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The Henry reaction: recent examples

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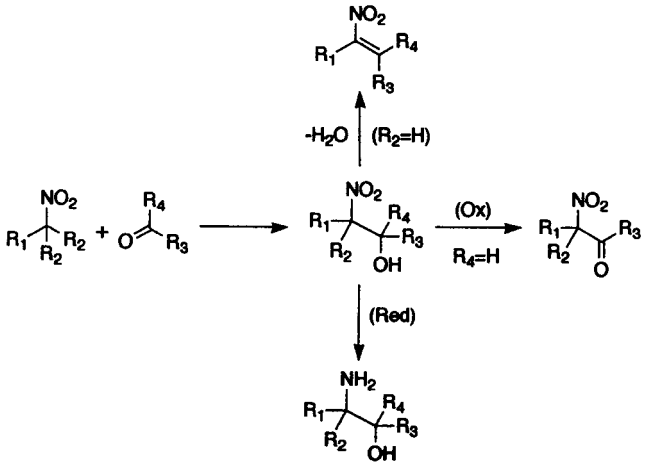
Contents

1. Introduction

The Henry or nitroaldol reaction is easily recognizable as one of the classical name reactions in organic synthesis.[1] Essentially a coupling reaction between a carbonyl compound and an alkylnitro compound bearing α hydrogens, the overall transformation enables the formation of a carbon–carbon bond with the concomitant generation of a new difunctional group, namely the β-nitroalcohol function.[2a,2b] Moreover, in more complex synthetic ventures, the Henry reaction will facilitate the joining of two molecular fragments, under mild conditions, with the formation of two asymmetric centers at the new carbon–carbon juncture. Typically, further transformations involving the newly formed β-nitroalkanol functionality, such as oxidation, reduction, and dehydration, will follow thereby depending on the requirements and overall goal of the multi-step synthetic plan (Scheme 1).[3]

An interesting aspect of the nitroaldol reaction is the high demand which is placed on selectivity during the subsequent synthetic steps involving reduction or removal of the nitro group. Nitroaldol reactions have seen increased utilization in syntheses where substructures bearing labile protecting groups and sensitive functionality are joined; however, these moieties will have to survive the subsequent operations such as removal of the nitro group, reduction to a



Scheme 1.

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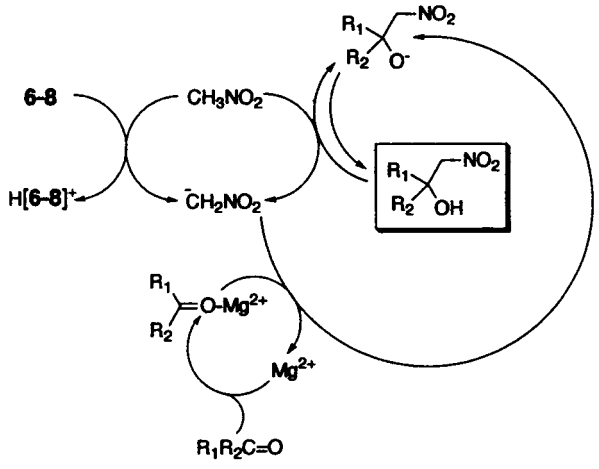


Scheme 2.

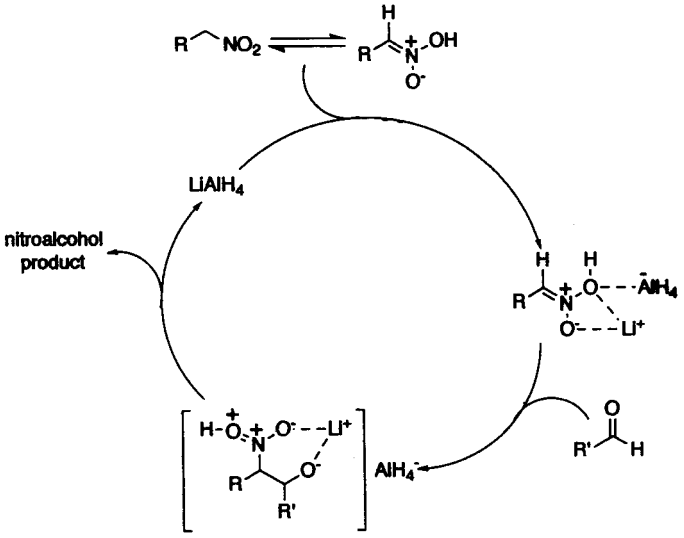
β-aminoalcohol, dehydration to a conjugated nitroalkene or the Nef reaction.[4] Furthermore, retroaldolization and/or epimerization may accompany any of the conversions of the β-nitroalkanol group. For example, the catalytic reduction of a nitroalcohol to the corresponding aminoalcohol function may be accompanied by significant retroaldolization, resulting in epimerization or complicated product mixtures containing unwanted stereoisomers and compromised yields of the desired products. In practice, once the nitroalcohol is formed and isolated, what are the options available to the synthetic chemist for arrival at the all-important goal? Several answers to this question may be found in this report. We have included a number of complex synthetic schemes which employ the nitroaldol reaction as the key step as well as simpler schemes which include at least the ensuing reduction step. Nitroaldol chemistry has driven the development of new methods for preparing alkylnitro compounds; therefore, schemes which include novel preparations of the alkylnitro precursors are included in this report as well. The exploration and development of asymmetric catalysis has enabled many of the classical organic reactions to approach their zenith of applicability. Along with serving as a guide, a goal of this report is to display the Henry reaction as an excellent example of a classical organic reaction which has undergone a maturation and fine-tuning process. The availability of newer types of chiral catalysts coupled with the ever-increasing requirements for stereochemically pure amino alcohols in pharmaceutical and natural product synthesis has made the evolution of the Henry reaction possible. As a result the scope of the Henry reaction has expanded from utilization in syntheses where the nitroalkanol functional group is interchanged (FGI),[5] with groups such as nitroalkenes, nitroketones and ketones, to employment as a highly efficient and reliable enantioselective transform. This report details the contributions in the area of nitroaldol chemistry which have spanned the last fifteen years 1985–1999 although some references to earlier work will be made to provide reasonable perspective and so that distinct advances may be recognized.

2. Catalysts

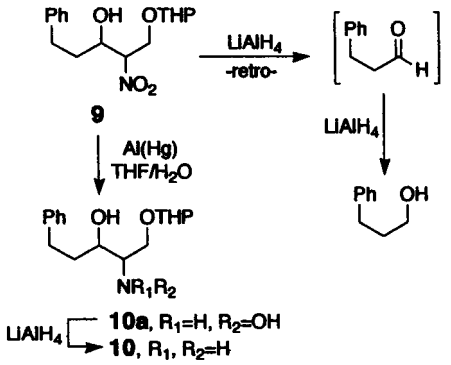
2.1. General catalysts and promotors

Nitroaldol reactions may be catalyzed or promoted by many different sets of conditions or catalysts. Organic bases, inorganic bases, quaternary ammonium salts, protic and aprotic solvents and solventless conditions have been used to name a few. The types of conditions which are employed for the reaction will largely depend on the type of functionality present, the solubility of the reactants and the ease to which the nitronate is generated. If the nitro compound is relatively inexpensive, then a large excess may be employed so that a high concentration may be maintained and the reaction will progress to completion. On the other hand a large excess of aldehyde may result in competing aldol condensations as well as epimerization.

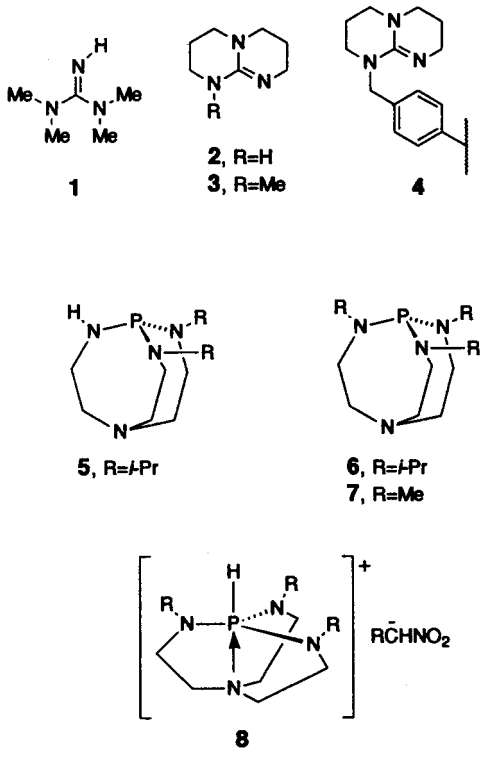
The first catalysts of choice for promoting nitroaldol reactions were variations of either alkoxides or hydroxides in alcoholic or aqueous solvent systems.[6] Such strong bases were normally used to promote reactions between relatively simple substrates bearing limited functionality. For some time, 1,1,3,3-tetramethylguanidine (TMG, **1**) has been



Scheme 3.

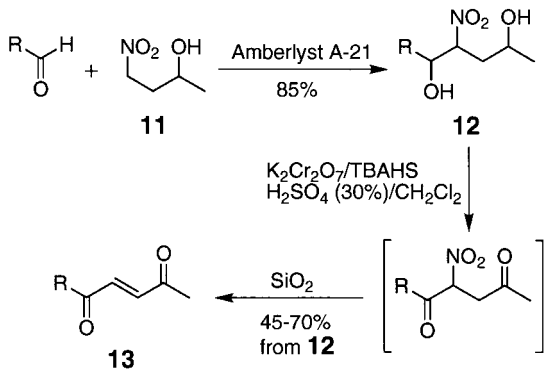


Scheme 4.



used to effectively promote the reaction in solvents such as diethyl ether and tetrahydrofuran, while amines such as triethylamine or diisopropylethylamine have been utilized in alcoholic solvents.[7,8,9] More recently the cyclic analogs of TMG, the bicyclic guanidines **2** and **3**, including the polymer-linked **4**, have been evaluated and appear to be useful additions to the already growing number of achiral nonionic bases which are known to catalyze or promote the Henry reaction.[10] In developing new promoters for the nitroaldol reaction, many investigators cite the need to avoid side reactions such as dehydration to the nitroalkene, normal aldol by-products, epimerization of centers remote from the nitro functionality and the formation of by-products as a result of the Nef-type reactions.

Verkade has developed a series of proazaphosphatranes **5**–**7** which efficiently promote nitroaldol reactions with ketones as well as aldehydes (Scheme 2).[11] Using ketones as substrates, the typical competitive side reaction is self-condensation of the carbonyl substrate. Since the proazaphosphatranes exist as the putative protonated complex **8**, the competing side-reaction involving ketone self-condensation is suppressed thereby allowing respectable yields of ketone-derived nitroalcohols. For optimal results, Verkade's reagent system includes magnesium sulfate as a Lewis-acid-type activator for the carbonyl group.

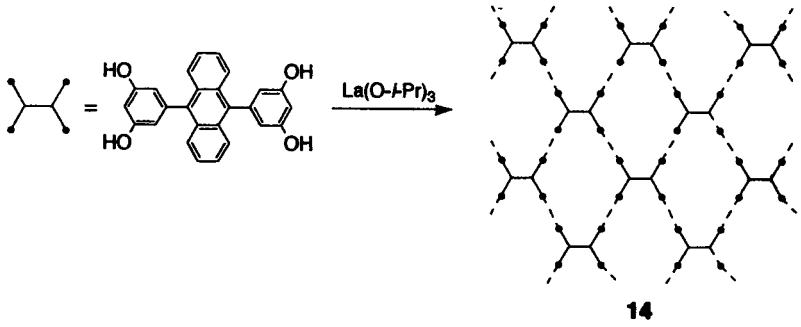


Scheme 5.

Lithium aluminum hydride (10 mol%) in tetrahydrofuran has been reported to catalyze the nitroaldol reaction between a variety of aromatic and aliphatic aldehydes and simple nitroalkanes such as nitromethane, nitroethane or nitropropane.[12] The reaction times vary from 2–8 h while the isolated yields range from 71% to quantitative. The *anti*/*syn* diastereoselectivity was determined by ^{1}H and ^{13}C NMR analysis and was found to range from 1:1.1 to 1:3.4. A proposed catalytic mechanism for the $LiAlH_4$-catalyzed reaction is detailed in Scheme 3. At first glance, the presence of moisture and adventitious base such as lithium hydroxide would immediately become suspect in the actual promotion of the reaction rather than $LiAlH_4$. In order to rule out promotion by moisture and basic impurities, the workers used carefully-dried solvents and performed control reactions with LiOH (10 mol%) in THF although the purity of the $LiAlH_4$ was not determined. Interestingly, the treatment of nitroalcohol **9** with excess $LiAlH_4$ in THF provided greater than 50% yield of hydrocinnamyl alcohol, apparently due to the retro-Henry reaction followed by reduction of hydrocinnamaldehyde. The method of choice for the reduction of nitroalcohol **9** to amino alcohol **10** was aluminum amalgam in THF/H_2O followed by reduction of the intermediate hydroxylamine **10a** with $LiAlH_4$/THF (Scheme 4).[13]

Ballini has employed Amberlyst A-21 under solventless conditions for the preparation of nitrodiols from a series of aldehydes and 4-nitro-2-butanol (Scheme 5). The nitrodiols were utilized as substrates for the preparation of *E*-α,β-unsaturated-γ-dicarbonyl compounds through modified chromic acid oxidation.[14]

Nitroaldol reactions may be run under aqueous conditions in order to avoid the use of organic solvents and their associated environmental concerns. Ballini and co-workers have



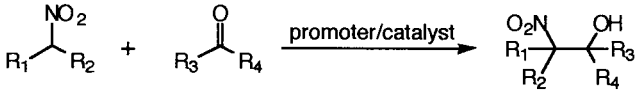
Scheme 6.

reported the use of cetyltrimethylammonium chloride as a phase-transfer agent for condensations in water containing sodium hydroxide.[15] Although the reactions are conducted under aqueous conditions, the protocol requires an extractive workup with ether prior to purification of the products. Solventless conditions have been employed when using microwave irradiation with promotion by ammonium acetate[16] as well as powdered potassium hydroxide.[17]

Admixture of lanthanum trisisopropoxide and the anthracene bisresorcinol results in the formation of an amorphous La^{+3} coordination polymer or La host 'network' **14**. The La host was found to catalyze the condensation of hydrocinnamaldehyde and nitromethane in benzene although no yields were reported (Scheme 6).[18] Catalysis by the La host is presumed to be attributed to the Lewis acid effect by La ions coordinated to the nitronate species while the metal ions are 'immobilized' in the polyphenoxide network. The heterogeneous catalyst has the consistency of being easily removed upon completion of the reaction thereby simplifying the subsequent purification steps. The preparation and use of the rare earth nitroaldol catalyst $Sm(HMDS)_3$ was reported by Shibasaki. $Sm(HMDS)_3$ can be easily prepared from $SmCl_3$ and NaHMDS and was used to catalyze simple nitroaldol reactions between nitromethane and aldehydes such as hydrocinnamaldehyde, benzaldehyde and cyclohexylcarboxaldehyde.[19] Additional catalyst/promoter systems for the mediation of the nitroaldol reaction, together with the conditions, yields and references, are listed in Table 1.

The reaction of nitroethane and a series of aldehydes gave only the corresponding nitroaldol products when promoted by the rhodium catalyst **15** and the silylketene acetal **16** (Table 2).[28] The reaction utilized nitroethane as the solvent since dichloromethane and tetrahydrofuran inhibit the reaction, presumably due to coordination with rhodium. The isolated yields of mixtures of *syn*/*anti* (2:3) products ranged from 24 to 62%. The mechanism for the rhodium-catalyzed reaction was proposed whereby a monomeric rhodium complex coordinates to nitroethane through the *aci* nitro species. Proton transfer from the coordinated *aci*-nitroethane-species to the silyl ketene acetal results in formation of the nitronate nucleophile which attacks the aldehyde thereby forming the nitroalkanol product. The proposed mechanism is somewhat consistent with the lower yields (18%) realized with nitromethane, which is more reluctant to exist in its *aci*-nitro form. Although the yields shown in Table 1 represented the isolated yields of product nitroalcohols, the crude product, which was obtained by removal of solvent from the reaction mixture, also consisted of silylated nitroalkanol. The occurrence of the silylated product required treatment with *tetra*-*n*-butylammonium fluoride (TBAF) prior to chromatographic

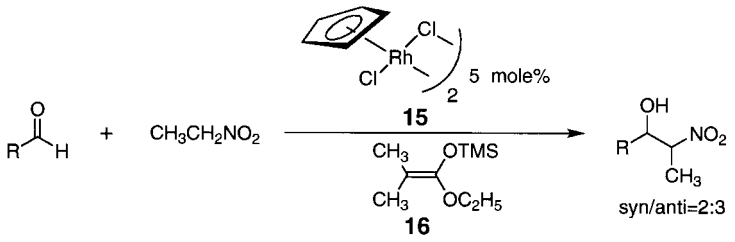
Table 1. Diversity of promoters, catalysts and conditions for simple nitroaldol reactions



Catalyst/Promoter	Conditions	Yield (%)	Ref.
KOH	Solventless, 0–5°C, 10 min	60–99	17
Mg–Al hydrotalcites	THF, reflux, 6–8 h	72–95	20
NH_4OAc	Solventless, microwaves, 2.5–8 h	80–92	16
$Bu_4N^+F^-$	Solventless, 0.3–0.95 kbar	63–100[a]	21
Alumina, Brockman I	Solventless, 0–5°C, 1 h	69–86	22
Amberlyst A-21	Solventless, 0–5°C, 20 h	70–87	23
KF/alumina	Solventless, 0°C, 5–15 h	50–78	24
Zr $(KOPO_3)_2$	Solventless, rt, 6–25 h	62–89	25
SiO_2	Solventless, microwaves	56–82	26
Triethanolamine-core dendrimer	Nitroalkane solvent	75–90[b]	27

[a] Experiments were conducted as a study of pressure effects
[b] Conversion was measured by ^1H NMR.

Table 2. Rhodium/silyl ketene acetal-catalyzed nitroaldol reactions



RCHO	$CH_3CH_3NO_2$ (equiv.)[a]	Yield (%)[b]
PhCHO	43	24
$PhCH_2CHO$	43	62
PhCH=CHCHO	43	48
$Ph(CH_2)_2CHO$	43	54

[a] Nitroethane was used as the solvent.
[b] Isolated yields.

purification for optimal yields. The yields of nitroalkanols were satisfactory when a stoichiometric amount of silyl ketene acetal was used.

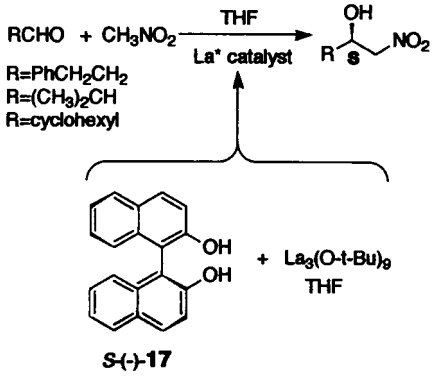
2.2. Asymmetric catalysts

Considerable effort has been directed toward the development of asymmetric catalysts for the Henry reaction. When coupled with an efficient, high-yield reduction of the product nitroalcohols the overall sequence offers an excellent expedient for the preparation of optically-enriched aminoalcohols.

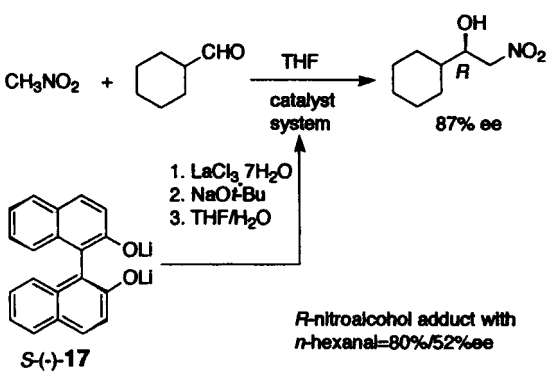
The first example of a catalytic asymmetric nitroaldol reaction was reported by Shibasaki who utilized (*S*)-(−)-binaphthol **17** in conjunction with a lanthanum alkoxide (Scheme 7).[29] Enantiomeric excesses of 79–91% were obtained with the chiral binaphthol/rare earth protocol. A more practical method for preparing the reagent system was later reported by the same workers as a result of an optimization study of several binaphthol reagent systems.[30] $LaCl_3$ heptahydrate in conjunction with the (*S*)-(−)-binaphthol ligand **17**, various inorganic salts, and alkoxides were optimal for the preparation of *R*-adducts from nitromethane and aldehydes such as *n*-hexanal and cyclohexane carboxaldehyde (Scheme 8).

High enantiomeric excesses (70–95%) were reported by Shibasaki for the asymmetric nitroaldol reaction of α,α′-difluoroaldehydes **19** and nitromethane with catalysis by the samarium-derived (*R*)-(+)-Binol **18** reagent systems (Scheme 9).[31] Several catalysts were first evaluated with the α,α′-difluoro-5-phenylpentanal series **20** which furnished the *S*-nitroalcohol **22** when reacted with nitromethane. Futher studies revealed that cyclohexyl carboxaldehyde gave a 58% chemical yield and 95% ee with the catalyst derived from bis-trimethylsilylethynyl-substituted **21** while *n*-heptanal gave a 73% chemical yield and 70% ee with catalyst system derived from the parent Binol **18**. The absolute configuration of the amino alcohol obtained from the catalytic hydrogenation of **22** was confirmed by X-ray crystallographic analysis. The catalytic system derived from **21** was employed to prepare *threo* nitroalkanol **23**, the immediate precursor for the preparation of *threo*-dihydrosphingosine **24**, in 97% ee with a *syn*/*anti* ratio of 91:9 (Scheme 10).[32]

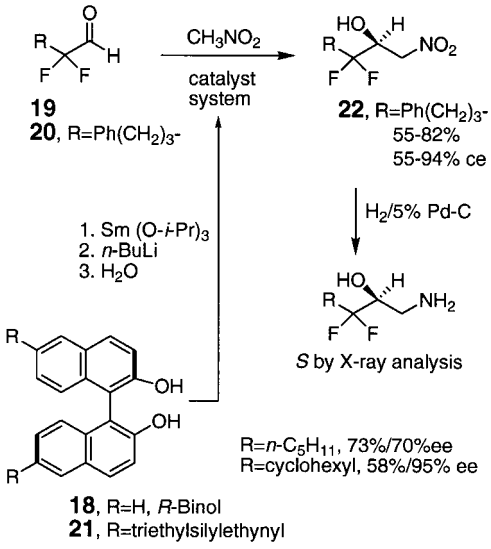
The effectiveness of the guanidine group in basic catalysis has been coupled with chiral design in producing enantiomeric guanidines for promoting the enantioselective Henry condensation. Guanidines **25**–**28** have been prepared and evaluated for their efficiency in catalyzing the Henry reaction between nitromethane and 3-methylbutanal or benzaldehyde.[33,34]



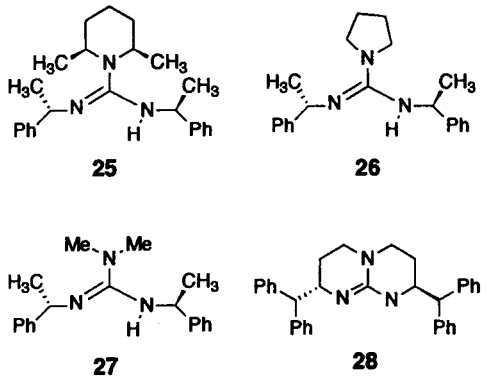
Scheme 7.



Scheme 8.

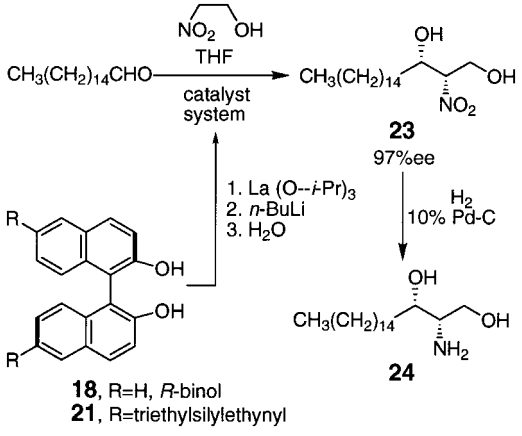


Scheme 9.

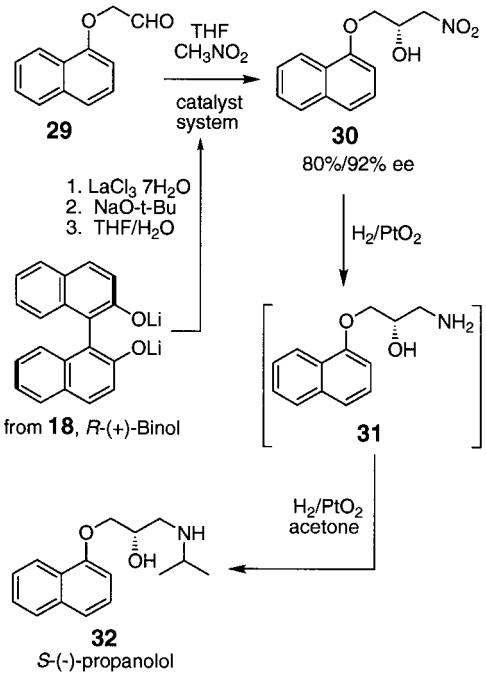


3. Stereoselective preparation of pharmaceuticals and pharmaceutical intermediates

Shibasaki and co-workers utilized the lanthanum-(*R*) binapthol complex in the preparation of (*S*)-propanolol (**32**) (Scheme 11).[35] The overall process employed the α-napthol-derived aldehyde **29**, nitromethane, $LaCl_3{\cdot}H_2O$,



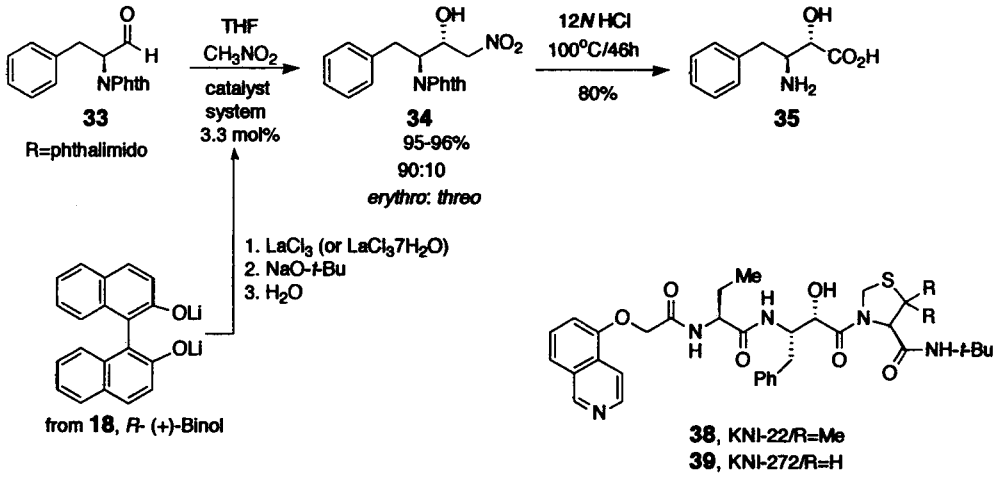
Scheme 10.



Scheme 11.

dilithium (*R*)-(+)-binapthoxide, sodium *tert*-butoxide and H_2O in THF. The chemical yield of the nitroaldol **30** was 80% accompanied by an ee of 92% as determined by chiral HPLC analysis (DAICEL CHIRALPAK AS or AD). Reduction/alkylation of the nitroalcohol function, through aminoalcohol **31**, was accomplished by hydrogenation over platinum oxide (MeOH/rt/2h) thereby furnishing **32**. The rare earth-catalyzed asymmetric aldol procedure was used by the same group to prepare 2*S*,3*S*-2-hydroxy-4-phenyl-3-*N*-phthalimido-1-nitrobutane **34**, an intermediate in their enantioselective synthesis of *erythro* 3-amino-2-hydroxy-4-phenylbutanoic acid **35**, a component of the HIV protease inhibitors, KNI-227 (**38**) and KNI-272 (**39**) (Scheme 12).[36] The sequence involved catalysis of the nitroaldol reaction of the freshly-prepared (*S*)-*N*-phthalimidoaldehyde **33** and nitromethane with dilithium-(*R*)-binapthoxide, La(O-*i*-Pr)$_3$, H_2O in THF. These results were part of a larger study in which the highest chemical yields and ee's of the resultant *erythro* nitro alcohol **34** were obtained with $LaCl_3{\cdot}H_2O$ and $LaCl_3$. Interestingly, hydrolysis of the nitro group and removal of the *N*-phthaloyl group of **34** was accomplished with 12N HCl (110°C/46 h) and thus demonstrated a serviceable method for stereoselective preparation of 3-amino-2-hydroxycarboxylic acid derivatives. By using the analogous *N*-Boc aldehyde **36** with nitromethane together with promotion by the disodium La-*R*-Binol system resulted in lower chemical yields and a less desirable *erythro*/*threo* ratio of the corresponding *N*-Boc nitroalcohol **37** (Scheme 13).

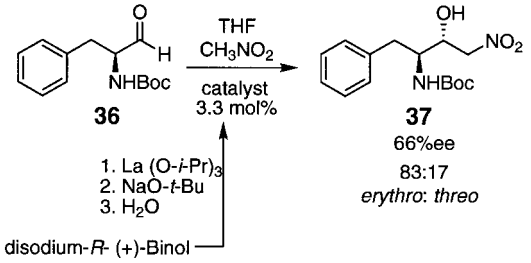
An asymmetric synthesis of *R*-(−)-arbutamine (**44**) was reported by the Shibasaki group which used a nitroaldol reaction in the preparation of key aminoalcohol **42** (Scheme 14).[37] The asymmetric nitroaldol reaction between aldehyde **40** and nitromethane was promoted by a reagent system composed of a samarium-derived *S*-Binol complex, water and *n*-butyllithium. The reagent system was prepared in



Scheme 12.

THF and used immediately by admixture with the aldehyde followed by an equivalent of nitromethane. The reaction was run at −50°C for 67 h and afforded nitroalcohol **41** in 92% ee and 93% chemical yield. Amide formation using acid **43** followed by reduction and deprotection completed the synthesis of **44**.

A lanthanum/potassium (*S*)-Binol complex[38] was employed in the stereoselective preparation of a 1α, 24*R*-dihydroxy-vitamin D_3 intermediate **48** (Scheme 15).[39] The reaction afforded 60–70% yields of the nitro-alcohol **47** from

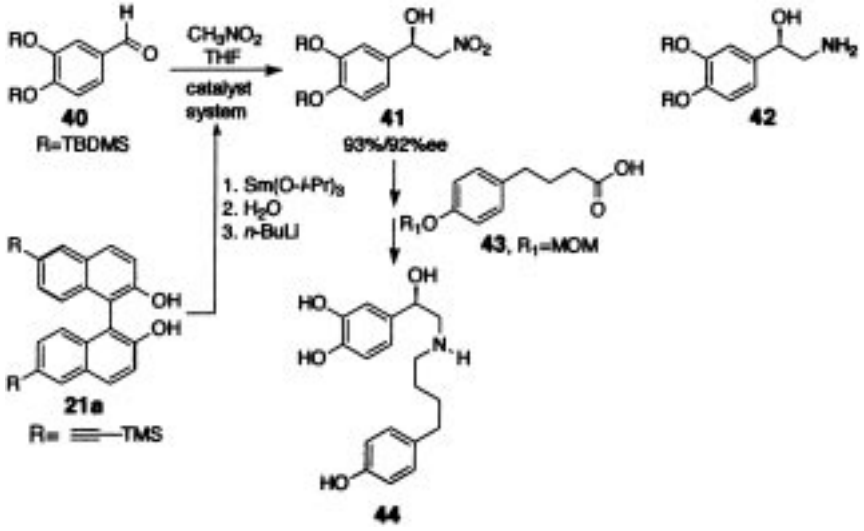


Scheme 13.

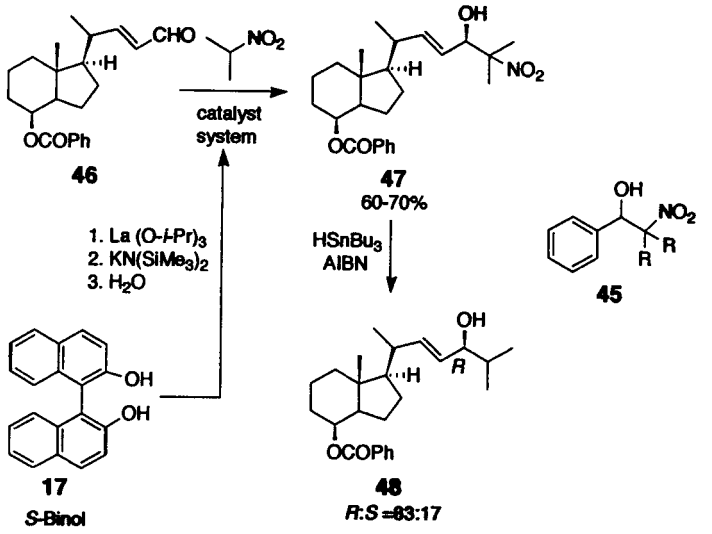
aldehyde **46** with *R*/*S* ratios ranging from 92:8 to 94:6. The report also contains data from experiments which employed the samarium and yttrium/alkali-earth (*S*)-Binol complexes. Adjustment of the reaction conditions was made through model nitroalcohol **45**. Denitration of **47** was accomplished with tri-*n*-butylstannane/AIBN in refluxing benzene.

S-(−)-Pindolol (**54**), a β-andrenergic antagonist with sympathomimetic activity, was prepared by the Shibasaki method which started with commercially-available 4-hydroxyindole **49**.[40] Treatment of the indole **49** with 3-chloro-1,3-propanediol followed by periodate cleavage of the intermediate diol ether **50** provided aldehyde **51**. Condensation of the indoloyloxyaldehyde **51** with nitromethane in the presence of the lanthanum-lithium (*R*)-(+)-Binol (LLB) catalyst (10 mol%) afforded the nitroalcohol **53** in 92% ee and 76% chemical yield (Scheme 16). The 'double Henry' product **52** was formed during an analogous synthesis of 3′-^{13}C pindolol, presumably from the utilization of excess **53**.

The new strategy for the stereocontrolled synthesis of the

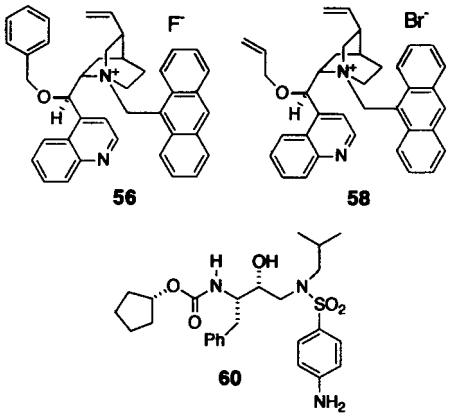


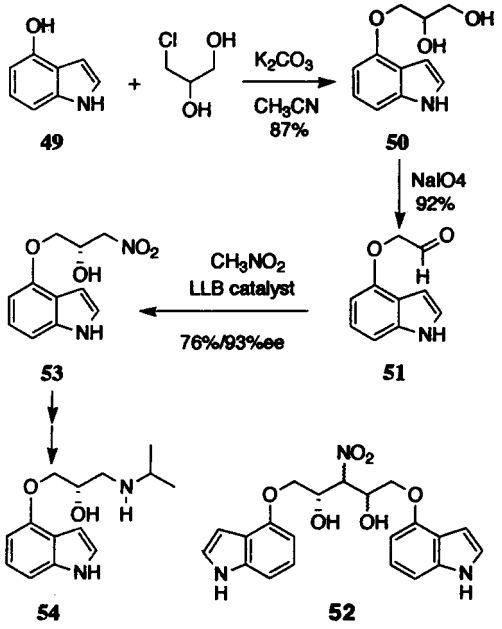
Scheme 14.



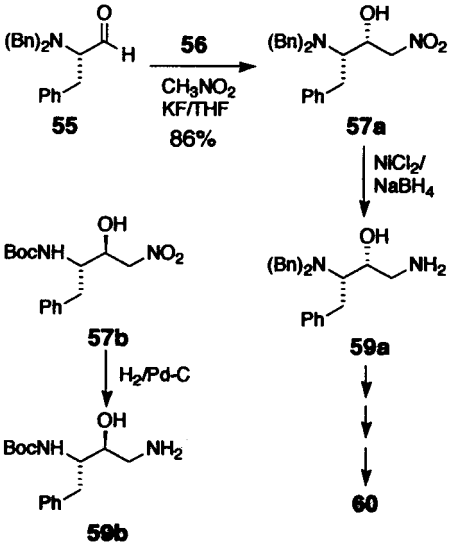
Scheme 15.

HIV protease inhibitor Amprenavir (**60**) (Vertex 478) was reported by Corey.[41] The key step in the sequence involved the diastereoselective nitroaldol reaction of the *S*-aldehyde **55** and nitromethane with promotion by the chiral quaternary salt **56**. The diastereoselectivity in favor of the 2*R*,3*S* nitro alcohol **57a** was found to be 17:1 while promotion with potassium fluoride alone provided 4:1 diastereoselectivity. The 2*S*,3*S*-nitroalcohol **57b** which leads to a diastereomeric derivative of Amprenavir was prepared from chiral quaternary catalyst **58** under similar conditions. Reduction of the diastereomeric nitroalcohols **57a** and **57b** to the diastereomeric amino alcohols **59a/59b** was effected by $NiCl_2$/$NaBH_4$ and Pd–C/H_2, respectively (Scheme 17).

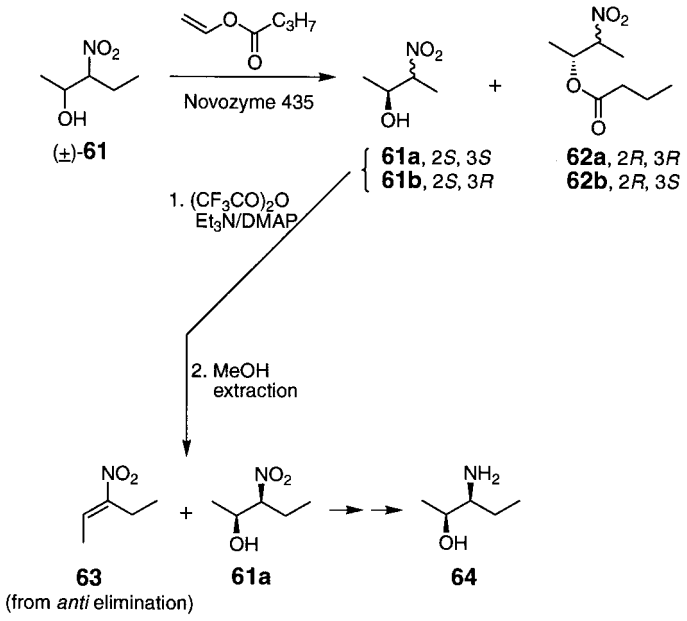




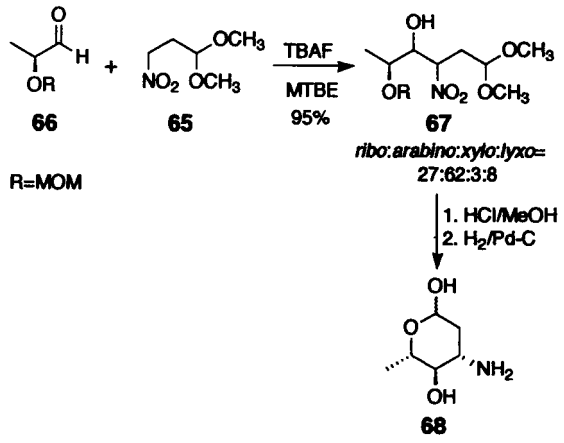
Scheme 16.



Scheme 17.



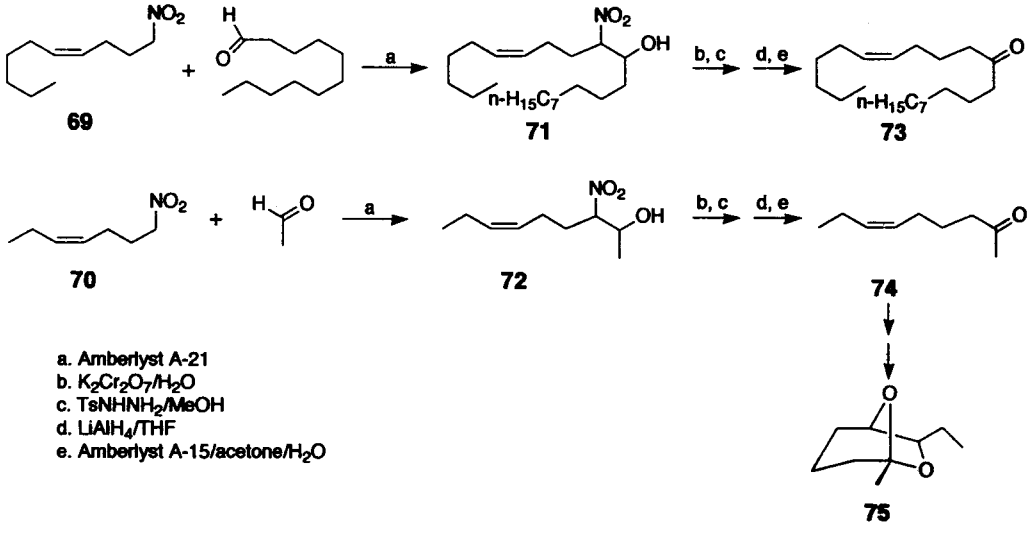
Scheme 18.



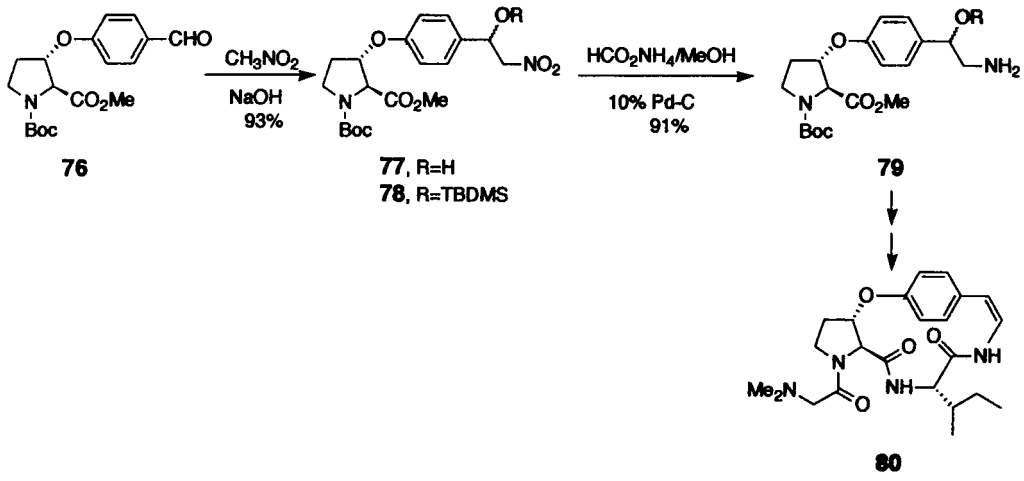
Scheme 19.

3-Nitro-2-pentanol **61**, either prepared by the Henry reaction of 1-nitropropane and acetaldehyde or commercially available, proved to be an excellent source of 2*S*,3*S*-amino-2-pentanol **64**, a unit of the azole antifungal SCH56592.[42] Nitroalcohol **61** was transacylated with vinylbutyrate and Novozyme 435 (Novo Nordisk) which gave a mixture of (2*S*,3*S*)- and (2*S*,3*R*)-3-nitro-2-pentanol (**61a** and **61b**) together with (2*R*,2*R*)-and (2*R*,3*S*)-3-nitro-2-(*n*-butyroyloxy)pentanol (**62a** and **62b**). The nitroesters **62a** and **62b** were removed by extraction and the remaining diastereomeric nitroalcohols **61a** and **61b** were acylated with trifluoroacetic anhydride and then eliminated under promotion by base. The *anti* trifluoroaceticnitroester of (2*S*,3*R*)-**61b** suffered elimination to the nitroalkene **63** while the *syn* (2*S*,3*S*)-nitroalcohol **61a** was recovered on workup and removal of the nitroolefin **63** (Scheme 18).

L-Acosamine (**68**), the carbohydrate subunit of the



Scheme 20.



Scheme 21.

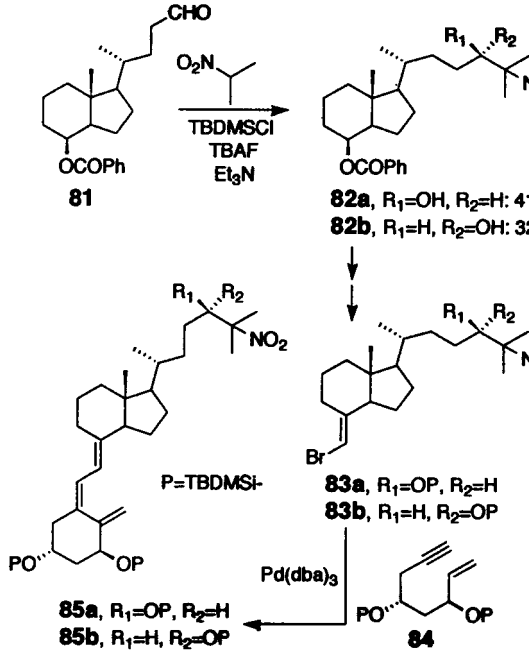
anthracycline class of antibiotics was prepared through a route which first involved the condensation of β-nitropropionaldehyde dimethyl acetal **65** and 2-*O*-methoxymethyl-L-lactaldehyde **66** (Scheme 19).[43] The nitroaldol reaction of **65** and **66** was studied extensively with respect to temperature, solvent effects and catalyst in order to increase the diastereomeric ratio of the desired L-*arabino* isomer **67**. The optimal conditions found for the procurement of **67** entailed the employment of excess **66** with 0.25 equiv. of *tetra-N*-butylammonium fluoride (TBAF) in methyl*tert*-butyl ether (MTBE) at −30°C for 17 days. While the optimal diastereomeric ratio was *ribo*/*arabino*/*xylo*/*lyxo*=27:62:3:8, as determined by HPLC analysis, the overall isolated chemical yield of the mixture was 95%.

4. Natural product synthesis

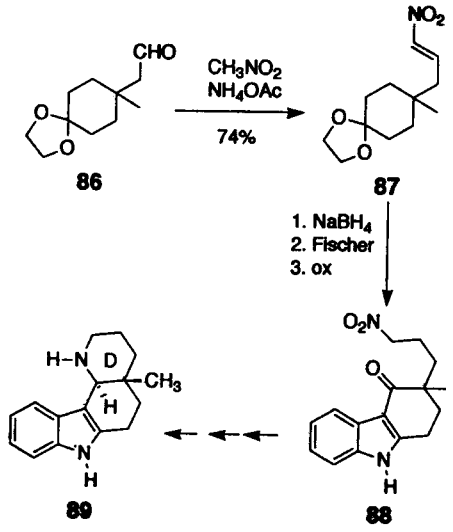
Ballini has detailed the synthesis of the sex pheromone of the Douglas Fir Tussock moth **73** and an intermediate **74** for the synthesis of brevicomin (**75**) using nitroaldol strategy as means for joining fragments such as the nitroalkenes **69** and **70** with *n*-undecanal and acetaldehyde without the use of organometallic reagents.[44] The condensation reaction was mediated with Amberlyst A-21. Further transformations entailed conversion of the nitroalcohols **71** and **72** to the corresponding nitroketones followed by formation of the corresponding α-nitrotosylhydrazone, α-denitration with $LiAlH_4$ and hydrolysis with Amberlyst/acetone/H_2O to the ketones **73** and **74**. Conversion of **74** to brevicomin was accomplished by oxidation with MCPBA followed by perchloric acid-mediated ring closure (Scheme 20).

A condensation of aldehyde **76** with nitromethane was employed during the synthesis of (−)-nummularine F (**80**), a cyclopeptide alkaloid.[45] Further steps included O-silylation of the nitroalcohol function of intermediate nitroalcohol **77** and reduction of the nitro group of the β-silyloxynitro compound **78** to the corresponding amine **79** (Scheme 21).

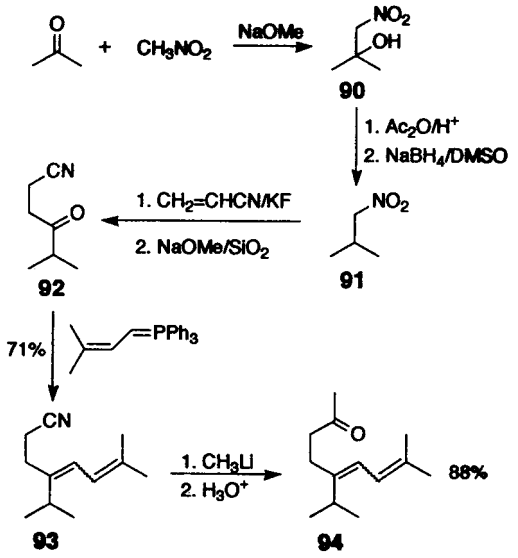
Okamoto and coworkers have reported the preparation of



Scheme 22.



Scheme 23.



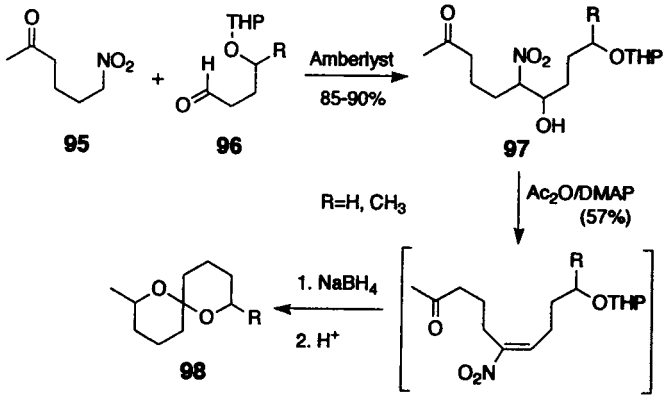
Scheme 24.

1α, 24*R*-dihydroxy-25-nitrovitamin D_3 **85a** and 1α, 24*S*-dihydroxy-25-nitrovitamin D_3 **85b** by the reaction of aldehyde **81** with 2-nitropropane promoted by *tert*-butyldimethylsilyl chloride/TBAF/triethylamine (Scheme 22).[46] The reaction afforded the mixture of diastereomeric nitroalcohols **82a** (41%) and **82b** (32%) which were separable by column chromatography. The separated nitroalcohols were taken through to the bromoalkenyl-β-nitrosilyl ethers **83a** and **83b** which then were coupled to the enyne **84** with a $Pd(dba)_3$ reagent system.

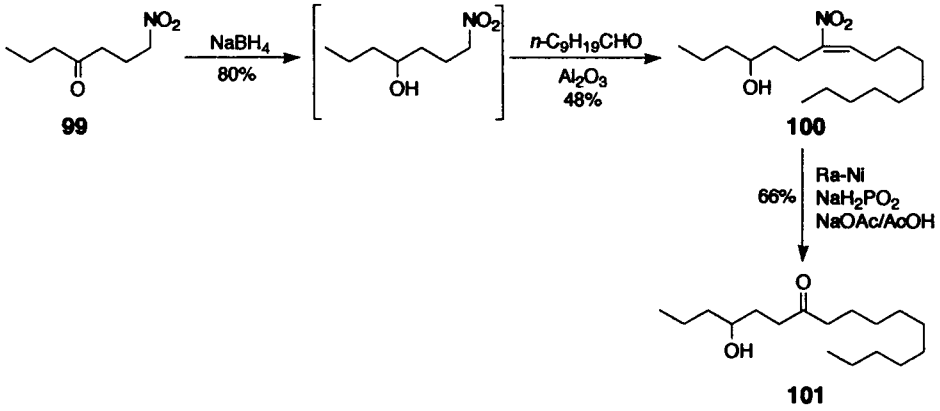
The synthetic route to a 20-methyl aspidospermidine analog **89** utilized an intermediate which was prepared by the nitroaldol reaction of aldehyde **86** and nitromethane under dehydrating conditions.[47] The resultant intermediate nitroolefin **87** was selectively reduced with sodium borohydride in ethanol at 0°C. A series of reductive steps followed which facilitated cyclization and D-ring saturation thereby affording the tetracyclic ABCD intermediate **88** en route to **89** (Scheme 23).

A synthesis of isosolanone (**94**) started with nitroisobutane **91** which was prepared by a nitroaldol route rather than the more common Kornblum method of halide displacement (Scheme 24).[48] Methoxide-promoted addition of nitromethane to acetone furnished the nitroalcohol **90**. Acetylation of nitroalcohol **90** followed by reduction of the corresponding nitroester afforded nitroisobutane **91**. Michael addition of **91** to acrylonitrile followed by a Nef conversion of the resultant Michael adduct provided cyanoketone **92**. Wittig reaction of the cyanoketone **92** with prenylidenetriphenylphosphorane gave the dienenitrile **93** which, upon exposure to methyllithium followed by hydrolysis, afforded the dienyl ketone target **94**.

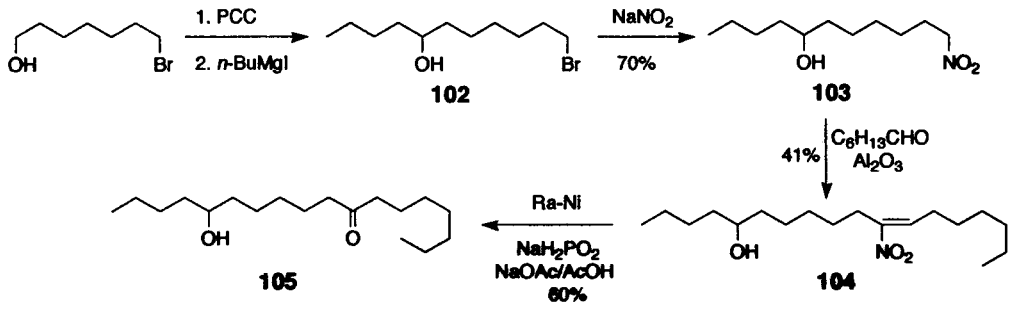
A synthesis of the 1,7-dioxaspiro[5.5]undecane ring system



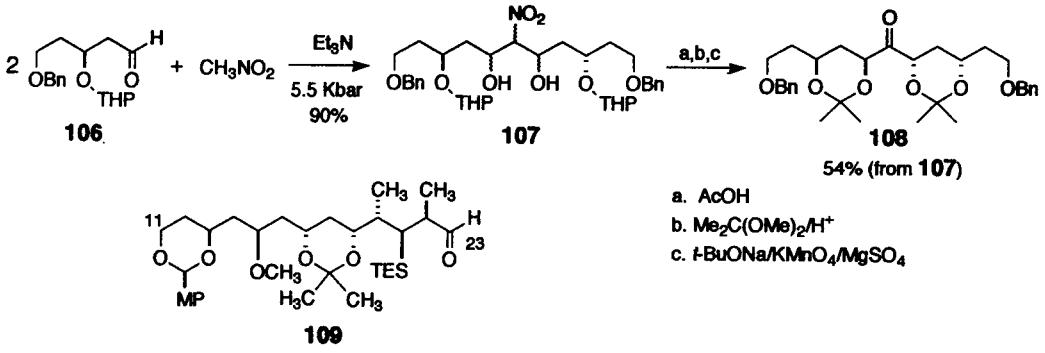
Scheme 25.



Scheme 26.



Scheme 27.



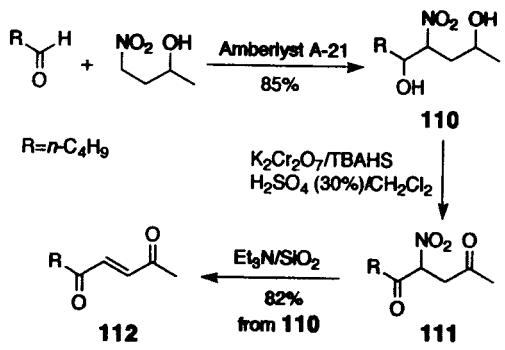
Scheme 28.

98, a component of various insect secretions, utilized nitroketone **95** and the THP-derived butyraldehyde **96**. Nitroaldol reaction of **95** and **96**, promoted by Amberlyst A-21, provided the THP-protected nitroalcohol **97** in 85–90% yield. Dehydration of nitroalcohol **97** with acetic anhydride/DMAP (57%) followed by reduction with sodium borohydride then hydrolysis of the THP group with aqueous acid afforded the spiroketal **98** in 65–70% yield (Scheme 25).[49]

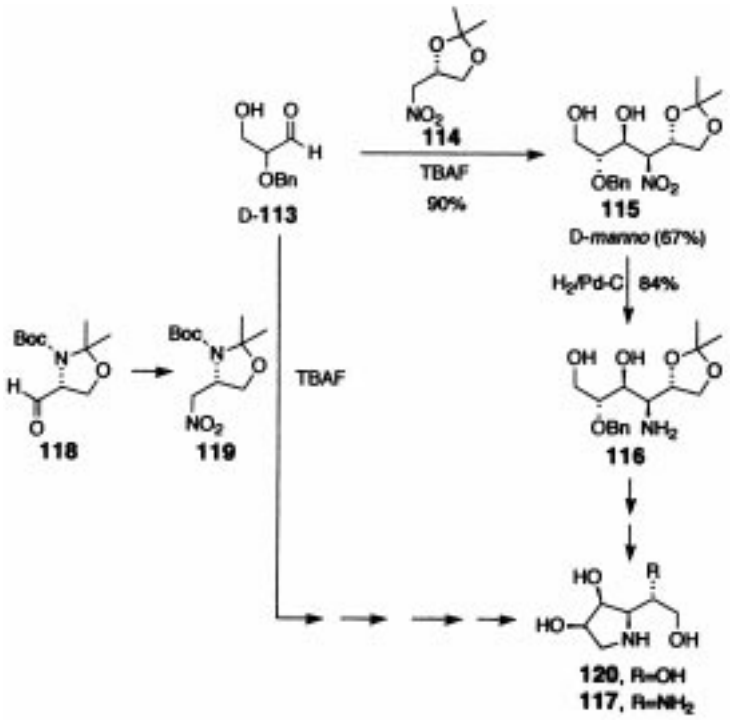
Nitroaldol strategy was used to prepare 4-hydroxyheptadecane-7-one **101** and 14-hydroxyoctadecane-8-one **105**, two new hydroxyketones isolated from the leaf extracts of *Chiccoca alba* (Rubiaceae).[50] Reduction of γ-nitroketone **99** with sodium borohydride followed by condensation with *n*-decanal provided the nitroolefin **100**. Direct Nef conversion of the nitroolefin **100** to the hydroxyketone **101** was effected with Raney nickel–sodium hypophosphite in 66% yield (Scheme 26). PCC oxidation of 7-bromoheptanol followed by treatment of the intermediate aldehyde with *n*-butylmagnesium iodide afforded the bromoalcohol **102** which was converted to the corresponding nitroalcohol **103** under Kornblum conditions in 70% yield. Condensation of 11-nitroundecan-5-ol **103** with *n*-heptanal furnished the nitroalkene **104** which was converted to the hydroxyketone **105** under the Raney nickel–hypophosphite Nef conditions (Scheme 27).

The utilization of an acyclic 'double Henry' reaction in the synthesis of the C_{11}–C_{23} segment **109** of the marine macrolide swinholide A has been reported by Nakata.[51] Two equivalents of the 3-tetrahydropyranyl-5-benzyloxyaldehyde **106** was reacted with one equivalent of nitromethane under high pressure in the presence of triethylamine to provide the bis-THP-bis-benzyloxynitrodiol **107** in 90% yield. Conversion of nitrodiol **107** to the symmetrical ketone **108** was through an isopropylidene protection protocol followed by a nitronate oxidation/epimerization sequence in 54% overall yield (Scheme 28).

Ballini's nitroaldol method for the preparation of 2,3-unsaturated-1,4-dicarbonyl compounds was applied to the synthesis of (*E*)-non-3-ene-2,5-dione **112** a component of the mandibular gland secretions of the fire bee *Trigona tataira*.[52] Condensation of 1-pentanal with 4-nitro-2-butanol in the presence of Amberlyst A-21, under solventless conditions, furnished 4-nitro-2,5-nonanediol **110** in 85% yield. Submission of the nitrodiol **110** to a two-phase reagent system composed of aqueous potassium dichromate, *tetra-n*-butyl ammonium hydrogen sulfate, 30% sulfuric acid and dichloromethane effected oxidation to the corresponding 4-nitro-2,5-nonanedione **111**. Direct exposure of the crude diketone **111** to triethylamine promoted α,β-elimination of



Scheme 29.



Scheme 30.

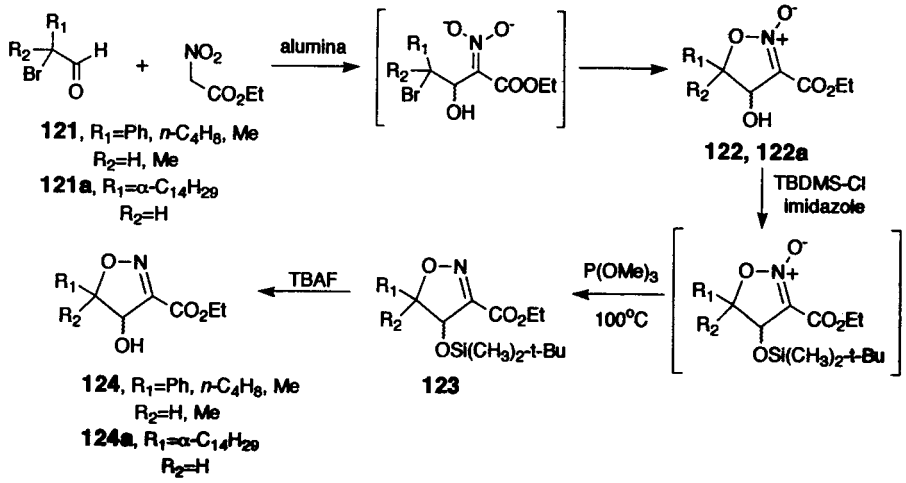
nitrous acid thereby affording the title compound **112** in 70% overall yield (Scheme 29).

5. Polyaminoalcohols and polyhydroxylated amines

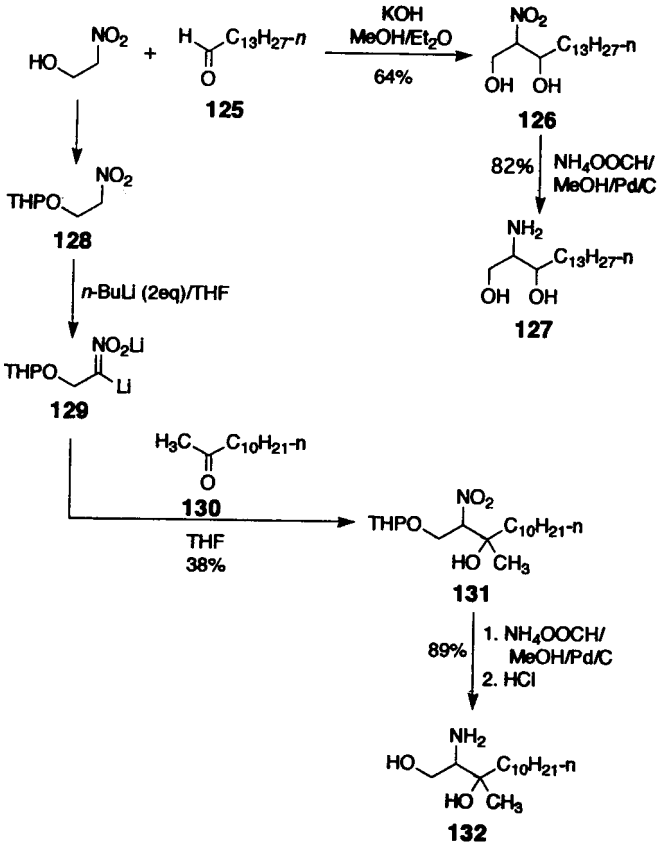
The α-mannosidase inhibitor 1,4-dideoxy-1,4-imino-D-mannitol (**120**) was prepared by the Henry reaction of benzyloxyaldehyde **113** and the nitroisopropylidene derivative **114** with promotion by TBAF. The conversion of nitroalcohol **115** to the corresponding aminodiol **116** was effected by catalytic hydrogenation. The same strategy was employed in preparing the amino analogs **117** by employment of the isopropylidene nitro compound **119** prepared from the Garner aldehyde (**118**) (Scheme 30).[53]

A tandem nitroaldol-cyclization sequence leading to a generalized preparation of 5-substituted-3-(ethoxy-carbonyl)-2-isoxazolin-4-ols **124** was reported by Rosini.[54] The sequence employed the alumina-promoted reaction of ethyl nitroacetate and a series of bromoaldehydes **121**. One of the intermediate 2-isoxazolin-4-ol-2-oxides **122** was silylated with *tert*-butyldimethylsilyl chloride/imidazole followed by deoxygenation with trimethylphosphite at 100°C to provide silyl ether **123** (99%). Desilylation of **123** under standard conditions using TBAF afforded the title compounds **124**, overall 1-amino-2,3-diol equivalents, in 87% yield (Scheme 31).

As part of a program directed toward the synthesis of sphinganine analogs modified in the head group, 2-nitroethanol was condensed with myristic aldehyde **125** using KOH/



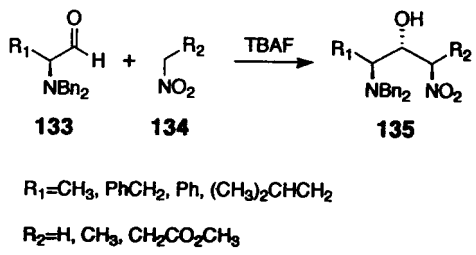
Scheme 31.



Scheme 32.

diethyl ether/methanol.[55] The resultant mixture of diastereomeric nitroalcohols **126**, obtained in 64% yield, was reduced with palladium on charcoal under phase-transfer conditions to afford the aminodiol derivatives **127** in 82% yield. In the same study Sandhoff and co-workers employed the dilithionitronate derivative **129** of THP nitroethanol **128** in conjunction with 2-dodecanone **130** thereby providing the THP nitroalcohol **131** in 38% yield. Phase-transfer reduction of the THP nitroalcohol **131** followed by direct hydrolysis with acid furnished the aminodiol **132** in 88% overall yield (Scheme 32).

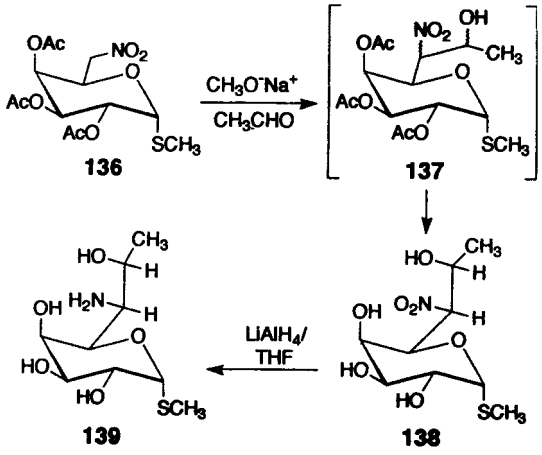
Hannesian reported a facile stereocontrolled route to acyclic 1,3-diamino-2-alcohols **135** which utilized optically-enriched *N*,*N*-dibenzyl-α-aminoaldehydes **133** and nitroalkanes **134** such as nitromethane, nitroethane and methyl 3-nitropropionate with promotion by 1–2 equiv. of TBAF. Promotion of the reaction by neutral alumina was found to be unacceptably slow and thereby less effective. The nitroaldol products exhibited mainly *anti*-,*anti*-stereochemistry with chemical yields ranging from 40–90% and diastereomeric ratios as high as 99:1 (Scheme 33).[56,57]



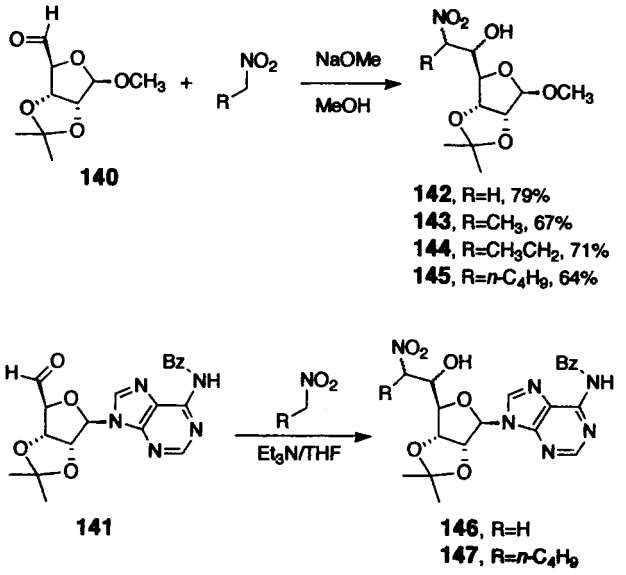
Scheme 33.

6. Extended carbohydrates

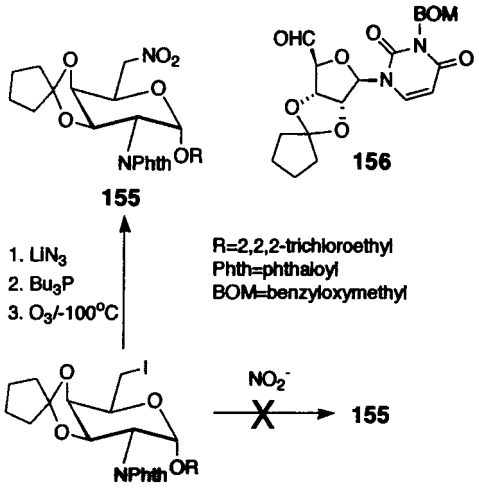
A classical nonstereoselective synthesis of the carbohydrate-derived antibiotic, lincomycin, utilized the nitroaldol reaction to prepare the extended eight-carbon carbohydrate backbone α-methylthiolincosaminide **139**.[58] The 6-nitro-2,3,4-tri-*O*-acetyl-1-(methylthio)galactoside **136** was condensed with acetaldehyde in the presence of sodium methoxide which furnished the diastereomeric



Scheme 34.



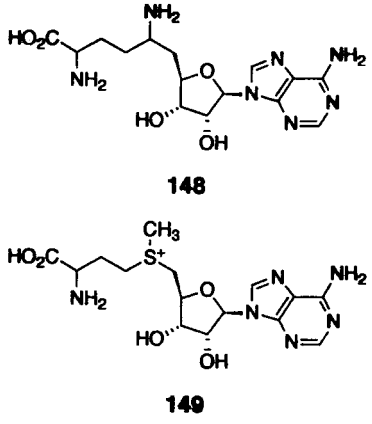
Scheme 35.

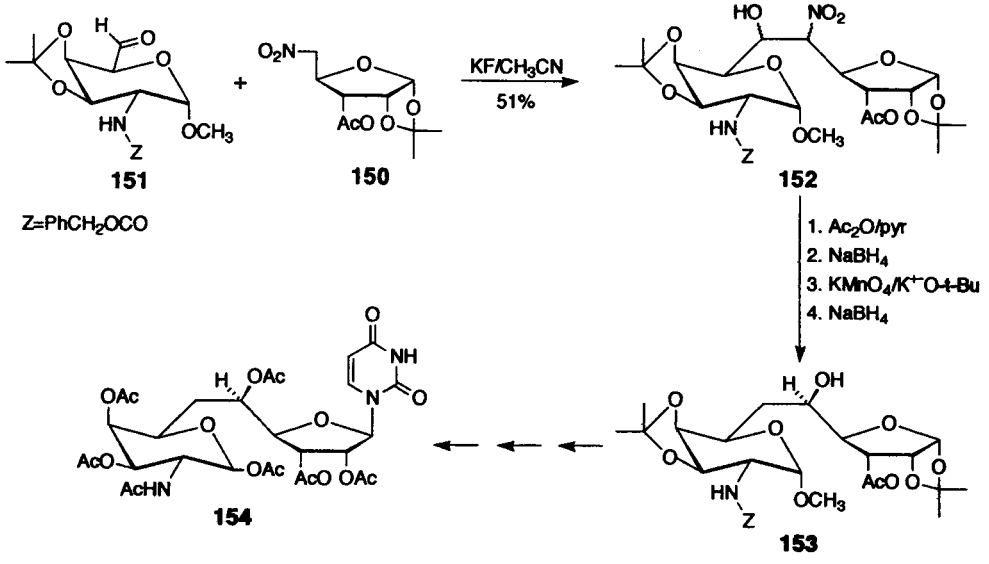


Scheme 37.

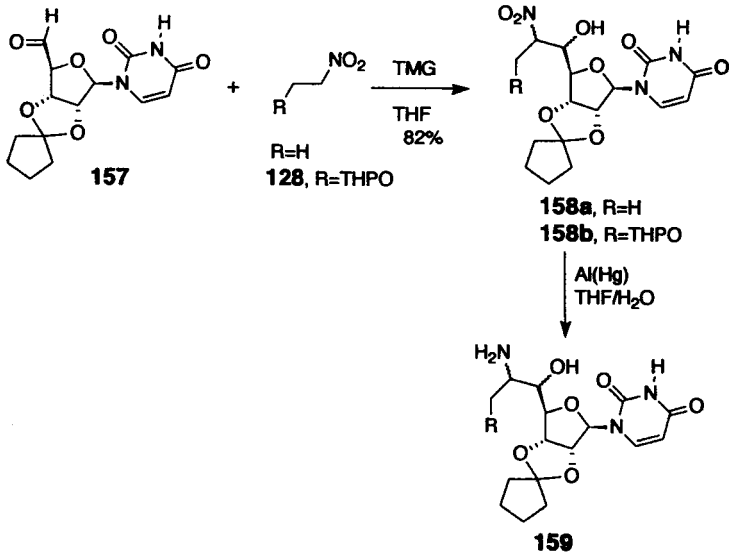
nitrotetraol **138**, through triacetate **137**, in 50% yield. The completion of the condensation reaction was facilitated by repeated addition of acetaldehyde and sodium methoxide to the 6-nitrogalactose **136**. The nitroalcohols **138** were reduced to the corresponding aminotetraol **139** with lithium aluminum hydride/THF. Chromatographic purification afforded the desired *erythro* diastereomer of **139** (Scheme 34).

During early sinefungin (**148**) and *S*-adenosylmethionine (**149**) support studies, Borchardt and coworkers explored the addition of simple nitroalkanes such as nitromethane, nitroethane, 1-nitropropane and 1-nitropentane to the β-adeninyl and β-methoxy-2,3-O-isopropylidene ribosyl-5-aldehydes **140** and **141**.[59] The nitroalcohol adducts **142**–**145**, formed with catalytic sodium methoxide in methanol, were isolated as diastereomeric mixtures in yields ranging from 64–79%. Triethylamine in tetrahydrofuran was used to promote the reaction between the nucleoside adeninyl substrates **141** and either nitromethane or 1-nitropentane thereby providing the nitroalcohols **146** and **147** in yields of 74 and 44% (Scheme 35).





Scheme 36.

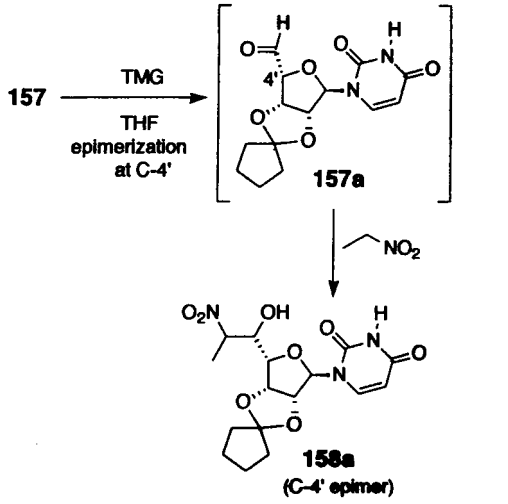


Scheme 38.

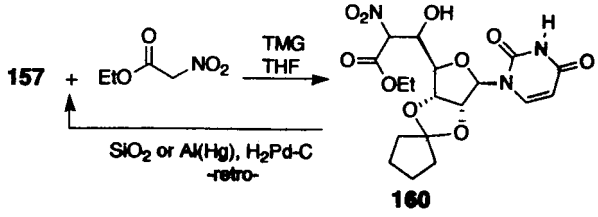
The use of the Henry reaction was exemplary in the first synthesis of the tunicamycin antibiotics as reported by the Suami group.[60] The key step in the Suami synthesis involved the condensation of nitrofuranose **150** and galactose aldehyde **151** which established the undecose backbone **152** of the tunicamycins.[61] The nitro group of **152** was removed and replaced with a hydroxyl by a sequence which involved acetylation and sodium borohydride reduction followed by $KMnO_4$/sodium *tert*-butoxide oxidation and sodium borohydride reduction (Scheme 36). Intermediate **153** was taken on to hexaacetyltunicaminyl uracil **154**, a product of exhaustive hydrolysis of the tunicamycins followed by peracetylation. Corey and coworkers reported the novel preparation of a 6-nitrogalactose derivative **155** for Henry condensation with a suitably-protected uridine aldehyde **156**.[62] While nitrogalactose **136** could be prepared by the usual Kornblum method, the 6-nitrogalactose **155** could not be prepared by 6-substitution with nitrite ion. Consequently, the 2-*N*-phthalimido-6-nitrogalactose required preparation of the 6-azide followed by phosphinimine formation. Ozonolysis of the in situ-prepared tri-*n*-butylphosphinimine at −100°C afforded the 6-deoxy-6-nitrogalactose coupling partner **155** (Scheme 37).

The treatment of 2′,3′-*O*-cyclopentylideneuridine aldehyde **157** with excess nitroethane (10 equiv.) and a catalytic amount of 1,1,3,3-tetramethylguanidine (TMG) in THF furnished a mixture of all four diastereomeric nitroalcohols **158a** in 82% yield (Scheme 38).[63] Using a 1:1 mixture of nitroethane and aldehyde with TMG resulted in a substantial amount of the *C*-4′ epimers of nitroalcohol **158a**. Presumably, with excess nitroethane, attack on aldehyde **157** is a more efficient process than its epimerization to **157a** and subsequent nitronate attack (Scheme 39). Similarly, during the course of liposidomycin core[64] support studies, the use of the THP nitroethanol **128** gives the expected nitroalcohol adducts **158b** in 62% yield. The nucleosidic nitroalcohols of the type **158a**, **158b** do not respond well to reductive conditions such as metal hydrides or palladium catalysts but afford the corresponding heptulose ribosyl amino alcohols **159** in 75–80% yield when treated with Al/Hg in THF/water. In contrast, TMG-catalyzed addition of ethyl nitroacetate to aldehyde **157** provided the nucleosidic nitroacetate adduct **160** as a mixture. Attempted chromatographic purification of nitroester **160** or in situ reduction of the nitro group led to facile retroaldolization (Scheme 40).[63]

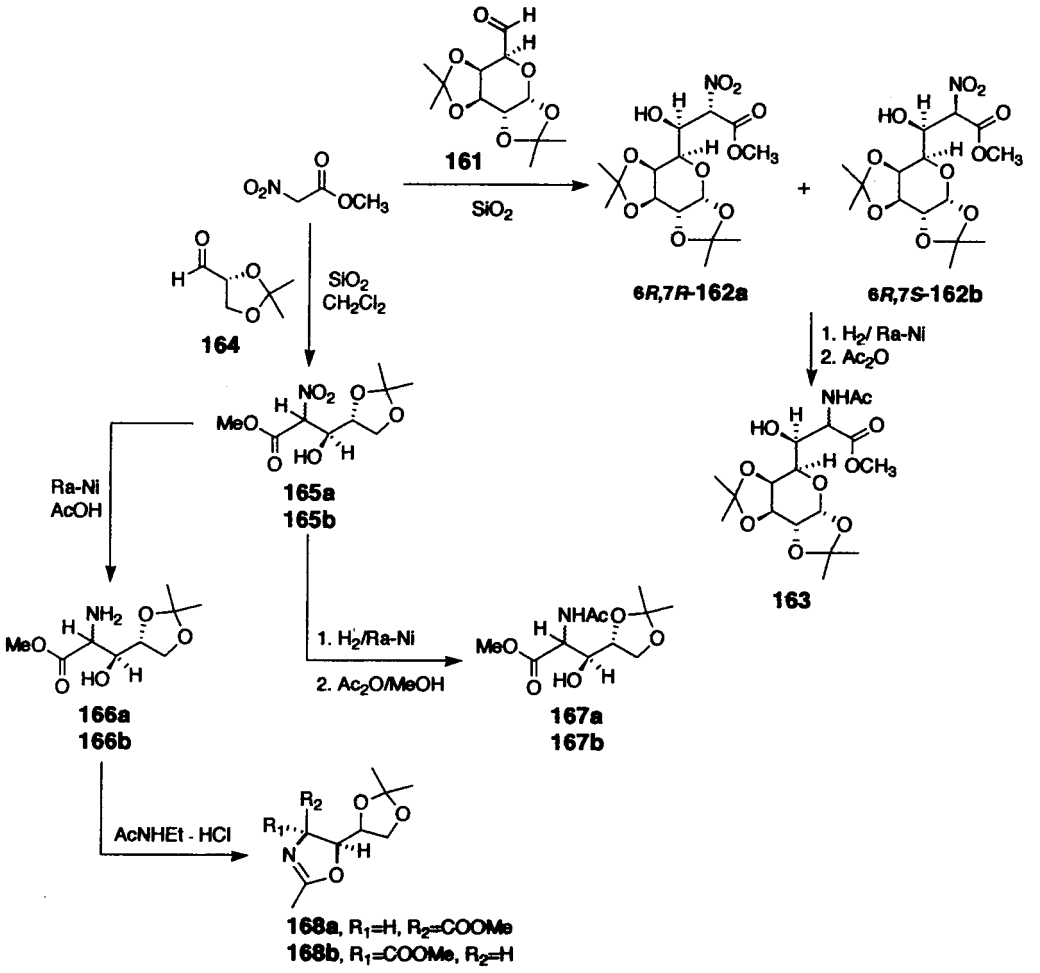
The stereochemistry of the reaction of methyl nitroacetate with the diisopropylidenegalactose-derived aldehyde **161** was examined by Gómez-Guillen and coworkers.[65] The silica gel-promoted addition of the nitroester to **161** gave



Scheme 39.



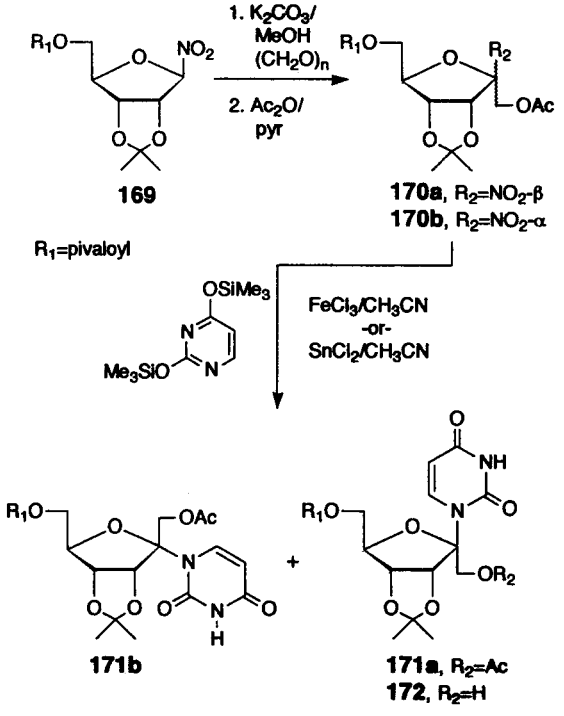
Scheme 40.



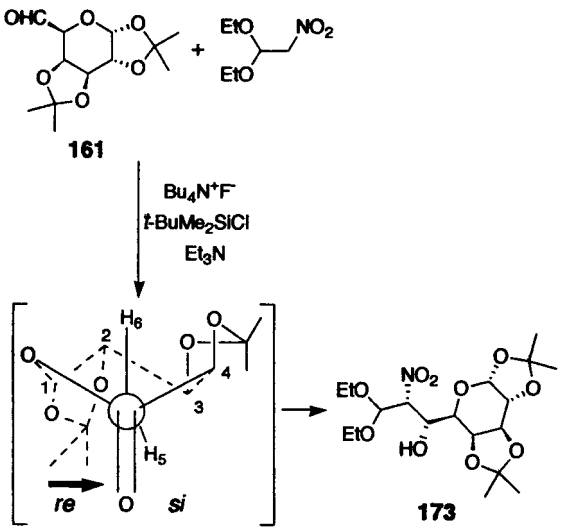
Scheme 41.

two of the four possible diastereomeric β-hydroxy-α-nitro-esters **162a** and **162b** in 55% yield after purification by preparative thin-layer chromatography. The configurations of the compounds were determined by single crystal X-ray analysis of one of the *N*-acetyl products 6*R*,7*S*-**163** obtained after Raney nickel reduction and acetylation. Silica gel-promoted reaction of 2,3-isopropylidene-D-glyceraldehyde **164**, the 3-carbon oxidative cleavage product of 1,2:5,6-di-*O*-isopropylidene-D-mannitol, with methylnitroacetate afforded mainly the 2-epimeric-3*S*-nitroalcohols **165a** and **165b**. Reduction of the epimeric nitroalcohols to the corresponding aminoalcohols **166a** and **166b** was effected by hydrogenation with Raney nickel in acetic acid. In contrast, Raney nickel-mediated hydrogenation of the nitroalcohols **165a** and **165b** in methanol followed by direct acetylation furnished the corresponding *N*-acetylaminoalcohols **167a** and **167b** in poor yield. The corresponding epimeric oxazolines **168a** and **168b** were prepared by the exposure of aminoalcohols **166a** and **166b** to ethyliminoacetate hydrochloride and their relative stereochemistries were correlated with the respective aminoalcohols and nitroalcohols as 4,5-*cis* (**168a**) and 4,5-*trans* (**168b**) (Scheme 41).

During synthetic studies directed toward the ketose-derived nucleosidic psicofuranosides **172**, the 1-nitro-2,3-isopropylidene-5-pivaloyl ribofuranose **169** and paraformaldehyde combined, under promotion with potassium carbonate in



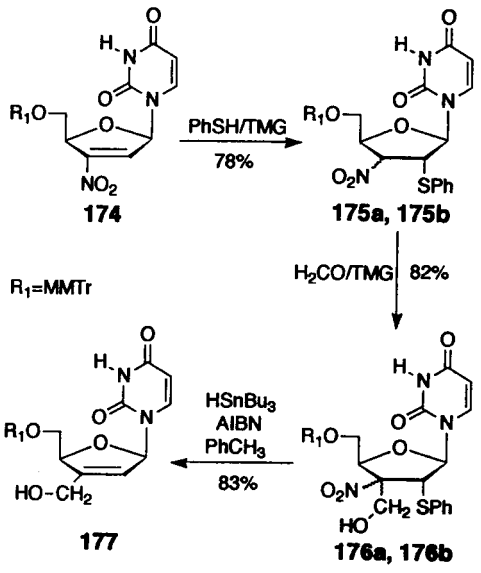
Scheme 42.



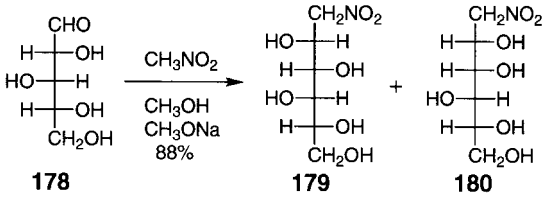
Scheme 43.

methanol, to afford the nitroketoses **170a** and **170b** in 86 and 4%, respectively.[66] Acetylation of nitroketose **170a** followed by glycosidation with 2,4-bis-(trimethylsilyloxy)-pyrimidine under Hilbert–Johnson conditions ($SnCl_4$/CH_3CN) provided the isopropylidene nucleoside **171a** in 15% yield while optimized conditions (3 equiv. $SnCl_2$/CH_3CN) gave **171a** and **171b** (60%) in a 1:4 ratio (Scheme 42).

A chain homologation study of diisopropylidenegalactose aldehyde **161** with 2,2-diethoxy-1-nitroethane was reported by Goméz-Sanchéz and coworkers.[67] The reactions were promoted by the TBAF/triethylamine/*tert*-butyldimethylsilyl chloride reagent system and resulted in the major diastereomer **173** as determined by X-ray structural analysis. The diastereoselectivity was rationalized on the basis of nitronate attack at the less hindered *re* face of the galactose aldehyde **161** (Scheme 43).



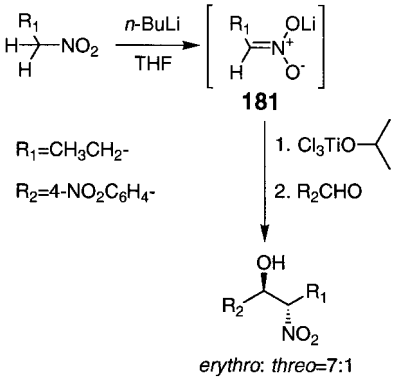
Scheme 44.



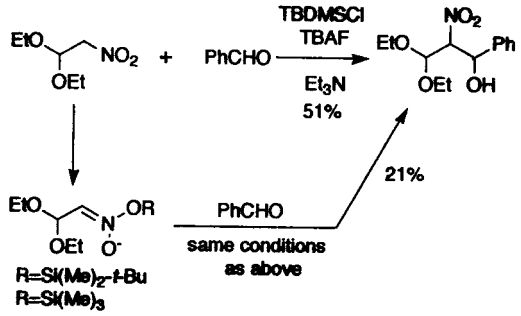
Scheme 45.

2′,3′-Dideoxy-2′,3′-didehydrothymidines can be homologated at the 3′ position through the agency of the 3′-nitroalkene nucleoside analogs.[68] Reaction of the nucleosidic nitroölefin **174** with thiophenol in the presence of 1,1,3,3-tetramethylguanidine (TMG) provided the mixture of 2′-phenylthio *ribo* and *xylo* derivatives **175a** and **175b** in 78% yield. Exposure of the mixture of 2′-phenylthionucleosides to 35% aqueous formaldehyde in acetonitrile with promotion by TMG afforded the chromatographically-separable 3′-hydroxymethyl-3′-nitro derivatives **176a** and **176b** in 82% combined yield. Removal of both the 2′-phenylthio and the 3′-nitrogroups of **176a** was effected with tri-*N*-butyltin hydride/azobisisobutyronitrile (AIBN) in toluene thereby providing the 3′-hydroxymethyl nucleoside olefin **177** in 83% yield (Scheme 44).

The extension of aldoses by the Henry addition of nitromethane, formally known as the Fisher–Sowden reaction, was the subject of a comprehensive ^{13}C NMR study by Koll and coworkers.[69] The adducts of nitromethane and D-glyceraldehyde, two aldotetroses, four aldopentoses and eight aldohexoses (C_3–C_6) were prepared by promotion with sodium methoxide in methanol and the resultant diastereomeric 1-nitroalditols were isolated. The nitroaldol reactions were found to be largely nonstereoselective and the ratios of the terminal-nitro tetritol, -pentitol, -hexitol and heptitol products varied from 1:0.8 to 1:2.9 with the average ratio of products 1:1.34. For example, the reaction of D-xylose **178**, on a 25-gram/166 mmol scale, with nitromethane gave an 88% yield of a mixture of 6-deoxy-6-nitro-L-glucitol **179** and 1-deoxy-1-nitro-D-iditol **180** in a 1:0.9 ratio (iditol, **180**/glucitol. **179**) (Scheme 45). The terminal iditol **180** was isolated as a crystalline solid $[\alpha]_D^{20}=+2.2$ (c=4.5, H_2O), while the terminal glucitol **179** was isolated as a syrup $[\alpha]_D^{20}=+3.8$ (c=1.9, H_2O).



Scheme 46.



Scheme 47.

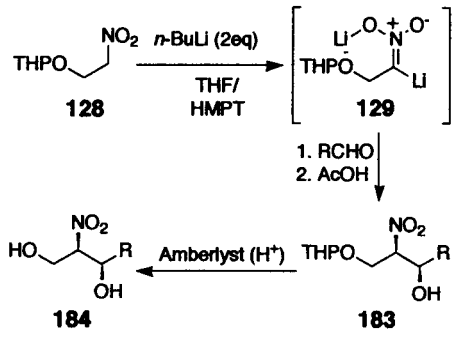
7. Variations of the nitroaldol reaction

7.1. Nitronate condensations

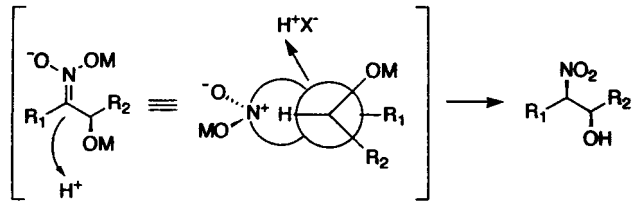
Lithioalkylnitronates **181**, derived from nitroalkanes and *n*-butyllithium, were reacted with various aldehydes in the presence of ispropoxytitanium trichloride (THF/−78°C) to afford the corresponding β-nitroalkanols.[70] The in situ-formed dichloroisopropoxytitanium nitronate promoted high *erythro* selectivity in the nitroalkanol products (Scheme 46).

Nitroaldol reactions of simple nitroalkanes and aldehydes were found to be promoted with a combination of TBAF, *tert*-butyldimethylchlorosilane and triethylamine.[71] The intermediacy of a silyl nitronate was explored; but was discounted when preformed silylnitronates were employed as starting materials under the same reaction conditions (Scheme 47).

Seebach and Eyer have detailed a useful variant of the nitroaldol reaction which employed dilithiated nitronates **182** as the reactive species (Scheme 48).[72] The versatility of the carbanion was demonstrated with a number of reactants such as benzylic halides and dimethyl carbonate as well as the carbonyl compounds required for the formation of nitroaldol products. For example, the tetrahydropyranyl nitroethanol **128** was treated with a twofold excess of *n*-butyllithium in tetrahydrofuran/hexamethylphosphoric acid triamide (HMPT) thereby forming the intramolecular-chelated dilithiated species **129**. The dilithionitronate **129** was then exposed to a range of aldehydes followed by quenching with acetic acid and aqueous workup. Hydrolysis of the tetrahydropyranyl-protected nitroalcohols **183** to the 2-nitro-1,3-alkanediols **184** was

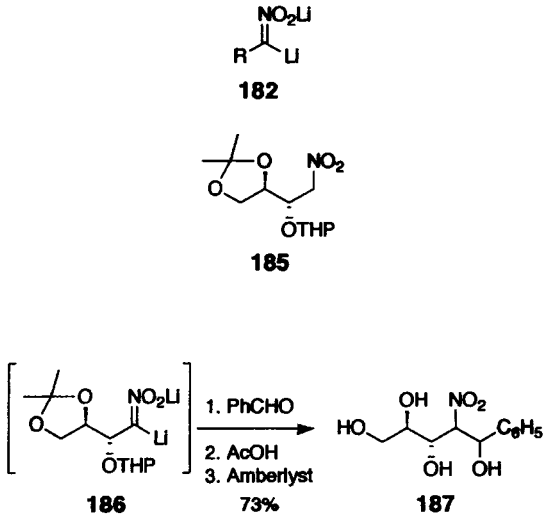


Scheme 48.

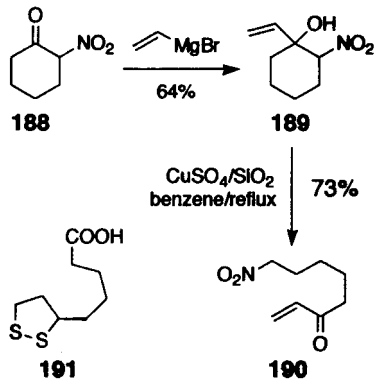


Scheme 49.

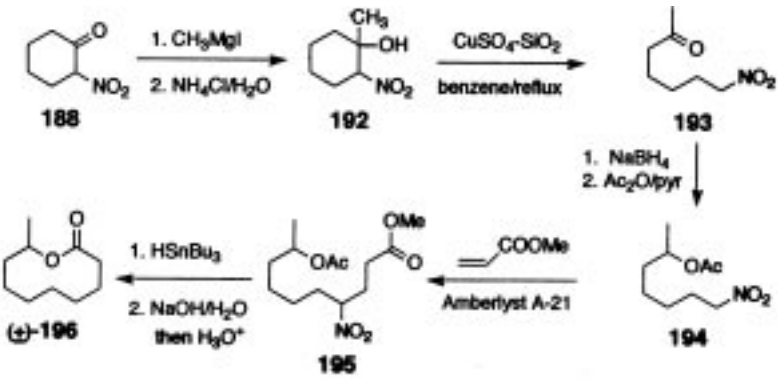
facilitated with the acidic ion exchange resin, Amberlyst, in methanol. The THP-protected nitroalcohols obtained were found to consist of the *threo* series and upon removal of the THP group, the single diastereomeric nitroalcohols could be separated by crystallization. A rationalization for formation of the *threo* configuration was presented in the form of a stereochemical model in which diastereotopic protonation with relative topicity was operative (Scheme 49). In separate experiments, the reaction of the 1,2-isopropylidene-3-THP (**185**) nitronate derivative **186** with benzaldehyde afforded the nitrotetrol **187** as a single diastereomer in 73% after workup and removal of the protecting groups (Scheme 50). Although the absolute stereochemistry of the newly-formed centers was undetermined, the use of nitronate **186** will undoubtedly offer a rapid access to 2-nitro-1,3,4,5-tetraols and the corresponding amino derivatives.



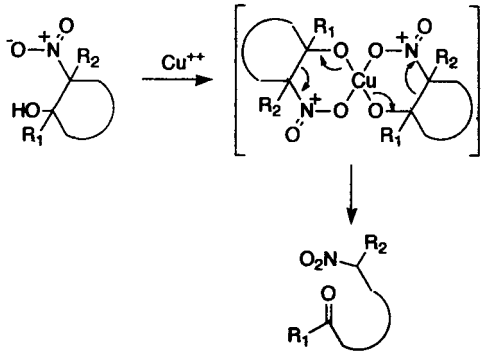
Scheme 50.



Scheme 51.



Scheme 52.



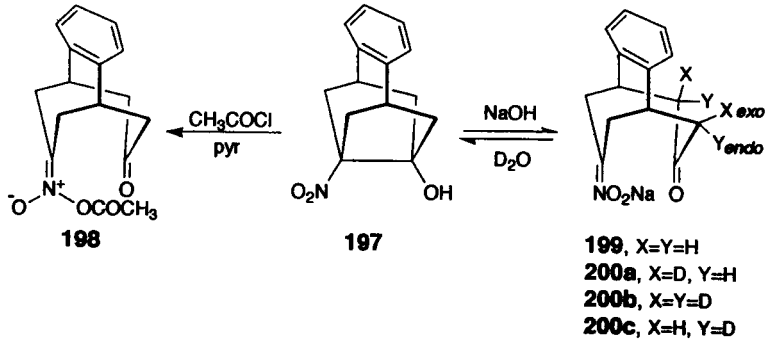
Scheme 53.

7.2. Retro-Henry reaction

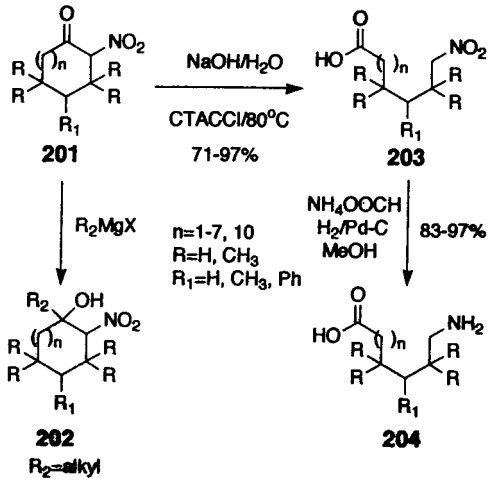
A retro-Henry reaction was employed as a method for preparing **190**, an intermediate in the synthesis of *R*-(+)-α-lipoic acid (**191**).[73] The cleavage was mediated by anhydrous copper sulfate adsorbed on silica gel in benzene under reflux (Scheme 51). Vinylic alcohol **189** was prepared from the Ballini ketone **188** by addition of vinylmagnesium bromide. The utilization of a retro-Henry reaction in the synthesis of (±)-phoracantholide (**196**) was reported by Barua.[74] Exposure of 2-nitrocyclohexanone to freshly-prepared methylmagnesium iodide provided 1-methyl-2-nitrocyclohexanol **192** in 70% yield. Treatment of the nitroalcohol **192** with anhydrous copper sulfate adsorbed on silica gel afforded the 7-nitroheptan-2-one **193** in 67% yield as a result of the retro-Henry reaction. Reduction of nitroketone **193** with sodium borohydride followed by acetylation gave the nitroester **194**. Michael addition of nitroester **194** with methyl acrylate furnished the nitrodiester **195**. Denitration of nitrodiester **195** with tri-*n*-butyltin hydride followed by saponification and acidification, with subsequent lactonization, provided (±)-phoracantholide (Scheme 52). A mechanistic pathway for the copper salt-mediated ring cleavage, which implicated the formation of a tetracoordinated square planar copper complex (Scheme 53), was proposed on the basis of observed pH changes during the progression of the reaction.

When exposed to acetyl chloride/pyridine, the tricyclic nitroalcohol **197** readily underwent the retro-Henry reaction to afford the isolable acetyl *aci*-nitroketone **198**.[75] Nitroalcohol **197** also undergoes the *retro*-Henry reaction when treated with aqueous sodium hydroxide thereby resulting in the ketonitronate **199** as an isolable solid. Extensive ^{13}C NMR analysis confimed the C_s symmetry of nitronate **199** and ^{1}H NMR analyses revealed that **197** suffered stereoselective deuterium exchange in methanol-D_4 to give the *exo* dideuterio isomer **200a** (X=D, Y=H) over 16 h. Complete deuteration of **197** to furnish **200b** (X=Y=D) was effected by refluxing with D_2O/NaOH for 30 minutes while selective *endo* dideuteration to give **200c** (X=H, Y=D) was accomplished by exposing the tetradeuterio compound to methanol for 16 h then concentration to dryness (Scheme 54).

Although cyclic α-nitroketones **201** are smoothly converted to cyclic 1-alkyl-substituted-2-nitroalkanols **202**, key substrates for the retro-Henry reaction, the cyclic nitroketones may also undergo a type of tandem nucleophilic



Scheme 54.

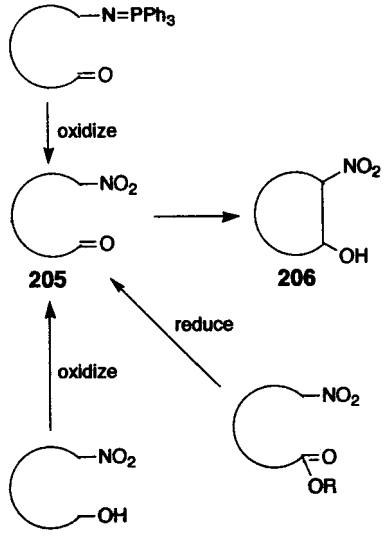


Scheme 55.

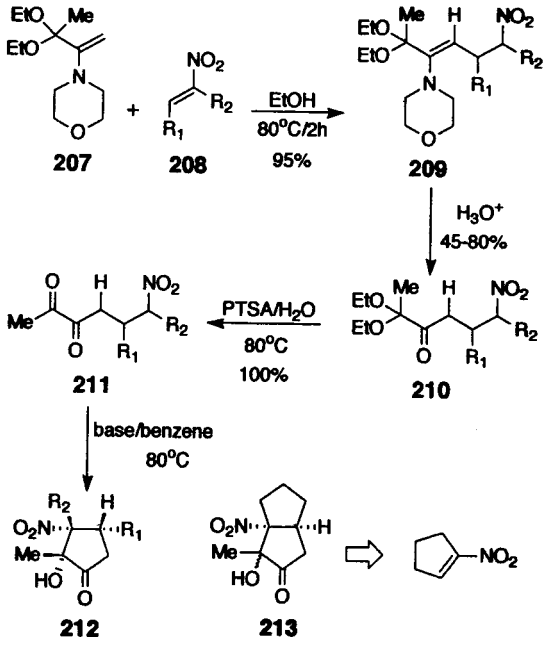
attack/retrocyclization by treatment with cetyltrimethylammonium chloride/aqueous sodium hydroxide at 80°C.[76] The resultant ω-nitrocarboxylic acids **203** may be used as substrates for Henry reactions or reduced with ammonium formate/10% palladium on carbon in methanol to provide the corresponding ω-amino acids **204**. The isolated yields of ω-nitrocarboxylic acids for the cleavage reaction ranged from 71–99% while the isolated yields for the reduction to the corresponding amino compounds **204** ranged from 83–97% (Scheme 55).

7.3. Intramolecular Henry reaction

Carbonyl compounds with suitably-disposed nitro groups will undergo cyclization thereby providing cyclic 2-nitroalkanols **206** through the intramolecular variant of the Henry reaction (Scheme 56). Interestingly,the preparation of such extended nitrocarbonyl precursors **205**, with both nucleophilic- and electrophilically-activated 'ends', in many cases, is not so straightforward. The efficient preparation of the bifunctional precursors requires effective methodology in the simultaneous adjustment of the required



Scheme 56.



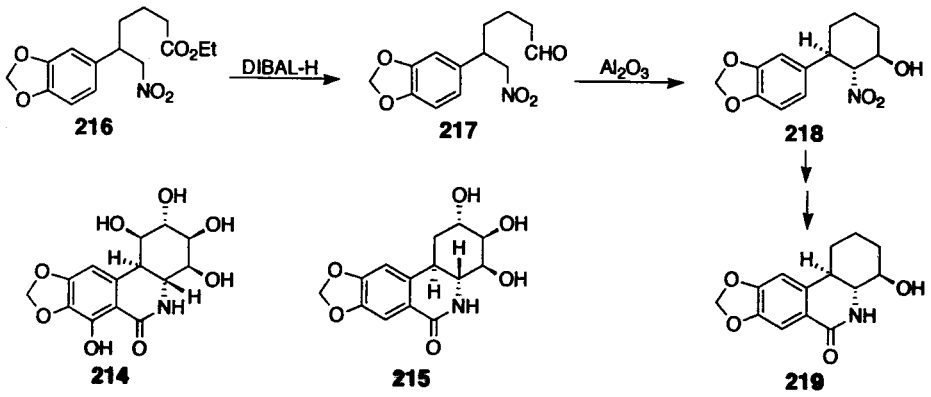
Scheme 57.

oxidation states of both carbon and nitrogen, an area in which there is still room for improvement.

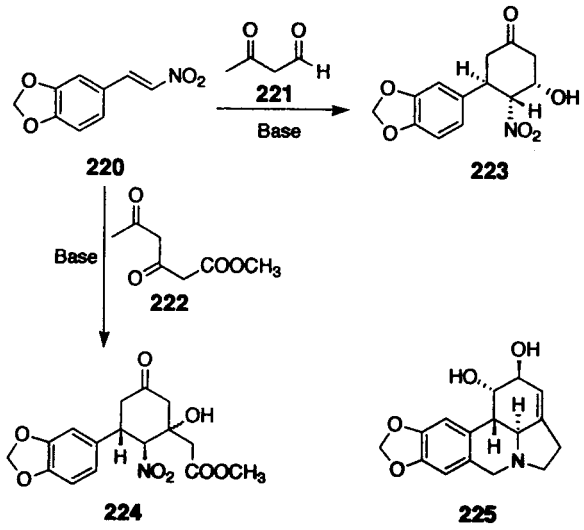
Addition of the morpholino enamine of 2,2-diethoxy-3-butanone (**207**) to nitroolefins **208** resulted in the nitroalkylated enamines **209** by Michael addition.[77] Treatment of the crude adducts **209** with dilute acetic acid resulted in selective hydrolysis of the enamine thereby providing the *gem*-dialkoxynitroketone **210**. Further treatment of **210** with *p*-toluenesulfonic acid/water hydrolyzed the ketal and furnished the nitrodiketone **211**. The nitrodiketone **211** could be cyclized under basic conditions to afford the cyclopentanone **212**. Starting with nitrocyclopentene, the morpholinoenamine/Michael/Henry route offered a direct route to the bicyclic pentalenone core structure **213** (Scheme 57).

The development of strategies for the synthesis of the pancratistatin (**214**) and lycoricidine (**215**) classes of alkaloids has been the proving ground for the intramolecular Henry reaction. McNulty has established an entry into the lycoricidine framework **219** which was based on the intramolecular cyclization of nitroaldehyde **217** to nitroalcohol **218** using neutral alumina.[78] Nitroaldehyde **217** was prepared from nitroester **216** by selective DIBAL-H reduction in dichloromethane at −78°C (Scheme 58). Similarly Seebach and Weller prepared nitro-alcohols **223** and **224** by a generalized tandem Michael–Henry approach which employed arylnitroolefin **220** and β-dicarbonyl compounds **221** and **222** (Scheme 59).[79] Activation of **221** and **222** required double deprotonation and triple deprotonation respectively and both processes led to the diastereomerically pure aryl nitroalcohols **223** and **224**. For further elaboration to the phenanthridine ring system present in lycorine class **225**, the nitro group was reduced with either Raney nickel or by catalytic hydrogenation.

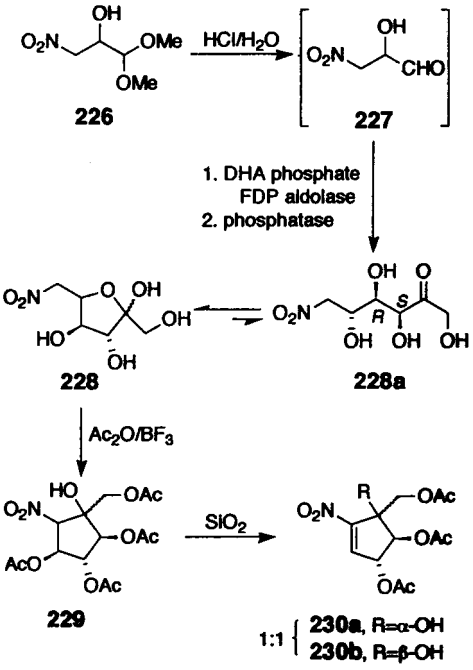
The nitroalcohol adduct **226** of nitromethane and glyoxal



Scheme 58.

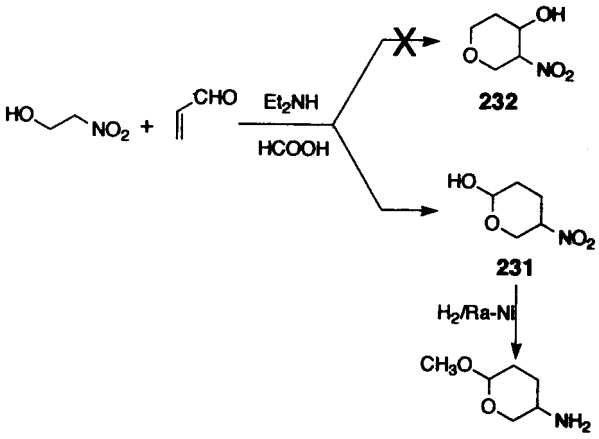


Scheme 59.

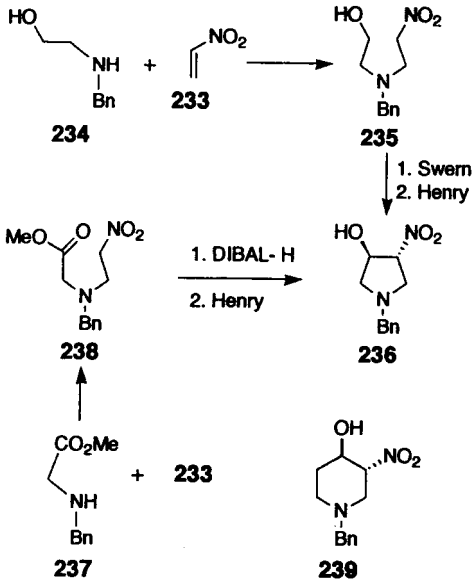


Scheme 60.

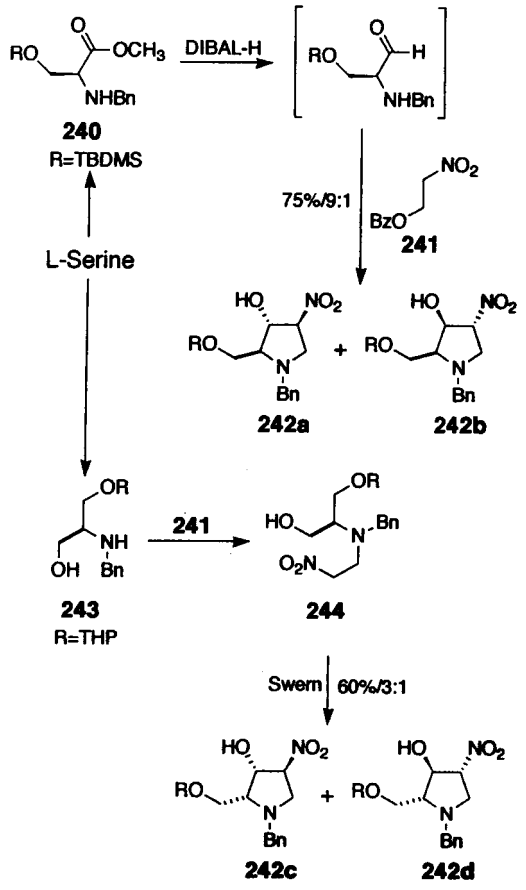
dimethylacetal was hydrolyzed to intermediate aldehyde **227** and condensed further with dihydroxyacetone (DHA) phospate under promotion by rabbit muscle (FDP) aldolase.[80] In situ treatment of the aldolase product with phosphatase was followed by concomitant cyclization of the phosphatase product **228a** to nitrotetrol **228**. Chemical



Scheme 61.



Scheme 62.



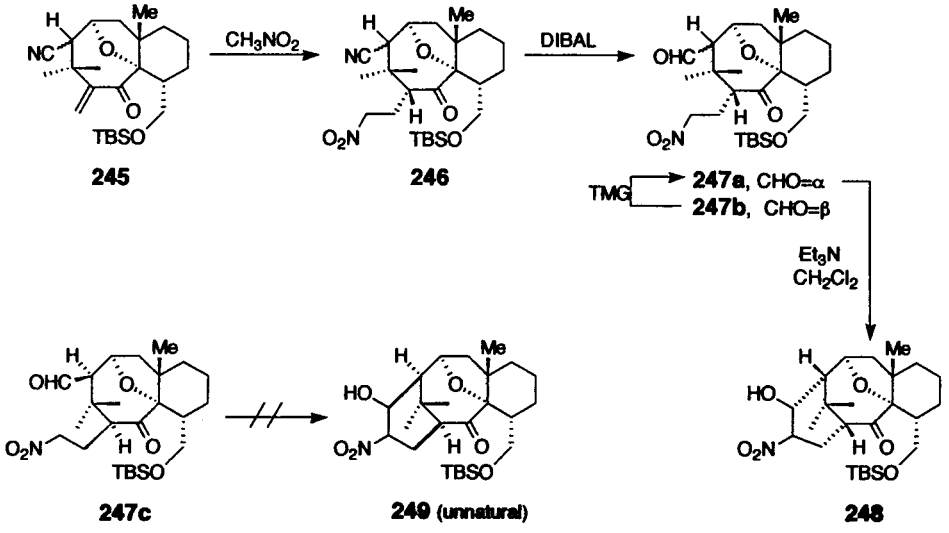
Scheme 63.

peracetylation of **228** with acetic anhydride/boron trifluoride provided nitrotetraacetate **229.** Silica gel chromatographic purification of **229** proceeded with β-elimination thereby affording the mixture of nitrocyclopentenetriacetates **230a** and **230b** (Scheme 60).

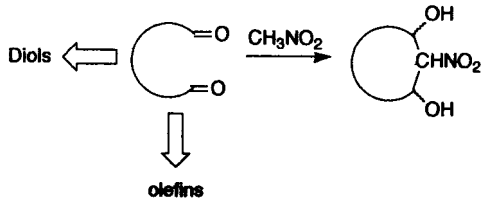
During early studies directed toward the synthesis of methyl D,L-tolyposaminides, the course of the intramolecular Henry reaction versus the tandem Michael/nitroaldol reaction between a β-hydroxynitrocompound and acrolein was investigated.[81] For example, the reaction of 2-nitroethanol and acrolein, promoted by diethylamine/formic acid (1:1.75), afforded the 3-nitrotetrahydropyran **231** rather than the 3-nitrotetrahydro-pyranyl alcohol **232** (Scheme 61).

A tandem Henry/Michael scheme was employed to prepare nitrohydroxylated pyrrolidine ring systems from nitroethylene **233** and *N*-benzylethanolamine **234** (Scheme 62).[82] Michael addition of the amine **234** to the nitrovinyl compound **233** provided the Michael adduct **235** which was oxidized via a Swern protocol to afford, presumably through an intermediate nitroaldehyde, the cyclic nitroalcohol **236**. Similarly, but with a different type of oxidation state adjustment, the Michael adduct **238** of *N*-benzylaminoester **237** and nitroethylene was reduced with diisobutylaluminum hydride thereby affording the cyclic nitroalcohol **236**. 4-Hydroxypiperidine derivatives **239** as well as pyrrolidine derivatives were prepared by the tandem route when the one-carbon homologous Michael donors were employed. Reduction of the nitro functions to the corresponding amino functions in both systems was effected by hydrogenation with W-4 Raney nickel. A Michael/Henry strategy similar to Scheme 62 utilized L-serine to prepare chiral hydroxylated pyrrolidine ring systems (Scheme 63).[83] *tert*-Butyldimethyl-silyloxy-*N*-benzylserine methyl ester **240** was reduced with DIBAL-H followed by condensation with 2-*N*-benzoyloxynitroethane **241.** The nitroester **241** was used as a latent Michael acceptor equivalent of nitroethylene thus providing the cyclized nitropyrrolidinones **242a** and **242b**. THP alcohol **243** was added to 2-*N*-benzoyloxy nitroethane **241** followed by concomitant cyclization to the pyrrolidinone derivatives **242c** and **242d** upon Swern oxidation of the intermediate Michael adduct **244**.

The Magnus group employed an intramolecular nitroaldol strategy to form the A-ring of the taxane system in high yield.[84] The strategy is of great interest both as a means for taxane A-ring construction and as a general intramolecular approach to the bicyclo[3.5.3]undecane ring



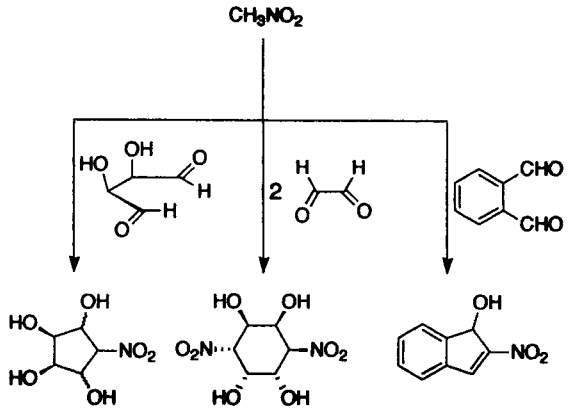
Scheme 64.



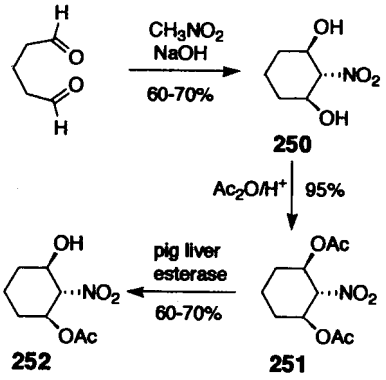
Scheme 65.

system (Scheme 64). Conjugate addition of methane to the epimeric γ-cyano-α-methylene enones **245** afforded the cyanonitrocompounds **246**. The generation of the requisite nitroaldehydes **247** was effected by the selective reduction of the cyanonitro compound **246** with DIBAL/CH_2Cl_2. Exposure of nitroaldehydes **247a** and **247b** to triethylamine at room temperature resulted in ring-A closure of the α-epimers to the nitroalcohol **248** which was obtained as a single stereoisomer in quantitative yield. The 11β-epimeric nitroaldehyde **247b** could be equilibrated by the agency of tetramethylguanidine to furnish the nitroalcohol **247a** which could be recycled through the nitroaldol reaction. The 1β,11β-nitroaldehyde **247c** resisted cyclization to the β-face (unnatural) ring A epimer **249**, noted Magnus, who reported that its resistance to cyclization was attributed to the conformational control exhibited by the C-19 methyl group.

The reaction of nitromethane with dialdehydes such as glutaraldehyde results in cyclization to give 2-nitro-1,3-diols (Scheme 65). Early accounts of the so-called 'double Henry' reaction were given by Lichtenthaler who compiled the many variations of the dialdehyde-nitromethane cyclization into a comprehensive review.[85] The basic constructs accessible by the double Henry reaction may be five or six membered rings which are accompanied by the assembly of 3–6 contiguous stereochemical centers. Since the versatility of the reaction depends on the dialdehyde or the nitro compound utilized, a great number of substitution patterns in the products may be realized (Scheme 66). For example, the reaction of glutaraldehyde and nitromethane may be conducted on a half-mole scale for the preparation of nitro-



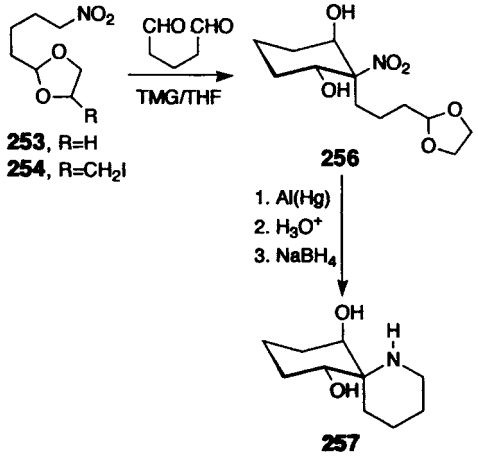
Scheme 66.



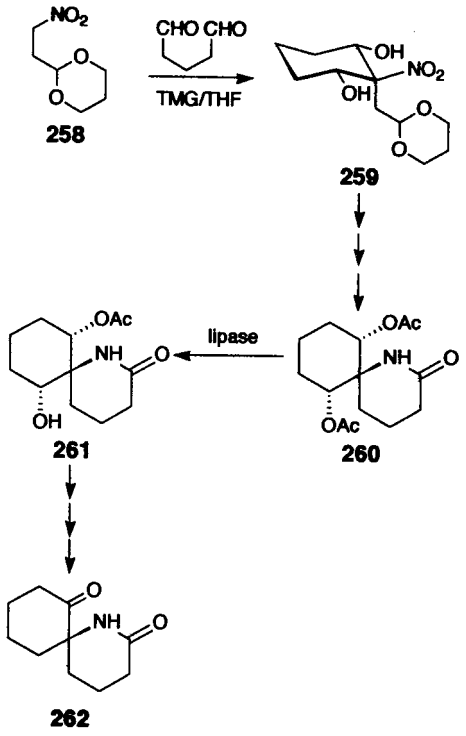
Scheme 67.

diol **250**. The predominantly *meso*-diastereomer that forms as the 'double Henry' product is then acetylated under acid conditions thereby providing an interesting substrate **251** for lipase-mediated desymmetrization to monoacetate **252** (Scheme 67).[86]

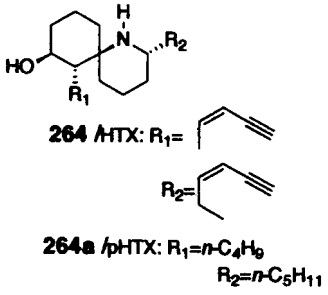
Extended nitroacetals such as **253** and **254** were used in the double Henry reaction as an entry into the azaspiro[5.5]-undecane ring system **255**, the core structure of the 'poison dart frog' alkaloids such as the histrionicotoxins **264** and **264a**.[87a,87b] For example, condensation of glutaraldehyde with the nitroacetal **253** provided the diastereomeric *cis*, *trans*-nitrodiols **256**. A reduction-hydrolysis-reduction sequence, using Al/Hg followed by aqueous acid then sodium borohydride, converted the nitrodiols **256** into the azaspiro system **257** (Scheme 68). With nitroacetals such as **258**, prepared by the method of Örlein,[88] the *meso*-nitrodiol **259** was the main product when condensed with glutaraldehyde in the presence of TMG/THF. Further elaboration provided the *meso*-lactamdiacetate **260** an excellent substrate for enzymatic desymmetrization to diolmonoacetate **261**. Further elaboration of **261** provided both antipodes of the Kishi lactam **262**, a perhydrohistrionicotoxin intermediate (Scheme 69).[89]



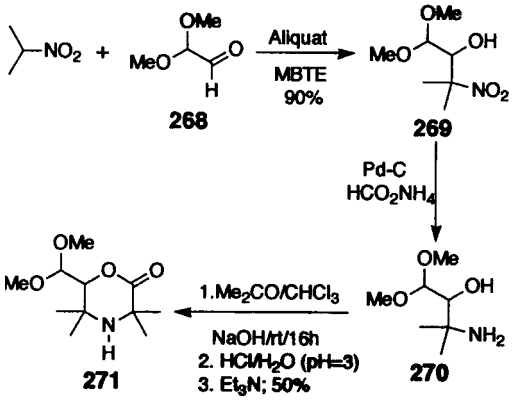
Scheme 68.



Scheme 69.



The oxidative cleavage of suitably-protected cyclic polyols or pyranosides to dialdehydes offers an efficient entry to *O*-protected dialdehydes which may participate in the double Henry cyclization with nitromethane.[90] For example, the dialdehyde **266**, obtained from the periodate-mediated oxidative cleavage of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **265**, was treated with nitromethane in the presence of sodium methoxide/methanol to afford mainly the four isomeric 3-nitroheptoseptanosides **267a** (42%), **267b** (36%), **267c** (12%) and **267d** (<10%). The configurations at C-2, C-3 and C-4 for the heptoseptanosides were correlated by conversion to the corresponding 3-acetamido derivatives and then to the characterized 3-amino-3-deoxyhexose derivatives (Scheme 70).

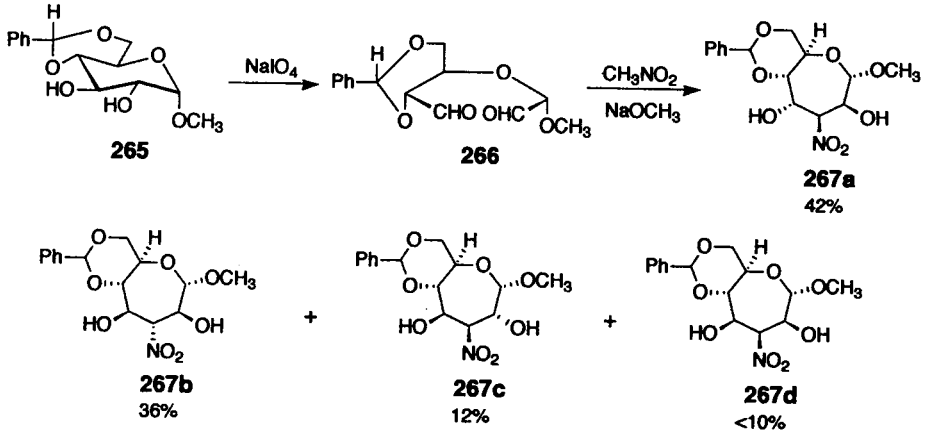


Scheme 71.

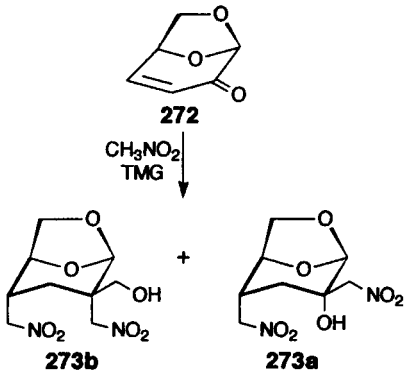
8. Miscellaneous substructures

A synthesis of 6-substituted-3,3,5,5-tetramethylmorpholinones **271** employed the nitroaldol reaction of 2-nitropropane and commercially-available glyoxal 1,1-dimethylacetal **268** in methyl *tert*-butyl ether (MBTE). The reaction was promoted by aqueou sodium hydroxide and Aliquat (tricaprylmethylammonium chloride) under two-phase conditions.[91] The nitroalcohol adduct **269** was obtained as an oil in 90% yield and was of sufficient purity to reduce to amino alcohol **270** with Pd/C and ammonium formate in THF. Amino alcohol **270** was transformed to the morpholinone **271** by means of the Lai protocol which employed acetone, chloroform and sodium hydroxide (Scheme 71).

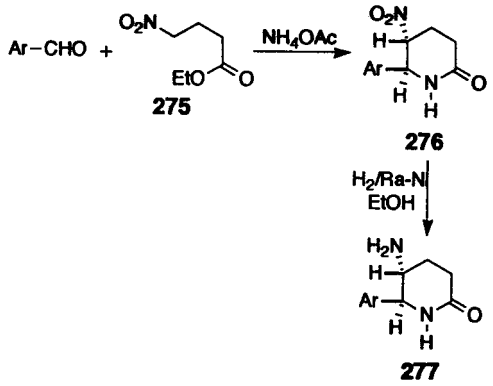
Levoglucosenone **272** reacts with an excess of nitromethane



Scheme 70.



Scheme 72.



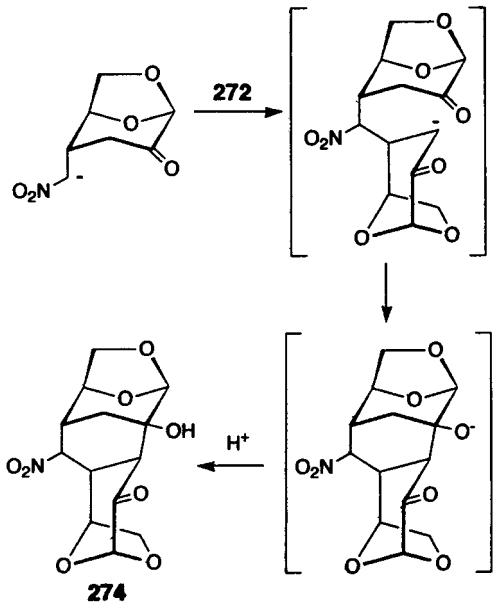
Scheme 74.

in the presence of 1,1,3,3-tetramethylguanidine (TMG) to afford the isomeric dinitroalcohols **273a** and **273b**.[7] The 2:1 adducts **273a** and **273b** are formed by Michael addition of nitronate followed by the standard Henry carbonyl attack which forms the two isomeric tertiary alcohols (Scheme 72). Interestingly, the 1:2 adduct **274** may form by a 'double Michael' followed by an intramolecular aldol-type ring closure (Scheme 73).

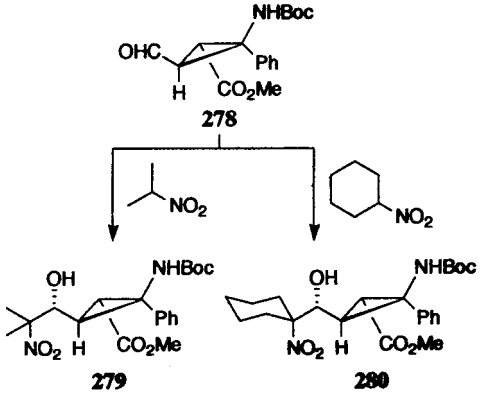
6-Aryl-substituted-5-nitro-2-piperidinones **276** have been prepared via a nitroaldol route by reacting an arylaldehyde, ethyl-4-nitrobutanoate **275** and and ammonium acetate.[92] The reactions may be conducted in a variety of solvents such as acetic acid, methanol or dimethylsulfoxide. The isolated yields of the nitropiperidinones **276** varied from 7 to 98%. Raney nickel in ethanol under two atm. of hydrogen was sufficient for reducing the nitro group of the piperidinones **276** to the corresponding amino group thereby furnishing the corresponding 5-amino-6-aryl-2-oxopiperidines **277** (Scheme 74).

The addition of 2-nitropropane and nitrocyclohexane to the cyclopropylcarboxaldehyde **278**, under catalysis with triethylamine, exhibited high Felkin-Anh control to furnish carbinols **279** and **280** with over 99:1 diastereoselectivity (Scheme 75).[93] During the same study the addition of cyanide, allyl silanes, enolsilanes, under Lewis acid catalysis (via Sakurai and Mukaiyama conditions), gave the same observed diastereoselectivity.

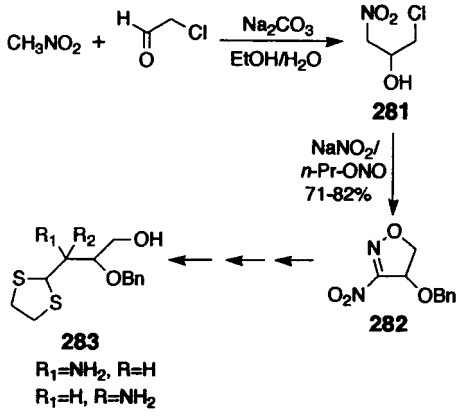
A general synthesis of 4-alkoxy-3-nitro-4,5-dihydroisoxazoles **282**, intermediates for conversion to 2-amino-2-deoxytetrose derivatives **283**, utilized a nitroaldol reaction between nitromethane and chloroacetaldehyde as the first step.[94] The resultant γ-chloro-β-hydroxynitrocompound **281** was *O*-benzylated followed by cyclization with sodium



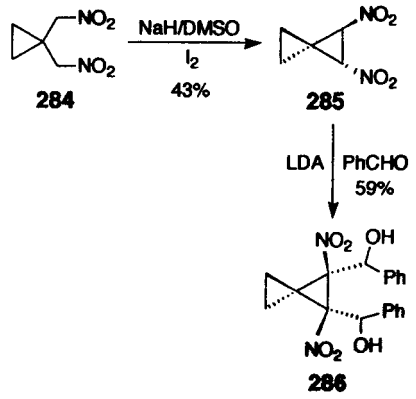
Scheme 73.



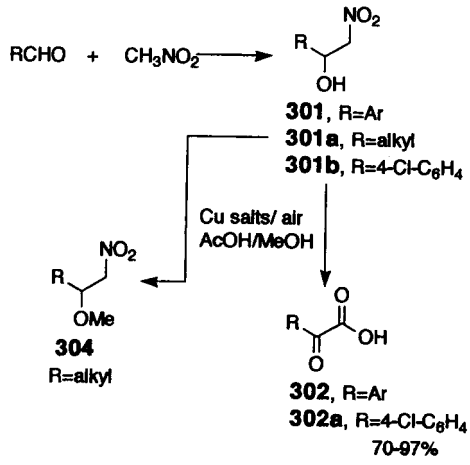
Scheme 75.



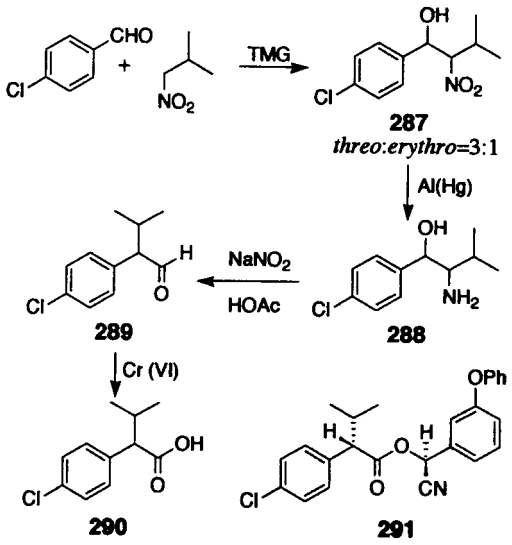
Scheme 76.



Scheme 77.



Scheme 80.



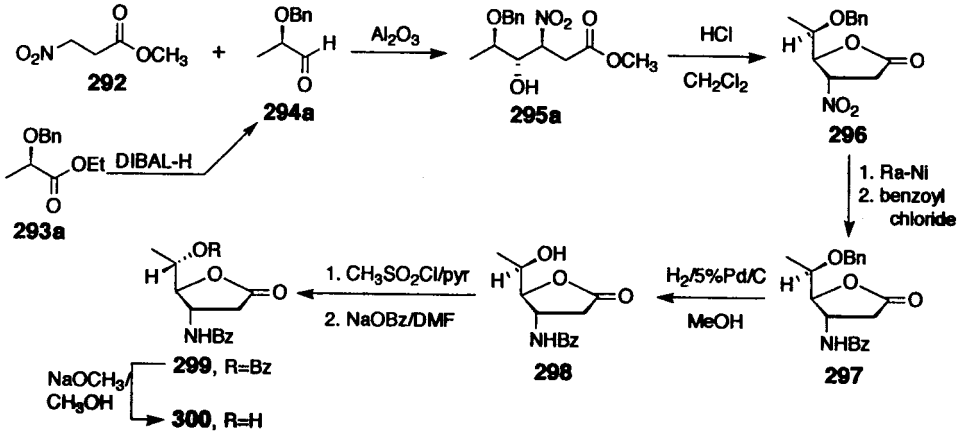
Scheme 78.

nitrite/*n*-propyl nitrite to furnish the dihydroisoxazole **282** in 82% yield (Scheme 76).

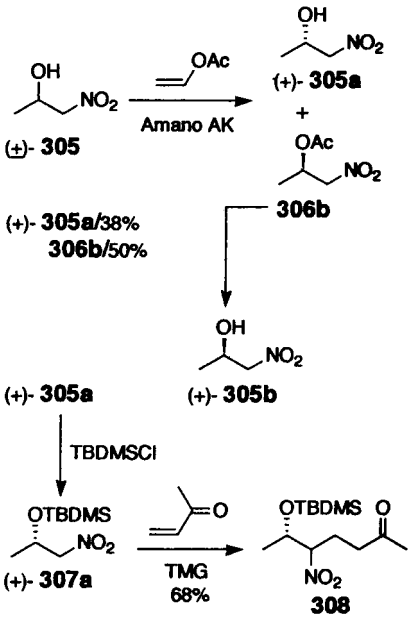
During their study of polynitro-substituted ring compounds, Wade and co-workers converted the 1,2-dinitrospiropentane **284** into the dinitromethylcyclopropane **285**, using dimsyl-sodium/iodine and reported its crystal structure.[95] Treatment of the dispironitro compound with excess LDA in the presence of excess benzaldeyde gave the dispirodinitrodiol **286** in 59% yield (Scheme 77).

The nitroalcohol **287**, obtained in 61% yield from the TMG-catalyzed reaction of 4-chlorobenzaldehyde and 2-methyl-1-nitropropane **91**, was utilized in a preparation of (±)-fenvaleric acid **290** a component of the synthetic pyrethroid pesticide esfenvalerate **291**.[96] The 3:1 *threo*/*erythro* mixture of **287** was reduced with Al/Hg to provide the corresponding amino alcohols **288**. Aminopinacol rearrangement of **288** with nitrous acid generated in situ, followed by Cr (VI)-mediated oxidation of the resultant aldehyde **289** furnished the (±)-fenvaleric acid **290** (Scheme 78).

Hanessian and Kloss have employed β-nitropropionates **292** in conjunction with *O*-benzyl D- or L-lactaldehyde **294a** or **294b** in a de novo synthesis of aminosugars in the deoxyhexose series.[97] DIBAL-mediated reduction of *R*-*O*-benzyl ethyl lactate **293a** afforded *O*-benzyl-D-lactaldehyde **294a**. Exposure of aldehyde **294a** to methyl-3-nitropropionate in the presence of neutral alumina provided a mixture of three nitroalcohols from which the major D-*ribo* isomer **295a** was isolated by crystallization in 62% yield. The overall distribution of nitroalcohols was determined to be *ribo*/*xylo*/



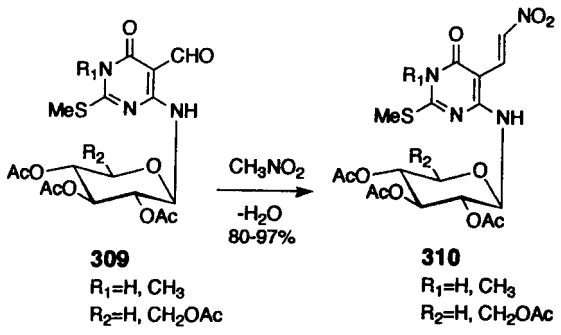
Scheme 79.



Scheme 81.

arabino, 15/1.5/1. Treatment of nitroalcohol **295a** with hydrochloric acid effected lactonization to furnish quantitatively the β-nitrolactone **296**, which upon reduction with Raney nickel followed by *N*-benzoylation, afforded benzamidolactone **297**. Correlation with the known L-*lyxo* lactone **300** was accomplished by debenzylation of benzamidolactone **297** followed by mesylation of the 5-hydroxylactone **298** and mesylate displacement with sodium benzoate in DMF. Hydrolysis of the inverted benzoate product **299** with sodium methoxide/methanol provided the *lyxo* lactone **300** in 79% yield. The same report revealed that the ratio could be increased to ribo:xylo:arabino, 1/3/1, by promotion of the nitroaldol reaction with potassium *tert*-butoxide/magnesium bromide in tetrahydrofuran (Scheme 79).

1-Aryl-2-nitro-1-phenethanols **301**, prepared by the nitroaldol reaction of nitromethane and various arylcarboxaldehydes, were converted to the corresponding α-ketocarboxylic acids **302** by treatment with copper salt catalysis in the presence of air.[98] Copper salts such as Cu $(OAc)_2$, $CuSO_4{\cdot}5H_2O$, $CuCl_2$ and CuI in an aqueous acetic acid/methanol solvent system promoted conversions of 1-(4-chlorophenyl)-2-nitroethanol **301b** to the corresponding title compound **302a** in isolated yields ranging from 70–97%. In contrast, under similar conditions, aliphatic-substituted nitroalcohols **301a** furnished the corresponding α-methoxy nitro compounds **304** albeit in lower yields (Scheme 80).



Scheme 82.

Racemic 1-nitro-2-propanol **305**, prepared by the method of Mélot[24] using alumina-supported KF, was used as an inexpensive, readily-available source of chiral starting materials for synthetic studies involving the pheromones of *Bactrocera negrotibialis*.[99] Nitroalcohol **305** was submitted to resolution by enzyme-mediated transesterification with Amano AK lipase and vinyl acetate. The resolution protocol furnished (+)-nitroalcohol **305a** and β-nitroacetate **306b** in 38% and 50% chemical yields respectively in greater than 99% enantiomeric purity. While the nitroacetate **306b** could be hydrolyzed to **305b**, (+)-**305a** was employed in futher studies. Silylation of (+)-**305a** with *tert*-butyldimethylsilyl chloride provided the β-silyloxynitropropane **307a**. Michael addition of **307a** in the presence of TMG afforded the β-silyloxynitroketone **308** in 68% yield (Scheme 81).

A study which involved the functionalization of C-5 in 4-glycosylaminopyrimidines utilized the 5-formyl pyrimidine analog **309** and nitromethane as a coupling partner in the nitroaldol reaction.[100] Under the reaction conditions, anhydrous pyridine/ammonium acetate/90°C, the intermediate nitroalcohols suffered dehydration to the corresponding nitroolefins **310**. The nitroolefinic pyrimidine derivatives were obtained in isolated yields of 80–97% (Scheme 82).

9. Conclusions

The Henry reaction continues to attract interest in several areas of synthetic organic chemistry. When employed as a key step in the total synthesis of natural products, sensitive functionality and protecting groups tolerate the reaction so that a high degree of selectivity in carbon–carbon bond formation may be achieved. Complex carbohydrate chemistry has especially benefited from the mild properties of the nitroaldol reaction in forming carbon–carbon bonds. The complex arrays of protecting groups and masked functionality encountered during the multistep synthesis of extended carbohydrates and carbohydrate-derived natural products are especially tolerant of even the most rigorous variants of the Henry reaction. The reaction has proven to be a viable testing ground for asymmetric synthesis and for the development of chiral catalysts, particularly in the area of pharmaceuticals and experimental therapeutics where the activity of the compounds depend on their relative chirality. The development and application of new promoters and solventless techniques will continually be emerging due to the increased interest in more efficient Henry catalysts and environmentally-friendly 'green' chemical technology.

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Biographical Sketch

Frederick Luzzio was born in Lawrence, Massachusetts. He graduated (BSc) from Vanderbilt University in 1976 where he majored in chemistry and biology. He worked as a development chemist at Arthur D. Little, Inc. in Cambridge, Massachusetts until entering the graduate program at Tufts University where he earned his MSc and PhD degrees in organic chemistry under the mentorship of Frank S. Guziec, Jr. After finishing graduate study he spent three years in the laboratories of E. J. Corey as a post-doctoral fellow, followed by two years in the Biomedical Products Department of DuPont. Since 1988 he has served on the faculty of the University of Louisville where he currently holds the rank of Associate Professor. His research interests are in the areas of organic synthesis, natural products and medicinal chemistry.