived from 6-nitrosugars, provided a direct entry to α- and β-(1,6)-linked *C*-disaccharides.[102] Thus, for example, protected *C*-isomaltoside **178**, an analogue of the

Scheme 34[a]



[a] Pyr = 2-pyridyl. Key: (a) Et_3N, DMAP,CH_2Cl_2; (b) SmI_2, THF; then TBAF, THF; then H_2, Pd/C, then Ac_2O, pyridine.

Scheme 35[a]

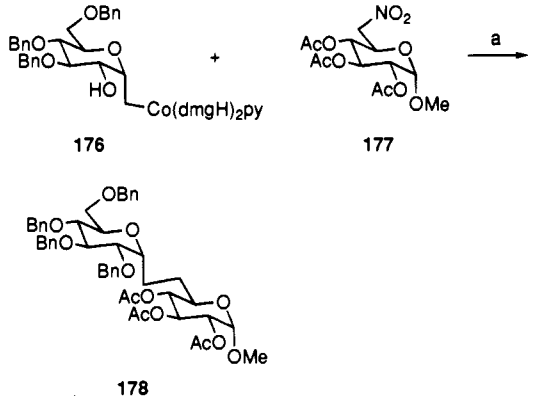


[a] Key: (a) THF, -50°C, (b) THF, -100°C; (c) Raney-Ni, THF; then $BF_3{\cdot}Me_2S$, THF, 0°C; then NaOH, H_2O_2.

previously disclosed compound **167**, was quickly assembled from (glycosylmethyl)cobaloxime **176** and D-glucose-based nitro derivative **177** under irradiation with a 300 W visible light lamp (Scheme 36).

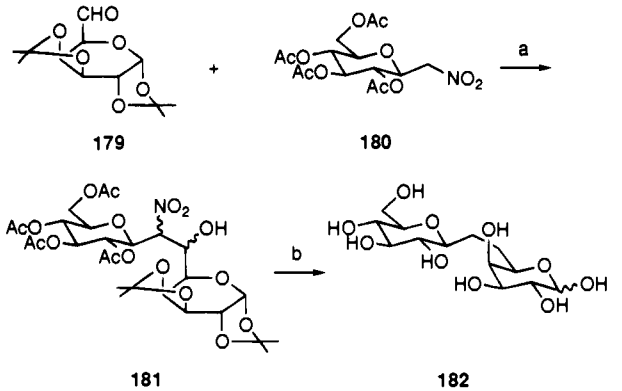
The condensation of *aldehydo*-sugars with glycosylnitromethanes, readily accessible from the parent sugars, was devised by Martin in a concise approach to (1,6)- and (1,1)-linked *C*-disaccharides.[103] As an example of this powerful technique, the synthesis of the carba analog of 6-*O*-β-D-glucopyranosyl-D-galactose (**182**) is detailed in Scheme 37.

Scheme 36[a]



[a] Key: (a) hv, NaOH, EtOH; then Ac_2O, pyridine; then Bu_3SnH.

Scheme 37[a]



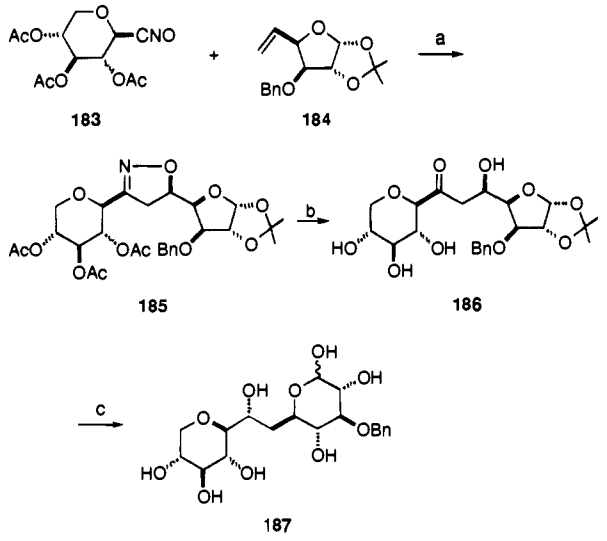
[a] Key: (a) KF, MeCN, DCH-18-crown-6; (b) Ac_2O, pyridine, $CHCl_3$; then $NaBH_4$, MeOH, CH_2Cl_2, 0°C; then Bu_3SnH, AIBN, reflux; then MeONa, MeOH; then H_3O^+.

The opening move was a nitroaldol condensation between galactose-derived aldehyde **179** and glucosylnitromethane peracetate **180**. When promoted by fluoride ion, the reaction proceeded successfully, providing the adduct **181** in reasonable yield and excellent diastereoselectivity (~90%). Three clean reactions, namely dehydration, reduction of the double bond, and radical denitration allowed transformation of the aldol intermediate **181** into *C*-disaccharide **182**. Enlarging the synthetic scope of this chemistry, β,β-(1,1)-linked systems, including *C*-β,β-threalose, were also produced.

A stereocontrolled route to higher-carbon sugars, comprising (1,6)-linked *C*-disaccharide derivatives, was recently introduced by Paton,[104-106] utilizing, as a key step, cycloaddition of carbohydrate-derived nitrile oxides with carbohydrate alkenes, followed by reductive hydrolytic cleavage of the formed isoxazolines. As a representative example of this remarkable approach, the synthesis of the (1,6)-hydroxymethylene-linked xylose–glucose derivative **187** is described in Scheme 38, utilizing D-xylose nitrile oxide (**183**) and alkene **184**, obtainable from D-glucose, as the two components.[104]

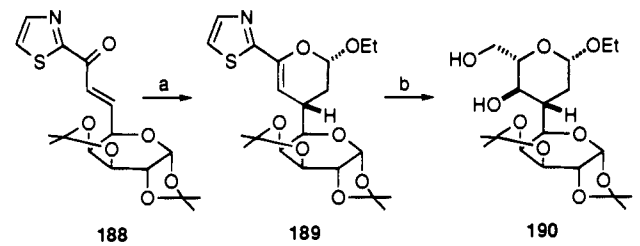
In situ-generated nitrile oxide **183** was thus reacted with **184** to produce the (5*R*)-isoxazoline **185** as the predominant adduct, accompained by 20% of the (5*S*)-epimer. Isoxazoline **185** was converted to β-hydroxy ketone **186** in acceptable yield, by deacetylation

Scheme 38[a]



[a] Key: (a) toluene, reflux; (b) KCN, MeOH; then H_2 / Raney-Ni; (c) H_3BO_3, MeOH, THF, H_2O; then L-Selectride; then aq. TFA.

Scheme 39[a]

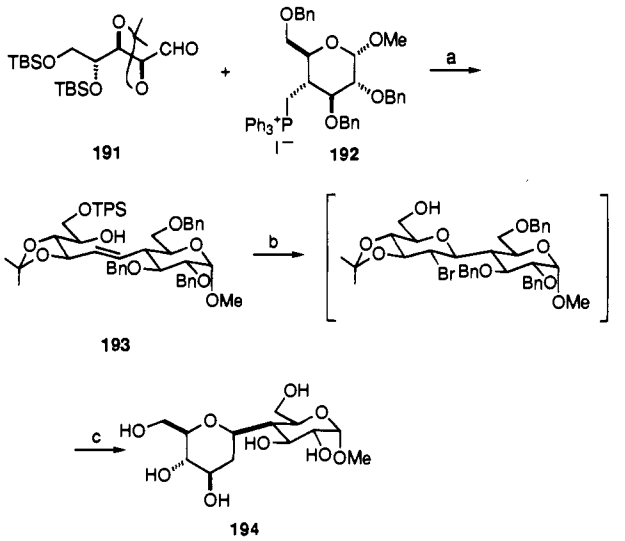


[a] Key: (a) ethyl vinyl ether, 80°C; (b) TfOMe, MeCN; then $NaBH_4$, MeOH, 0°C, then $HgCl_2$, MeCN, H_2O; then $NaBH_4$, MeOH; then BH_3·THF; then H_2O_2, NaOH, 60°C.

followed by reductive hydrolytic cleavage of the isoxazoline ring. Compound **186** is only few steps away from disaccharide **187** which was obtained by stereoselective reduction of the C=O function (L-Selectride) and final acid-promoted deacetalization and furanose-to-pyranose ring expansion. The method is capable of connecting various combinations of monosaccharide units, permitting syntheses of a variety of higher-carbon aldoses[105] and dialdoses,[106] as well as variously linked *C*-disaccharide derivatives.

A stereoselective hetero-Diels–Alder reaction was applied by Dondoni in designing a versatile approach to carbon-carbon disaccharides.[107] As illustrated for the C(3)–C(5)-linked dipyranoside **190**, the second sugar fragment was created *de novo*, its chirality dictated by the chirality of the starting sugar matrix (Scheme 39). The route started with oxabutadiene **188** readily available by Wittig olefination of *dialdo*-D-galactose with the thiazole carbonyl ylide **40**, as previously disclosed for the synthesis of KDN **15** (*vide supra*). The key reaction was the asymmetric cycloaddition reaction of this heterodiene with neat ethyl vinyl ether, providing **189** as the predominant cycloadduct (4:1 diastereomeric ratio). Elaboration of the dihydropyran fragment of **189** into a 2,3-dideoxy-pyranosyl unit was carried out by first deblocking of the formyl moiety embodied in the thiazole ring and then submitting the glycal double bond

Scheme 40[a]



[a] Key: (a) KF, THF; then TBAF, THF; then TPSCl, imidazole, DMF; (b) NBS, Br_2, MeCN; then TBAF, THF; (c) Na / NH_3; then *p*-TsOH, MeOH.

to *cis*-specific hydroboration. This provided pseudodisaccharide **190** wherein the two aldoses are directly joined by a carbon–carbon link.

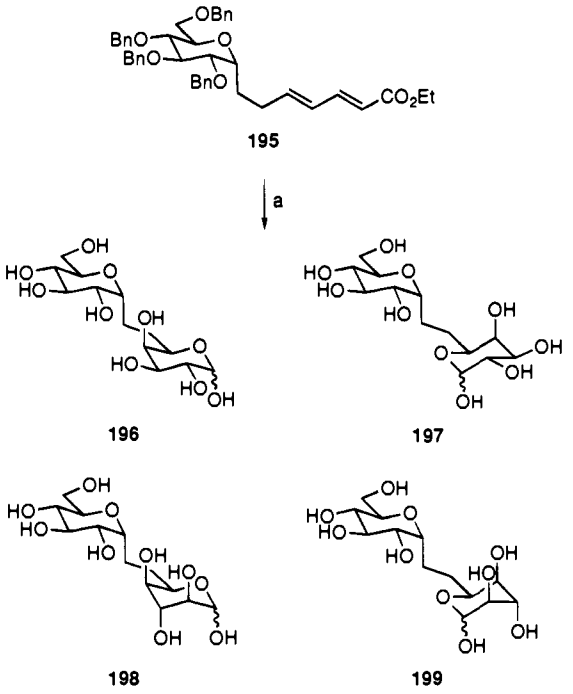
An analogous (1,4)-*C*-disaccharide bearing direct connectivity of the two carbohydrate rings, namely α-methyl 1′,2′-dideoxycellobioside (**194**), was synthesized by Armstrong by a homologative procedure based on a Wittig-type olefination (Scheme 40).[108]

Condensation of *aldehydo*-D-arabinose **191** with the phosphonium salt **192** in the presence of potassium fluoride afforded a mixture of olefins which was photochemically isomerized and easily transformed into a major compound **193**. After some trials, satisfactory cyclization conditions were found (NBS, Br_2) allowing formation of a brominated disaccharide intermediate as a single diastereoisomer, albeit in low yield. Conventional debromination and deprotective workup finally afforded cellobioside analog **194**. It should be noted that regiochemical control governing the crucial 6-*endo* (versus 5-*exo*) cyclization is exerted by the trans-fused dioxolane ring connecting the *erythro*-disposed allylic and homoallylic oxygens in **193**. This restricts the scope of the synthesis to glucono-β-*C*-glycosides and their derivatives.

In a quest for water-soluble *C*-oligosaccharide units to be used as tethers to covalently link biomolecules, the same author[109] recently described syntheses of certain interesting dipyranosyl sugars containing an acetylenic linker. The chemistry involved preparation of a lithiated C-1 acetylenic carbohydrate which was coupled to suitable electrophilic sugar acceptors.

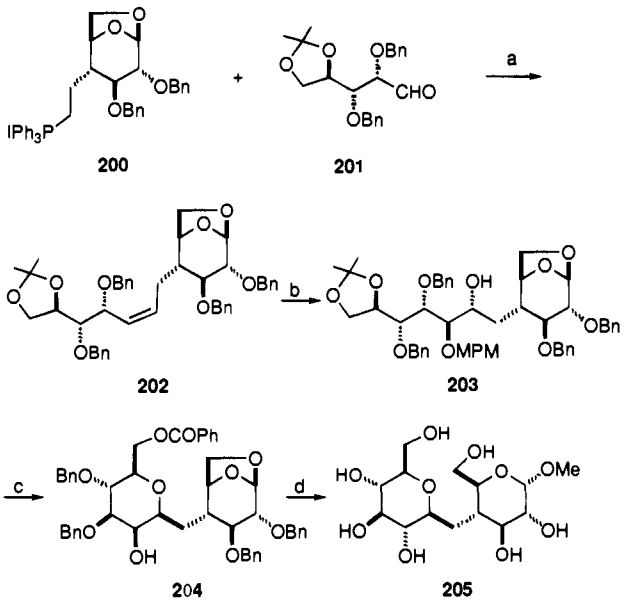
Paralleling recent combinatorial approaches to peptide libraries,[110] Armstrong[111] designed a skill growth technique to homologate a given carbohydrate template with maximal constitutional and stereochemical versatility. That is, keeping constant the stereochemistry of a unit in the oligomer, while varying the structure and shape of the newly emerging one. A representative example (Scheme 41) highlights the preparation of several D-glucose-α-(1,6)-hexose *C*-disaccharides by starting with a common C-1 homologated monosaccharide template bearing a fixed sugar. Diene ether **195**, readily available

Scheme 41[a]



[a] Key: (a) OsO_4, NMO; then DIBALH, -32°C; then H_2, $Pd(OH)_2/C$, MeOH.

Scheme 42[a]



[a] Key: (a) n-BuLi, THF, -78°C to 0°C; (b) OsO_4, *N,N'*-bis(mesitylmethyl)-(*R,R'*)-1,2-diphenyl-1,2-diaminoethane, CH_2Cl_2, -80°C; then MPMBr, NaH, THF; (c) Swern oxidation; then aq. HCl, THF; then PhCOCl, pyridine; then n-Pr_3SiH, BF_3 etherate, MeCN, -20°C; (d) Swern oxidation; then $BH_3 \cdot Et_3N$, THF; then NaOMe, MeOH; then H_2, $Pd(OH)_2/C$, MeOH; then MeOH, HCl, 90°C.

by Wittig-type homologation of perbenzylated 1-*C*-allylglucose, was subjected to normal osmylation (OsO_4, NMO) followed by selective reduction of the ester moiety to give two pairs of lactols in a 5:1 ratio.

The more abundant pair of adducts was separated and deprotected to afford D-Glu-α-(1,6)-D-Gal (**196**) and the hybrid D-Glu-α-(1,6)-L-Gal (**197**). D-Glu-α-(1,6)-D-Ido (**198**) and D-Glu-α-(1,6)-L-Ido (**199**) emerged from the less abundant pair of lactols. To make a detailed structure assignment, these diastereomeric *C*-disaccharides were also prepared individually according to a Sharpless asymmetric dihydroxylation protocol.

Extremely flexible synthetic routes to carba di- and trisaccharides have been developed by Kishi and coworkers with the principal aim to investigate the conformational properties of this nonnatural sugar subclass and to get a further insight into the relationship between the conformation of the carbohydrates and their binding affinity toward biomolecular conjugates. Of the numerous synthetic achievements of that laboratory, three relevant examples are selected herein, which emphasize the creativity of the authors and the beauty of the chemistry involved.

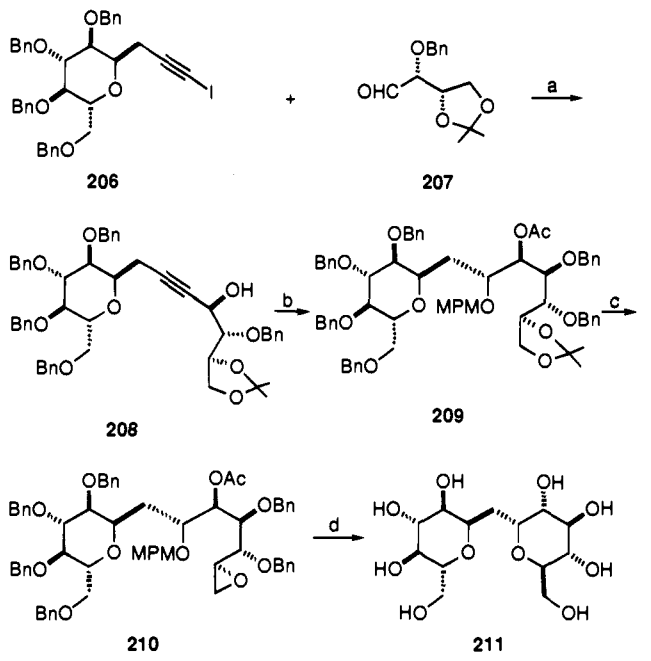
For the carbon analogue **205** of cellobioside,[112] the opening synthetic move was a Wittig olefination of the ylide generated from anhydro sugar **200** and the five-carbon aldehyde **201** (Scheme 42). This reaction provided the *cis*-olefin **202** bearing the complete 13-carbon skeleton of the disaccharide target. Catalytic osmylation under the usual conditions proceeded with good selectivity giving, after suitable protection, the higher carbohydrate **203**. The selectivity of this reaction was greatly improved to 60:1 by using asymmetric catalysis. Compound **203** was converted into protected disaccharide **204** according to a sequence of four successive reactions, namely alcohol to ketone oxidation, deprotection of the terminal acetonide moiety and spontaneous annulation, protection of the terminal hydroxymethylene function, and reductive removal of the ketal hydroxyl. Compound **204** was not too far from target compound **205**. The final conversion entailed configurational inversion of the C-2′ stereocenter. This was achieved by Swern oxidation–borane reduction. Remarkably, a 2′-epimeric glycoside was also synthesized, employing **204** as a common intermediate.

The flexibility and efficiency of this synthetic tactic was also demonstrated by syntheses of deoxy and deshydroxymethyl derivatives. For a C-3-deoxy-*C*-maltoside, a nickel(II)/chromium(II)-mediated coupling of D-threose aldehyde and a branched iodopropynyl pyranose was employed as a pivotal step (*vide infra*). A single unified strategy[113] for the stereocontrolled syntheses of α,α-, α,β-, and β,β-trehaloses was also developed by the same research group, taking advantage of extensive previous work in this field. Thus, as shown in Scheme 43 for pseudotrehalose **211**, the synthesis started with the reaction of the iodopropynyl derivative **206** with L-threose aldehyde **207** through the well-exploited Ni(II)/Cr(II)-mediated coupling to give, as the major diastereoisomer, **208** (4:1 ratio). Acetylenic alcohol **208** was subjected to partial hydrogenation to the alkene followed by selective dihydroxylation of the double bond producing, after suitable protecting group manipulations, compound **209**.

Selective removal of the acetonide, tosylation of the primary alcoholic moiety, and basic treatment afforded terminal epoxide **210** which was annulated according to a 6-exo-tet mechanism first to a protected disaccharide unit and then, by full deprotection, to the target trehalose **211**.

An extremely flexible synthesis of certain carbon trisaccharides, including trisaccharide **222** related to

Scheme 43[a]



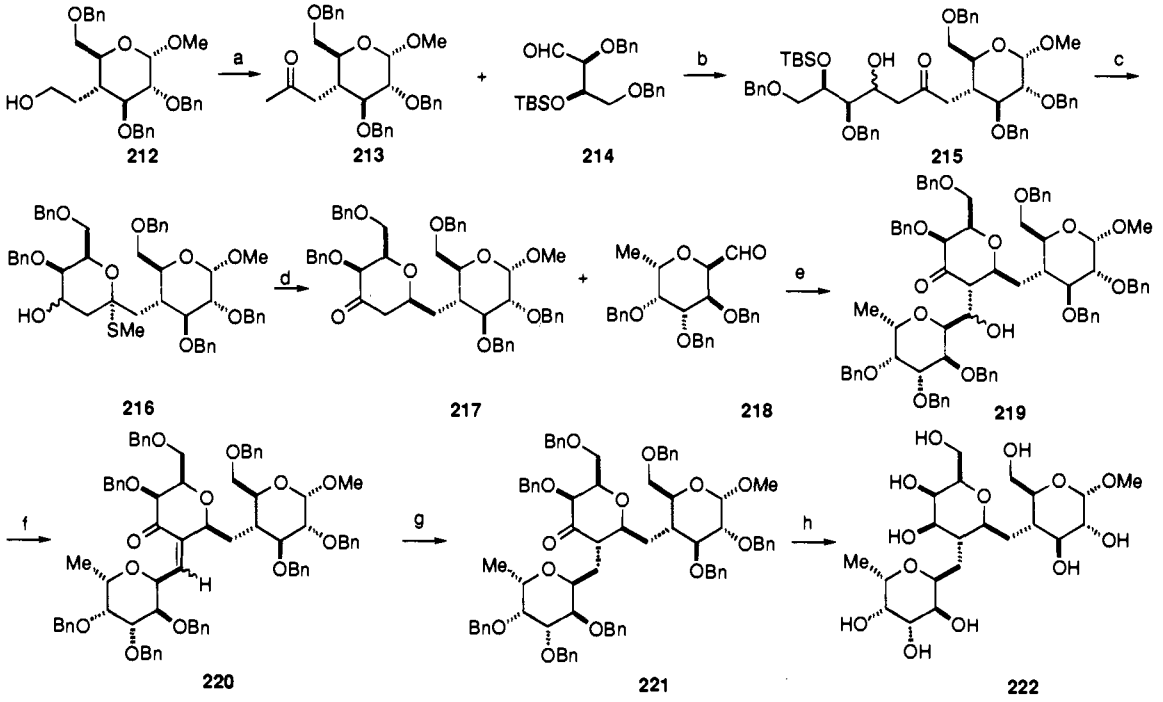
[a] Key: (a) $NiCl_2$, $CrCl_2$, THF, DMF; (b) H_2, Pd, Pb on $CaCO_3$, MeOH; then BnBr, NaH, imidazole, TBAI, THF, DMF; then OsO_4, THF, pyridine; then Bu_2SnO, toluene; then CsF, MPMCl, TBAI, DMF; then Ac_2O, DMAP, pyridine; (c) aq. AcOH; then *p*-TsCl, pyridine; then NaH, imidazole, THF; (d) DDQ, CH_2Cl_2; then *p*-TsOH, CH_2Cl_2; then MMTrCl, pyridine; then K_2CO_3, MeOH; then Swern oxidation; then BH_3, THF; then aq. AcOH, THF; then H_2, $Pd(OH)_2$/C, MeOH.

the type II O(H) blood group determinant, was also developed.[114]

This admirable synthesis (Scheme 44) started with the carbinol **212**, available in large scale from glucose, which was converted to ketone **213** by routine reactions. Aldol condensation with aldehyde **214** yielded **215** as a 4:1 diastereomeric mixture, which was used directly in the subsequent step. Selective removal of the TBS protecting group followed by thioketalization afforded **216**, which was first reduced and then oxidized to give the carbon-linked disaccharide ketone **217**. The ketone in THF at −79 °C was treated with 3 equiv of LiHMDS and TMEDA, followed by the addition of $MgBr_2$. This furnished a magnesium enolate which reacted with the aldehyde **218** obtained, in turn, from 2,3,4-*O*-tribenzyl-L-fucose. There was obtained the equatorial *C*-trisaccharide **219** as a 2:1 epimeric mixture. Mesylation of the mixture followed by treatment with liquid NH_3 gave **220** as a mixture of isomers, which was reduced to the methylene-linked protected trisaccharide **221** using Bu_3SnH in the presence of catalytic AIBN. In the event, the C-2′ equatorial ketone forms, exclusively. This was stereoselectively reduced using $NaBH_4$ creating the last chiral center with the desired configuration. Finally, full debenzylation by hydrogenolysis provided the polyol target **222**.

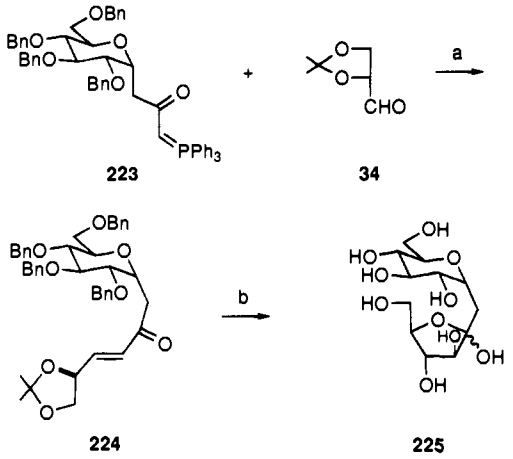
A strategy based on *de novo* construction of an additional sugar unit by stereocontrolled manipulation of a carbon frame appended to a given carbohydrate template was developed by Nicotra and coworkers[115] in connection with a remarkable synthesis of *C*-disaccharide antimetabolites of sucrose. As displayed in Scheme 45, treatment of D-glucose-based phosphorane **223** with D-glyceraldehyde acetonide (**34**) allowed preparation of the α,β-unsaturated ketone **224** in high yield. Osmylation of the double bond, followed by a series of manipulations led to the carbon analogue of sucrose **225**, as a mixture of

Scheme 44[a]



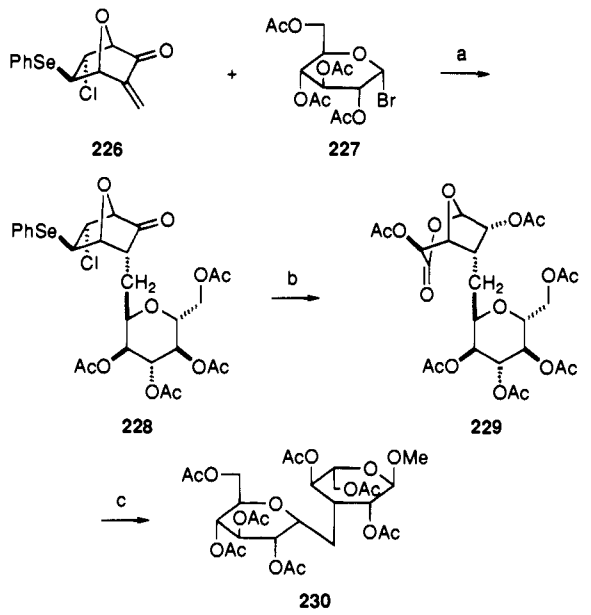
[a] Key: (a) Swern oxidation; then MeMgBr, THF; then Swern oxidation; (b) LiHMDS, THF; then **214**; (c) TBAF, THF; then MeSH, BF_3 etherate, CH_2Cl_2; (d) Bu_3SnH, AIBN, toluene; then Swern oxidation; (e) LiHMDS, TMEDA, THF, -79°C; then $MgBr_2$; then **218**; (f) MsCl, Et_3N, Et_2O; then NH_3, THF; (g) Bu_3SnH, AIBN, toluene; (h) $NaBH_4$, MeOH; then H_2, $Pd(OH)_2$/C, MeOH.

Scheme 45[a]



[a] Key: (a) MeCN; (b) OsO_4, NMO, -30°C; then Ac_2O, pyridine; then $FeCl_3$, SiO_2, Et_2O; then K_2CO_3, EtOH; then H_2, Pd / C, MeOH.

Scheme 46[a]

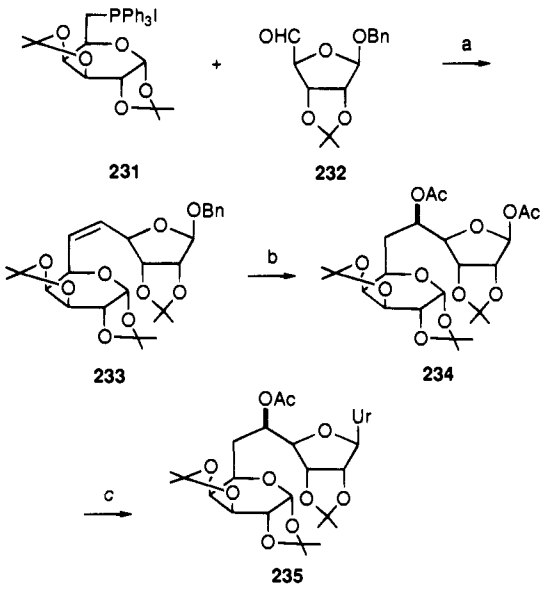


[a] Key: (a) Bu_3SnH, AIBN; (b) $NaBH_4$, THF, MeOH, 0°C; then MCPBA, CH_2Cl_2, -78°C; then Ac_2O, pyridine, DMAP; then OsO_4, CCl_4, $NaHCO_3$, H_2O_2, THF, 0°C; then Ac_2O, pyridine, DMAP; then $NaHCO_3$, MCPBA, CH_2Cl_2; (c) $SOCl_2$, MeOH; then Ac_2O, pyridine, DMAP; then $LiAlH_4$, THF, then Ac_2O, pyridine, DMAP.

pyranosidic and furanosidic forms. Also, the same research group succeeded in preparing an additional analogue of sucrose through BF_3-mediated dimerization of *exo*-methylene glucose.[116]

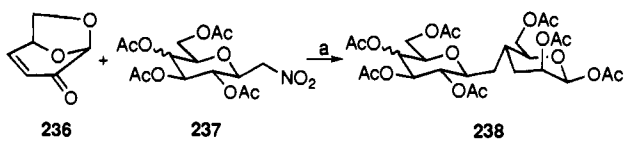
A versatile methodology to access a variety of α-(1,2)-, α-(1,3)-, α-(1,4)-, and α-(1,5)-*C*-linked disaccharides was introduced by Vogel[117] employing his "naked sugar" chemistry.[19,118] Scheme 46 illustrates how fully protected α-D-Glc*p*-*C*-(1,3)-β-L-Man*p*-OMe (**230**) was prepared. The opening move was the radical addition of oxabicyclo[2.2.1]heptan-2-one **226** to α-acetobromoglucose **227** according to a conventional protocol (Bu_3SnH/AIBN). There was obtained the exo ketone **228** as a major adduct along with a minor amount of an anomeric isomer. A set of clean transformations including Baeyer–Villiger oxidative ring expansion led to urono-6,1-lactone **229** which

Scheme 47[a]



[a] Ur=uracil. Key: (a) LiHMDS, THF, HMPA, -70°C to -10°C; (b) BH_3· THF, -20°C to 10°C; then NaOH, H_2O_2; then Ac_2O, pyridine, DMAP; then H_2, Pd / C, EtOH; then Ac_2O, pyridine, DMAP; (c) $Ur(TMS)_2$, TMSOTf, MeCN.

Scheme 48[a]



[a] Key: (a) Et_3N, THF, 0°C; then Bu_3SnH, ABCN, toluene; then $NaBH_4$; then Et_3SiOTf, Ac_2O.

was transformed to the target disaccharide **230** by acidic methanolysis followed by $LiAlH_4$ reduction and full acetylation.

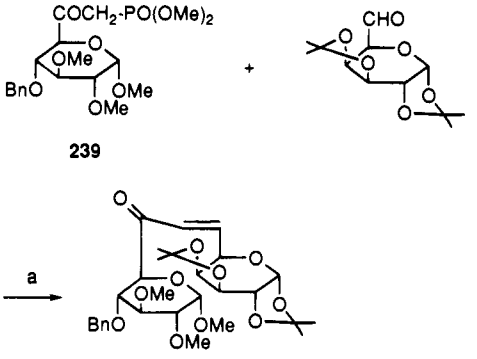
A simple five-step approach to *O*-protected deaminotunicaminyluracil **235**, an 11-carbon nucleoside disaccharide with potential inhibitory effect on the biosynthesis of polysaccharides and glycoproteins, was engineered by Banaszek and Karpiesiuk (Scheme 47),[119] utilizing, as a key operation, a Wittig coupling "tail to tail" between two sugar units.

Thus, treatment of phosphonium salt **231** with D-*ribo*-pentodialdo-1,4-furanoside **232** (LiHMDS, THF-HMPA) stereoselectively resulted in formation of undecose **233**, which was then converted to hydroxylated compound **234** through a moderately selective hydroboration–oxidation reaction followed by appropriate protection. Final condensation of compound **234** with 1,3-bis-*O*-(trimethylsilyl)uracil led to the target compound **235**.

Levoglucosenone (**236**) is an excellent substrate for C–C bond formation through Michael addition of sugar-based carbon nucleophiles. Accordingly, disaccharide **238** was obtained by conjugate addition of nitro derivative **237** to **236** followed by a denitration–reduction sequence (Scheme 48).[120] In addition, a carbon–trisaccharide was prepared by Henry reaction of 4-formyl levoglucosenone with the Paton adduct of nitromethane to levoglucosenone.

Utilizing scantly exploited sugar-derived β-keto phosphonates, Narkunan and Nagarajan have re-

Scheme 49[a]



[a] Key: (a) Cs_2CO_3, Pr^iOH.

cently proposed a quite general approach to higher sugar enones, by Wadsworth–Emmons reaction with aldehydo sugar derivatives.[121] As shown for **240** (Scheme 49), the glucose-derived phosphonate **239** was coupled with isopropylidene-protected α-D-*galacto*-hexodialdo-1,5-pyranose using, as a base solvent, cesium carbonate in 2-propanol. According to a bilateral version of this technique, higher C-2 symmetric bis enones were assembled by starting with a L-tartrate derived bis-phosphonate.

Very recently Johnson[122] succeeded in synthesizing a novel 1,6-linked aza-*C*-disaccharide related to 6-*O*-β-D-mannopyranosyl-D-galactose utilizing, as a key step, a Suzuki coupling of an alkyl boron reagent derived from D-galactose.

III. Synthesis of Hydroxylated Alkaloids

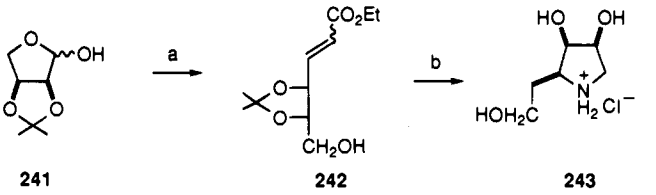
Alkaloidal sugar mimics with a nitrogen in the ring (azasugars), including naturally occurring and synthetic monocyclic and bicyclic derivatives, constitute a realm of important functional molecules which have drawn considerable attention by virtue of their potent and varied biological activities.[47,49,123] Many azasugar representatives have been reported to inhibit various glycosidases in a reversible and competitive manner. Glycosidases are involved in a number of processes, such as digestion, the biosynthesis of glycoproteins, and the catabolism of glycoconjugates. Since inhibitors of glycosidases have shown remarkable therapeutic potentialities in the treatment of metabolic diseases, in the inhibition of tumoral metastasis, and as antiviral substances, including the human immunodeficiency virus, an impressive number of synthetic routes to such compounds and structural variants thereof have been recently developed. It is the intention of this section of the review to bring together the range of totally synthetic methodologies for producing nonracemic monocyclic and bicyclic azafuranose and azapyranose derivatives from simple chirons.[124] For the purpose of this survey some widely exploited approaches such as chemoenzymatic methods and conventional carbohydrate-to-azasugar interconversions are not considered.

A. Monocyclic Compounds

1. Pyrrolidine Derivatives

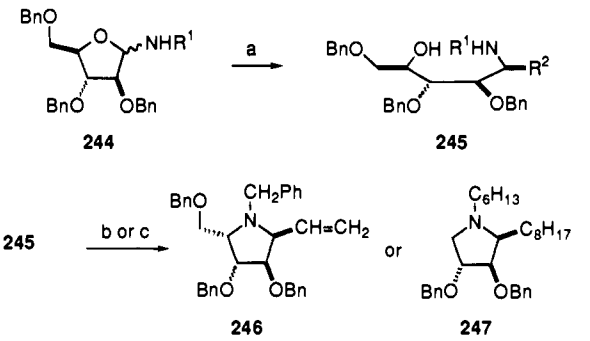
A number of compounds in this subgroup display interesting bioactivity, as for example the inhibition

Scheme 50[a]



[a] Key: (a) $Ph_3PCH{:}CO_2Et$; (b) MsCl, pyridine; then NH_3, EtOH; then, $LiAlH_4$; then TFA, HCl.

Scheme 51[a]



[a] Key: (a) R^2MgX, THF; (b) R^1 = Bn, R^2 = CH:CH_2, Tf_2O, pyridine; (c) R^1 = *n*-C_6H_{13}, R^2 = *n*-C_8H_{17}, PCC; then $BH_3{\cdot}Me_2S$; then TMEDA.

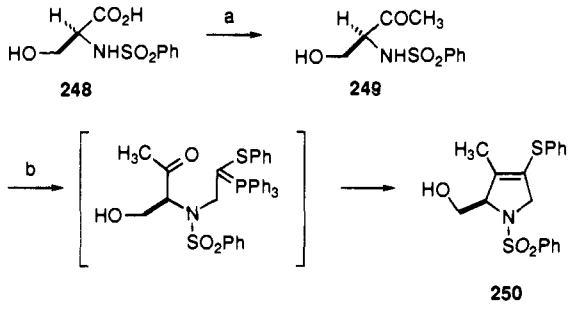
of α-glucosidase I of glycoprotein processing or inhibition of yeast α-glucosidase.[123] Enantiospecific syntheses of a series of 1,4-dideoxy-1,4-imino alditols have been reported on the basis of elongation of short aldehyde or carbohydrate templates. According to Wightman[125] (Scheme 50), two-carbon Wittig homologation of 2,3-*O*-isopropylidene-L-erythrose (**241**) with (ethoxycarbonylmethylene)triphenylphosphorane allowed preparation of the key six-carbon enoates **242** which were converted to L-*lyxo*-iminohexitol (**243**) via mesylation of the terminal hydroxymethyl function followed by ammonia-promoted annulation and deprotection. In a similar fashion, octitol derivatives were synthesized by starting with suitably protected *aldehydo*-hexoses.

A novel expedient procedure for the synthesis of alkylated azafuranose derivatives was introduced by Nicotra,[126] involving, as a key reaction, stereoselective additions of Grignard reagents to protected furanosyl amines (Scheme 51).

Aminosugar **244** was thus treated with saturated and unsaturated magnesium derivatives to afford open-chain aminoalditols **245** with excellent margin of diastereoselection favoring *threo* products (chelation control). Intermediates **245** were transformed to either **246** or **247** by conventional cyclization procedures.

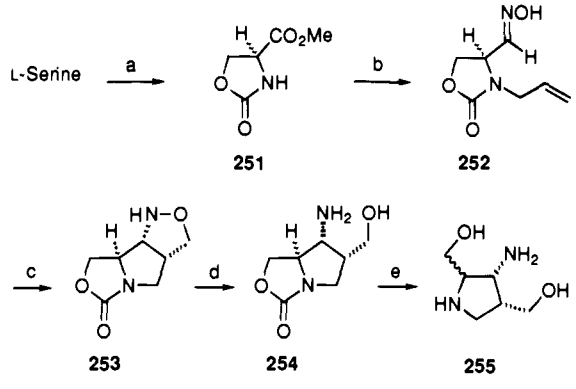
A recent approach[127] relies upon the use of an intramolecular Wittig reaction to generate the five-membered heterocycle. Thus, for example, the *N*-protected α-amino acid **248** was first converted to enantiopure ketone **249** by direct reaction with a lithium reagent (Scheme 52). The ketone was then treated with NaH followed by the appropriate phosphonium salt. There was obtained pyrroline **250**, likely arising from an intramolecular olefination–cyclization. Noticeably, the L-serine-derived pyrro-

Scheme 52[a]



[a] Key: (a) CH_3Li; (b) NaH; then $CH_2{:}C(SPh)P^+Ph_3$.

Scheme 53[a]



[a] Key: (a) Triphosgene, NaOH; then MeOH; (b) NaH, DMF, allyl iodide; then DIBALH; then NH_2OH; (c) toluene, 170°C; (d) Ra-Ni, MeOH, H_2O; (e) aq. Cs_2CO_3, 100°C.

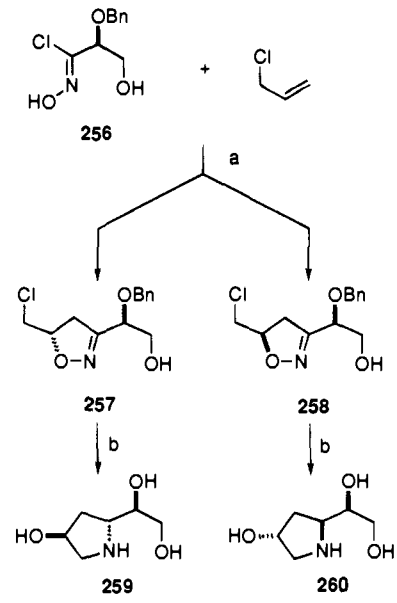
line **250** allowed access to novel hydroxylated pyrrolidines via diastereoselective dihydroxylation or epoxidation procedures.

Starting with L-serine and utilizing intramolecular oxime–olefin cycloaddition, Hassner and co-workers established a nice synthetic route to certain selective inhibitors of α-glucosidase.[128] As shown in Scheme 53, oxazolidone **251**, obtained from L-serine by treatment with triphosgene, was converted to unsaturated oxime **252** by a sequence of three reactions, namely *N*-allylation, ester-to-aldehyde reduction, and oxime formation. Thermolysis of **252** provided the cycloadduct **253** in high yield and stereoselectivity, which was then reduced to enantiopure amino alcohol **254**. At this point all that remained was the removal of the carbamoyl protection at nitrogen, and this was performed by catalytic aqueous Cs_2CO_3 treatment. Disappointingly, epimerization at C-2 took place under these rather forcing conditions, resulting in formation of a 1:3 mixture of isomers **255**.

Isoxazolines **257** and **258** have been viewed by Jäger as five-membered aza-aldol ring structures. These heterocycles, readily available by 1,3-dipolar cycloaddition of alkene derivatives with hydroxylated nitrile oxides, provide key intermediates which are elaborated into a variety of glycosidase inhibiting iminopolyols.[129] This clever plan is detailed by the sequences in Scheme 54, leading to iminohexitols **259** and **260**.

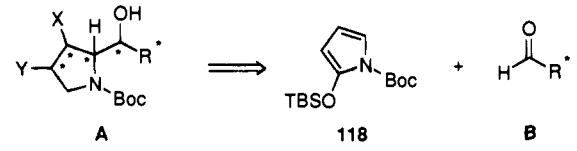
1,3-Dipolar cycloaddition of the nitrile oxide derived from hydroxamic acid chloride **256** (ex 2-*O*-benzyl-L-glyceraldehyde) with allyl chloride according to Huisgen's *in situ* method gave, as expected, the

Scheme 54[a]



[a] Key: Et_3N, Et_2O; then chromatogr. separation; (b) H_2, Pd/C, MeOH; then H_2, Pd / C, MeOH, HCl.

Scheme 55

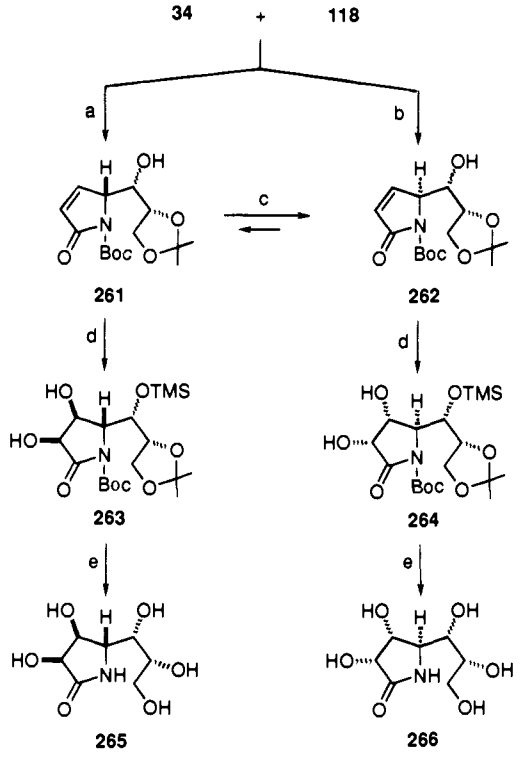


oxazoles **257** and **258** as an approximately 1:1 mixture of diastereoisomers. Separation of individual compounds was carried out by chromatography allowing preparation of gram quantities of pure intermediates. In a divergent manner, each compound was elaborated into iminohexitols **259** or **260** via the respective amino triol intermediates by hydrogenolytic ring opening and deprotection.

Retrosynthetically, polyhydroxylated pyrrolidine derivatives of type **A**[130] can be envisioned as deriving from pyrrole-based silyl dienol ether **118** and chiral aldehydes of type **B** (Scheme 55). Accordingly, **118** can be considered as a masked pyrrolidine. In our own laboratory, the synthetic potential of **118** was explored with diastereomeric polyhydroxylated pyrrolidinones **265** and **266** as the first objectives (Scheme 56).

Treatment of 2,3-*O*-isopropylidene-D-glyceraldehyde (**34**) in anhydrous Et_2O with **118** at −85 °C in the presence of $SnCl_4$ gave crystalline D-*arabino* α,β-unsaturated γ-lactam **261** as the sole reaction product. Doubling the scope of the synthesis, when **34** was allowed to react at the same temperature with **118** in Et_2O in the presence of BF_3 etherate, reversal of stereochemistry occurred, resulting in predominant formation of crystalline D-*ribo* epimer **262**, along with minor amount of **261**. Also, clean and almost quantitative epimerization at C-4 was observed when lactam **261** was subjected to treatment with Et_3N in CH_2Cl_2 at room temperature in the presence of DMAP, and this provided a good alternative preparation of the thermodynamically more stable D-*ribo* lactam **262**. Next, after protection of the free OH group as the trimethylsilyl ether, the double bond of

Scheme 56[a]



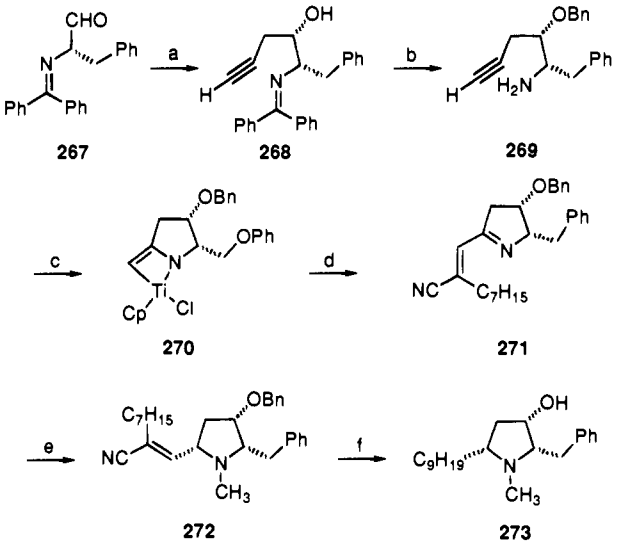
[a] Key: (a) $SnCl_4$, Et_2O, -85°C; (b) BF_3 etherate, CH_2Cl_2, -85°C; (c) Et_3N, CH_2Cl_2, DMAP; (d) TMSCl, pyridine; then $KMnO_4$, DCH-18-crown-6, CH_2Cl_2; (e) TFA, CH_2Cl_2.

both epimers was selectively dihydroxylated ($KMnO_4$) producing diastereoisomeric pyrrolidinones **263** and **264**. In the event, the compounds were obtained as 2,3-*cis*-3,4-*anti* diastereoisomers only, as functionalization of the double bond is strictly governed by the presence of a bulky substituent at C-4 which hinders the *syn* face of the lactam ring. Finally, the acetonide, TMS, and Boc protections in **263** and **264** were cleanly removed by acidic treatment giving the free lactams **265** and **266**.

The hydroxy pyrrolidine frame is also embodied in a variety of naturally occurring alkaloidal compounds displaying antibiotic, anthelmintic, and antitumoral activities. An efficient stereoselective total synthesis of the potent antifungal agent (+)-preussin (**273**), was achieved via an intramolecular imidotitanium–alkyne [2 + 2] cycloaddition–acyl cyanide condensation sequence (Scheme 57).[131]

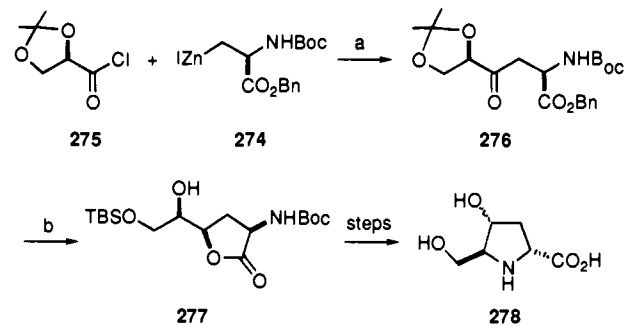
The first reaction of the elegant sequence of Livinghouse was the addition of allenylmagnesium bromide to imino aldehyde **267** which is readily accessible from L-phenylalanine by a trivial procedure. A 3.2:1 mixture of *threo* and *erythro* homopropargyl alcohols were obtained in high yield from which the desired *threo* isomer **268** was isolated by chromatography. Compound **268** was then transformed to the key intermediate **269** by *O*-benzylation followed by mild acidic hydrolysis of the imino group. Exposure of **269** to $CpTi(CH_3)_2Cl$ in THF gave rise to the reactive azatitanetine **270** which was directly transformed to the α,β-unsaturated nitrile **271** by treatment with octanoyl cyanide. Stereoselective *N*-methylation of **271** followed by direct reduction of the resulting iminium salt provided pyrrolidine **272**

Scheme 57[a]



[a] Key: (a) CH_2:C:CHMgBr; (b) KH, THF, BnBr; then aq. $H_2C_2O_4$; (c) $CpTi(CH_3)_2Cl$, THF; (d) octanoyl cyanide, THF; (e) MeOTf; then $NaBH_3CN$; (f) Mg, MeOH; then K, HMPA, Et_2O, toluene; then H_2, Pd / C.

Scheme 58[a]



[a] Key: (a) Pd catalysis; (b) L-Selectride, THF, -78°C; then I_2, MeOH; then TBSCl, Et_3N, DMAP, DMF.

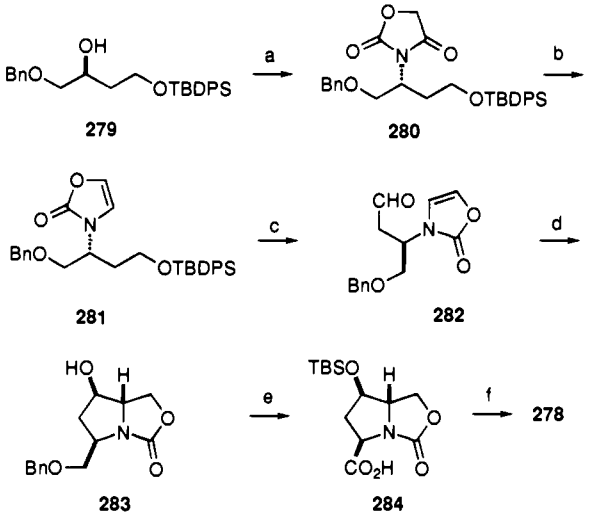
as a single stereoisomer. Chemoselective reduction of the double bond in **272** followed by reductive removal of both the cyano and *O*-benzyl groups gave rise to (+)-preussin (**273**).

Two brief syntheses of (+)-bulgecinine (**278**), the enantiomer of the naturally occurring constituent of the bulgecin glycopeptides, were recently executed by the Jackson and Shibuya groups. The English researchers[132] utilized the coupling of the D-serine-derived zinc reagent **274** with (*R*)-isopropylideneglyceryl chloride (**275**) to afford, in a single step, the protected oxonorleucine derivative **276** (Scheme 58).

Selective reduction of the carbonyl function in **276** using L-Selectride and appropriate deprotection–protection operations produced the advanced intermediate **277**, which was employed to synthesize the alkaloid **278** according to the sequence used by Fleet in his synthesis of natural (−)-bulgecinine.[133]

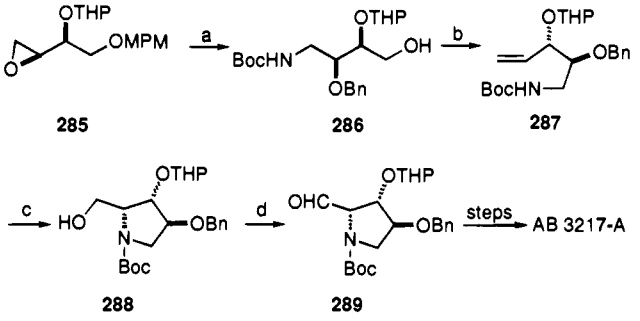
A novel synthesis of the same alkaloid was developed by Shibuya[134] employing, as the key operation, an intramolecular radical cyclization of a *O*-stannyl ketyl with a proximate alkene function (Scheme 59). Thus, condensation of partially protected triol **279**, derived from (*S*)-malic acid through trivial chemistry, with oxazolidine-2,4-dione according to the Mitsunobu protocol provided compound **280**.

Scheme 59[a]



[a] Key: (a) PPh_3, $(Pr^iOCON:)_2$, oxazolidine-2,4-dione; (b) $NaBH_4$; then MsCl, Et_3N; (c) NBu_4F, THF; then Swern oxidn.; (d) Bu_3SnH, AIBN; (e) TBSCl, imidazole, DMF; then H_2, Pd/C; then $RuCl_3$, $NaIO_4$; (f) NaOH, EtOH.

Scheme 60[a]



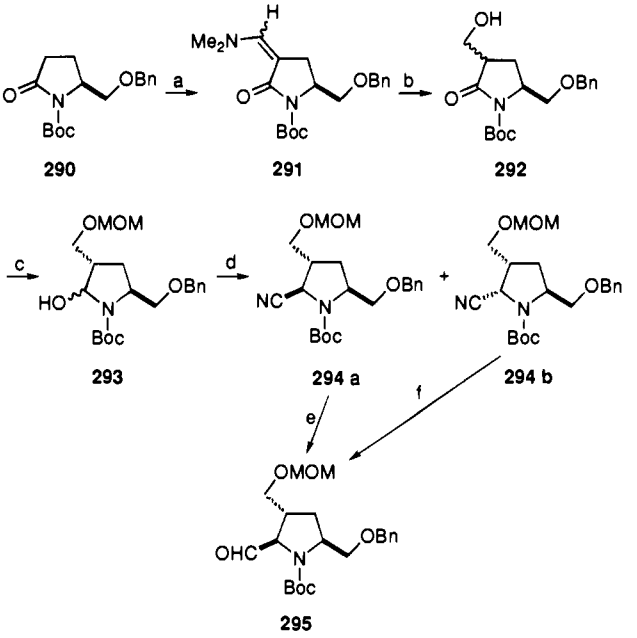
[a] Key: (a) NaN_3, MeOH; then BnBr, NaH, Bu_4NI; then PPh_3, THF; then Boc_2O, $NaHCO_3$; then DDQ; (b) Swern oxidn.; then CH_2:PPh_3; (c) MCPBA; then BF_3 etherate; (d) Swern oxidn.

Reduction of **280** with $NaBH_4$ followed by treatment with methanesulfonyl chloride in the presence of triethylamine gave **281** through spontaneous elimination of methanesulfonic acid. Desilylation of **281** and subsequent Swern oxidation of the resulting alcohol afforded the key aldehyde intermediate **282** which was treated with tributyltin hydride in the presence of AIBN to afford the desired bicyclic compound **283** together with its C-7 epimer (1:1 diastereomeric mixture) which is conveniently convertible to **283** via oxidation and subsequent stereoselective reduction. Protection of the hydroxyl group of **283** as the TBS ether, debenzylation of the *O*-silylated adduct, and subsequent oxidation of the hydroxymethylene function afforded carboxylic acid **284** which was finally transformed to (+)-bulgecinine (**278**) by base-promoted cleavage of the oxazolidinone ring followed by ion exchange chromatography.

In their total synthesis of AB3217-A, a recently isolated natural substance showing marked activity against the two spotted spidermite, Nakata and coworkers[135] were able to develop a viable synthesis of the pyrrolidine subunit **289** (Scheme 60).

Starting from enantiopure epoxy alcohol **285**, which was in turn prepared through a seven-step procedure

Scheme 61[a]



[a] Key: (a) $(Me_2N)_2CHOBu^t$; (b) HCl, THF; then $NaBH_3CN$; (c) MOMCl, Pr^i_2EtN; then DIBALH; (d) PPTS, MeOH; then TMSCN, BF_3 etherate; (e) DIBALH; (f) DIBALH; then K_2CO_3, MeOH, reflux.

from dimethyl L-tartrate, the authors effected epoxide-opening with NaN_3–NH_4Cl to give an azido alcohol intermediate which was then easily manipulated to produce the *N*-Boc-protected amino triol **286**. Swern oxidation followed by Wittig methylenation then gave olefin **287**. Epoxidation of the olefin with MCPBA followed by BF_3 treatment gave a 3:1 diastereomeric mixture of two pyrrolidines, the major being the desired stereoisomer **288**. Swern oxidation of the terminal hydroxyl gave aldehyde **289**, an advanced intermediate for the synthesis of AB3217-A.

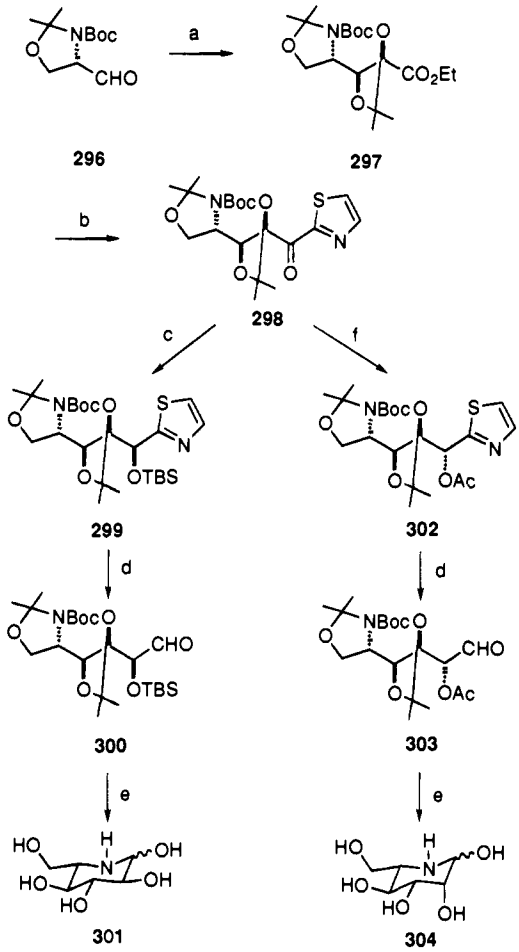
The key D-ring fragments of enantiomeric pairs of quinocarcin[136] and 10-decarboxyquinocarcin, *Streptomyces* metabolites exhibiting prominent antitumor activity, have been recently obtained by Terashima by employing each enantiomer of glutamic acid and pyroglutamic acid as chiral starting materials. As an example, the synthesis of 3,5-disubstituted 2-formylpyrrolidine **295** required for the total synthesis of quinocarcin is detailed in Scheme 61.

Pyrrolidinone **290**, obtainable from (*S*)-glutamic acid, was first treated with the Bredereck reagent providing enamine **291** which was next transformed to epimeric alcohols **292** as a 88:12 mixture. After suitable protection, the thermodynamically more stable isomer was reduced to 2-hydroxypyrrolidine **293** (anomeric mixture) which was directly homologated at the 2-position with cyanide anion to give a 30:70 mixture of *cis* and *trans* isomers **294a** and **294b**. To complete the synthesis of the key intermediate **295**, the minor isomer was directly reduced (DIBALH) while the major one was first reduced and then epimerized under basic conditions.

2. Piperidine Derivatives

Piperidinose alkaloids have been mainly prepared by simple elaboration of suitable carbohydrate pre-

Scheme 62[a]



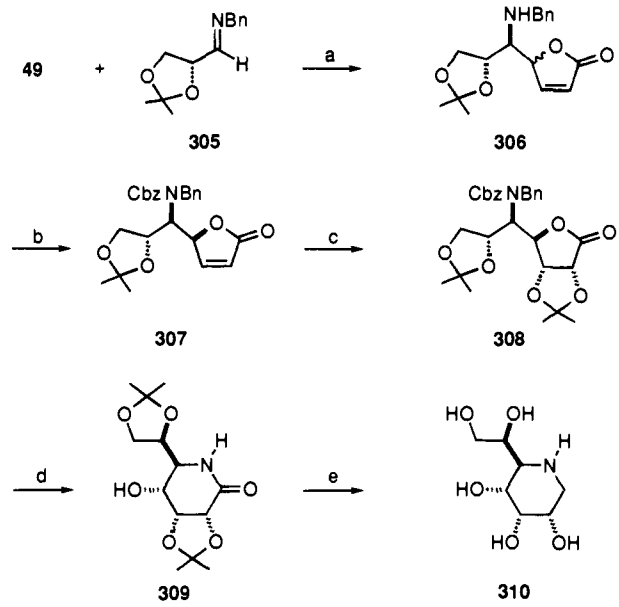
[a] Key: (a) Ph_3P:$CHCO_2Et$; then OsO_4, NMO; then DMP, TsOH; (b) 2-lithiothiazole, Et_2O; (c) $NaBH_4$; then TBSCl, imidazole; (d) MeI, MeCN; then $NaBH_4$; then $HgCl_2$, MeCN, H_2O; (e) TFA, H_2O; (f) Red-Al, toluene; then Ac_2O, pyridine, DMAP.

cursors. Only a few recent reports involving totally chemical approaches based on chiron homologation have appeared. Exploiting his elegant chemistry based on thiazole intermediates, Dondoni[137] engineered a divergent synthetic route to the (−)-antipodes of nojirimycin **301** and mannonojirimycin **304** via a common advanced intermediate from protected L-serinal **296** (Scheme 62).

Two-carbon Wittig elongation of **296** with (ethoxycarbonylmethylene)triphenylphosphorane followed by OsO_4 dihydroxylation of the resulting adduct and acetonide protection gave rise to intermediate **297** accompained by a small amount of a diastereomer. Elongation by one more carbon was effected employing 2-lithiothiazole as a masked formyl anion equivalent giving the masked keto aldehyde **298**. Conveniently, access to the same intermediate **298** was provided by direct three-carbon homologation of serinal by using a thiazole-based carbonyl phosphorane as an equivalent of a formyl ketophosphorane (not shown). To access either L-(−)-nojirimycin (**301**) or L-(−)-mannonojirimycin (**304**) from the common precursor **298**, a stereocontrolled reduction of the carbonyl function to carbinol of either (*R*)- or (*S*)-configuration had to be performed.

For **301**, ketone **298** was reduced by using $NaBH_4$ in methanol to afford the masked aminohexose **299**

Scheme 63[a]



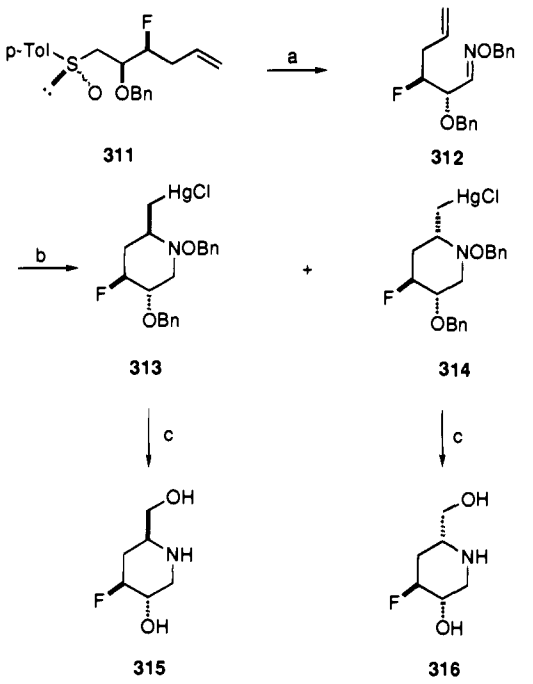
[a] Key: (a) BF_3 etherate, CH_2Cl_2; (b) CbzCl, $NaHCO_3$; (c) $KMnO_4$, DCH-18-crown-6 ether, CH_2Cl_2; then DMP, TsOH; (d) H_2, $Pd(OH)_2$, MeOH; (e) $BH_3 \cdot Me_2S$, THF; then aq. TFA.

as a single diastereoisomer. Deblocking of the formyl function within the thiazole ring to aldehyde **300** and subsequent removal of all the protecting groups furnished the unnatural alkaloid **301** in high yield. On the other hand, alternative reduction of the same precursor **298** with Red-Al proceeded with a stereochemistry opposite to that previously observed, allowing synthesis of the L-*manno* compound **302** which was easily converted to **304** via mannose **303** by the same set of reactions as described for **301**. By utilizing similar chemistry, it was possible to synthesize 3-deoxy derivatives from L-serine using 2-substituted thiazoles as homologative reagents and aldehyde equivalents.

By exploiting the synthetic utility of enantioenriched butenolide matrices,[138] iminoalditol **310** containing five consecutive stereocenters, was synthesized from D-glyceraldehyde imine **305** and 2-(trimethylsiloxy)furan (**49**) as outlined in Scheme 63, utilizing the single chiral element in the precursor imine.

The target called for D-*ribo*-butenolide **307** as the chiral matrix. Four-carbon homologation of imine **305** with 2-(trimethylsiloxy)furan (**49**) in CH_2Cl_2 in the presence of BF_3 etherate resulted in formation of butenolide **306**. This was isolated as a 1:1 mixture of two epimers at C-4, which could not be separated owing to rapid equilibration. Mixture **306** was smoothly converted into the *N*,*N*-diprotected butenolide **307** by reaction with benzyloxycarbonyl chloride under the usual Schotten–Baumann conditions. Although the intermediate **306** was a mixture of isomers, the Cbz-protected butenolide **307** was isolated as the D-*ribo* stereoisomer only. Presumably, the formation of **307** is controlled by thermodynamics of base-catalyzed lactone equilibration, strongly favoring, in this instance, the D-*ribo* isomer. On the basis of precedents for related compounds, butenolide **307** was selectively hydroxylated at C-2 and C-3 by

Scheme 64[a]



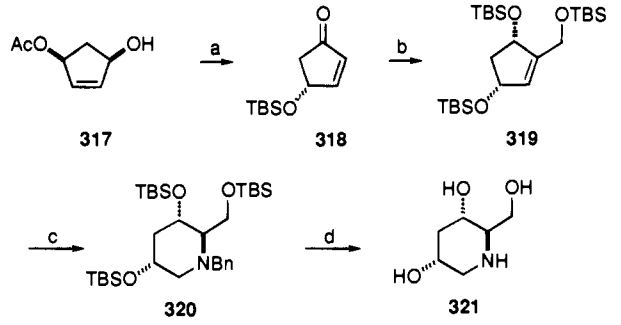
[a] Key: (a) $(CF_3CO)_2O$, 2,4,6-trimethylpyridine, MeCN; then $CuCl_2$, K_2CO_3; then $BnONH_2$; (b) $NaCNBH_3$, HCl, MeOH; then $(CF_3CO_2)_2Hg$, THF; then KCl, H_2O; (c) $NaBH_4$, $(CF_3)_2CHOH$, O_2; then H_2, Pd / C, TFA.

using $KMnO_4$ under solid–liquid phase-transfer conditions. There was obtained, after protection (DMP, TsOH), D-*glycero*-D-*allo*-heptono-1,4-lactone (**308**) as a homogeneous material with no trace of other stereoisomers. Hydrogenolytic cleavage of the protective groups at the C-5 nitrogen of **308** using Pd-$(OH)_2$ in methanol gave the δ-lactam **309** which was then transformed to **310** in excellent yield by reduction with the BH_3·Me_2S complex in CH_2Cl_2, subsequent deprotection, and chromatography on DOWEX OH^- and lyophilization.

The substitution of a fluorine for a hydroxy group in a bioactive substance often results in improved activities. Recently, Resnati and co-workers described a total asymmetric synthesis of fluorinated analogues of 1-deoxynojirimycin by utilizing, as ultimate chiral source, (*S*)-methyl *p*-tolyl sulfoxide.[139] The sequences to piperidines **315** and **316** is shown in Scheme 64.

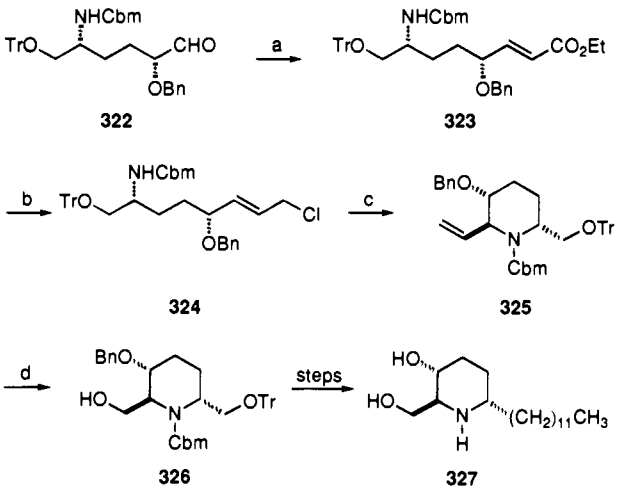
Thus, the fluorosulfinylhexenol **311**, obtained in three steps from the above chiral sulfoxide, was first subjected to Pummerer rearrangement to generate a geminal thioacetoxy moiety. Deblocking of the masked aldehyde function and subsequent reaction with *O*-benzylhydroxylamine afforded oxime **312** as a 10:1 mixture of *E* and *Z* isomers. After reduction of the oxime double bond, intramolecular aminomercuration allowed the assembly of the piperidine ring of the target compounds. Unfortunately, the cyclization proved to be unselective resulting in formation of a 1:1 C-5 epimeric mixture of two piperidines **313** and **314**, which were separated by flash chromatography. The individual compounds were finally elaborated to fluorinated pyrrolidine derivatives **315** and **316** according to the chemistry illustrated in the scheme.

Scheme 65[a]



[a] Key: (a) TBSCl, imidazole; then CO, Bu_3SnH, $Pd(Ph_3P)_4$; then $NaBH_4$, $CeCl_3$; then O_3, MeOH; then Me_2S; (b) I_2, pyridine, CCl_4; then $NaBH_4$, $CeCl_3$; then TBSCl, imidazole; then CO, Bu_3SnH, $Pd(Ph_3P)_4$; then $NaBH_4$, $CeCl_3$; then TBSCl, imidazole; (c) O_3, MeOH; then DMS; then $BnNH_2$, $NaCNBH_3$; (d) HCl, MeOH; then H_2, Pd/C.

Scheme 66[a]



[a] Key: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (b) DIBALH; then TsCl, DMAP (c) NaH, $Pd(PPh_3)_4$, Bu_4NI, THF; (d) O_3, MeOH, PPh_3; then $NaBH_4$.

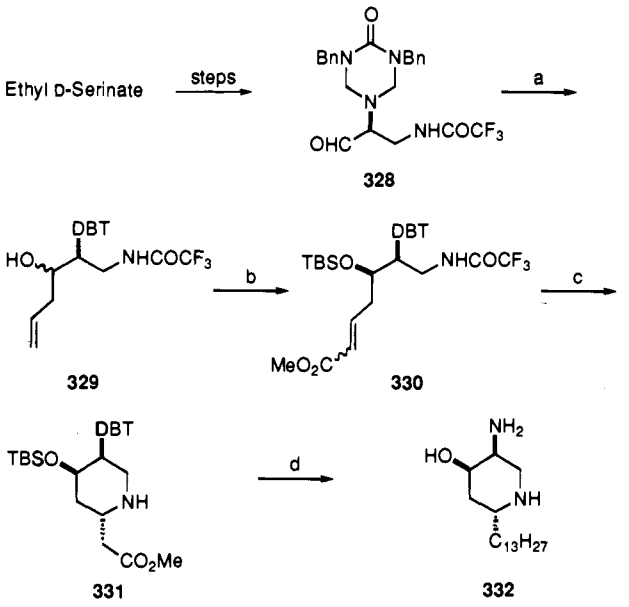
Using optically pure cyclopentene diol monoacetate **317** as a chiron, Johnson[140] designed a nice diastereoselective route to 1,3-dideoxynojirimycin (**321**) (Scheme 65). Compound **317** was obtained by enzymatic asymmetrization (*Candida antarctica*) of *meso*-3,5-cyclopentenediol.

First, **317** was transformed into enone **318** by simple chemistry. The trihydroxylated cyclopentene derivative **319** was prepared from **318** by α-iodination, Luche reduction, and Pd(0)-mediated carbon monoxide coupling. Ozonolysis of **319**, followed by reductive workup gave the corresponding keto aldehyde which was then transformed into trisilylated piperidine **320** by a highly stereoselective double reductive amination with benzylamine and sodium cyanoborohydride in methanol. Acidic hydrolysis followed by hydrogenation finally afforded enantiopure 1,3-dideoxynojirimycin (**321**).

In a recent paper, Tadano[141] and co-workers reported total syntheses of certain congeners of Prosopis piperidine alkaloids using Pd(0)-catalyzed intramolecular *N*-alkylation to forge the key piperidine ring. As an example, the total synthesis of (−)-desoxoprosopinine (**327**) is outlined in Scheme 66.

Protected amino aldehyde **322** was obtained from D-glucose according to a sequence of conventional

Scheme 67[a]

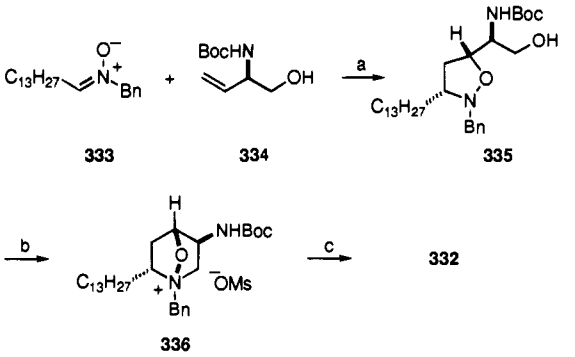


[a] Key: (a) allyltrimethylstannane, BF_3 etherate; (b) TBSOTf; then OsO_4, NMO; then $NaIO_4$; then Ph_3P:$CHCO_2Me$; (c) $NaBH_4$, MeOH; (d) Cbz_2O, DIPEA; then $LiBH_4$; then Swern oxidn.; then Ph_3P:CH-$C_{10}H_{21}$; then H_2, Pd/C; then TBAF; then TFA; then diethanolamine.

reactions. Two-carbon Wittig homologation gave rise to the eight-carbon enoate **323** as a 10:1 diastereomeric mixture. Although the authors utilized in the next stages of the sequence the enoate mixture, Scheme 66 depicts only transformations involving the most abundant isomer. Thus, **323** was transformed to unsaturated chloro derivative **324** by selective reduction of the carbethoxy moiety followed by treatment with an excess of TsCl. Chloride **324** underwent intramolecular *N*-alkylation yielding the piperidine intermediate. With NaH-Pd(PPh_3)-THF-Bu^n_4NI, the cyclization occurred with good diastereoselectivity allowing for synthesis of dihydroxylated piperidine **325**. Ozonolysis followed by reduction of the resulting aldehyde gave the key trihydroxypiperidine intermediate **326** which is endowed with all the chirality of the target compound **327**. A series of several reactions, including elongation of the chain at C-6 by the Wittig protocol, finally permitted the synthesis of (−)-desoxoprosopinine (**327**). To expand the synthetic scope of this chemistry, intermediate **327** was also utilized to complete the synthesis of the C-6 epimer (−)-desoxoprosophylline.

Pseudodistomins are hydroxylated amino piperidine alkaloids isolated from tunicate species which possess *in vitro* activity against leukemia cells. Recently, in order to confirm the absolute stereochemistry of this important class of compounds, Knapp and Hale[142] projected a total synthesis of (+)-tetrahydropseudodistomin (**332**) by utilizing D-serine as the starting chiral synthon. As shown in Scheme 67, protected diamino aldehyde **328**, obtained in nine steps from D-serine ethyl ester, was homologated to allyl alcohol derivative **329** with high diastereoselection. After hydroxyl protection, the carbon chain was extended by oxidative cleavage of the alkene and by Wittig reaction of the resulting aldehyde to afford ester **330** as a *trans*/*cis* mixture.

Scheme 68[a]



[a] Key: (a) toluene, reflux; (b) MsCl, pyridine; (c) $Pd(OH)_2$, H_2; then TFA, CH_2Cl_2.

Treatment of this mixture with $NaBH_4$ resulted in removal of the *N*-trifluoroacetyl protection and subsequent intramolecular 1,4-addition wherein piperidine **331** formed as the only product. To reach the target **332**, all that remained was to elongate the chain at C-2; and this was effected by reduction of the ester moiety, Swern oxidation, and Wittig elongation. The entire scheme required 24 steps with an overall yield of ~6% from D-serine ethyl ester.

More recently, a Japanese group[143] reported a practical asymmetric synthesis of the same piperidine alkaloid **332** along with some stereoisomeric derivatives. For **332** (Scheme 68), cycloaddition of the nitrone **333** to enantiopure 2-aminobutenol **334** led to the key intermediate **335**. Of note, the cycloaddition proved unselective, giving a separable mixture of all four of the possible diastereoisomers with **335** as a minor component.

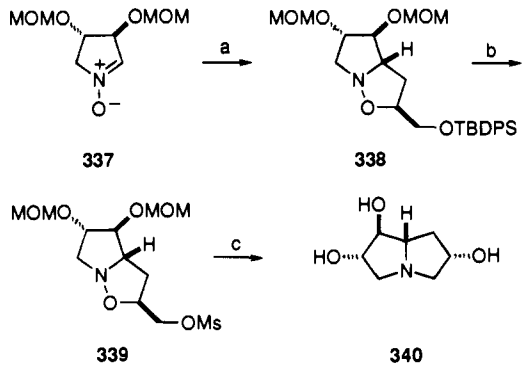
Mesylation of the free hydroxyl group of **335** transformed this compound into bicyclic iminium salt **336**, allowing formation of the piperidine framework. Hydrogenolysis of the benzyl protecting group and cleavage of the N−O bond followed by acidic deprotection, finally generated pseudodistomin **332**. Compared to the above-mentioned procedure, this route appears to be shorter; however, the lack of selectivity during the crucial cycloaddition step in the Japanese approach represents a severe drawback, only partially mitigated by the synthetic divergence of the plan and by the possibility of converting an unwanted isomer into a desired one.

B. Bicyclic Compounds

1. Pyrrolizidine Derivatives

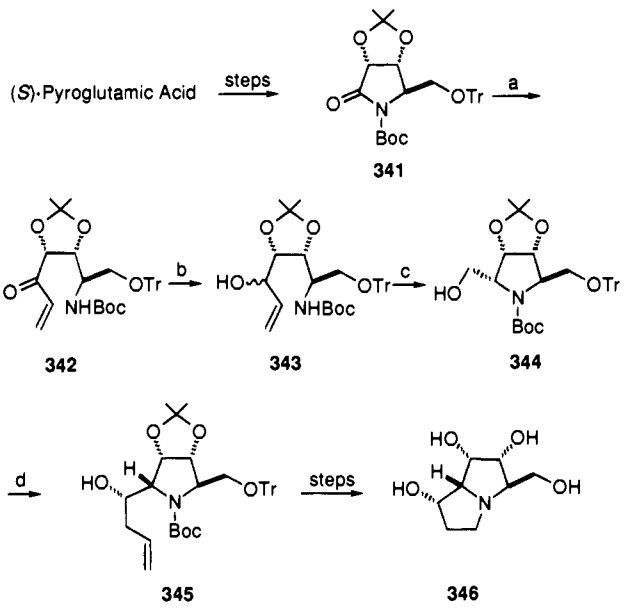
The pyrrolizidine subgroup includes a number of naturally occurring alkaloids, many of which exhibit useful activities as glycosidase inhibitors as well as antiviral and anticancer agents.[144−146] In spite of these remarkable biological applications, only a few reports dealing with the design and implementation of totally chemical approaches to hydroxylated pyrrolizidines have appeared during the period covered by this article. Most syntheses in this area have used pentoses or hexoses as chiral sources while employing extensive manipulation of functional groups. To gain access to hydroxylated pyrrolizidines, McCaig and Wightman[147] utilized 1,3-dipolar cycloaddition reac-

Scheme 69[a]



[a] Key: (a) CH_2:$CHCH_2OTBDPS$; (b) TBAF, THF; then MsCl, Et_3N; (c) H_2, Pd/C; then HCl.

Scheme 70[a]



[a] Key: (a) CH_2:CHMgBr, THF; (b) $NaBH_4$, $CeCl_3$; (c) O_3, CH_2Cl_2; then $NaBH_4$; then TBSCl, imidazole; then MsCl, TEA; then Bu^tOK; then TBAF, THF; (d) Swern oxidn.; then allylation.

tions of suitable cyclic nitrone units. For compound **340**, for example, the key four-carbon nitrone intermediate **337**, easily obtained from diethyl L-tartrate, was treated with allyl *tert*-butyldiphenylsilyl ether to give in high yield a single cycloadduct **338**. Desilylation and mesylation gave **339**, which on hydrogenolysis of the *N-O* linkage followed by removal of all the protecting groups, gave the pyrrolizidine **340** (Scheme 69).

A novel approach to 1,7a-diepialexine (**346**) starting with (*S*)-pyroglutamic acid is shown in Scheme 70.[148] Thus, the advanced intermediate **341** was first homologated to ketone **342** which was then reduced to allylic alcohols **343** (1:2.4 diastereomeric ratio). Ozonolysis of the double bond and subsequent reductive workup allowed transformation of **343** into a mixture of polyols, the major isomer being then converted to pyrrolidine **344** by ring-closure through sequential mesylation and desilylation. Swern oxidation of the terminal hydroxymethylene and subsequent homologation by two carbon atoms gave rise to allyl alcohol **345** predominantly, which was finally converted to the bicyclic target **346** by conventional chemistry.

N-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-pyrrole (**118**) served admirably to forge the skeleton of these important alkaloids. From D-glyceraldehyde acetonide (**34**) (or its L-enantiomer) all four isomers of *cis*-1,2-dihydroxypyrrolizidine (**349**, **350**) and their enantiomers were recently prepared in our laboratory according to a divergent protocol (Scheme 71).[149]

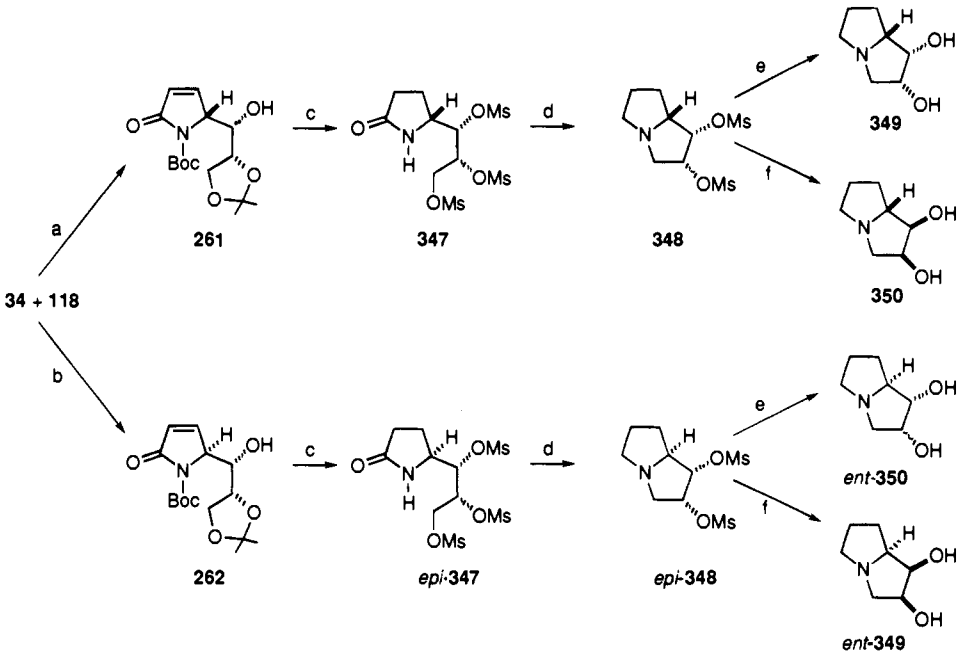
Unsaturated γ-substituted γ-lactams of type **261** and **262** were envisioned to be ideal building blocks for the preparation of the oxygenated pyrrolizidine ring systems. These compounds incorporate the complete seven-carbon skeleton of the final pyrrolizidines and are already equipped with proper substitution and chirality. Starting with these intermediates, the sequences shown in Scheme 71 were executed in a parallel and repetitive fashion. Thus, unsaturated lactam **261** was converted to **347** by hydrogenation followed by acidic treatment and mesylation. This compound was transformed into the protected pyrrolizidine **348** by a two-step protocol consisting of carbonyl reduction followed by DBU-assisted ring closure. For the intermediate **348** to be converted to either **349** or **350**, a divergent protocol had to be employed. Enantioconservative demesylation to the free base **349** was performed by exposing **348** to sodium amalgam in 2-propanol. Conversely, exposure to tetrabutylammonium benzoate in refluxing toluene resulted in efficient displacement of the two adjacent OMs groups by the benzoate anion with inversion to produce a benzoyl derivative which was transformed to the free base **350** upon treatment with catalytic sodium methoxide in methanol. Paralleling this scheme and exploiting the same chemistry, but reversing the mode of execution of the final transformation, *ent*-**349** and *ent*-**350** were prepared from **262**, via intermediates *epi*-**347** and *epi*-**348**.

The necine alkaloids, such as hastanecine (**358**) and a variety of hydroxylated congeners, have received much attention due to their interesting physiological activities. Practical multistep syntheses of both hastanecine (**358**) and dihydroxyheliotridane (not shown), involving a regioselective Claisen rearrangement, have been devised by Mulzer.[150] The exchiral pool route to **358** is shown in Scheme 72.

From known enantiopure triol **351**, aldehyde intermediate **352** was first prepared which was homologated to unsaturated ester **353** and then transformed to the key alcohol **354**. Heating this compound with triethyl orthoacetate resulted in clean formation of the *C*-branched ester **355** by stereoselective orthoester Claisen rearrangement. Three subsequent reactions, namely reduction of the ester moiety, Mitsunobu amination, and epoxidation, allowed conversion of **355** to the major epoxide **356** which was elaborated into the suitable pyrrolidine derivative **357** by regioselective ring closure and functional group manipulation. Acidic cleavage of the carbamoyl protection at nitrogen easily permitted the second annulation to take place producing the expected hastanecine (**358**).

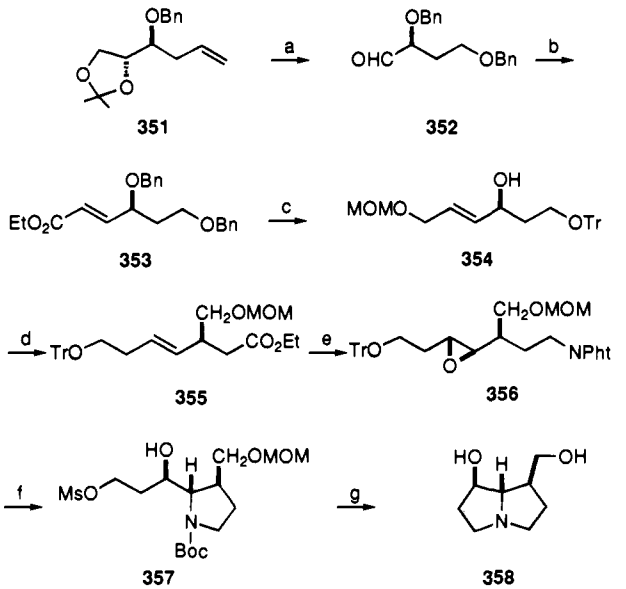
The first synthesis of petasinecine (**362**), the necine base of the natural alkaloid petasinine, was recently reported by the same author using L-proline as the

Scheme 71[a]



[a] Key: (a) $SnCl_4$, Et_2O, -85°C; (b) BF_3 etherate, Et_2O, -85°C; (c) H_2, Pd/C; then 6N HCl; then MsCl, pyridine; (d) BH_3·DMS; then DBU, benzene, reflux; (e) Na/Hg, Pr^iOH; (f) $Bu_4N^+BzO^-$, toluene; then NaOMe, MeOH.

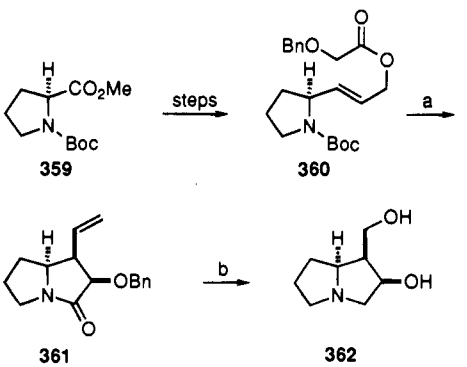
Scheme 72[a]



[a] Key: O_3, MeOH; then $NaBH_4$; then BnBr, NaH; then AcOH, H_2O; then $Pb(OAc)_4$; (b) $(EtO)_2PCH_2CO_2Et$, NaH; (c) DIBALH; then MOMCl, Pr^i_2EtN; then Na, NH_3; then TrCl, DMAP; (d) $MeC(OEt)_3$, $EtCO_2H$, 100°C; (e) DIBALH; then PPh_3, PhtNH, DEAD; then MCPBA; (f) N_2H_4, EtOH; then Boc_2O, Pr^i_2NH, then H_2, Pd/C, cat. HCl; then MsCl, pyridine; (g) TFA, MeOH.

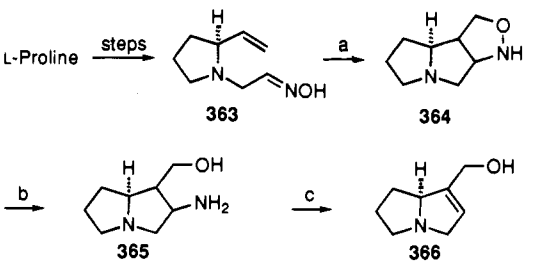
chiral component. As shown in Scheme 73, the sequence features an Ireland–Claisen rearrangement.[151] Protected L-proline methyl ester **359** was thus homologated by two carbons and transformed to the key intermediate **360**. Treatment of **360** with LiHMDS/TMSCl resulted in formation of pyrrolizidinone **361** in a single operation. The synthesis of the alkaloid **362** was then completed by conversion of the vinyl group to hydroxymethylene, reduction of the lactam carbonyl, and removal of the benzyl protection.

Scheme 73[a]



[a] Key: (a) LiHMDS, TMSCl, THF; then TFA, BuOH; (b) O_3, MeOH; then $NaBH_4$, MeOH; then BH_3, THF; then H_2, Pd/C, MeOH.

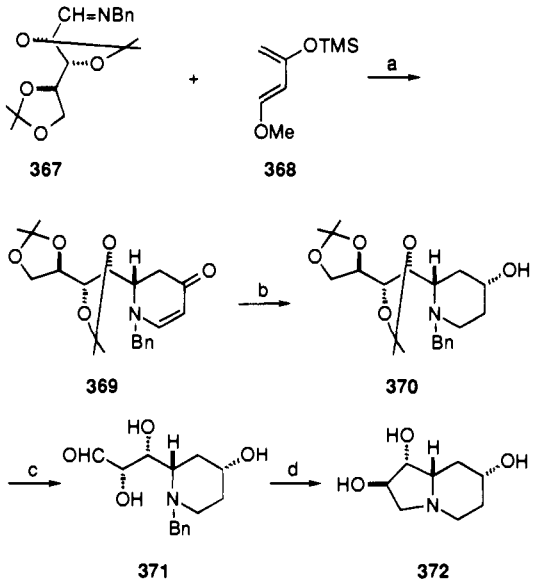
Scheme 74[a]



[a] Key: (a) 180°C, neat; (b) $LiAlH_4$, THF; (c) $NaNO_2$, 2N HCl, THF; then K_2CO_3, $CHCl_3$.

A short synthesis of (−)-supinidine (**366**) from L-proline was described by Hassner and co-workers[152] employing, as the crucial operation, a thermal intramolecular oxime–olefin cycloaddition. Thus, L-proline was converted to the key oxime **363** through one-carbon elongation and *N*-allylation (Scheme 74). Heating of **363** afforded the tricyclic derivative **364** which was converted to hydroxylated 2-amino-

Scheme 75[a]



[a] Key: (a) $ZnCl_2$, dioxane; (b) $NaBH_4$, EtOH; (c) aq. AcOH; then $Pb(OAc)_4$; then aq. TFA; (d) H_2, Pd/C, AcOH.

pyrrolizidine **365**, the immediate precursor of (−)-supinidine (**366**).

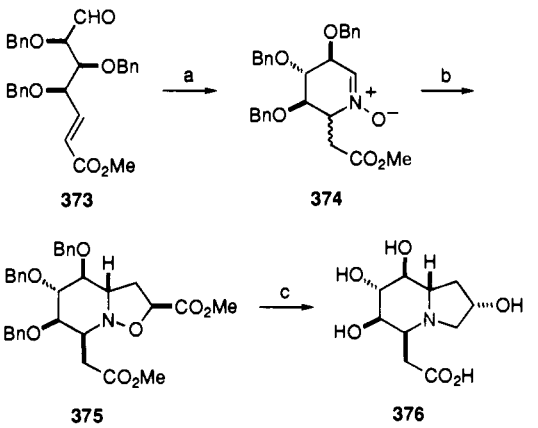
2. Indolizidine Derivatives

The chemistry, biochemistry, and biological implications of hydroxylated indolizidine alkaloids, both natural and synthetic, have attracted enormous interest in recent years. Aspects of the chemistry and biology of castanospermine (**404**) and swainsonine (**409**), two remarkable naturally occurring representatives of this subgroup, have been surveyed in noteworthy reviews.[26,153–155] An important article summarizing a variety of synthetic approaches to stereoisomers and analogues of castanospermine has been recently compiled by Burgess and Henderson.[8] Because of the unique value of these alkaloids as glycoprocessing inhibitors and therapeutic agents, a plethora of publications focused on their preparation have appeared. This forced us to limit the present discussion to those approaches which are, in our opinion, relevant as far as chemistry and synthetic viability are concerned.

Due to close resemblance between sugars and polyhydroxyindolizidines, a number of homologative approaches utilize carbohydrates as starting materials and sources of chirality. As depicted in Scheme 75,[156] swainsonine analogue **372** was synthesized from D-arabinose, through $ZnCl_2$-promoted cyclocondensation of azomethine derivative **367** with Danishefsky's diene **368**. The major cycloadduct **369** so obtained was then stereoselectively reduced to the nine-carbon pyrrolidine **370** which was first shortened to aldehyde **371** and finally cyclized to 1,2,7-trihydroxyindolizidine (**372**) by reductive amination.

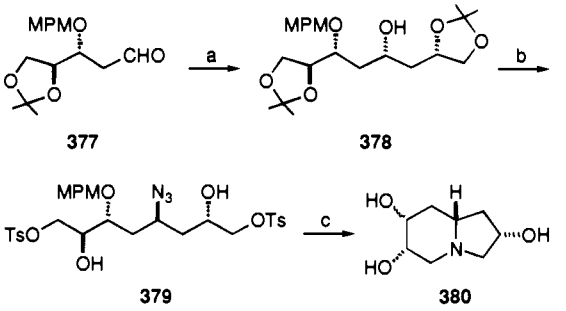
The same research group[157] utilized D-xylose to assemble the tetrahydroxyindolizidine derivative **376** (Scheme 76). Thus, unsaturated ester **373**, obtained by two-carbon Wittig elongation of a dialdose mercaptal (ex D-xylose), was first transformed to the key nitrone derivative **374** by an intramolecular conjugate addition involving an *in situ* generated oxime.

Scheme 76[a]



[a] Key: (a) NH_2OH, EtOH; (b) methyl acrylate; (c) Zn, AcOH; then $BH_3 \cdot Me_2S$; then $Ba(OH)_2$, EtOH, H_2O; then H_2, Pd/C, AcOH.

Scheme 77[a]



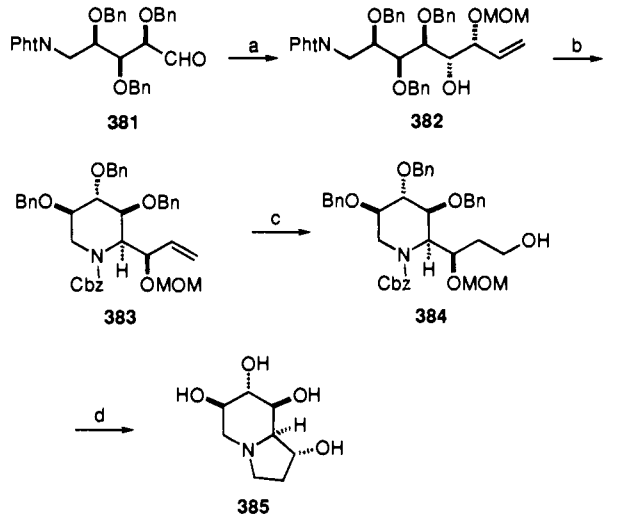
[a] Key: (a) $IcF_2BCH_2CH{:}CH_2$. Et_2O; then TBSCl, imidazole; then Sharpless AD; then DMP, TsOH; then TBAF, THF; (b) MsCl, Et_3N; then NaN_3, DMF; then Dowex H^+; then TsCl, pyridine; (c) H_2, $Pd/CaCO_3$, EtOH; then K_2CO_3, EtOH; then DDQ; then HCl, MeOH.

Remarkably, the subsequent 1,3-dipolar cycloaddition of **374** with methyl acrylate gave **375** as the major adduct. This was converted to indolizidine **376** by a four-step sequence involving reduction, lactamization, reduction, and deprotection.

The synthesis of trihydroxyindolizidine **380** employed L-arabinose-derived aldehyde **377** as a chiral template to control the installation of all the stereocenters of the target.[158] Diastereoselective chain elongation of **377** was effected by allylation to form a homoallylic alcohol intermediate which was converted to C_8-polyol **378** by means of a Sharpless asymmetric dihydroxylation (Scheme 77). The nitrogen at C-5 (C-8a in the target compound) was installed by conventional azide-S_N2 displacement to produce, after deprotection−protection, the requisite advanced intermediate **379** which was cyclized, in the final stages of the sequence, to indolizidine **380**.

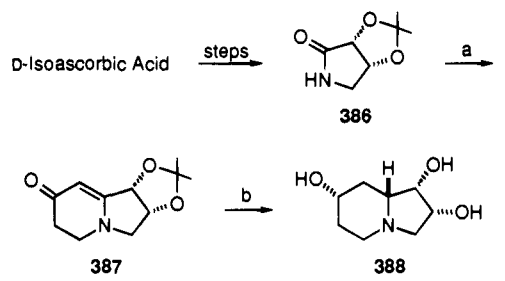
In searching for a flexible unified protocol amenable to preparation of several castanospermine-related stereoisomers, Burgess and his colleagues[159] developed a methodology of wide synthetic applicability. The envisioned strategy was based upon preliminary formation of an acyclic precursor endowed with the required stereochemistry via diastereoselective allylation of suitable homochiral aldehyde precursors. As illustrated for indolizidine **385** (Scheme 78), the synthesis begins with D-xylose-derived aldehyde **381**.

Scheme 78[a]



[a] Key: (a) $Ipc_2BCH_2CH{:}CH(OMOM)$, BF_3 etherate; (b) MsCl, Et_3N; then $MeNH_2$; then Cbz-Cl, $NaHCO_3$; (c) BH_3, THF; then H_2O_2; (d) MsCl, Et_3N; then H_2, Pd/C, MeOH; then aq. HCl.

Scheme 79[a]



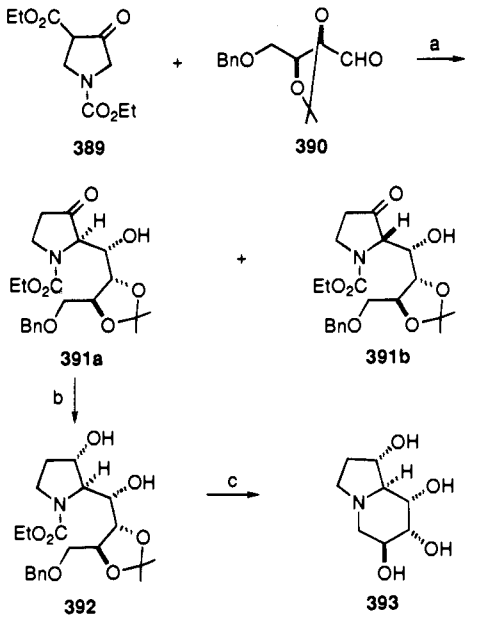
[a] Key: (a) Lawesson's reagent; then methyl acrylate, NaOH, THF; then aq. NaOH, MeOH; then $ClCO_2Et$; then CH_2N_2; then $[Rh(OAc)_2]_2$, benzene, reflux; then Ra-Ni, acetone; (b) $LiAlH_4$, THF; then MeOH; then H_3O^+.

Stereospecific allylation to **382** was effected with a chiral borane reagent taking advantage of double stereodifferentiation (matched sense). Mesylation of **382** and *N*-deprotection gave rise to piperidine **383** which was transformed to intermediate **384** by hydroboration−oxidation. Mesylation and hydrogenolysis facilitated the second cyclization and almost complete deprotection. Acid-catalyzed hydrolysis of the methoxy methyl ether finally gave the target compound **385**. In an analogous manner other stereoisomers were also synthesized by employing suitable aldehydopentoses.[159,160]

A total synthesis of trihydroxyindolizidine **388** was achieved in few steps from dihydroxy lactam **386** which was obtained in turn from readily available D-isoascorbic acid.[161] As shown in Scheme 79, isopropylidene-protected lactam **386** was transformed to bicyclic enaminone **387** by a set of reactions involving, as a key step, rhodium(II)-catalyzed cyclization of a diazo ketone intermediate. Reduction of both the double bond and carbonyl function in **387** followed by removal of the acetonide protection, resulted in selective formation of the target indolizidine **388**.

Enantioselective syntheses of certain castanospermine congeners, based on the C-2 enolate of *N*-substituted pyrrolinone **389**, were recently illustrated

Scheme 80[a]



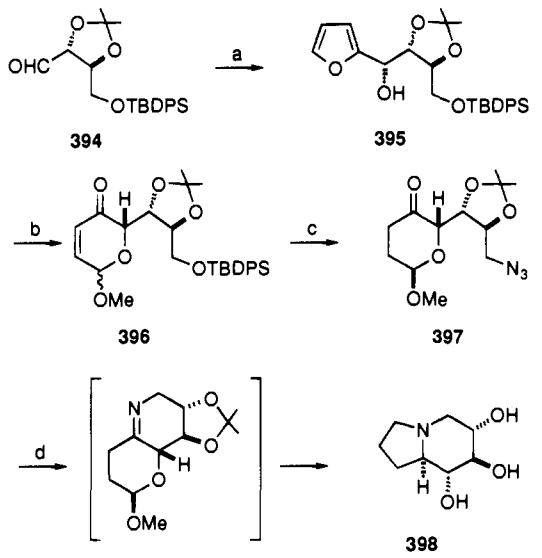
[a] Key: (a) LDA, DMPU, THF; then NaCl, DMSO, H_2O, 130°C; (b) $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (c) KOH, MeOH, 120°C; then $(ClSiPr^i_2)_2O$,pyridine; then H_2, Pd/C; then Ph_3P, CBr_4, Pr^i_2NEt; then aq. HCl.

by Gallagher.[162,163] Homologation of L-*threo* aldehyde **390** with the above anion furnished a mixture of four diastereomeric adducts of which the *anti* isomers **391a,b** were predominant (1:1 ratio) (Scheme 80). To access (+)-8,8a-diepicastanospermine (**393**), for example, pure isomer **391a** was utilized. Stereoselective reduction of the carbonyl group of this precursor was accomplished with hydroxy direction providing pyrrolidine **392** in high yield. After suitable manipulation of the hydroxy functions, the indolizidine skeleton of **393** was completed by intramolecular *N*-alkylation and deprotection during workup.

By utilizing protected L-threose **394** and 2-furyllithium as a four-carbon homologative nucleophile, a clever approach to 1-deoxycastanospermine (**398**) was recently devised by Martin and colleagues (Scheme 81).[164] When the coupling reaction of the aldehyde substrate with the organolithium reagent was conducted in the presence of $ZnBr_2$, the *threo*-furylcarbinol **395** was obtained predominantly (12:1 ratio) along with a minor amount of the *erythro* isomer. Compound **395** was then transformed into a 2:1 mixture of hydroxypyranones **396** by oxidation and methylation of the anomeric hydroxyl. The major α-anomer was transformed to the key azido intermediate **397** by reduction and subsequent nucleophilic displacement of the terminal hydroxyl. To reach 1-deoxycastanospermine (**398**) a reductive annulation was performed by a two-step sequence consisting of azide-to-amine conversion (PPh_3) and subsequent stereoselective reduction of the intermediate bicyclic imine. Alternatively, reduction of the azido ketone **397** by catalytic hydrogen furnished exclusively 1-deoxy-8a-*epi*-castanospermine (not shown).

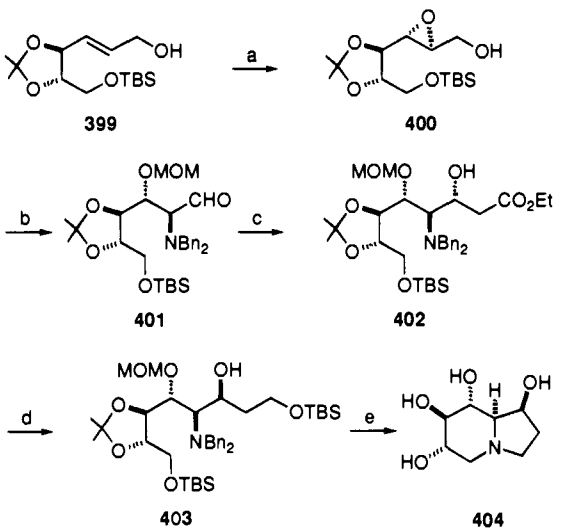
In a non-carbohydrate-based approach, total syntheses of (+)-castanospermine (**404**) and its 1-*epi*-derivative have been achieved by Kibayashi starting

Scheme 81[a]



[a] Key: (a) 2-furyllithium, $ZnBr_2$; (b) Bu^tO_2H, $VO(acac)_2$; then MeI, Ag_2O; (c) K-Selectride; then Bu_4NF; then MsCl, Et_3N, DMAP; then NaN_3, DMF; then Swern oxidn.; (d) PPh_3, benzene; then $TiCl_4$, $LiAlH_4$; then H_3O^+; then H_2, Pd/C, MeOH.

Scheme 82[a]

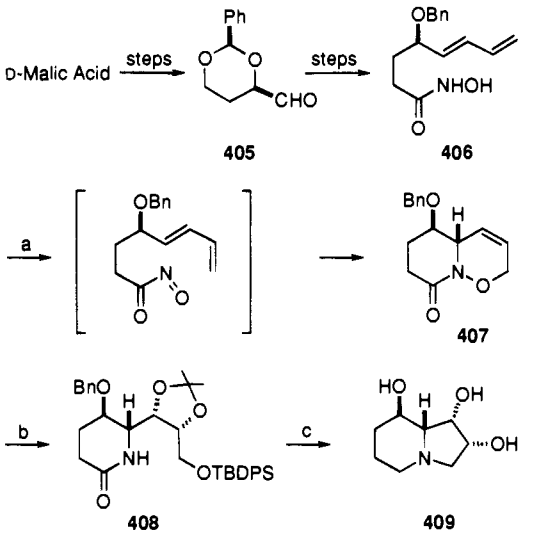


[a] Key: (a) Sharpless epoxidn.: (b) Et_2AlNBn_2; then AcCl,Et_3N; then MOMCl, Pr^i_2NEt; then $LiAlH_4$; then Swern oxidn.; (c) LiHMDS, EtOAc; (d) $LiAlH_4$; then TBSCl, imidazole, DMF; then Mitsunobu inversion; (e) TBAF, THF; then TsCl, pyridine; then H_2, $Pd(OH)_2$; then Et_3N, MeOH, reflux; then HCl, MeOH.

from a tartrate precursor.[165] For **404** (Scheme 82), the key building block **399**, obtained in six steps from dimethyl-L-tartrate, was first subjected to asymmetric Sharpless epoxidation in a matched sense (L-tartrate) to generate epoxide **400** whose oxirane ring was cleaved, regio- and stereoselectively, by exposure to Et_2AlNBn_2.

The formed amino intermediate was then converted to the six-carbon α-amino aldehyde **401** by suitable manipulation of the protective groups followed by Swern oxidation. Two-carbon elongation of aldehyde **401** was carried out according to a diastereoselective aldol reaction using lithio ethyl acetate to afford a major *anti* ester **402** (89:11 ratio) accompanied with its *syn* isomer. The diastereomeric mixture was reduced ($LiAlH_4$) and protected at the terminal hydroxyl. The major *anti* product, with the undesired configuration at C-3, was converted to the requisite *syn*-β-carbinol **403** by the Mitsunobu protocol and subjected to a series of transformations culminating in the formation of the target castanospermine (**404**). In the same study, through use of common intermediates, syntheses of anti-HIV active 1-epicastanospermine and certain 1-*O*-acetyl derivatives were also performed.

Scheme 83[a]



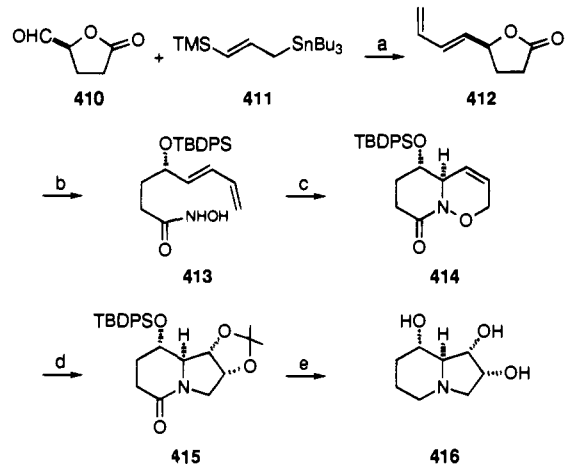
[a] Key: (a) Pr_4NIO_4, H_2O; (b) Na(Hg), Na_2HPO_4; then TBSCl, imidazole; then OsO_4, NMO; then DMP, PPTS; (c) $LiAlH_4$, THF; then CBr_4, PPh_3, Et_3N; then H_2, $PdCl_2$; then HCl, THF.

D-Malic acid was the chiron from which Kibayashi synthesized (−)-swainsonine (**409**).[166] The remarkable chemistry, featuring an intramolecular hetero-Diels–Alder reaction of a homochiral acylnitroso derivative, is outlined in Scheme 83. Dioxane aldehyde **405**, obtained in three steps from D-malic acid, was homologated by three-carbon atoms in a Wittig protocol to generate, after a series of conventional transfomations, the key eight-carbon hydroxamic acid **406** in preparatively useful yield.

The pivotal step was an intramolecular cycloaddition of an intermediate acylnitroso diene. Optimally, oxidation of **406** was conducted with tetrapropylammonium periodate in aqueous solution which ensured formation of the *trans* cycloadduct **407** with a high degree of stereoselection (4.1:1). The next stages of the sequence involved reductive cleavage of the N–O bond, dihydroxylation of the double bond in **407** and suitable protection to prepare **408**, which was subjected to carbonyl reduction, desilylation of the terminal hydroxyl, and CBr_4–PPh_3–Et_3N-assisted cyclocondensation to generate swainsonine (**409**).

Quite similar chemistry was independently adopted by Keck and Romer[167] in an important study designed to provide a general means to prepare densely oxygenated indolizidine alkaloids. As shown in Scheme 84, the opening move of the synthesis of (−)-8,8a-diepiswainsonine (**416**) was the BF_3-catalyzed homologation of lactone carboxaldehyde **410** with

Scheme 84[a]



[a] Key: (a) BF_3 etherate; then Bu^tOK; (b) LiOH; then TBDPSCl; then LiOH; then Suc-OCOCF$_3$; then NH_2OH; (c) Pr_4NIO_4; (d) OsO_4; then DMP, H^+; then Na(Hg); then MsCl; then Na_2CO_3; (e) F^-; then BH_3·DMS; then H^+.

vinyl silane **411** to produce, after basic treatment, the eight-carbon lactone **412**.

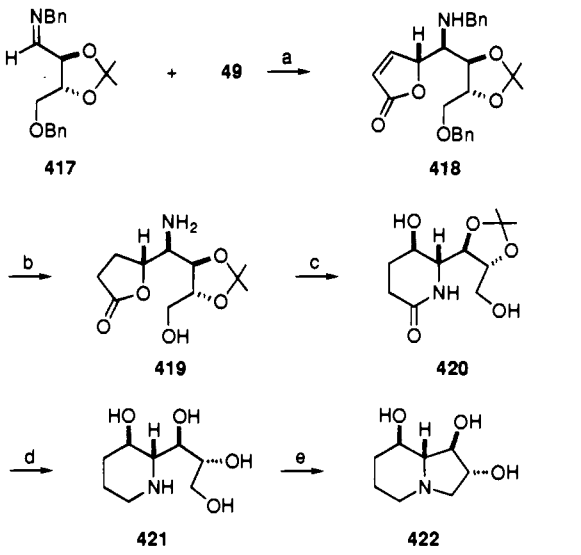
The dienyl lactone **412** was then converted to hydroxamic acid **413** which was next subjected to the crucial acylnitroso Diels–Alder reaction step. Under nonaqueous conditions, the reaction afforded a major cycloadduct **414** with low level of stereoselectivity (2.3:1). This cycloadduct was first dihydroxylated and then subjected to N–O bond cleavage. This allowed preparation of bicyclic lactam intermediate **415** which was elaborated directly into indolizidine **416** by simple chemistry.

In our continuing effort to utilize furan-, pyrrole-, and thiophene-based siloxy dienes for syntheses of densely oxygenated compounds, viable routes to indolizidine alkaloids have been devised and executed. Protected D-threose imine **417** was the enantiopure substrate from which, by reaction with siloxy diene **49**, the swainsonine derivative **422** was generated.[168]

The route to **422** is outlined in Scheme 85. The reaction of **417** with **49** in the presence of BF_3 etherate gave the expected butenolide **418** with no detectable stereoisomeric contamination. Double-bond saturation with concomitant reductive cleavage of the C–N and C–O benzylic bonds to provide aminobutanolide **419** was effected under controlled hydrogenation conditions. Next, upon treatment with DBU in benzene at reflux, amino γ-lactone **419** underwent clean ring expansion to provide δ-lactam **420** in good yield. Treatment of this compound with 3 equiv of BH_3·DMS complex in THF effected the reduction of the lactam carbonyl to the corresponding amine-borane adduct. Deprotection of the crude adduct was accomplished by acidic treatment giving the fully deprotected piperidine derivative **421**. Finally, the amino alcohol was exposed at room temperature to PPh_3–CCl_4–Et_3N in anhydrous DMF. This led cleanly to intramolecular dehydration, resulting in formation of the target compound **422** in good yield.

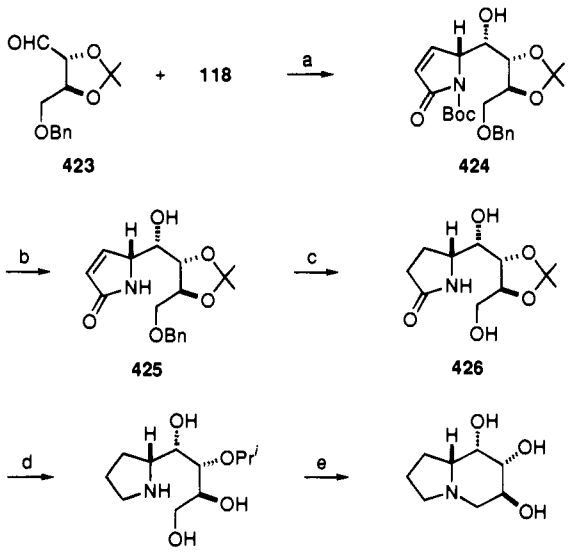
An expedient synthesis of (+)-1-deoxy-8-epicastanospermine (**428**) called for the use of 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose (**423**) as a chiral source

Scheme 85[a]



[a] Key: (a) BF_3 etherate, CH_2Cl_2; (b) H_2, Pd/C; (c) DBU, benzene, reflux; (d) BH_3·Me_2S, THF; then TFA; then DOWEX OH^-; (e) PPh_3, CCl_4, Et_3N, DMF.

Scheme 86[a]

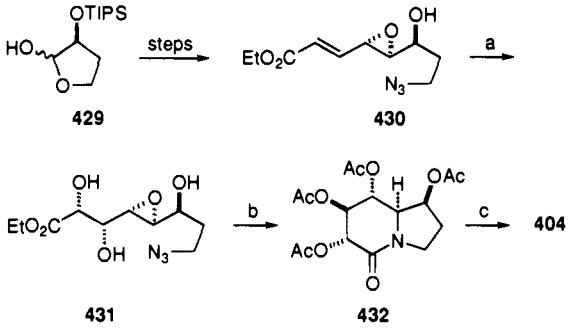


[a] Key: (a) $SnCl_4$, Et_2O; (b) PhSH, TMSOTf, CH_2Cl_2; (c) H_2, Pd/C; (d) BH_3·Me_2S, THF; then aq. HCl; (e) PPh_3, CCl_4, Et_3N, pyridine; then BBr_3, CH_2Cl_2.

and pyrrole-based siloxy diene **118** as a four-carbon nucleophile.[169] The approach (Scheme 86) envisaged double-bond saturation in the lactam adduct **424** followed by ring closure to create the indolizidine skeleton.

Optimally, threose **423** was treated with **118** in diethyl ether at −80 °C in the presence of $SnCl_4$. The addition occurred regio- and stereoselectively at the C-5 carbon of **118** to form α,β-unsaturated lactam **424** exclusively. Treatment of **424** with TMSOTf in CH_2Cl_2 in the presence of thiophenol cleanly afforded lactam **425**, which was hydrogenated and deprotected to compound **426**. Lactam **426** was directly exposed to an excess of BH_3·DMS in THF at room temperature and the crude amine–borane adduct thus formed was subjected to acidic treatment at room temperature.

Scheme 87[a]



[a] Key: (a) OsO_4, $(DHQ)_2PHAL$; (b) H_2, Pd/C, EtOH; then EtOH reflux; then Ac_2O, pyridine; (c) $BH_3{\cdot}Me_2S$; then NH_3.

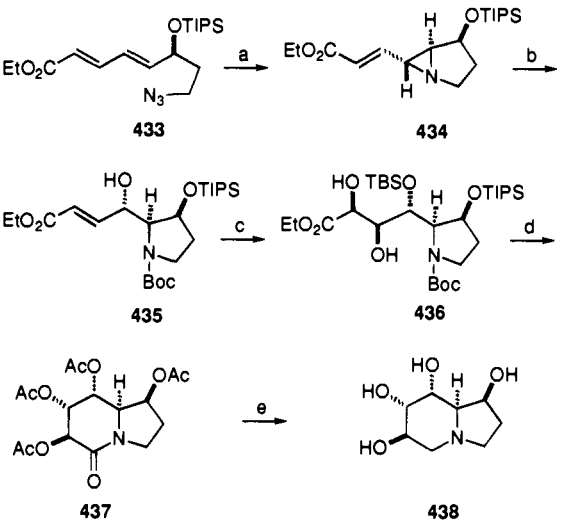
Surprisingly, this treatment afforded isopropyl ether **427** likely to have arisen from reduction of the lactam with concomitant regioselective opening of the acetonide at the O(7)−$C(Me)_2$ linkage and overreduction. Amino alcohol **427** was ready for the final and crucial cyclization step. This was achieved by subjecting this compound to PPh_3−CCl_4−Et_3N in pyridine at room temperature. There was obtained, after ion-exchange resin purification and BBr_3-promoted dealkylation, the indolizidine **428** in high yield.

A concise, enantioselective synthesis of natural castanospermine (**404**) was recently achieved by Cha and colleagues[170] utilizing readily available lactol **429** as a chiral source (Scheme 87). Wittig homologation followed by azide introduction and Sharpless enantioselective epoxidation resulted in clean production of the eight-carbon intermediate **430**. An enantioselective Sharpless osmylation led to the acyclic ester **431**. Double cyclization of this material to indolizidine **432** was accomplished by reduction of the azide group, thermal cyclization, and peracetylation. Finally, reduction of the lactam carbonyl and global deprotection afforded castanospermine (**404**).

Exploiting quite similar chemistry, the same research group[171] also succeeded in preparing 6,7-diepicastanospermine (**438**, Scheme 88). Thus, azidodiene **433** was prepared from the same lactol precursor **429** as that used for castanospermine (**404**) (*vide supra*). Intramolecular 1,3-dipolar cycloaddition took place with complete diastereoselectivity to provide aziridine **434**. A regio- and stereoselective ring opening was efficiently accomplished by the action of di-*tert*-butyl dicarbonate to furnish protected alcohol **435** which was converted to the eight-carbon pyrrolidine **436** by Sharpless catalytic asymmetric dihydroxylation. Subsequent removal of the *N*-Boc was selectively achieved by HF in acetonitrile permitting clean cyclization (Et_3N) to pyrrolizidinone **437**. The final stages to the target indolizidine **438** entailed lactam reduction and deprotection.

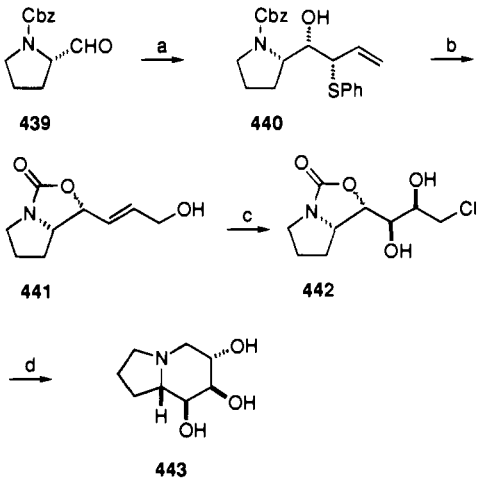
Four different isomers of 1-deoxycastanospermine were prepared by St-Denis and Chan utilizing L-proline as a common chiral precursor.[172] As illustrated for trihydroxyindolizidine **443** (Scheme 89), stereocontrolled homologation of L-prolinal **439** with the titanium salt of allyl phenyl sulfide gave a 2:1 mixture of two isomers which could be easily separated. The major compound **440** was first transformed into cyclic carbamate **441** and then elaborated into diol **442** by chlorination and subsequent diastereoselective (3:1 diastereomeric ratio) dihydroxylation (OsO_4). The indolizidine skeleton was generated next, after acetonide formation and decarbamoylation, by conventional base-promoted nucleophilic displacement of the terminal chlorine function. The protected indolizidine so formed was finally deprotected by acidic treatment and then converted to the free base **443**. From the different isomeric intermediates, three further hydroxylated indolizidines were also prepared, thus enlarging the synthetic scope of the entire plan.

Scheme 88[a]



[a] Key: (a) pyridine, 50-70°C; (b) Boc_2O, THF, H_2O; (c) TBSOTf; then OsO_4, (DHQD)-PHAL; (d) HF, MeCN; then Et_3N, Δ; then Ac_2O, pyridine; (e) $BH_3{\cdot}Me_2S$; then NH_3.

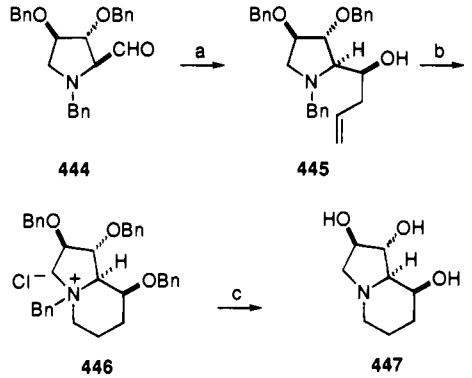
Scheme 89[a]



[a] Key: (a) CH_2:$CHCH_2SPh$, BuLi, $Ti(OPr^i)_4$; (b) MCPBA, CH_2Cl_2; then $(MeO)_3P$, MeOH; then NaOH, Pr^iOH, H_2O; (c) PPh_3, CCl_4; then OsO_4, NMO; (d) DMP, CSA; then NaOH, aq. MeOH, 80°C; then TFA.

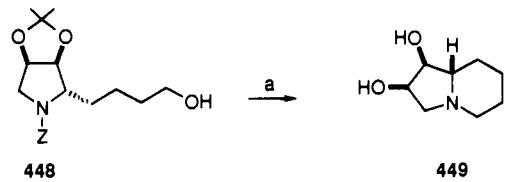
An elegant approach to swainsonine-related alkaloids from noncarbohydrate sources was reported by Ikota[173] utilizing (*S*)-pyroglutamic acid as the precursor of the pyrrolidine moiety. As shown for (+)-1,8-diepiswainsonine (**447**, Scheme 90), diastereospecific $TiCl_4$-promoted allylation of hydroxylated aldehydo pyrrolidine **444**, easily obtained from pyroglutamic acid by trivial chemistry, afforded homologated com-

Scheme 90[a]



[a] Key: (a) CH_2:$CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2; (b) NaH, BnBr; then BH_3, THF; then NaOH, H_2O_2; then MsCl, TEA; (c) H_2, Pd/C, HCl, EtOH; then Dowex H^+.

Scheme 91[a]



[a] Key: (a) MsCl, pyridine; then H_2, $Pd(OH)_2$; then aq. K_2CO_3; then H_3O^+.

pound **445** as the dominant product, with all stereochemistry correctly implemented.

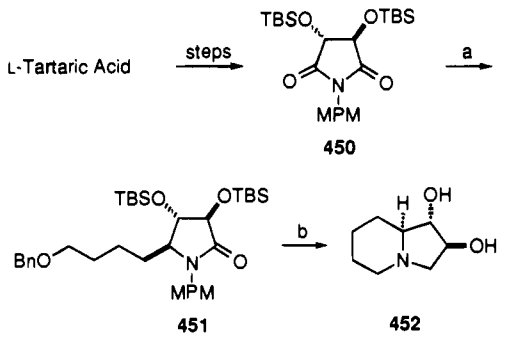
After benzylation of the free hydroxyl, hydroboration–oxidation and subsequent mesylation directly afforded the bicyclic compound **446** which was transformed to swainsonine derivative **447** by catalytic hydrogenolysis. The use of a different catalysis during the allylation stage allowed preparation of an epimeric adduct which was used to prepare (−)-1-episwainsonine (**422**).

Rather similar chemistry allowed preparation of (−)-*cis*-1,2-dihydroxyindolizidine (**449**).[174] In the event, the eight carbon pyrrolidine **448** was directly cyclized to the target compound upon mesylation, ring closure, and deprotection (Scheme 91).

Lentiginosine (**452**), first isolated from *Astragalus lentiginosus*, was indicated to inhibit fungal α-glucosidase. To synthesize this alkaloid, Yoda *et al.* converted L-tartaric acid to the C_2-symmetric imide **450** which was next elongated by four atoms using [ω-(benzyloxy)butyl]magnesium bromide.[175] After deoxygenation, there was obtained intermediate **451** endowed with all carbons and chirality of lentiginosine. Annulation through mesylation, desilylation, and reduction of the lactam carbonyl finally provided the target indolizidine **452** (Scheme 92).

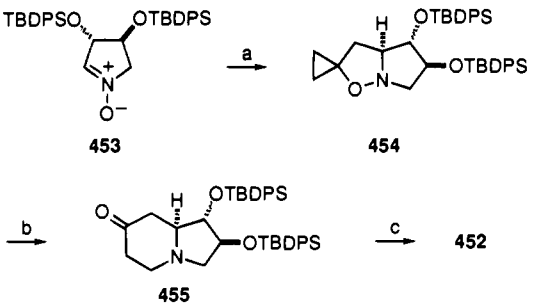
A total synthesis of the same alkaloid **452** was recently introduced by Brandi,[176] employing L-tartaric acid. Thus, protected nitrone **453**, easily prepared from L-tartrate, was treated with methylenecyclopropane to give isoxazolidine **454** predominantly (10:1 ratio). Thermal rearrangement provided indolizidinone **455** in moderate yield along with an unwanted monocyclic derivative. Reduction of the ketone function in **455** via the tosylhydrazone and subsequent desylilation afforded lentiginosine **452** (Scheme 93).

Scheme 92[a]



[a] Key: (a) $BnO(CH_2)_4MgBr$, THF; then Et_3SiH, BF_3 etherate; (b) CAN, MeCN, H_2O; then Pd, HCO_2H, $PrOH$; then MsCl, Et_3N; then NaH, THF; then HCl, MeOH; then $LiAlH_4$.

Scheme 93[a]



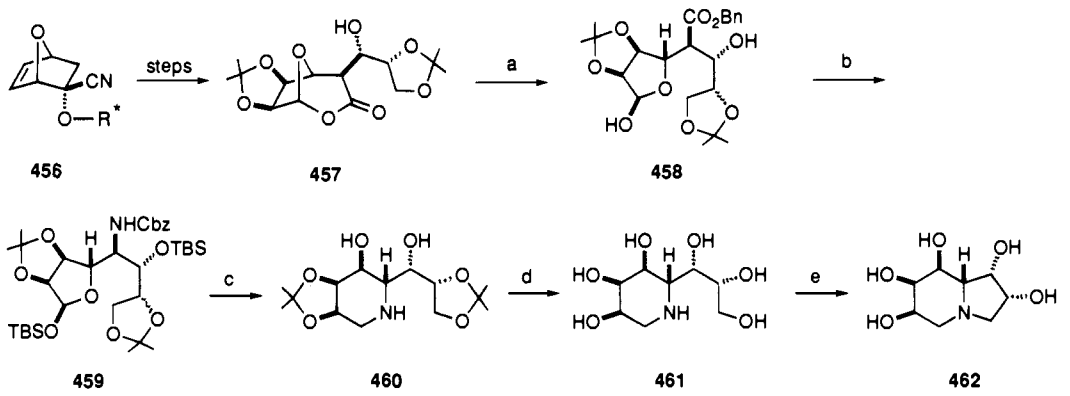
[a] Key: (a) methylenecyclopropane; (b) xylenes, 140°C; (c) $TsNHNH_2$, MeOH; then $NaBH_4$; then aq. HF, MeCN.

Enlarging further the scope of homochiral "naked sugars" in the organic synthesis domain, Vogel synthesized hyperoxygenated indolizidine **462** (Scheme 94).[177] The optically pure Diels–Alder adduct **456** of furan and 1-cyanovinyl (1*R*′)-camphanate was the synthetic chiron from which the key precursor **457** was generated.

Clean opening of the lactone ring to form benzyl ester **458** was then achieved by exposure to benzyl alcohol/cesium fluoride in DMSO. Silylation of the anomeric hydroxyl in **458** and debenzylation followed by Curtius rearrangement provided the corresponding isocyanate that was treated with benzyl alcohol to give the protected aminofuranose **459**. Remarkably, desilylation of the anomeric function and hydrogenolytic removal of the carbobenzyloxy protection effected ring expansion to **460** according to an efficient intramolecular reductive amination. Acidic hydrogenolysis of the two dioxolane moieties in **460** resulted in quantitative formation of the free octitol **461** which was finally cyclized to indolizidine **462** by exposure to PPh_3/CCl_4 in the presence of triethylamine.

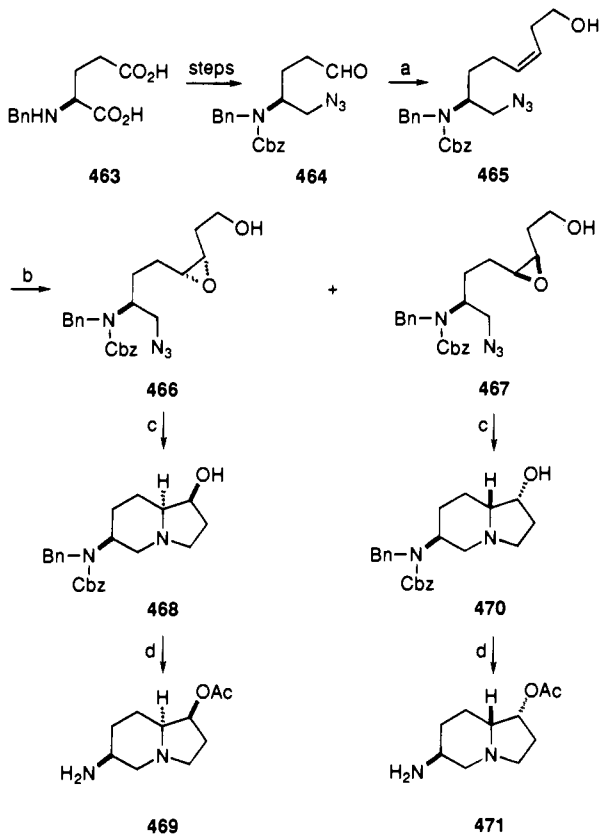
Indolizidine alkaloid slaframine (**469**), a mycotoxin produced by the fungus *Rhizoctonia leguminicola*, has been shown to be the causative agent for a disease in ruminants (black patch) who graze on fungus contamined feeds. Only two synthetic approaches to nonracemic slaframine were reported during the period antecedent to this review, while four elegant studies on this subject have appeared in the subsequent period. The Pearson approach to **469** (Scheme 95) utilizes *N*-benzyl-L-glutamic acid

Scheme 94[a]



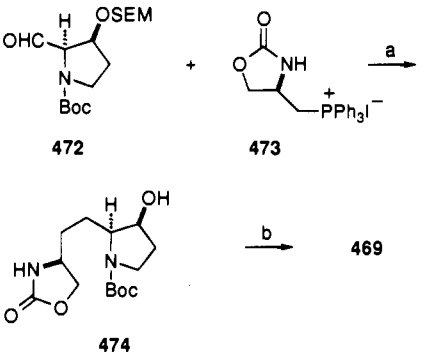
[a] Key: (a) BnOH, CsF, DMSO; (b) TBSOTf, 2,6-lutidine; then H_2, Pd/C; then $N_3PO(OPh)_2$, toluene, Et_3N; (c) TBAF; then H_2, Pd/C; (d) aq. TFA; (e) Ph_3P, CCl_4, Et_3N, pyridine.

Scheme 95[a]



[a] Key: (a) Ph_3P:$CHCH_2CH_2OTMS$, THF; (b) MCPBA; (c) TsCl, pyridine; then H_2, Pd/C; then K_2CO_3, EtOH; (d) Ac_2O, pyridine; then H_2, Pd/C.

Scheme 96[a]



[a] Key: (a) BuLi; then H_2, Pd/C; then TBAF, HMPA; (b) 270°C; then Ac_2O.

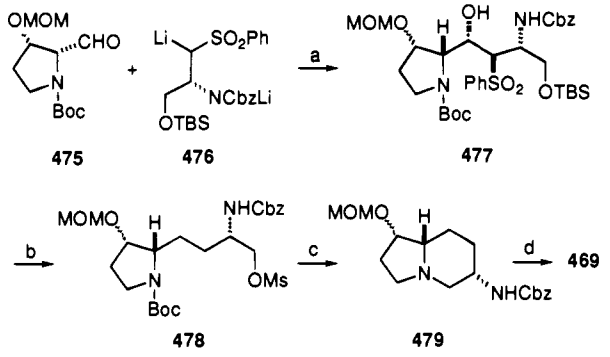
(**463**) as the starting chiral precursor.[178] Conversion of this acid to azido-aldehyde **464** was accomplished in six steps. Then, a stereoselective Wittig homologative alkenylation of the five-carbon aldehyde **464** using a siloxy substituted ylide afforded the key (*Z*)-azidoalkene **465** which was subjected to epoxidation with *m*-chloroperoxybenzoic acid. In the event, epoxides **466** and **467** were produced in equal amounts, but in excellent yields. Once separated, the individual epoxides **466** and **467** were processed independently by the same sequence, to reach slaframine (**469**) and its 1,8a-diepi derivative **471**, respectively.

Thus, after activation of the terminal hydroxyl as a tosylate and azide-to-amine conversion by catalytic hydrogen, the epoxide underwent clean base-promoted double annulation to give the *N*-diprotected indolizidine **468** from which (−)-slaframine (**469**) was obtained through acetylation of the free hydroxyl and hydrogenolytic *N*-deprotection. Paralleling this protocol, (−)-1,8a-diepislaframine (**471**) was also synthesized from the protected derivative **470**.

In a concise entry to the same alkaloid **469**[179] (Scheme 96), the aldehyde **472**, obtained from D-proline ethyl ester, was treated with the ylide derived from the chiral phosphonium salt **473** to afford, after hydrogenation of the double bond and desilylation, the saturated intermediate **474**. The crucial step was ring closure to form the piperidine ring; the process involved concomitant removal of the Boc protection in **474**, ring closure at the 5-position of the oxazolidinone, and loss of carbon dioxide under pyrolytic conditions. Remarkably, the reaction produced in high yield an indolizidine whose acetylation afforded natural slaframine **469**.

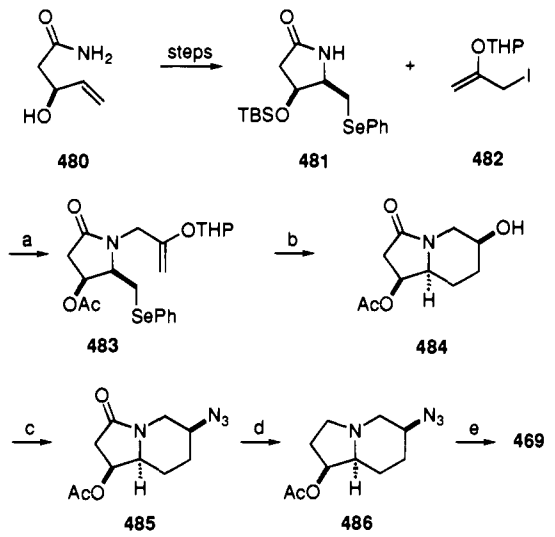
The prolinal derivative **475** was the chiron utilized by Knight[180] to synthesize **469**, by homologation with the dianion derived from chiral β-amino sulfone **476** (Scheme 97). The condensation proceeded with an acceptable level of diastereoselectivity (3:1) affording intermediate **477** as the dominant isomer. A sequence of four simple reactions allowed conversion of **477** into the key pyrrolidine **478** bearing all the required atoms and stereochemistry. Removal of the *N*-Boc group followed by basic treatment led to the desired indolizidine **479**, the immediate precursor of slaframine **469**.

Scheme 97[a]



[a] Key: (a) Julia condensation; (b) Na(Hg), Na_2HPO_4, MeOH; then trisylhydrazide, Et_3N, Et_2O; then TBAF, THF; then MsCl, pyridine; (c) TFA, CH_2Cl_2; (d) HCl, MeOH; then Ac_2O, CH_2Cl_2; then H_2, Pd/C.

Scheme 98[a]



[a] Key: (a) NaH, DMF; then TBAF, THF; then Ac_2O, pyridine; (b) $(TMS)_3SiH$, AIBN; then aq. AcOH, THF; (c) MsCl, Pr'_2EtN, CH_2Cl_2; then NaN_3, DMF, 105°C; (d) $BH_3 \cdot Me_2S$, THF; then TMEDA; (e) H_2, Pd/C; then Ac_2O, pyridine.

An elegant synthesis of **469**, in 11 steps and 25% overall yield, has been executed by Knapp and Gibson[181] utilizing resolved (3*S*)-hydroxy-4-pentenamide (**480**, Scheme 98). Thus, **480** was first transformed into the lactam intermediate **481** by a five-reaction sequence involving iodolactamization and replacement of iodo with phenylseleno. The required substrate for the crucial free radical-initiated annulation, compound **483**, was then obtained by *N*-alkylation of **481** with THP-protected iodo derivative **482**, followed by suitable exchange of the protecting groups. Radical cyclization of **483** was carried out using the AIBN–tris(trimethylsilyl)silane system to afford, after removal of the THP protection, indolizidinone **484** predominantly (7:1), along with a minor C-6 epimeric alcohol. Conversion of **484** to its methanesulfonic ester, followed by S_N2 displacement of the *O*-mesyl group with azide, gave azidoindolizidinone **485** which was converted to stable slaframine azide **486** by BH_3 reduction of the lactam carbonyl and then transformed to (−)-slaframine (**469**) by catalytic hydrogenation and acetylation.

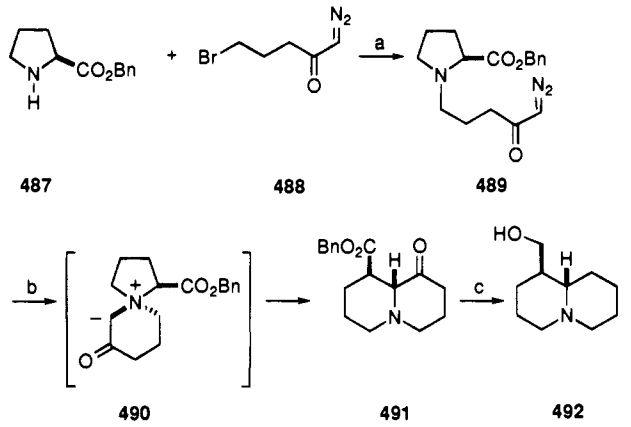
Quite recently, Gmeiner[182] and co-workers reported a chirospecific synthesis of 1,8a-diepislaframine (**471**) and 8a-epislaframine from natural aspartic acid.

3. Quinolizidine Derivatives

While considerable effort has been devoted to prepare a wide number of polyhydroxylated indolizidines as well as ring-contracted versions, few studies dealing with the assembly of chiral ring-expanded analogues, namely the hydroxylated quinolizidines, have appeared. Some work in this area was aimed at the bicyclic quinolizidine alkaloids of the lupinine family, ranging from simple lupinine and epilupinine to more elaborated bioactive tetracyclic assemblies.[153,183]

A concise stereoselective route to enantiomerically enriched (−)-epilupinine (**492**) from L-proline benzyl ester (**487**) has been recently reported by West and Naidu[184] (Scheme 99). Thus, *N*-alkylation of **487**

Scheme 99[a]

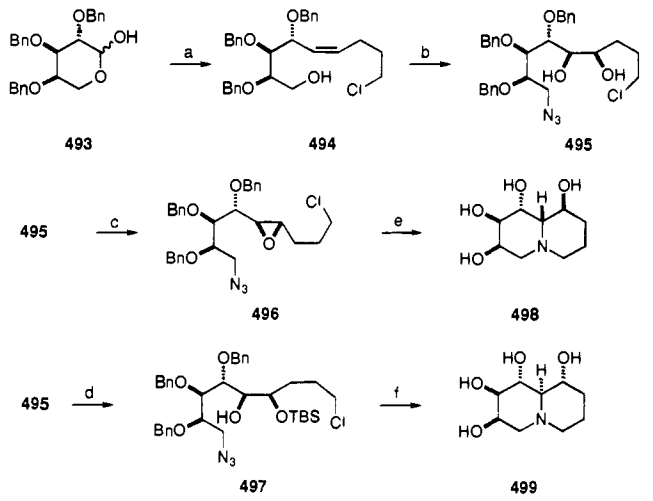


[a] Key: (a) Et_3N, EtOAc; (b) $Cu(acac)_2$, toluene, reflux; (c) $(CH_2SH)_2$, BF_3 etherate; then $LiAlH_4$; then Na, N_2H_4, $(CH_2OH)_2$.

with diazopentanone **488** gave in excellent yield diazo ketone **489** which was subjected to transition metal-catalyzed annulation. Under optimal conditions, exposure of **489** to catalytic copper(II) acetylacetonate in toluene at reflux resulted in preferential formation of quinolizidinone **491** accompained by only a few percent of its 9a-epimer. NMR analysis of **491** (chiral shift reagent) indicated an ee of 65–75%. The stereochemical outcome of the reaction suggested formation of ylide **490** and stereospecific [1,2]-shift to give enantiopure **491**. The racemic portion of **491** would arise from a homolytic coupling mechanism with concomitant randomization. The final conversion of **491** to epilupinine **492** (75% ee) was carried out in three steps, involving thioketalization, reduction of the carbobenzyloxy moiety, and desulfurization with Na/hydrazine. From proline ester **487**, the entire sequence required five steps proceeding in 30% overall yield.

Very recently, Pearson[185] concluded a detailed study directed toward the synthesis of polyhydroxylated quinolizidine alkaloids. His remarkable research culminated in a successful entry to four novel tetrahydroxyquinolizidine stereoisomers, by exploiting, as a key synthetic operation, a reductive double alkylation of suitable α,ω-chloro azide intermediates. Scheme 100 illustrates how diastereomeric indolizidines **498** and **499** were assembled from a common precursor, namely the hydroxylated α,ω-chloro azide **495**.

Scheme 100[a]

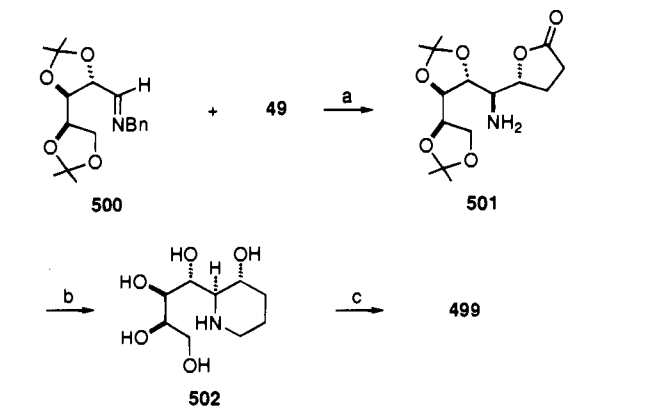


[a] Key: (a) PPh_3:$CH(CH_2)_3Cl$, THF; (b) PPh_3, HN_3, DEAD; then OsO_4, NMO; (c) MsCl, Et_3N; then NaH, THF; (d) TBSCl, imidazole; (e) H_2, Pd/C; then K_2CO_3, EtOH; then H_2, Pd/C, HCl, MeOH; (f) Swern oxidn.; then H_2, Pd/C; then $NaBH_4$, MeOH; then K_2CO_3, EtOH; then H_2, Pd/C, HCl, MeOH.

Easily available tri-*O*-benzyl-D-arabinopyranose (**493**) was first elongated by four carbon atoms by a Wittig protocol to give alkene **494** which possesses the requisite nine-carbon skeleton of the targets. The key divergent intermediate **495** was next created by azidation of **494** at one terminal and subsequent diastereoselective (85:15) double-bond hydroxylation. For **498**, epoxide **496** was required, while for the isomeric quinolizidine **499**, intermediate **497** had to be prepared. Epoxide **496** was directly cyclized to **498** through azide reduction, base-promoted double annulation, and deprotection, whereas transformation of ketone **497** into **499** required preliminary reductive amination and subsequent ring closure and deprotection.

Preparation of the same quinolizidine **499** was also reported by us in a recent publication focused on the use of the siloxy diene reagent **49** for syntheses of densely oxygenated quinolizidines (Scheme 101).[186]

Scheme 101[a]



[a] Key: (a) BF_3 etherate, CH_2Cl_2; then H_2, Pd/C; (b) DBU, xylenes, 140°C; then BH_3·Me_2S, THF; then aq. TFA; (c) Ph_3P, CCl_4, Et_3N, DMF.

By starting with arabinose-derived imine **500** and paralleling exactly the chemistry previously applied to the synthesis of the swainsonine analogue **422** (*vide supra*), amino-γ-lactone **501** was prepared and then converted to the key piperidine intermediate **502**. The final cyclization was achieved upon exposure of **502** to PPh_3–CCl_4–Et_3N. This treatment allowed formation of an alkaloid to which structure **499** was assigned upon the basis of ^1H and ^{13}C NMR analyses. However, inspection of the NMR spectral data provided by Pearson for **499** revealed profound discrepancies.[187]

IV. Concluding Remarks

Highlighted in this article have been conceptually diverse syntheses of carbohydrates and variants thereof, including preparation of aminated derivatives and carbon–carbon-linked oligosaccharides, a rapidly growing subclass of carbohydrate mimics. Also emphasized have been total syntheses of certain hydroxylated alkaloids ranging from monocyclic pyrrolidine and piperidine derivatives to bicyclic pyrrolizidine, indolizidine, and quinolizidine compounds. All these alkaloids represent *N*-containing sugar mimics which have gained increasing attention recently as inhibitors of the glycoprotein processing and as potential chemotherapeutic agents.[123]

The described chemistry demonstrates the usefulness of the chiron approach and the various substrate-controlled asymmetric tranformations for syntheses of complex chiral compounds. The flexibility embodied in chiron-based synthesis coupled with its divergent and/or convergent nature has now rendered a multitude of constitutionally and stereochemically diverse compounds accessible by total synthesis.

Future improvements of this mature technique for the assembly of multifunctional bioactive substances will include novel synthetic strategies minimizing protection–deprotection, or combining, in a rational way, the chiron protocol with other complementary techniques, such as chemical and enzymatic asymmetric catalysis. Furthermore, application of combinatorial chemistry[110,188] by exploiting the constitutional and stereochemical diversity of a number of readily available chirons, will ensure rapid assembly of small-compound libraries to be used in the development of novel drugs. This exciting prospect, while providing a new tool for chemists to discover bioactive lead compounds, will encourage the search for unified chemo- and stereoselective protocols to assemble active components or even simplified and superior agents.

V. An Overview of Reviews on Related Topics

A large number of papers on the stereoselective preparation of bioactive carbohydrates and hydroxylated alkaloids were found on searching the literature. We tried to cover the majority of those related to the present topics that appeared in the period of 1992 to the present, and we apologize for inevitable omissions. For the convenience of the readers a compilation of relevant review articles, books, and book chapters, some of which are mentioned throughout the text, is presented here.

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