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Perspective

Synthesis of mono- and di-hydroxylated prolines and 2-hydroxymethylpyrrolidines from non-carbohydrate precursors

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Dedicated to Professor Hassan S. El Khadem on the occasion of his 80th birthday

Abstract

Natural and synthetic imino sugars are biologically important as glycosidase inhibitors. This review includes selected syntheses of 3-hydroxyproline, 4-hydroxyproline, 3,4-dihydroxyproline, 2-hydroxymethyl-3-hydroxypyrrolidine and 2-hydroxymethyl-pyrrolidine-3,4-diol, which exhibit glycosidase inhibitory and various other biological activities.

Keywords: Hydroxyproline; Dihydroxyproline; Hydroxypyrrolidine; Glycosidase inhibitors; Deoxy imino sugars

1. Introduction

Imino sugars are well known as glycosidase inhibitors and many of them are naturally occurring.[1,2] 1,4-Dideoxy-1,4-imino-D-arabinose and -D-ribose are naturally occurring imino sugars exhibiting activity as glycosidase inhibitors,[2] and hydroxylated pyrrolidines constituted one of the main classes of naturally occurring sugar mimics having nitrogen in the ring.[1] Much attention has been focused on this class of compounds because of their potential for cell-biological and therapeutic applications as a consequence of their role as glycosidase inhibitors.[1,2] A wide range of analogues has been synthesized.[1–3] Because of their sugar-like struc-

Abbreviations: AIBN, azobis(isobutyronitrile); All, allyl; Bn, benzyl; BMS, borane–dimethylsulfide complex; Boc, *tert*-butoxcarbonyl; Bu, butyl; Bz, benzoyl; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; CSA, camphorsulfonic acid; DAMP, 4-(dimethylamino)pyridine; DAST, diethyl aminosulfur trifluoride; DBAD, di-*t*-butyl azodicarboxylate; DBU, 1,8-diazabicycloundecane; DEAD, diethyl azodicarboxylate; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DHQ-CLB, Sharpless asymmetric dihydroxylation reagent; DIBAL, di-*i*-butyl aluminium hydride; DIPT, di-*i*-propyl tartrate; DMP, 2,2-dimethoxypropane; Me_2SO, dimethyl sulfoxide; DPPA, diphenylphosphorazidate; HMDS, hexamethyldisilazane; HMPA, hexamethylphosphoramide; LDA, lithium di-*i*-propylamide; LHMDS, lithium hexamethyldisilazide; *m*CPBA, *m*-chloroperoxybenzoic acid; MEM, methoxyethoxymethyl; MOM, methoxymethyl; MoOPH, oxodiperoxymolybdenum(pyridine)hexamethylphospharamide; MPM, methoxyphenylmethyl; Ms, mesyl; MS, molecular sieves; NBS, *N*-bromosuccinimide; NMO, *N*-methylmorpholine *N*-oxide; NSA, 2-naphthalenesulfonic acid; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; Ph, phenyl; PhFIBr, 9-(9-phenylfluorenyl)bromide; PPTS, pyridinium salt, *p*-toluenesulfonic acid; Py, pyridine; rt, room temperature; Ru-Cat, bis-(tricyclohexylphosphane) benzylidene ruthenium dichloride; TBAF, tetrabutylammonium fluoride; TBS, *t*-butyldiphenylsilyl; TBDPS, *t*-butyldimethylsilyl; Tf, trifluoromethylsulfonyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; THF, tetrahydrofuran; TIPS, triisopropylsilyl; Me_3Si, trimethylsilyl; Me_3SiOfuran, 2-(trimethylsiloxy)furan; Tol, tolyl.

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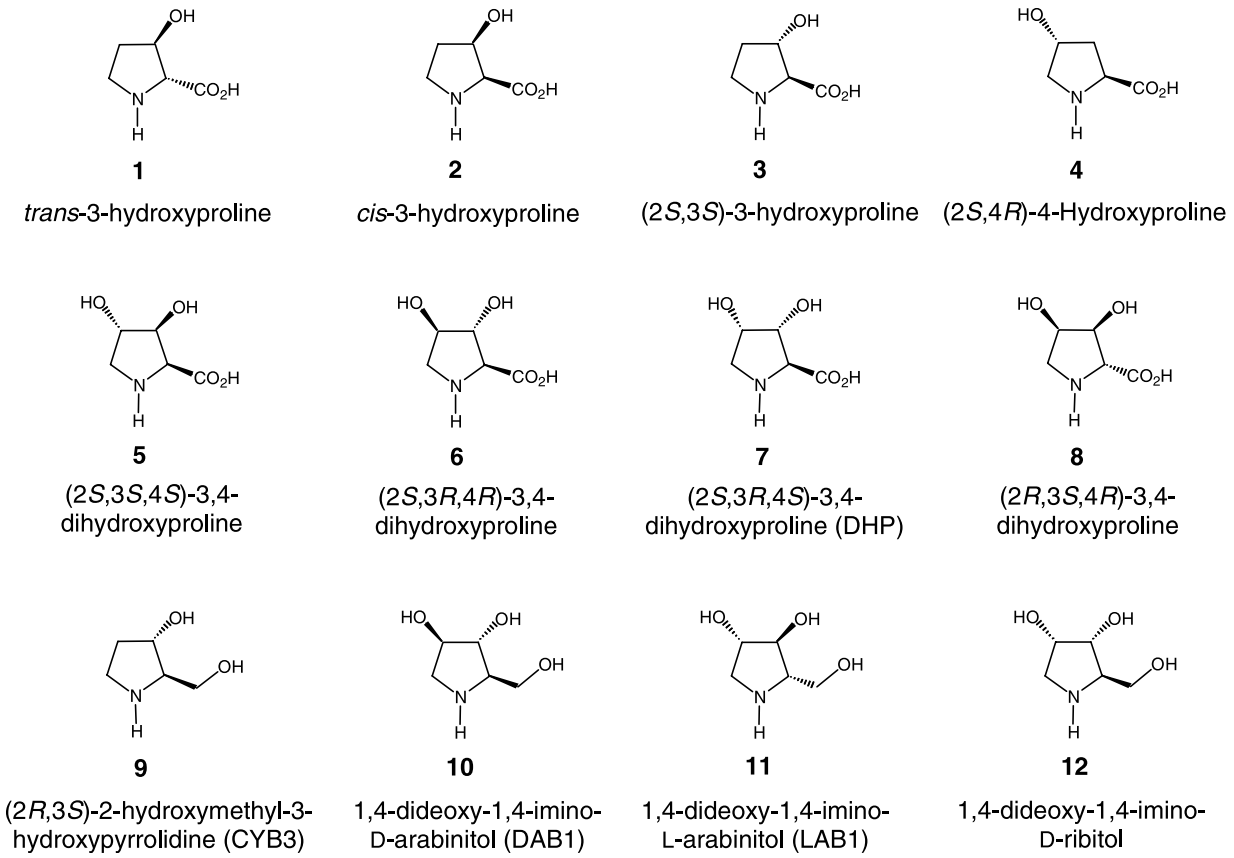
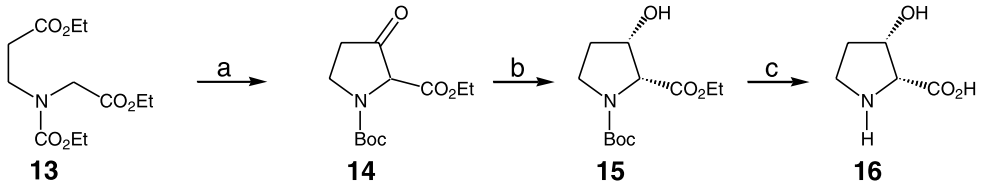
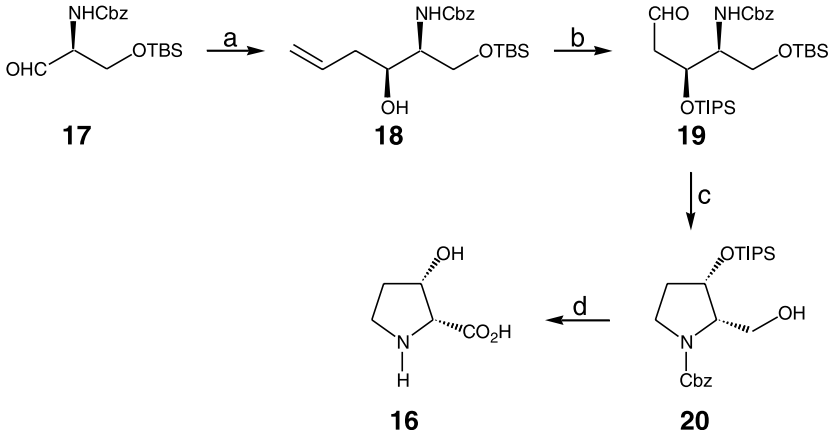


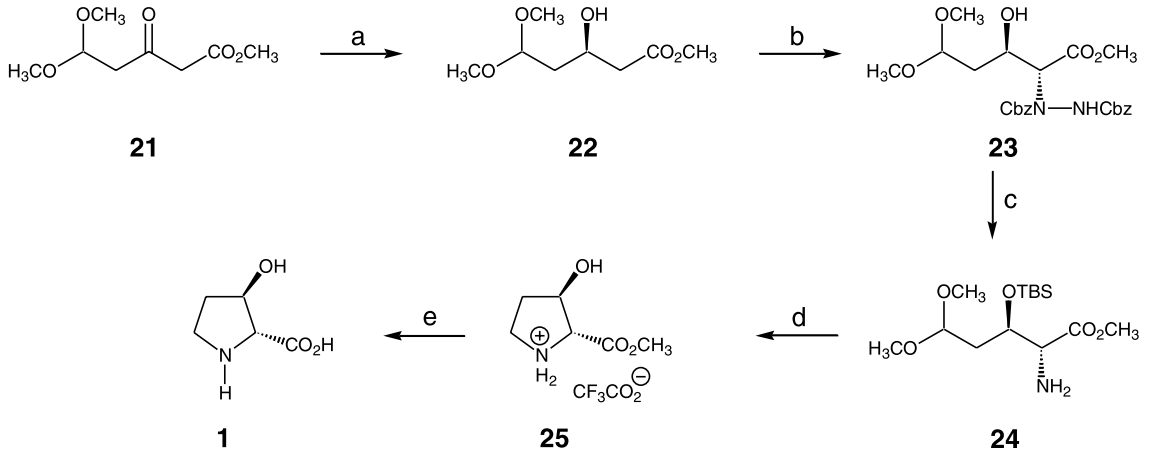
Fig. 1. Natural mono- and di-hydroxylated prolines and 2-hydroxymethylpyrrolidines.



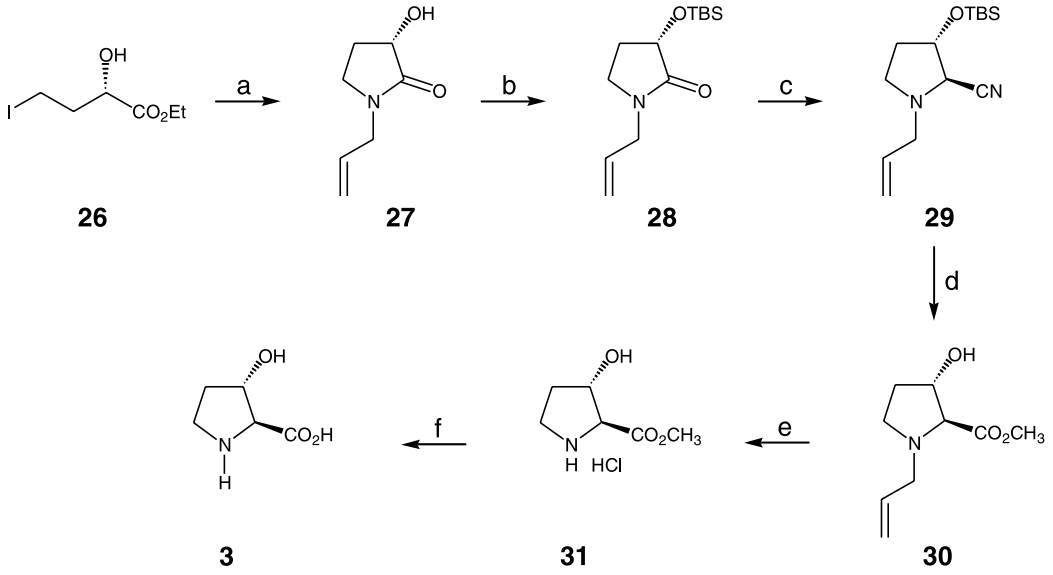
Scheme 1. (a) *t*-BuOK, toluene, 0 °C, 0.5 h, 45%; (b) sucrose, dried bakers' yeast, 30 °C, 24 h, 75%; (c) 1. TFA, CH_2Cl_2, rt, 2 h; 2. KOH, CH_3OH, H_2O, rt, 16 h; 3. Dowex 50W (H^+), elution with aqueous NH_3, 70%.



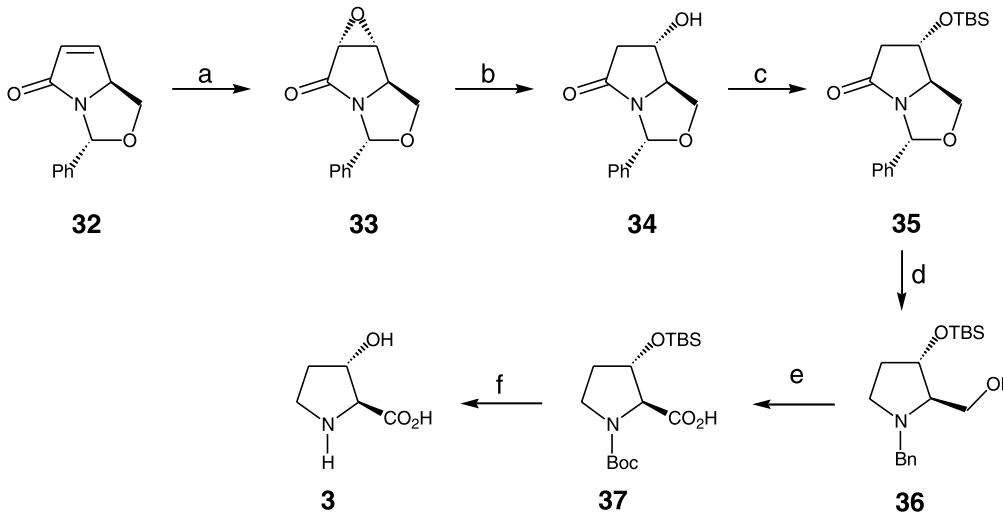
Scheme 2. (a) $(CH_3)_3SiCH_2CH{=}CH_2$, $SnCl_4$, CH_2Cl_2, −78 °C, 60%; (b) 1. TIPS-Tf, 2,6-lutidine, CH_2Cl_2, 0 °C; 2. OsO_4, NMO, acetone, H_2O, rt; 3. $NaIO_4$, silica gel, CH_2Cl_2, rt, 81%; (c) 1. $NaBH_3CN$, AcOH, CH_3OH, rt; 2. AcOH, CH_3OH, reflux, 1 h; d) 1. NaOCl, TEMPO, KBr, $NaHCO_3$, Et_2O, H_2O, 0 °C; then acetone, $NaIO_4$, $RuCl_3$, rt, 91%; 2. H_2SiF_6, CH_3CN, H_2O, 55 °C, 50 min; 3. 10% Pd on C, H_2, CH_3OH, rt, 86% for two steps.



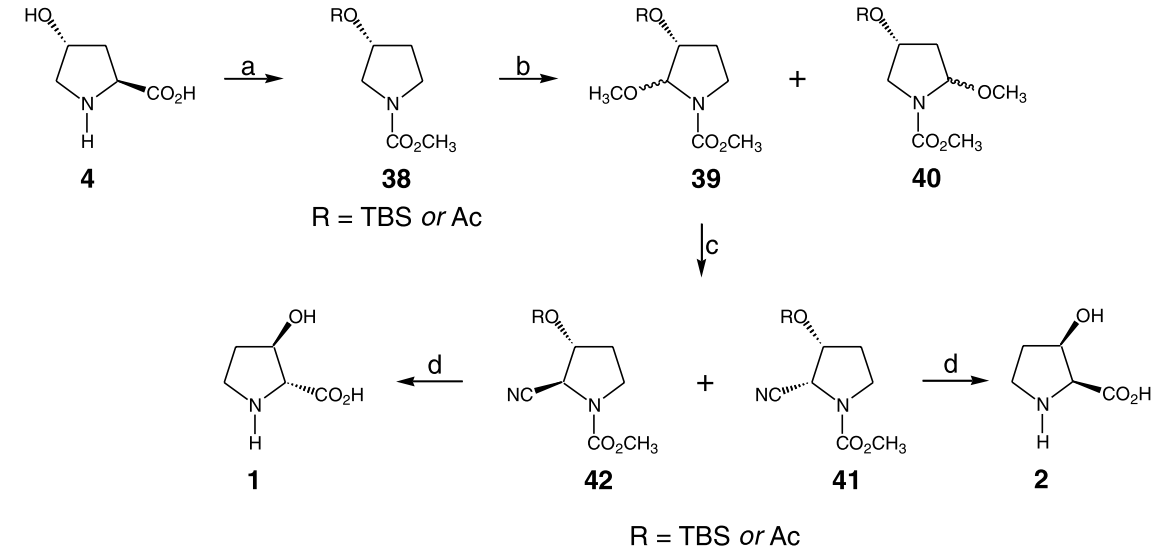
Scheme 3. (a) H_2, (*R*)-Binap $RuBr_2$, 2% mol; CH_3OH; 1 atm, rt, 18 h, 86%; (b) CH_3ZnBr, LDA, CbzN=NCbz, −78 °C, 66%; (c) 1. TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 96%; 2. H_2, PtO_2, H_2O, CH_3OH, H_2O, rt, 71%; (d) 1. TFA, H_2O; 2. H_2, PtO_2, H_2O, rt; (e) KOH, CH_3OH, H_2O, rt, Dowex 50 × 4, 84%.



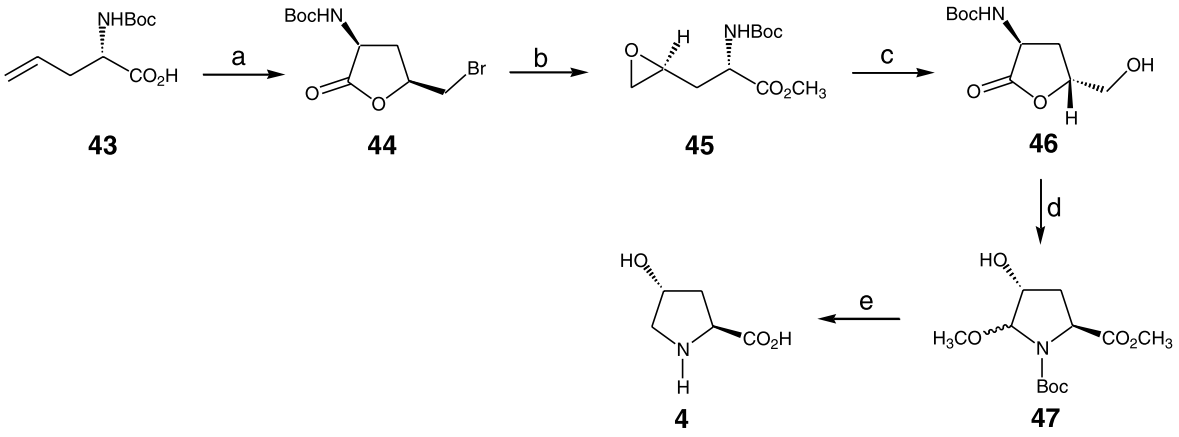
Scheme 4. (a) CH_2=$CHCH_2NH_2$, THF, rt, 90%; (b) TBSCl, imidazole, DMF, rt, 80%; (c) 1. DIBAL-H, THF, −35 to −15 °C; 2. KCN, H_2O, −10 °C to rt, 93%; (d) 1. HCl, CH_3OH, −20 °C; 2. Amberlyst 15, CH_3OH, 65 °C, 83%; (e) 1. $Pd(dba)_2$, Dppb, mercaptobenzoic acid, THF, rt; 2. 1 M HCl, 70%; f) KOH, CH_3OH, H_2O, rt, 88%.



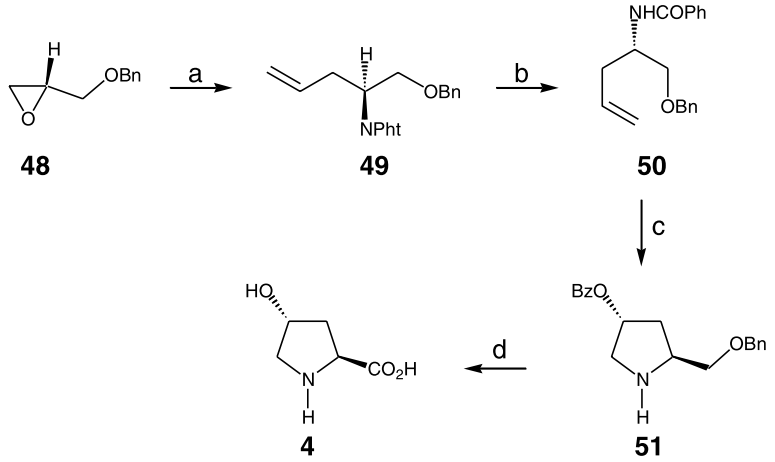
Scheme 5. (a) *t*-BuOOH, *n*-Bu_4NF, K_2CO_3, DMF; (b) Al/Hg, EtOH, acetone, 2:1; (c) TBSCl, imidazole, DMF; (d) BH_3-$S(CH_3)_2$, THF, 70 °C; (e) 1. H_2, Pd on C, Boc_2O, CH_3OH; 2. $RuCl_3$, $NaIO_4$, CH_3CN, H_2O; (f) 1. 6 M HCl; 2. Dowex 50 W X2, NH_4OH.



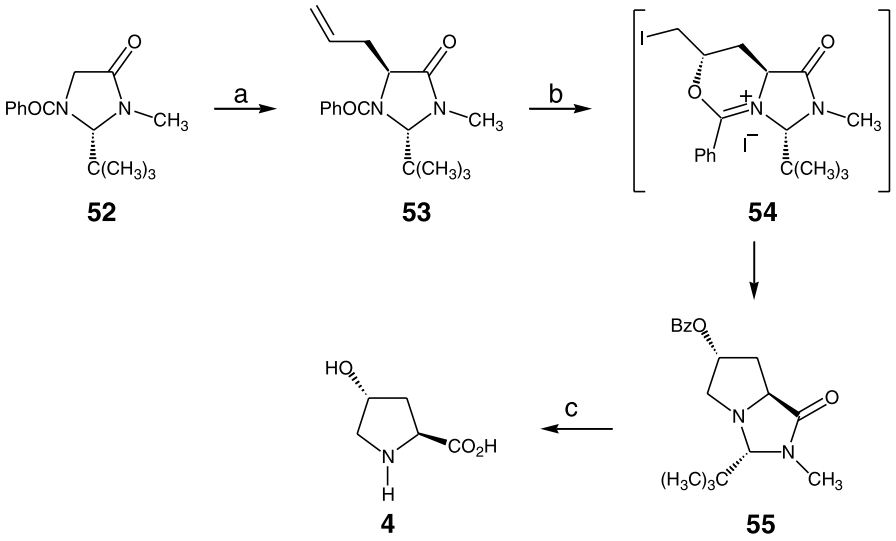
Scheme 6. (a) 1. Cyclohexanol; 2. $ClCO_2CH_3$, 95%; 3. TBSCl or Ac_2O; (b) Anodic oxidation, CH_3OH, 43% for R = TBS; (c) Me_2SiCN, $TiCl_4$, −78 °C, 86%; **42**:**41** (R = TBS, 14:86 ratio), (R = Ac, 48:52 ratio); (d) 5 M HCl.



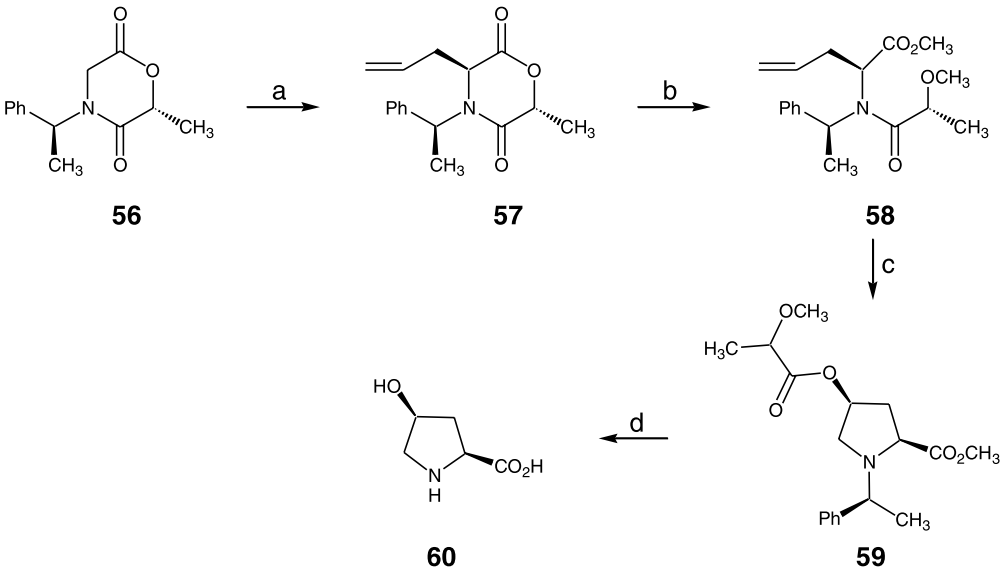
Scheme 7. (a) NBS, THF, 0 °C, 30 min, 73%; (b) K_2CO_3, CH_3OH, 0 °C, 30 min, 100%; (c) 1. 1N HCl, 0 °C, 14 h; 2. CSA, CH_2Cl_2, rt, 20 h, 74%; d) 1. $(COCl)_2$, CH_2Cl_2, Me_2SO, −78 °C (15 min) to −45 °C (1 h); then Et_3N, 0 °C, 15 min; 2. CSA, CH_3OH, rt, 14 h, 58%; (e) 1. 60% AcOH, rt, 48 h; 2. $NaCNBH_3$, EtOH, 60% AcOH, rt, 45 min, 41%; 3. 1N NaOH, 0 °C, 14 h; 4. 1N HCl, CH_2Cl_2, 0 °C, 30 min.



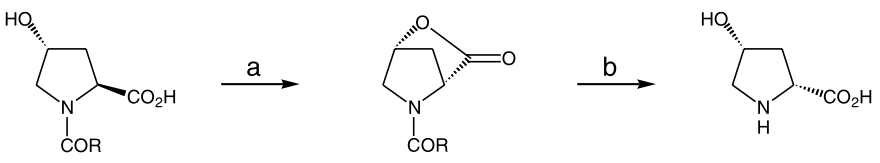
Scheme 8. (a) 1. C_2H_2, NaH, Me_2SO, 2. H_2, Pd, $CaCO_3$; 3. Phthalimide, PPh_3, DEAD, 61%; (b) 1. N_2H_4, EtOH; 2. BzCl, Et_3N, 87%; (c) 3 equiv I_2, H_2O, THF, 78%; (d) 1. Boc_2O, Et_3N; 2. K_2CO_3; 3. H_2, $Pd(OH)_2$; 4. $RuCl_3$, $NaIO_4$; 5. TFA, 61%.



Scheme 9. (a) LDA, *n*-BuLi, $BrCH_2CH{=}CH_2$, −78 °C to −20 °C; (b) I_2, THF, H_2O; (c) HCl, heat in sealed tube.

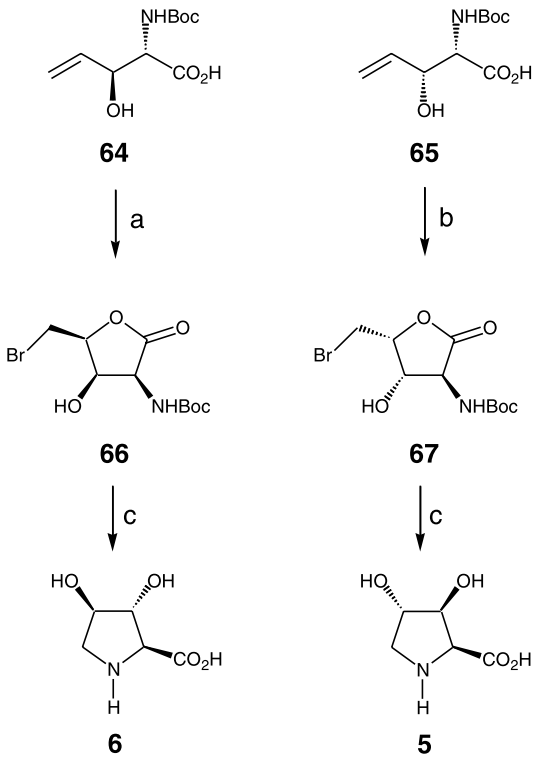


Scheme 10. (a) 1 M LHDMS, THF, −40 °C; then (*Z*)-$BnOCH_2CH{=}CHCH_2OMs$; (b) 1. 1 M NaOH, CH_3OH, 4 h; 2. NaH, THF, 0 °C, 1 h; then CH_3I, 60 °C, 1 h, 90%; (c) I_2, THF, H_2O, rt, 2 h, 80%; (d) 1. H_2, $Pd(OH)_2$, CH_3OH, rt, 5 h; 2. 1 M NaOH, CH_3OH, rt, 2 h; then 1 M HCl, Amberlyst H-15, eluted by 5 M NH_4OH, 90%.



R = CH_3 *or* Ph

Scheme 11. (a) Ac_2O, 90 °C, 7 h, CH_2Cl_2, (b) 1. 2 M HCl, gentle reflux, 2 h; 2. 5 M NaOH; then Dowex 50 × 8 eluted with 5 M NH_4OH, 75%.



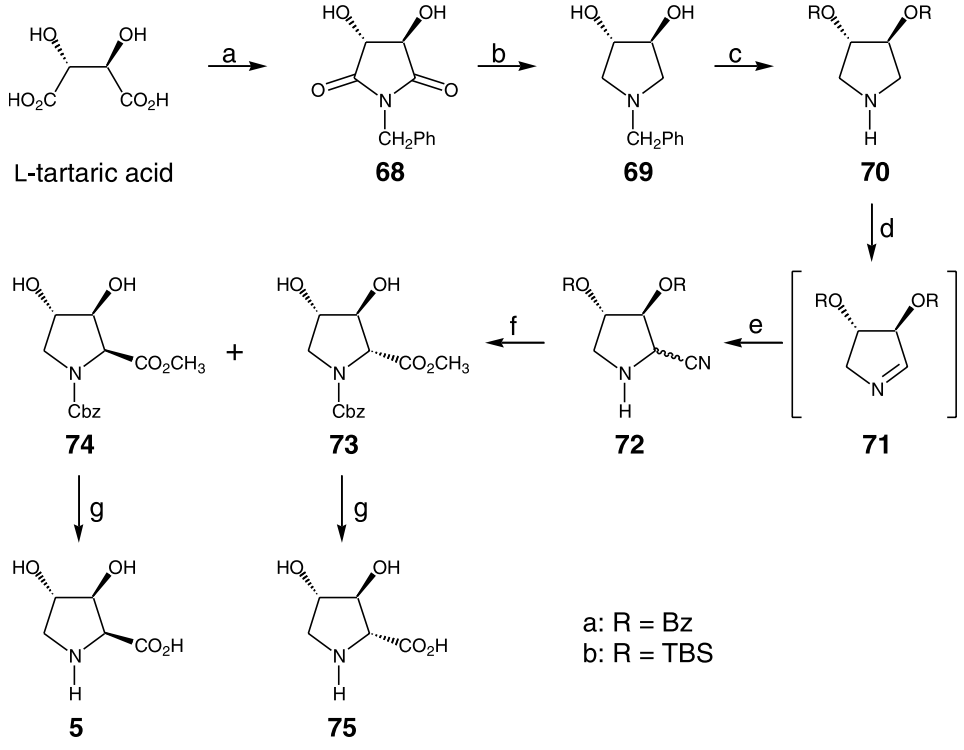
Scheme 12. (a) NBS, THF, 0 °C, 20 min (70%); (b) $Hg(OAc)_2$, THF, 0 °C, 20 h; then, NBS, 56%; (c) 1. TFA; 2. 0.5N NaOH, **5** (75%), **6** (60%).

tures it is not surprising that many syntheses of hydroxylated pyrrolidines utilize carbohydrates as starting materials. There are also strategies that employ inexpensive non-carbohydrates as starting materials. The synthesis of mono- and di-hydroxylated pyrrolidines with a carboxyl or hydroxymethyl group at position 2 of the ring is the subject of the present review. Those having carboxyl groups are named hydroxylated prolines.

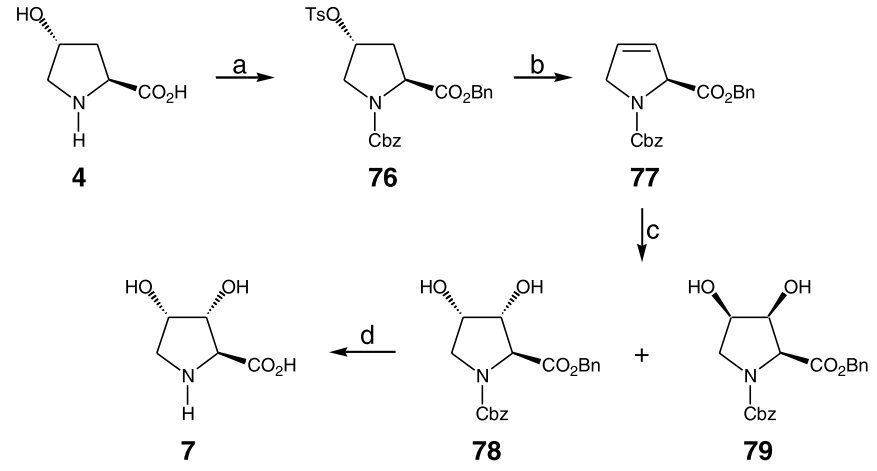
2. Natural occurrence

A number of hydroxylated prolines and 2-hydroxymethyl pyrrolidines have been isolated from natural sources[4–44] (see Fig. 1). *trans*-3-Hydroxyproline (**1**) was isolated from a dried Mediterranean sponge and from telomycin,[4–6] while its *cis* isomer (**2**) was obtained from telomycin only.[7,8] (2*S*,3*S*)-3-Hydroxyproline (**3**) was found in naturally occurring peptides, namely mucrorin-D,[9] telomycin[10] and in bovine Achilles tendon collagen.[11]

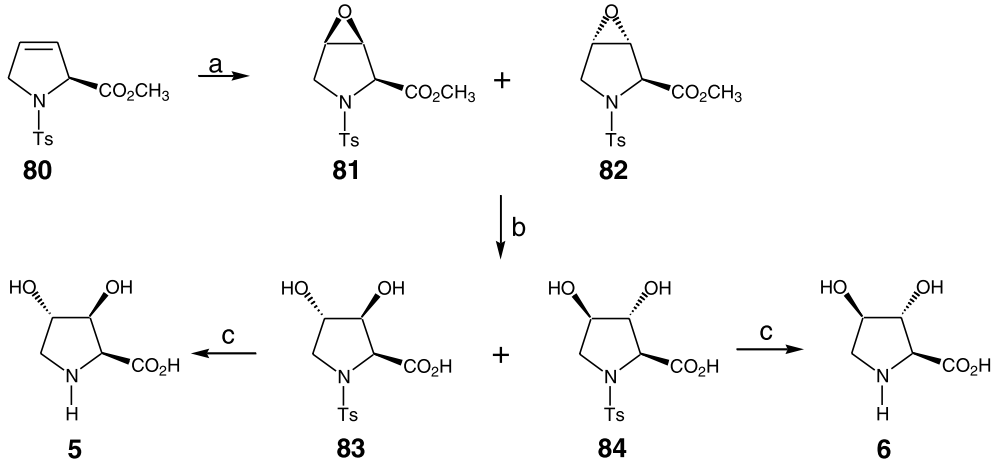
(2*S*,4*R*)-4-Hydroxyproline (**4**) was found in the oligopeptide antibiotics echinocandin B, C, and D, isolated from strains of *Aspergillus ruglosus* and *Aspergillus nidulans*. They are characterized by their high antifungal and anti-yeast activities.[12–14]



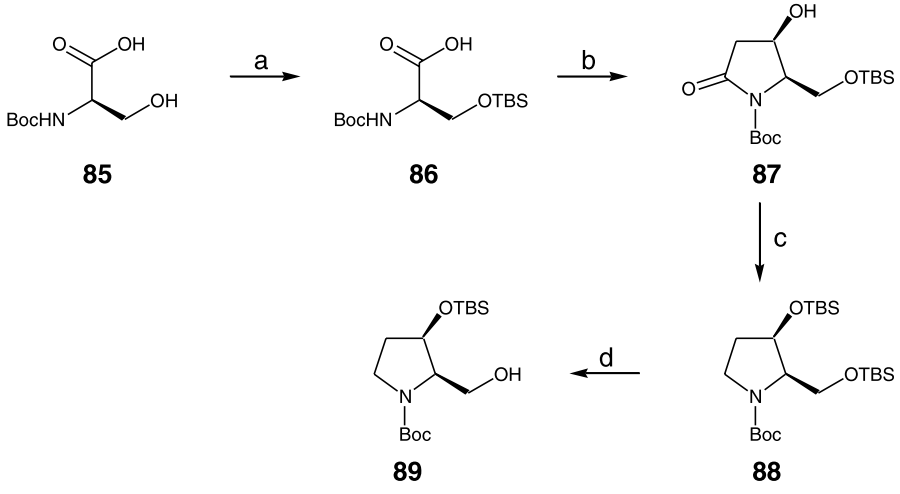
Scheme 13. (a) $BnNH_2$, xylene; (b) $LiAlH_4$, THF; (c) 1. BzCl, aqueous Na_2CO_3, CH_2Cl_2, 83%; or NaH, TBSCl, 93%; 2. H_2, $Pd(OH)_2$ on C, AcOH or CH_3OH, **70**,100%, 83%; (d) 1. NCS, Et_2O; 2. DBU, benzene; (e) $(CH_3)_3SiCN$, ZnI_2; (f) 1. 6N HCl, AcOH; 2. CH_3OH, $SOCl_2$; 3. CbzCl; 4. dioxane, aqueous $NaHCO_3$; (g) 1. 1N NaOH, CH_3OH; 2. Amberlite 200C; 3. H_2, 10% Pd on C, 50% aqueous AcOH.



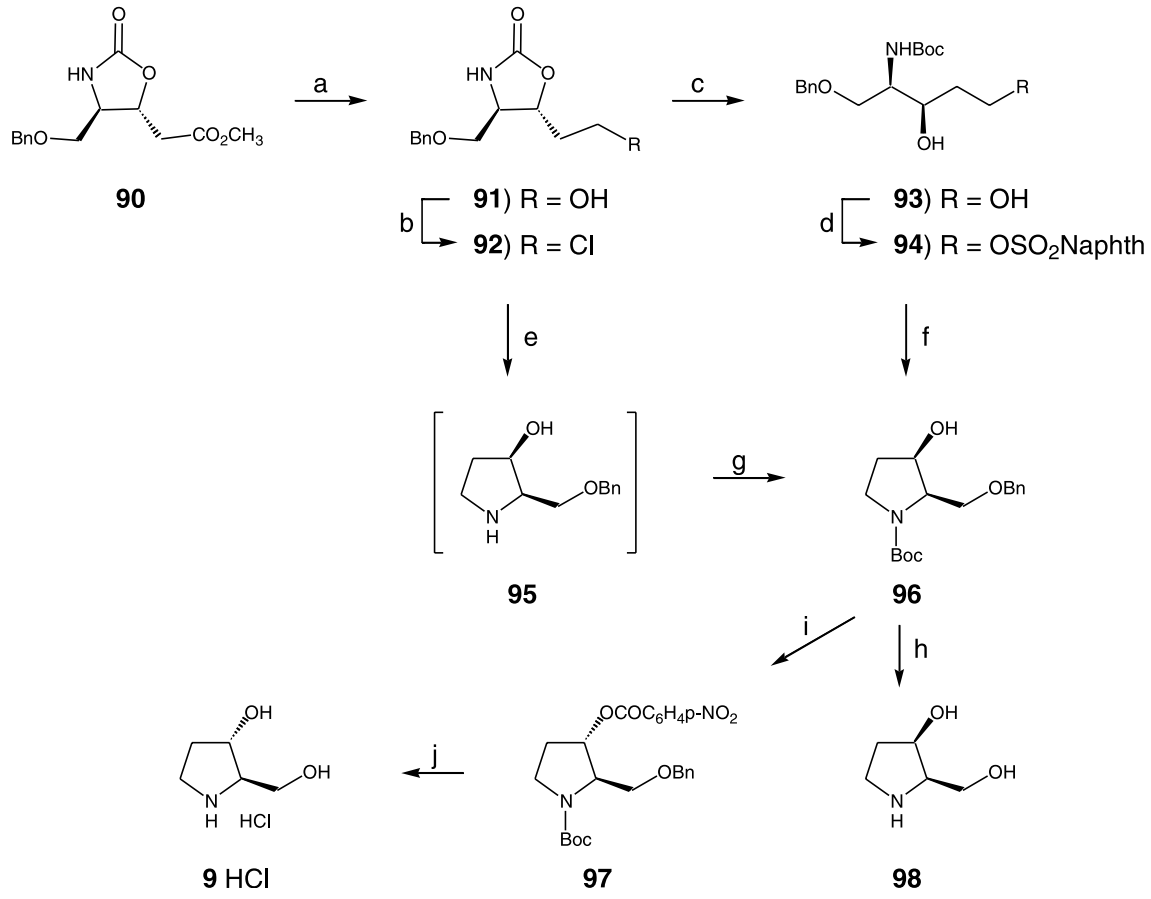
Scheme 14. (a) 1. CbzCl, $NaHCO_3$; 2. BnBr, NaI, K_2CO_3; 3. Ts-3-CH_3-Im$^+$TfO$^-$, 60%; (b) 1. PhSeSePh, $NaBH_4$; 2. H_2O_2, Py, 58%; (c) OsO_4, NMO, 79%; (d) H_2, 10% Pd on C, 92%.



Scheme 15. (a) TFAA, CH_2Cl_2, H_2O_2, 92%; (b) 1. 2.5 M H_2SO_4, acetone, 8 h; 2. 1 M NaOH; 3. 1 M HCl; (c) Na, naphthalene, NH_3.



Scheme 16. (a) 1. TBSCl, DMF, imidazole, rt, 24 h; 2. CH_3OH, THF, 1 M K_2CO_3, rt, 6 h, 87% for two steps; (b) 1. isopropenyl chloroformate, DMAP, Meldrum's acid, CH_2Cl_2, 0 °C, 2 h; 2. EtOAc, reflux, 0.5 h; 3. $NaBH_4$, AcOH, CH_2Cl_2, 0 °C, 4 h, 41% for three steps; (c) 1. TBSCl, DMF, imidazole, rt, 5 h; 99%; 2. $BH_3 \cdot S(CH_3)_2$, THF, reflux, 70 °C, 3 h, 74%; (d) AcOH, THF, H_2O, 0 °C, 8 h, 93%.



Scheme 17. (a) $NaBH_4$, THF, −10 °C, 30 min; then CH_3OH, rt, overnight, 88%; (b) CCl_4, CH_2Cl_2, K_2CO_3, Ph_3P, 50 °C, overnight, 93%; (c) 1. $Ba(OH)_2$, EtOH, H_2O, reflux, overnight; then Amberlyst IR 120, eluted by 30% NH_4OH; 2. Boc_2O, Et_3N, THF, rt, overnight, 68%; (d) β-naphthalen-2-sulfonyl chloride, Py, −10 °C, 3 h, 67%; (e) CH_3OH, H_2O, NaOH, 80 °C, 16 h; (f) NaH, THF, rt, 3 h, 86%; (g) Boc_2O, Et_3N, THF, 16 h, 65%; (h) 1. TBSCl, imidazole, DMAP, THF, rt, 24 h, 76%; 2. H_2, 10% Pd on C, EtOH, rt, 16 h, 83%; 3. TEMPO, NaBr, NaOCl, $NaHCO_3$, toluene, EtOAc, H_2O; 4. *t*-BuOH, NaH_2PO_4, $KMnO_4$, Na_2SO_3; 5. HCl, CH_3OH, 0 °C to rt, 2 h, Dowex 50 × 8, 200–400 mesh, eluted by 1.5 M NH_3, 63%; (i) Ph_3P, *p*-nitrobenzoic acid, benzene, diethylazodicarboxylate, rt, 6 h, 90%; (j) 1. NaOH, CH_3OH, rt, overnight, 90%; 2. H_2, 10% Pd on C, EtOH, rt, 18 h, 98%; 3. 3 M HCl, EtOAc, rt, 30 min, 91%.

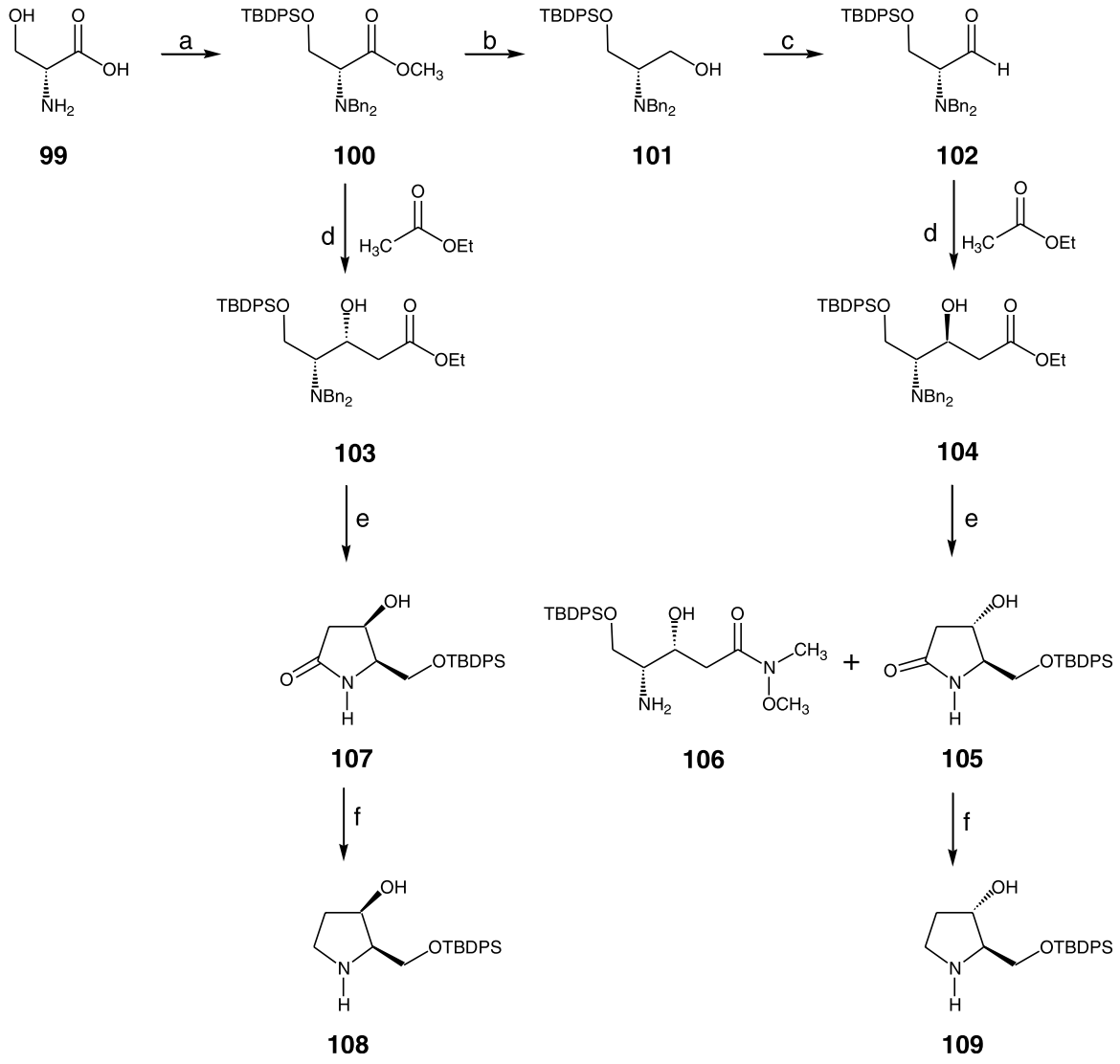
The (2*S*,3*S*,4*S*)- (**5**) and (2*S*,3*R*,4*R*)-3,4-dihydroxyprolines (**6**) have been isolated from diatom cell walls[15] and *Amanita vitosa* mushrooms.[16,17] It is believed that dihydroxyprolines act in plants as defense agents against predators and parasites.[18] (2*S*,3*R*,4*S*)-3,4-Dihydroxyproline (**7**) was isolated from animal adhesive protein (Mefp 1) found in the mussel *Mytilus edulis*.[19–21] (2*R*,3*S*,4*R*)-3,4-Dihydroxyproline (**8**) was also isolated from natural sources.[22,23]

(2*R*,3*S*)-2-Hydroxymethyl-3-hydroxypyrrolidine (**9**) (L-*trans*-3-hydroxyprolinol or CYB3) was isolated from the legume *Castanospermum australe*; and it has no significant biological activity.[24]

1,4-Dideoxy-1,4-imino-D-arabinitol (**10**) (DAB1) has been found in both *Arachniodes standishii*[25,26] and *Angylocalyx boutiqueanus*[27] and is a potent inhibitor of yeast α-glucosidase (50% inhibition at 1.8×10^{-7} M)[28,29] and different mouse gut disaccharidases to various degrees.[30] DAB1 (**10**) inhibits the hydrolysis of sinigrin and progoitrin by thioglucosidases from mustard and the cabbage aphid *Brevicoryne brassicae*.[31] It also inhibits phloem unloading and/or utilization of sucrose, resulting in insufficient sucrose transport from cotyledons to roots and hypocotyls.[32] The mechanism of insect antifeedant activity of DAB1 (**10**) has been studied[33] and it may be carcinogenic to rodents.[34] The enantiomer LAB1 (**11**) occurs as a component of bacterial lipopolysaccharides[35,36] but shows a weaker inhibition of α-glucosidase (50% inhibition at 1.0×10^{-5} M)[37,38] and exhibits several other biological activities.[39–42] 1,4-Dideoxy-1,4-imino-D-ribitol (**12**) has been isolated from *Morus* spp.[43,44]

3. Synthetic approaches

Various methods for the synthesis of hydroxyprolines and pyrrolidines have been reported from



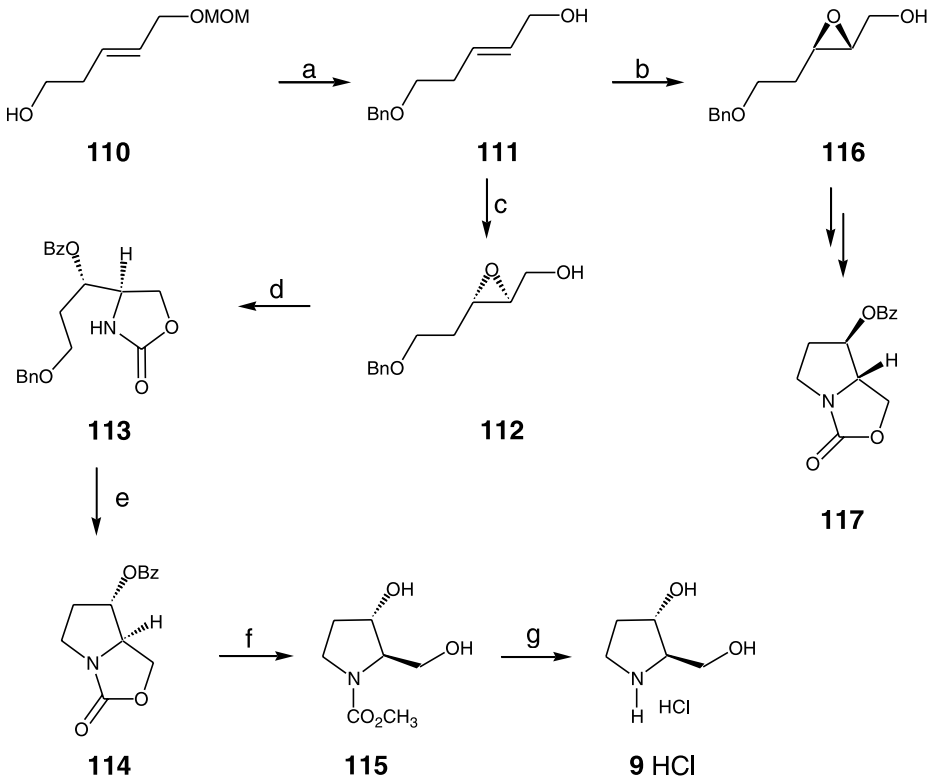
Scheme 18. (a) 1. CH_3COCl, CH_3OH, reflux, 3 h, 98%; 2. K_2CO_3, BnBr, CH_3CN, rt, 24 h, 95%; 3. TBDPSCl, imidazole, DMF, rt, 18 h, 100%; (b) DIBAL-H, toluene, −78 °C, 30 min, 93% or $LiBH_4$, Et_2O–CH_3OH (60:1), 0 °C to reflux, 4 h, 95%; (c) $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C, 1 h, Et_3N, 100%; (d) LiHMDS, THF, −78 °C to 0 °C, 3–4 h, (e) 1. $(CH_3O)NHCH_3$-HCl, $(CH_3)_3Al$, THF, 0 °C to 35 °C, 3 h, 98%; 2. H_2, $Pd(OH)_2$ on C, CH_3OH, rt, 12 h; (f) BH_3–THF, THF, 0 °C to reflux, 24 h, 85%.

carbohydrates[45–59] and from non-carbohydrates. This mini review includes mainly selected methods for those synthesized from non-carbohydrate precursors. They are subdivided according to the substituent on position 2 (carboxyl or hydroxymethyl) and the number of hydroxyl group on the ring.

3.1. Synthesis of 3-hydroxyproline

Bakers' yeast reduction of the β-oxo proline derivative **14** has been used to synthesize the (+)-*cis*-(2*R*,3*S*)-3-hydroxyproline (**16**)[60] (Scheme 1). The acyclic ester **13** was treated with *t*-BuOK in toluene to produce the 1,2-dicarboxylate **14** (45%), which underwent reduction of Bakers' yeast to give the 3-hydroxyproline derivative **15** in 75% yield as a single diastereoisomer. Removal of the protecting groups from **15** led to **16** in 70% yield.

Stereoselective synthesis of *cis*-(2*R*,3*S*)-3-hydroxyproline (**16**) from *N*-benzyloxycarbonyl-*O*-*tert*-butyldimethylsilyl-L-serinal (**17**) has been reported[61] (Scheme 2). Addition of allyltrimethylsilane to the aldehyde **17** in the presence of $SnCl_4$ afforded the *syn*-adduct **18** in 60% yield. Protection of the hydroxyl group with triisopropylsilyl (TIPS) triflate, followed by *cis*-hydroxylation and subsequent oxidative cleavage by periodate afforded the aldehyde **19** in 81% yield. Treatment of **19** with $NaBH_3CN$, followed by selective deprotection of the primary hydroxyl group furnished the pyrrolidine derivative **20** (91%), which was subjected to two-step oxidation with $NaIO_4$ and $RuCl_3$ followed by removal of the protecting groups to give **16** in 86% yield.



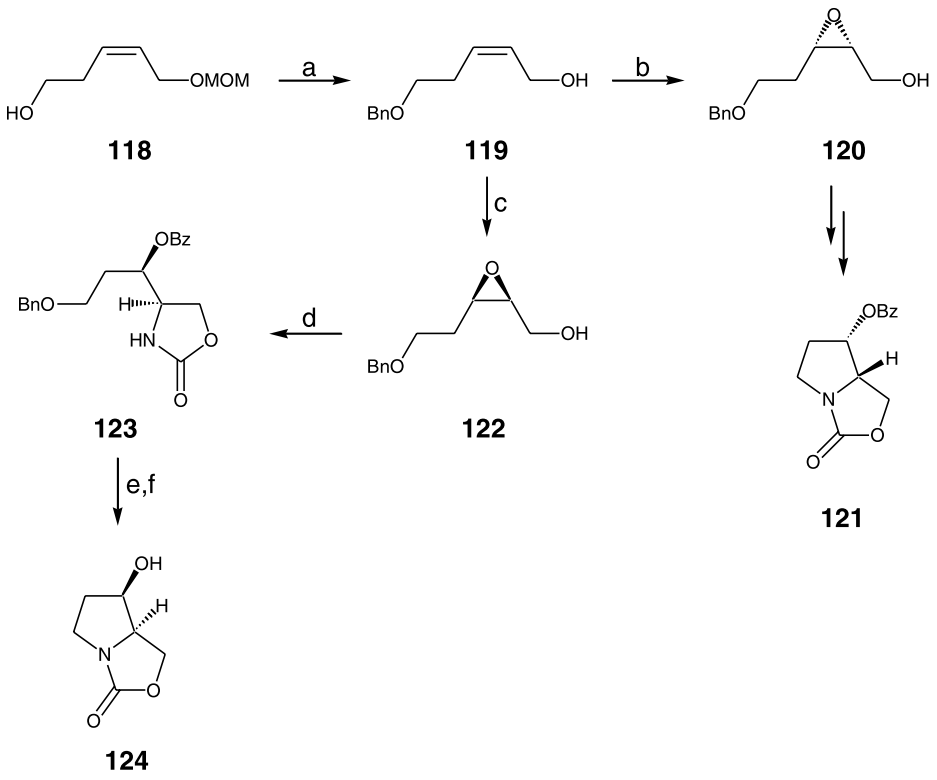
Scheme 19. (a) 1. BnBr, NaH; 2. conc HCl, CH_3OH, 84% for two steps; (b) 1. Ti(*i*-PrO)$_4$, *t*-BuO_2H; 2. *d*-DIPT, 4 Å MS, 80%; (c) 1. Ti(*i*-PrO)$_4$, *t*-BuO_2H; 2. *l*-DIPT, 4 Å MS, 72%; (d) 1. O=C=NCOPh, 100%; 2. K_2CO_3, $(C_8H_{17})_3NCH_3Cl$; K_2CO_3, CH_3OH, 96%; (e) 1. H_2, $PdCl_2$; 2. MsCl, Py; (f) NaH, THF; (g) 20% HCl, 93%.

A stereocontrolled synthesis of (2*R*,3*R*)-3-hydroxyproline (**1**) has been achieved from methyl 5,5-dimethoxy-3-oxopentanoate (**21**, Scheme 3).[62] Hydrogenation of **21** under mild conditions gave the β-hydroxy ester **22**, which underwent diastereoselective amination with dibenzylazodicarboxylate as electrophilic reagent to produce the *anti* diastereomer **23**. This was silylated, followed by removal of the benzyl carbamate group by hydrogenation, to produce amine **24** which was cyclized to the proline using TFA followed by hydrogenation to give the trifluoroacetic salt of methyl *trans*-hydroxyprolinate (**25**). Saponification of the methyl ester in **25** with KOH, followed by purification with Dowex afforded (2*R*,3*R*)-*trans*-3-hydroxyproline (**1**).

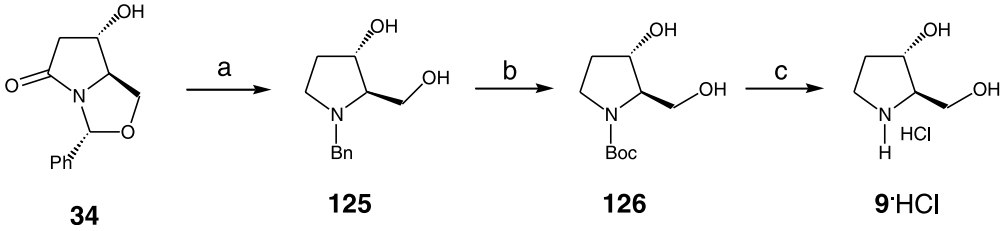
A stereoselective synthesis of (−)-(2*S*,3*S*)-3-hydroxyproline **3** has been achieved from L-malic acid by conversion[63] into ethyl (2*R*)-2-hydroxy-4-iodobutanoate (**26**, Scheme 4).[64] Cyclization of **26** using allyamine gave the lactone **27**, which was silylated to give **28**. Reductive cyanation of **28** afforded the nitrile **29**, which underwent hydrolysis and hydroxyl group deprotection with HCl in methanol to give the ester **30**. This was hydrogenated to produce **31**, which underwent saponification to afford (−)-(2*S*,3*S*)-3-hydroxyproline (**3**).

trans-(2*S*,3*S*)-3-Hydroxyproline (**3**) has been synthesized[65] (Scheme 5) by stereoselective epoxidation of the pyroglutamic acid derivative **32** using *t*-BuOOH to give **33** which underwent regioselective ring-opening to give **34** whose subsequent hydroxyl group protection with TBS gave **35**. Reduction of the amide group of **35** resulted in a concomitant transformation of the acetal moiety to give the *N*-benzyl derivative **36**. Replacement of the benzyl group by a Boc group followed by oxidation gave the *N*-Boc proline derivative **37**. Removal of the protecting group from **37** furnished the enantiopure *trans*-(2*S*,3*S*)-3-hydroxyproline (**3**).

trans-4-Hydroxy-L-proline (**4**) has been used as a starting material for the synthesis of both *cis*- (**2**) and *trans*-3-hydroxyproline (**1**)[66] (Scheme 6). Thus, it was converted via three-step sequence into the pyrrolidinol derivative **38**, which underwent electrochemical methoxylation using anodic oxidation in methanol to afford a mixture of compounds **39** and **40**. Substitution of the 2-methoxy group by a cyano group, via an iminium ion intermediate, was shown to occur predominantly in *cis* fashion when a *tert*-butyldimethylsilyl substituent was at the OH group on C-3. On the other hand, when the protecting group was acetyl, an almost equal ratio of both isomers was formed. Hydrolysis of the resulting cyano compounds **41** and **42** gave the *cis*- and *trans*-(3*R*)-3-hydroxyprolines **2** and **1**, respectively.



Scheme 20. (a) 1. BnBr, NaH; 2. conc. HCl, CH_3OH, 70% for two steps; (b) 1. Ti(*i*-PrO)$_4$, *t*-BuO_2H; 2. *d*-DIPT, 4 Å MS; (c) 1. Ti(*i*-PrO)$_4$, *t*-BuO_2H; 2. *l*-DIPT, 4 Å MS; (d) 1. O=C=NCOPh, 100%; 2. K_2CO_3, $(C_8H_{17})_3NCH_3Cl$, 88%; (e) 1. H_2, $PdCl_2$; 2. MsCl, Py; 3. NaH, THF, 73% for three steps; (f) aqueous K_2CO_3, 91%.



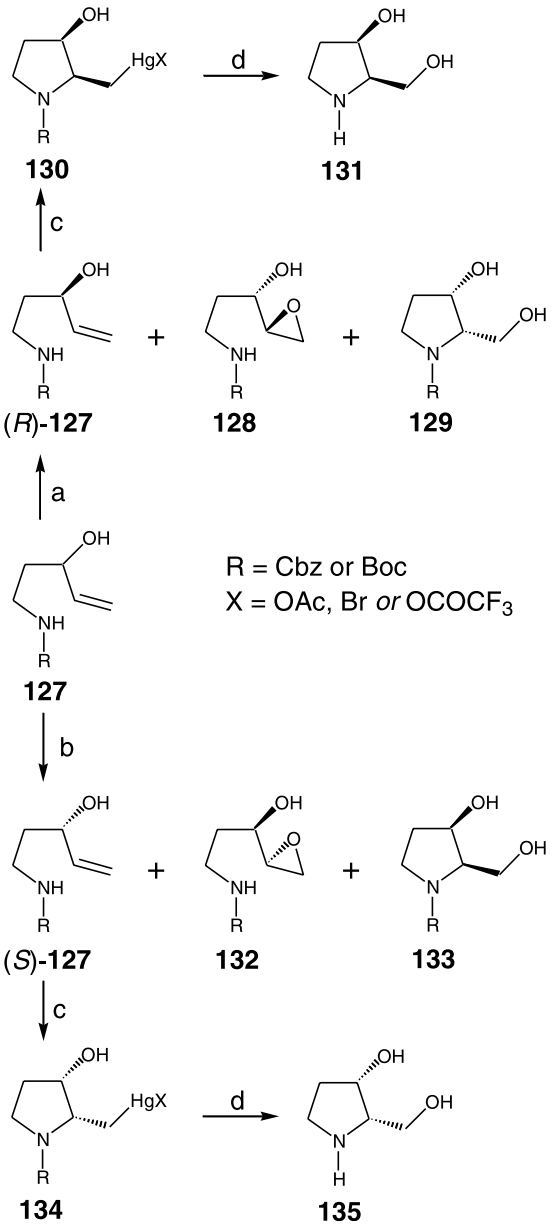
Scheme 21. (a) BMS, THF, 70 °C; (b) H_2, Pd on C, Boc_2O, CH_3OH; (c) 5 M HCl.

3.2. Synthesis of 4-hydroxyproline

(2*S*,4*R*)-4-Hydroxyproline (**4**) has been synthesized[67] from the chiral allylglycine derivative **43** (Scheme 7). Bromolactonization of the latter with *N*-bromosuccinimide afforded the *cis*-butyrolactone **44** in 73% yield together with its *trans* isomer in 9% yield. The major isomer was converted into its epimer **46** via the epoxide **45** in 74% overall yield. Swern oxidation of **46** followed by methanolysis furnished the pyrrolidine **47** (58%), which was subjected to acid hydrolysis followed by sodium cyanoborohydride reduction and subsequent removal of the protecting groups to give **4**.

Another efficient synthesis of (2*S*,4*R*)-4-hydroxyproline (**4**), using (*S*)-*O*-benzylglycidol (**48**), has been reported[68] (Scheme 8). Reaction of acetylene with the epoxide **48** followed by reduction of the resulting pentynol derivative and subsequent Mitsunobu reaction with phthalimide furnished alkene **49**. This was reacted with hydrazine followed by benzoylation to afford **50**, which underwent intramolecular cyclization in the presence of iodine to furnish the 2-prolinol 4-benzoate **51**. Protection of the secondary amine in **51** with a Boc group followed by debenzylation, oxidation, and further deprotection furnished **4** in 25% overall yield from **48**.

An enantioselective three-step synthesis of **4** in 67.5% overall yield starting from lactam **52** has been reported[69] (Scheme 9). Diastereoselective introduction of an allyl group into **52** using allyl bromide afforded the lactam **53**, which underwent cyclization with iodine via intermediate **54** to furnish the bicyclo derivative **55**. Finally, acidic hydrolysis of **55** in a sealed tube led to (2*S*,4*R*)-4-hydroxyproline (**4**).



Scheme 22. (a) L-(+)-DIPT, TBHP, Ti(O-*i*-Pr)$_4$, MS 3 Å, CH_2Cl_2, −20 °C, 15 days, *R*-**127** (36%), **128** (5%), **129** (33%); (b) D-(−)-DIPT, TBHP, Ti(O-*i*-Pr)$_4$, MS 4 Å, *S*-**127** (46%), **132** (11%), **133** (33%); (c) 1. $Hg(OAc)_2$; 2. KBr, $NaHCO_3$, 88–90%; d) O_2, $NaBH_4$, DMF, 64–66%.

Enantioselective syntheses of (−)- and (+)-*cis*-4-hydroxyprolines from chiral synthons **56** and its epimer have been reported[70] (Scheme 10). Complete 1,4-*trans* alkylation of **56** gave **57**, which was treated with sodium hydroxide followed by methyl iodide to produce the ester **58**. Intramolecular cyclization of **58** using iodine gave the proline derivative **59** in 80% yield. Complete deprotection of **59** gave (−)-*cis*-4-hydroxyprolines **60**. Similarly, the epimer of chiral **56** was converted into (+)-*cis*-4-hydroxyprolines.

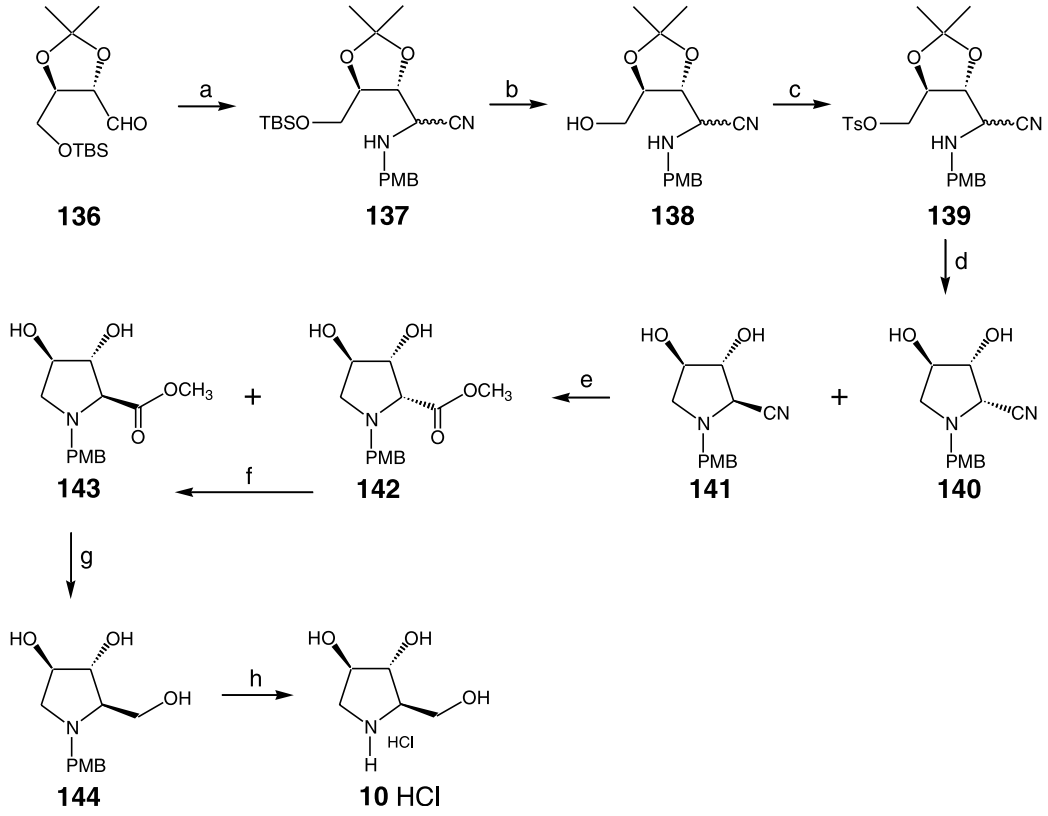
Synthesis of *cis*-4-hydroxyproline (**63**) from the *trans*-4-hydroxyproline derivatives **61** has been reported[71] (Scheme 11). Hydroxyprolines **61** were treated with acetic anhydride to give *N*-acetyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one or *N*-benzoyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one **62**, which were heated in 2 M HCl to afford *cis*-4-hydroxyproline (**63**) in 75% yield.

3.3. Synthesis of 3,4-dihydroxyproline

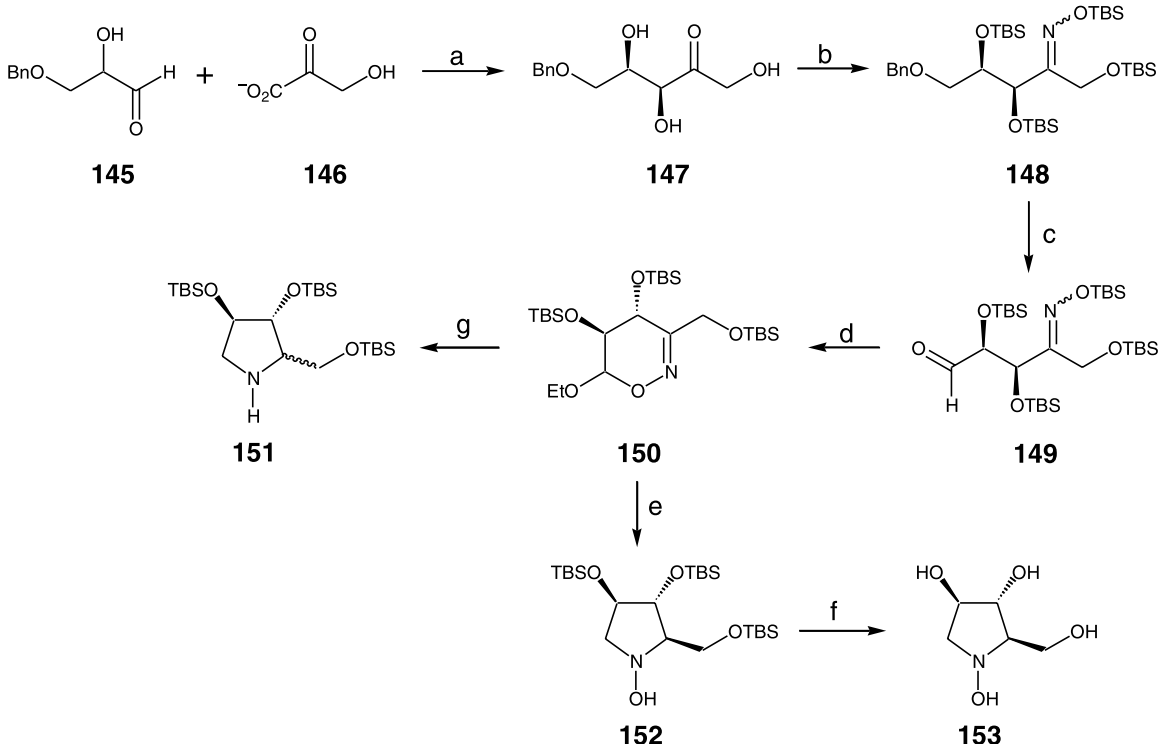
Stereoselective synthesis of (2*S*,3*R*,4*R*)-(**6**) and (2*S*,3*S*,4*S*)-3,4-dihydroxyprolines (**5**) from the isomeric β-hydroxyallylglycines **64** and **65** has been reported[22] (Scheme 12). Halolactonization of the isomer **64** with *N*-bromosuccinimide yielded the (2*S*,3*R*,4*R*)-bromolactone **66** in 70% yield as the sole product. Bromolactone **66** was treated with trifluoroacetic acid to remove the N-protecting group, and subsequent hydrolysis with NaOH provided **6** in 60% yield. On the other hand treatment of the isomer **65** with N-bromosuccinimide gave a poor yield (10%) of **67**. However, mercurilactonization of **65** gave **67** in 56% yield, which was transformed in the same manner as before to **5** in 75% yield.

(2*S*,3S,4*S*)-3,4-Dihydroxyproline (**5**) and its (2*R*,3*S*,4*S*) isomer (**75**) have been synthesized from L-tartaric acid[72] (Scheme 13) by conversion into (3*S*,4*S*)-1-benzyl-3,4-dihydroxypyrrolidine (**69**) in 42% yield via (3*R*,4*R*)-1-benzyl-3,4-dihydroxy-2,5-dioxopyrrolidine (**68**). Protection of the hydroxyl group in **69** as the benzoyl ester or *tert*-butyldimethylsilyl ether, followed by hydrogenation over palladium hydroxide afforded **70**. Treatment of **70** with *N*-chlorosuccinimide followed by dehydrochlorination with DBU in benzene afforded the corresponding cyclic Schiff base **71**, which without isolation was reacted with cyanotrimethylsilane in the presence of ZnI_2 to give **72**. Heating of **72a** in AcOH–6N HCl and subsequent esterification followed by *N*-benzyloxycarbonylation of the resulting epimeric mixture of amino acids gave a mixture of epimers **73** (26%) and **74** (17%). On the other hand, **72b** was converted into **73** and **74** in 42 and 28% yields, respectively. Compounds **73** and **74** were deprotected and hydrolyzed to give (quantitatively) **75** and **5**, respectively.

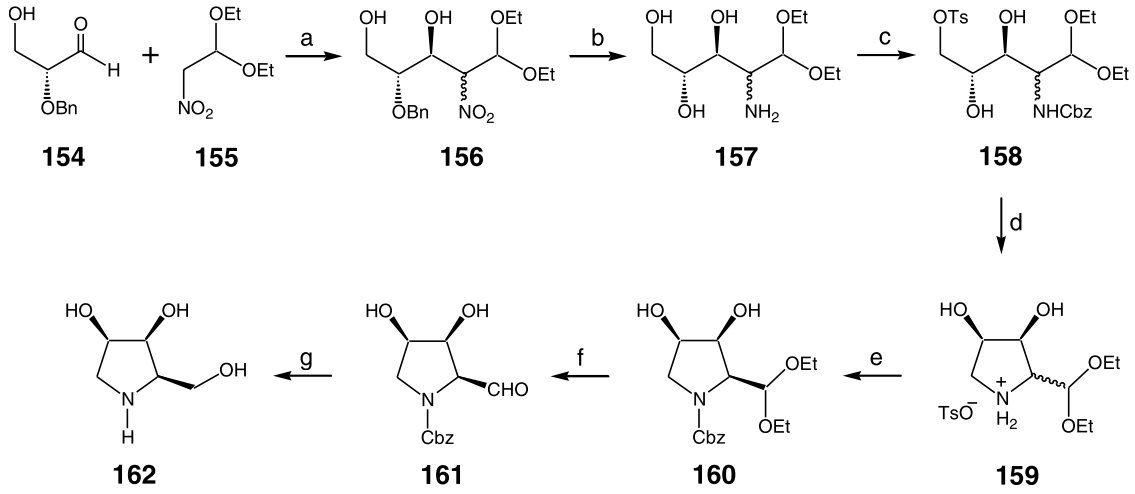
trans-4-Hydroxy-L-proline (**4**) can be converted into (2*S*,3*R*,4*S*)-3,4-dihydroxyproline (**7**)[73,74] (Scheme 14). Thus, its N-protection with CbzCl followed by esterification with BnBr and then tosylation of the C-4 hydroxyl group with the triflate of 1-methyl-3-tosylimidazole afforded **76**. This was treated with PhSeSePh followed by H_2O_2 to give 3,4-dehydroproline **77** (58%), which was dihydroxylated with osmium tetraoxide in the presence of NMO to give predominantly **78** along with **79**, by addition to the face opposite the ester group. Debenzylation of **78** gave 3,4-dihydroxyproline (**7**).



Scheme 23. (a) *p*-$(CH_3O)C_6H_4CH_2NH_2$, $(EtO)_2P(O)CN$, THF, 86.7%; (b) TBAF, THF, quantitative; (c) *p*-TsCl, Py, 84%; (d) TFA, H_2O, THF, 5:1:1, 70–75 °C; (e) $NaOCH_3$, CH_3OH; then 2M HCl, 87%; (f) $NaOCH_3$, CH_3OH, 65–70 °C, 2 h; then 2M HCl, 78%; (g) $NaBH_4$, EtOH, 89%; (h) 1. H_2, 20%, $Pd(OH)_2$ on C, HCO_2H, EtOH; 2. conc HCl, 94%.



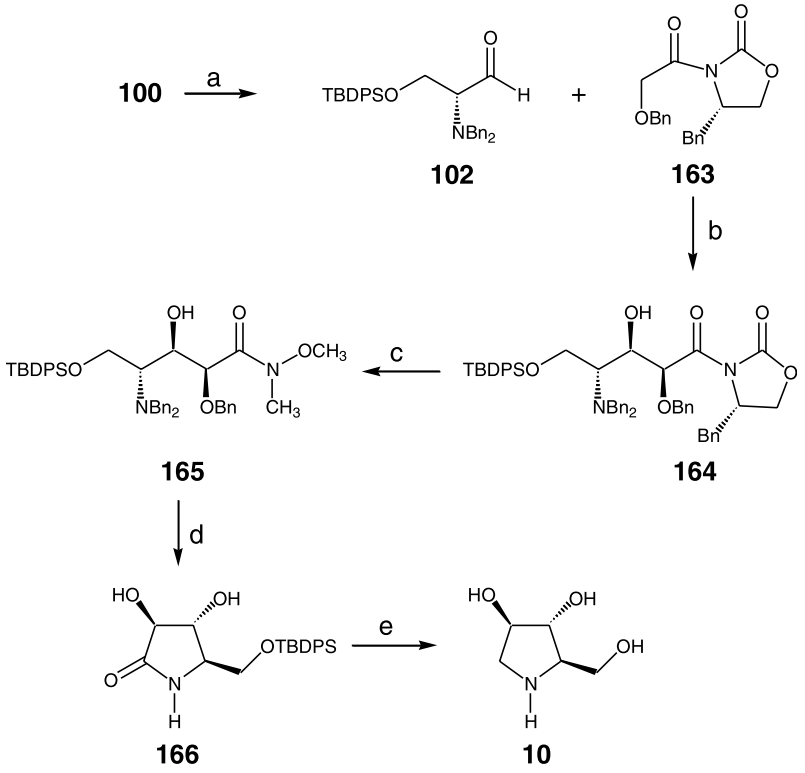
Scheme 24. (a) Transketolase, TPP, Mg^{2+}, pH 7, 80%; (b) 1. TBSOTf, Et_3N, 83%; 2. NH_2OH–HCl, $KHCO_3$, 71%; 3. TBSOTf, Et_3N, 95%; (c) 1. H_2, 10% Pd on C, near-quantitative; 2. NaOCl, TEMPO, 66% or Swern oxidation, 40–60%; (d) $(EtO)_3CH$, *p*-TsOH, EtOH; (e) $NaCNBH_3$, acetic acid, 37%; (f) aqueous HF, (1:1) THF–CH_3CN, quantitative; (g) H_2, 10% Pd on C, EtOH, 59% yield.



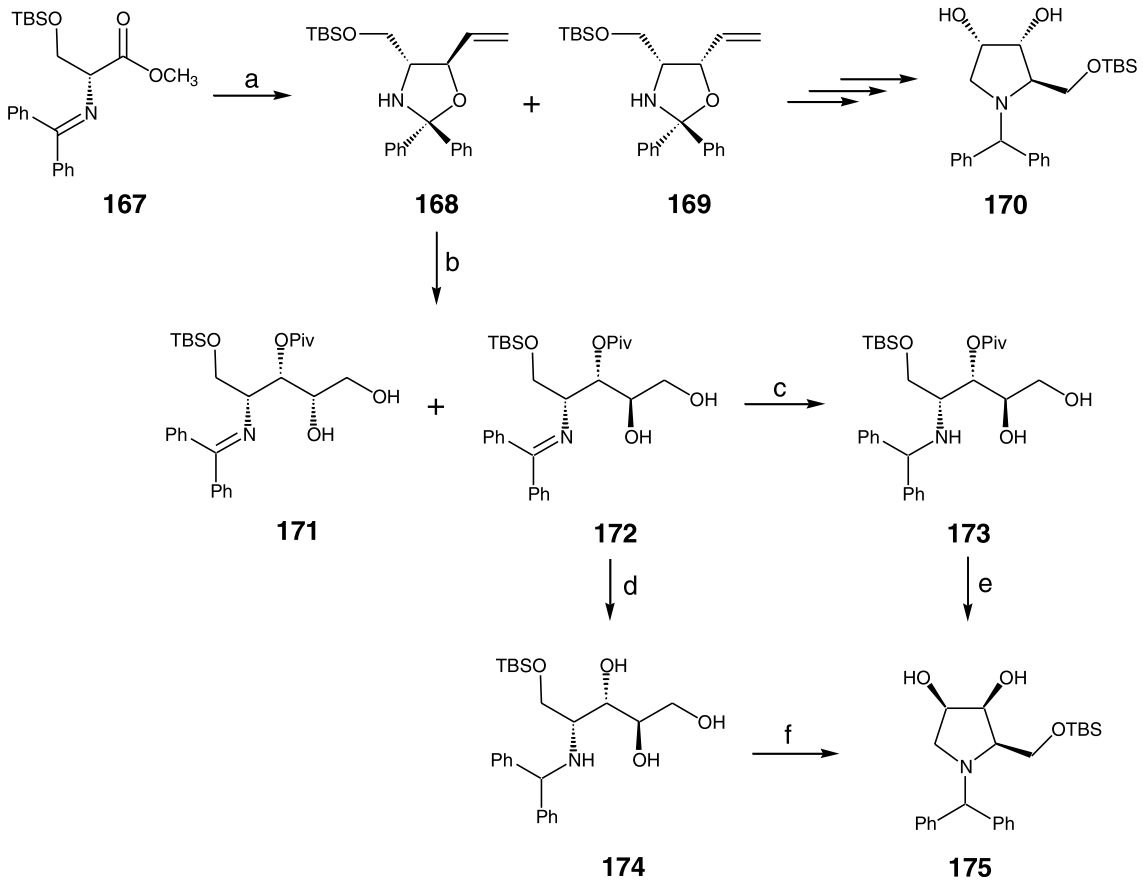
Scheme 25. (a) Bu_4NF-3H_2O, THF, −78 to −5 °C, 17 h, 89–92%, *arabino*/*ribo* 22:3; (b) H_2, Pd on C, CH_3OH, 25 °C, 24 h, 100%; (c) CbzCl, H_2O, $NaHCO_3$, 25 °C, 20 h, 60%; (d) *p*-TsCl, Py, ether, 25 °C, 3 days, 70%; 3. H_2, 10% Pd on C, CH_3OH, 25 °C, 18 h, 88%; (e) CbzCl, $NaHCO_3$, H_2O, 25 °C, 22 h, 70–75%; (f) 0.1N HCl, THF, 25 °C, 13 h, DC-kontrolle; (g) 1. $NaBH_4$, EtOH, 25 °C, 6 h, 87%; 2. H_2, 10% Pd on C, 99%.

On the other hand, the *N*-tosyl-3,4-dehydro-L-proline methyl ester (**80**)[17] has been converted into 2,3-*trans*-3,4-*trans*-3,4-dihydroxy-L-proline (**6**) and its 2,3-*cis* diastereoisomer (**5**) (Scheme 15) via a *trans* dihydroxylation process. Thus epoxidation of **80** with TFAA and H_2O_2 gave the 3,4-epoxy esters **81** and **82**, which were converted without separation into *N*-tosyl-3,4-dihydroxy-L-prolines **83** and **84**. Separation and removal of the tosyl protecting group then afforded **5** and **6**, respectively.

Enantioselective synthesis of pyrrolidine derivative **89** has been achieved starting with D-serine as a source of



Scheme 26. (a) 1. DIBAL-H, toluene, −78 °C, 30 min, 93%; 2. $(COCl)_2$, Me_2SO, CH_2Cl_2, −78 °C, 1 h; then Et_3N, 100%; (b) Et_3N, *n*-Bu_2BOTf, CH_2Cl_2, −78 °C to 0 °C, 3 h, 82%; (c) $(CH_3O)NHCH_3$–HCl, $(CH_3)_3Al$, THF, −30 °C to 0 °C, 2 h, 100%; (d) $Pd(OH)_2$, H_2 (1 atm), CH_3OH, 72 h, 71%; (e) 1. BH_3–THF, THF, reflux, 18 h, 100%; 2. 48% aqueous HF, CH_3CN, rt, 15 min; then $CH_3OSi(CH_3)_3$; Dowex OH^-, 100%.



Scheme 27. (a) 1. *i*-Bu_5Al_2H; 2. $H_2C{=}CHMgBr$, THF, −78 °C to rt; 3. $NaHCO_3$ workup, **168**:**169** (1.7:1); (b) 1. $(CH_3)_3CCOCl$, Py, DMAP; 2. $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, *t*-BuOH, H_2O, K_2CO_3, $NaHCO_3$, **171**:**172** (1:10); (c) $NaCNBH_3$, AcOH, CH_3CN, 4 Å MS; (d) $LiBH_4$, THF, reflux; (e) 1. Ph_3P, CCl_4, Et_3N, DMF; 2. $NaOCH_3$, CH_3OH; (f) Ph_3P, CCl_4, Et_3N, DMF.

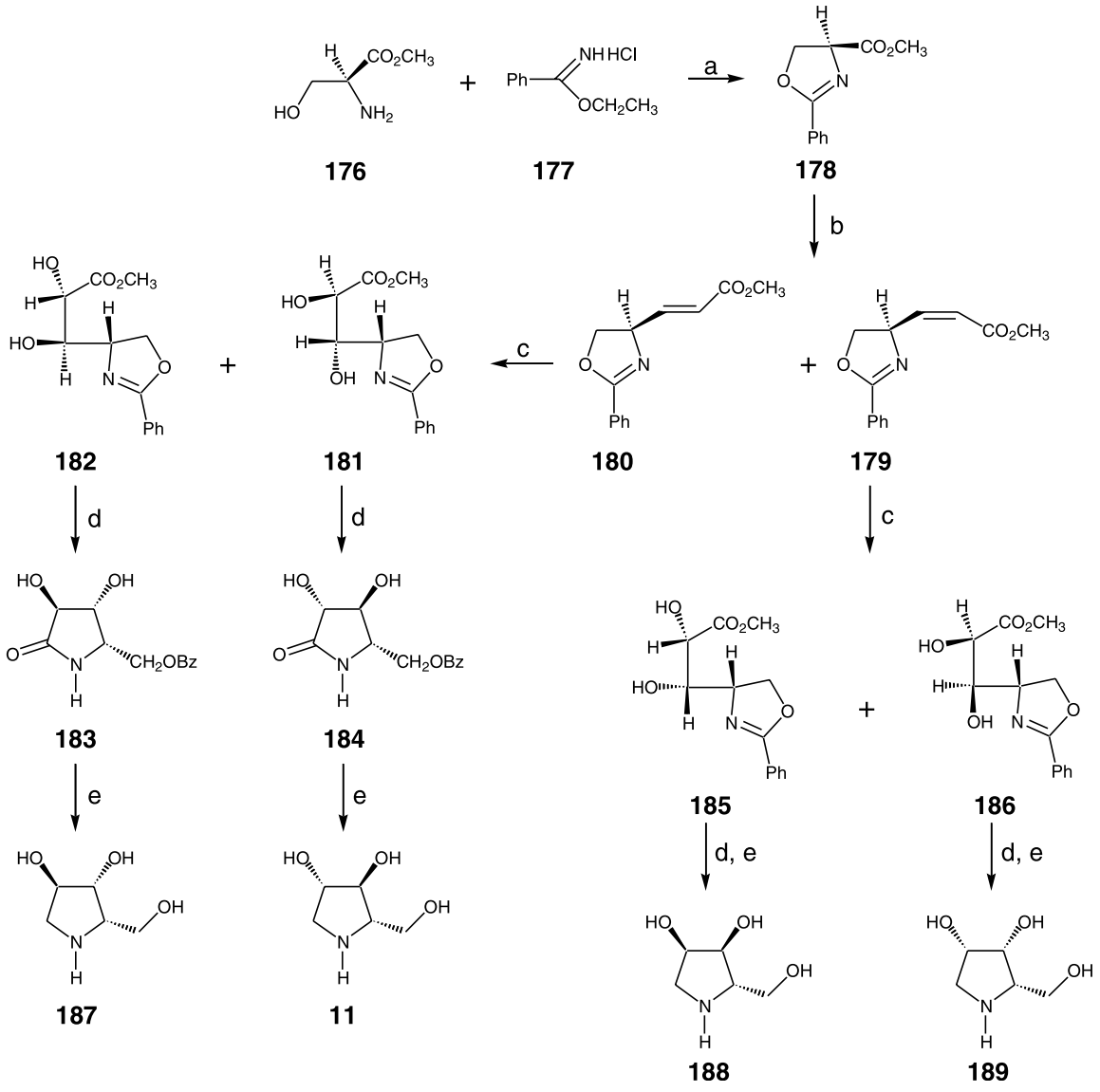
chirality[75] (Scheme 16). The D-serine derivative **85** was silylated to give **86**, which could be transformed into the pyrrolidinone **87** in 41% yield. The secondary hydroxyl group of **87** was protected, followed by treatment with borane–dimethyl sulfide complex, to give **88** in 74% yield. Regioselective cleavage of the silyl group on the primary hydroxyl group afforded **89**.

Syntheses of *cis*-3-hydroxyproline **98** and *trans*-3-hydroxyproline **9** have been achieved[76] from ester **90** (Scheme 17). Reduction of the ester **90** gave the alcohol **91** whose chloride **92** was cyclized to give the intermediate **95**, which was then converted into the *N*-Boc derivative **96**. Alternatively, the oxazolidin-2-one **91** was treated with $Ba(OH)_2$ to cleave the cyclic ring, and then converted into the *N*-Boc amino alcohol **93** in 68%, followed by treatment with NaH to give the pyrrolidine **96**. The corresponding *tert*-butyldimethylsilyl ether was debenzylated by catalytic hydrogenolysis and converted into (2*S*,3*R*)-3-hydroxyproline (**98**). (2*R*,3*S*)-2-Hydroxymethyl-3-hydroxypyrrolidine (**9**) was obtained from **96** by using a Mitsunobu reaction to produce *p*-nitrobenzoate **97** in 90% yield, followed by conversion into the *trans*-3-hydroxypyrrolidine **9**.

3.4. Synthesis of 2-hydroxymethyl-3-hydroxypyrrolidine

The synthesis of (2*R*,3*S*)-2-*tert*-butyldiphenylsilyloxymethylpyrrolidin-3-ol (**109**) and its *C*-3 epimer (**108**) were achieved in nine and eight steps, respectively, from D-serine[77] (Scheme 18). The aldehyde **102** was obtained from D-serine (**99**) in five steps via intermediates **100** and **101**. Condensation of **100** and **102** with ethyl acetate in the presence of LiHMDS gave the esters **103** and **104**, respectively. Their intramolecular cyclization in the presence of $(CH_3O)NHCH_3$–HCl and $(CH_3)_3Al$ followed by hydrogenation over palladium hydroxide afforded **107** (78%) from **103**, whereas **104** gave **105** (81%) together with **106** (12%), respectively. Reduction of the lactams **105** and **107** with BH_3 afforded **109** and **108**, respectively.

The *trans*-allyl alcohol **110** could be used for the synthesis of 3-hydroxypyrrolidine hydrochloride **9** by benzylation and subsequent removal of the MOM group to afford **111** (84%), which was subjected to Sharpless asymmetric epoxidation in the presence of *I*-DIPT to afford stereoselectively the 2,3-epoxy alcohol **112** (Scheme 19).[78] Treatment of **112** with *N*-benzoyl

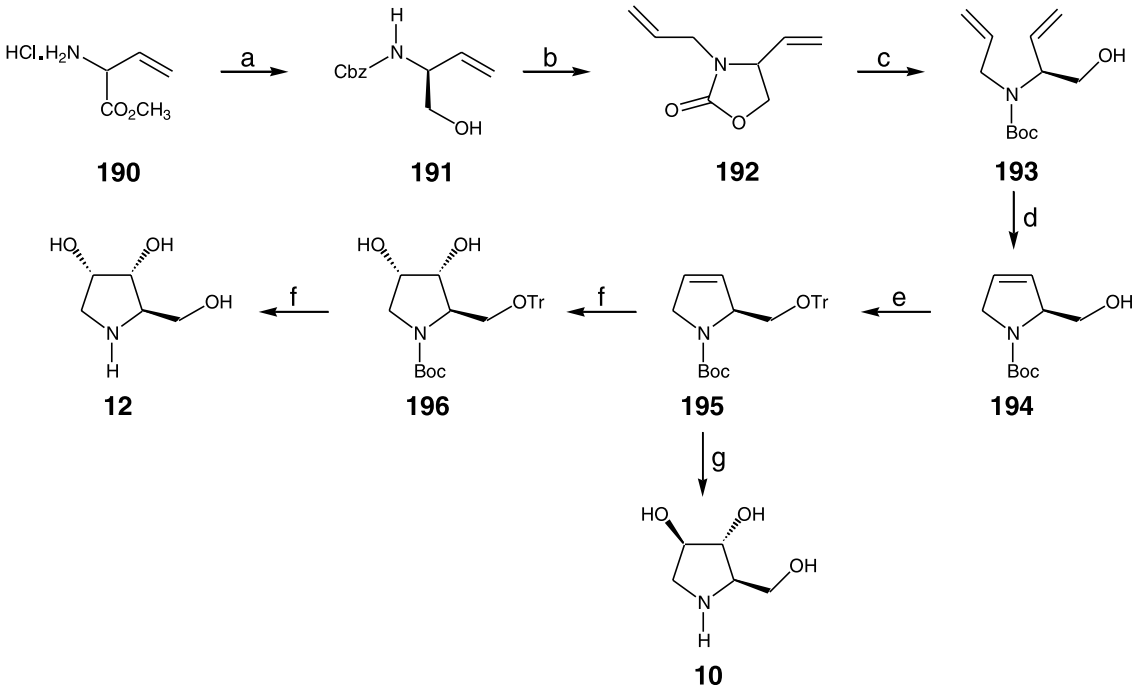


Scheme 28. (a) CH_2Cl_2, Et_3N, reflux, 4 h; then rt, overnight, basic workup, 80%; (b) 1. DIBAL-H, toluene, −78 °C, 3 h; 2. $Ph_3P{=}CHCO_2CH_3$, CH_3OH, rt, overnight, **179** (64%), **180** (8.4%); (c) 1. OsO_4, NMO, acetone, rt, 36 h; then sodium hydrogensulfite solution, **181** (43%), **182** (27%), **185** (17.5%), and **186** (55.5%); or $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH, OsO_4, rt, 48 h, **181** (67%), **182** (4.5%), and **186** (84.8%); (d) aqueous HCl, THF, rt, 20–24 h, **184** (60.4%), **183** (66%); (e) B_2H_6, THF, reflux, overnight, 86–96%.

isocyanate, followed by cyclization with K_2CO_3, gave the 2-oxazolidinone **113** where migration of the *N*-benzoyl group took place. Hydrogenation over palladium chloride followed by mesylation and intramolecular cyclization with sodium hydride afforded the pyrrolidine derivative **114**, which was debenzoylated with aqueous K_2CO_3 followed by basic hydrolysis to afford **115** (96%), which was then subjected to acid hydrolysis, giving **9** in 93% yield. Similarly, the precursor **117** and its isomer could be obtained from the isomeric epoxide **116**.

In a similar sequence of reactions, the *cis*-allyl alcohol derivative **118** was used as the precursor for the two isomeric epoxides **120** and **122**, which could be converted into the respective oxazolidinones. Conversion of **123** into the pyrrolidine derivative **124** was achieved as in the former scheme; also **120** was converted into **121** (Scheme 20).[78]

(2*R*,3*S*)-2-Hydroxymethyl-3-hydroxypyrrolidine (castanodiol **9**) has been synthesized from the pyroglutamic acid derivative **23**[65] (Scheme 21). Reduction of the amide group in **23** resulted in concomitant transformation of the acetal moiety into the *N*-benzyl protecting group to furnish **125**, which was hydrogenated over palladium in the presence of Boc_2O to give the Boc-derivative **126** in 71% yield from **23**. Removal of the Boc group from **126** using 5 M HCl afforded the hydrochloride of the castanodiol **9**.



Scheme 29. (a) 1. CbzCl, $NaHCO_3$, CH_2Cl_2, H_2O, rt, 30 min, 45%; 2. $LiBH_4$, CH_3OH, Et_2O, rt, 2 h, 81%; (b) NaH, DMF, rt, 24 h; then $BrCH_2CH{=}CH_2$, rt, 24 h, 92%; (c) 1. NaOH, H_2O, EtOH, 80 °C, 4 h; 2. Boc_2O, Et_3N, CH_2Cl_2, rt, 6 h, 82%; (d) 4 mol% $Cl_2(PCy_3)_2Ru{=}CHCH{=}CPh_2$, PhH, rt, 32 h, 95%; (e) TrCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 days, 93%; (f) 1. OsO_4, $(CH_3)_3NO$, Py, *t*-BuOH, H_2O, 80 °C, 42 h, 96%; 2. HCl, CH_3OH, $AcOCH_3$, rt, 1 h, 78%; (g) 1. *m*CPBA, Et_2O, rt, 21 days, 75%; 2. KOH, H_2O, Me_2SO, 95 °C, 64 h, 87%; 3. HCl, CH_3OH, $AcOCH_3$, rt, 1 h, 89%.

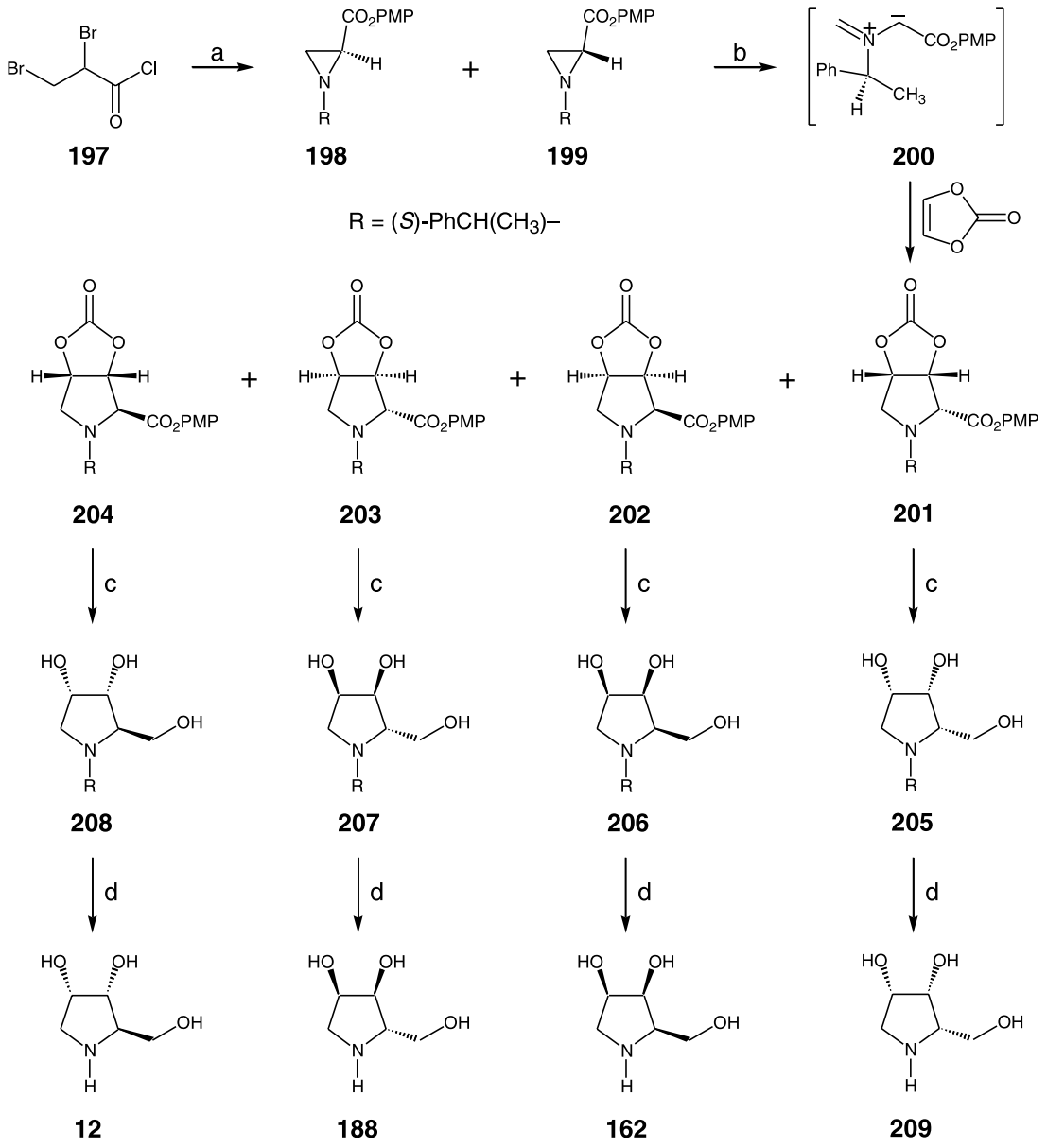
Syntheses of four stereoisomers of 2-hydroxymethyl-pyrrolidine-3-ol have been achieved from the racemic **127** using the Sharpless asymmetric epoxidation[79,80] (Scheme 22). Epoxidation of **127** using L-(+)-DIPT gave (*R*)-**127** (36%), **128** (5%) and **129** (33%), while similar reaction but using D-(−)-DIPT afforded (*S*)-**127** (46%), **132** (11%) and **133** (33%). The pyrolidines **129** and **133** could have resulted from **128** and **132**, respectively, by Ti(O-*i*-Pr)$_4$-mediated intramolecular cyclization. Stereoselective amidomercuration of (3*R*)-**127** and (3*S*)-**127** was carried out to give **130** and **134**, respectively, which without purification were converted into **131** and **135**.

cis-2-Hydroxymethyl-3-hydroxypyrrolidine hydrochloride (**135**·HCl) has been synthesized from the pyrrolidine derivative **20**, which was obtained from *N*-benzyloxycarbonyl-*O*-*tert*-butyldimethylsilyl-L-serinal[67] by reaction with tetra-butylammonium fluoride, followed by catalytic hydrogenation.

3.5. Synthesis of 2-hydroxymethyl-pyrrolidine-3,4-diol

Syntheses of DAB-1 (**10**) and LAB-1 (**11**) have been effected[81] (Scheme 23) by conversion of the aldehyde **136**, readily available from diethyl D-(−)-tartrate, to the aminonitrile **137** (86.7%) as an inseparable diastereomeric mixture. Subsequent deprotected with TBAF gave the alcohol **138** (quantitative), which was esterified with *p*-TsCl to afford the tosylate **139** (84%). Treatment of the tosylate **138** with TFA–H_2O–THF afforded the cyclized diastereomeric mixture **140** and **141** in 1:4 ratio (74%). Subsequent treatment with sodium methoxide in methanol gave a chromatographically separable mixture of methyl ester **142** (21%) and **143** (28%), along with recovered starting material (48.7%), which could be recycled. Treatment of **142** with sodium methoxide in methanol afforded a 1:1 mixture of **142** and **143** in 75–80% yield. Reduction of **143** with sodium borohydride gave the alcohol **144** (89%). Removal of the PMB group in **144** by catalytic hydrogenolysis provided **10**, which was conveniently isolated as its crystalline hydrochloride by treatment with conc HCl (94%). The enantiomeric **11** was synthesized from diethyl L-(+)-tartrate, following the same set of reactions just described for **10**.

The synthesis of **153**, the *N*-hydroxypyrrolidine analogue of **10**, from racemic 3-*O*-benzylglyceraldehyde (**145**) via its coupling with hydroxypyruvate **146** to give 5-*O*-benzyl-xylulose **147** (80%) has been reported[82] (Scheme 24). The conversion of **147** into silylated oxime **148** was accomplished by silylation, oxime formation, and resilylation. Hydrogenation of **148** over 10% palladium–charcoal followed by NaOCl/TEMPO oxidation (66%) or Swern oxidation (40–60%) of the resulting alcohol gave the aldehyde **149**, which was treated with triethyl orthoformate and *p*-toluenesulfonic acid to give the 1,2-oxazine **150**. Hydrogenation of **150**

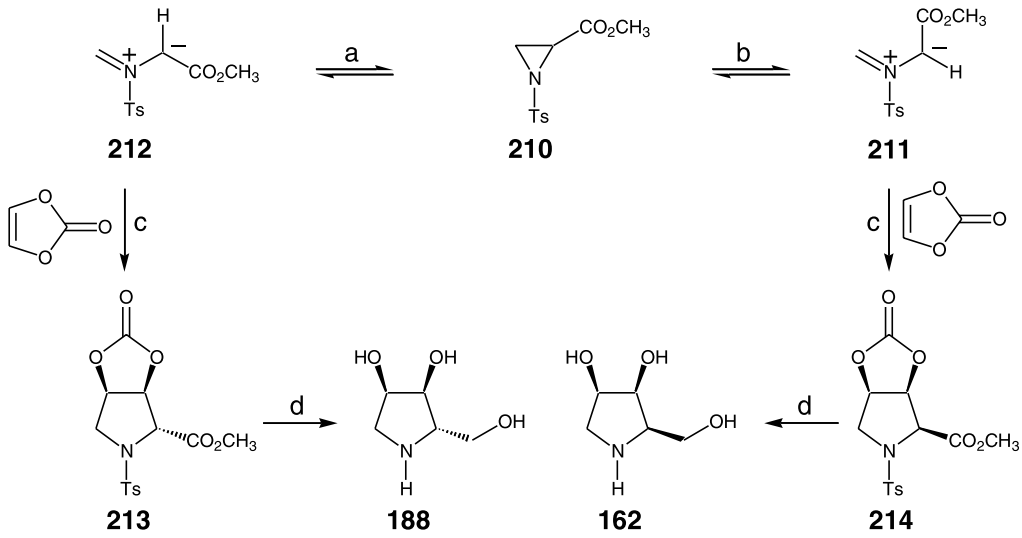


Scheme 30. (a) $CH_3OC_6H_4OH$, Et_3N; then (*S*)-$PhCH(CH_3)NH_2$, CH_2Cl_2, 0 °C to rt; (b) vinylene carbonate, toluene, 280 °C, 30 min, **201** (30%), **202** (33%), **203** (10%), and **204** (11%); (c) 1. $LiAlH_4$, THF, rt; 2. H_2, $Pd(OH)_2$, CH_3OH, conc HCl, **162** (64%), **188** (56%), **12** (48%), and **209** (83%) for two steps.

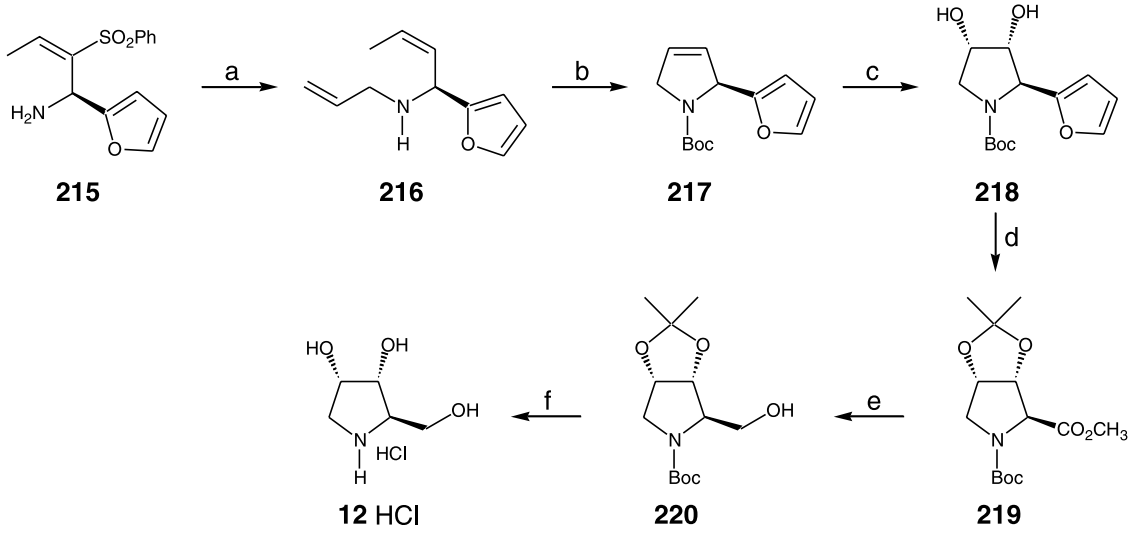
over 10% palladium–charcoal afforded the trisilylated derivatives **151** as a mixture of diastereomers in 59% yield. On the other hand, treatment of **150** with $NaCNBH_3$ in acetic acid led to the formation of *N*-hydroxypyrrolidine **152** (37%) which was desilylated by aqueous HF to give **153** quantitatively.

Synthesis of (2*R*,3*S*,4*R*)-2-hydroxymethylpyrrolidine-3,4-diol (**162**) from 2-*O*-benzylglyceraldehyde (**154**) has been described[14,83] (Scheme 25). Treatment of **154** with the nitro acetal **155** in the presence of tetrabutylammonium fluoride trihydrate afforded an 22:3 mixture of *arabino* and *ribo* **156** in 90% yield. Hydrogenation of **156** in the presence of palladium on charcoal led to formation of amine **157**. N-protection of the amine **157** with benzyl chloroformate followed by selective tosylation of the primary hydroxy group afforded **158**, which was hydrogenated in the presence of palladium on charcoal to afford the pyrrolidine **159**. Treatment with benzyl chloroformate in aqueous $NaHCO_3$ afforded the carbamate **160**. This was hydrolyzed with 0.1N HCl to the corresponding aldehyde **161**, followed by reduction with sodium borohydride and subsequent hydrogenation to produce the pyrrolidine **162** in 17% yield from **154**.

1,4-Dideoxy-1,4-imino-D-arabinitol (**10**) has been synthesized in ten steps from D-serine (**99**) with an



Scheme 31. (a) Photochem.; (b) thermal; (c) vinylene carbonate, benzene, sealed under argon, 160 °C, 3 days, 62–64%; (d) 1. $LiBH_4$, THF; 2. Na naphthalenite, THF, rt, 70–72%.

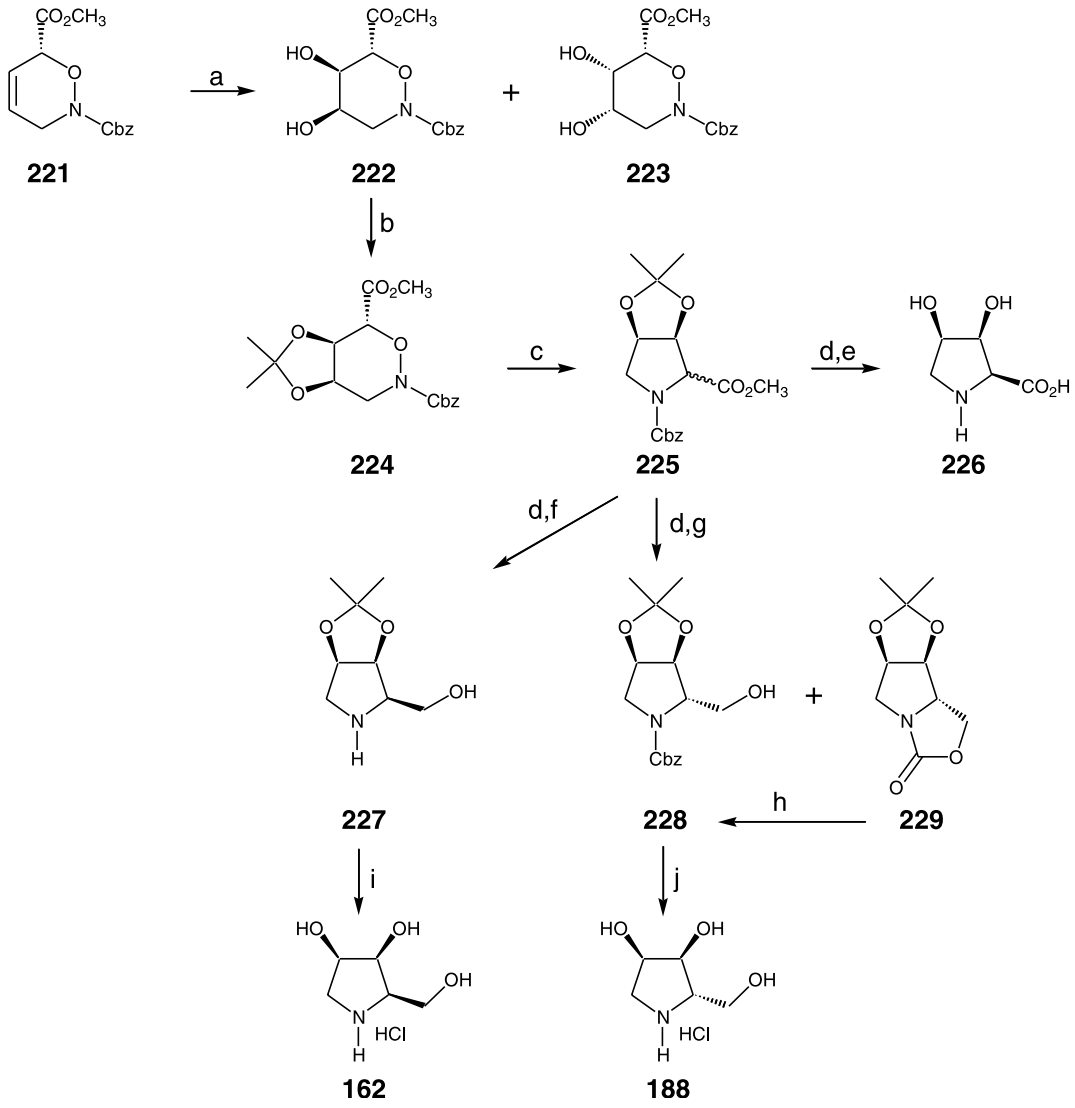


Scheme 32. (a) 1. $BrCHCH{=}CH_2$, K_2CO_3, CH_3CN, 0 °C to rt, 3 days, 78%; 2. SmI_2, THF, HMPA, −20 °C. 20 min, 59%; (b) 1. *N*-TBCBT, CH_2Cl_2, rt, overnight, 80%; 2. [Ru]=, CH_2Cl_2, rt, 2.5 h, 92%; (c) OsO_4, NMO, *t*-BuOH, THF, H_2O, 6 h, 92%; (d) 1. 2,2-DMP, *p*-TsOH, CH_2Cl_2, rt, 30 min, 83%; 2. RuO_2, $NaIO_4$, *t*-BuOH, CH_3CN, CCl_4, 35 min; 3. CH_2CN, Et_2O, 82% for two steps; (e) DIBAL-H, Et_2O, −78 °C, 15 min, 80%; (f) 1. 80% aqueous TFA, 24 h, rt; 2. aqueous HCl, 75% for two steps.

overall yield 49% (Scheme 26).[84] The aldehyde **102**, obtained from **100**, was condensed with **163** in the presence of *n*-Bu_2BOTf to produce the *syn* aldol adduct **164** as a single diastereomer in 82% yield. This was converted into amide **165** which, without protection, was hydrogenated over palladium hydroxide to remove the benzyl protecting group and in situ intramolecular cyclization to give the pyrrolidinone **166** in 71%. Reduction of the lactam **166** with borane, followed by desilylation with aqueous HF and ion-exchange chromatography, furnished **10**.

D-Serine has been used for the synthesis of protected pyrrolidines **170** and **175** (Scheme 27).[85] Thus, the protected D-serine **167** was treated with *i*-Bu_5Al_2H followed by $H_2C{=}CHMgBr$ to give the chromatographically separable 1.7:1 mixture of diastereomers, *threo* **168** and *erythro* **169**, in 76% yield. The *threo* **168** was protected as the corresponding pivalate, and the product subjected to hydroxylation using $K_2OsO_2(OH)_4$ and $K_3Fe(CN)_6$ to afford a 1:10 mixture of diols **171** and **172** in 70% yield. The major product (**172**) was converted into the protected pyrrolidine **175** via either **173** or **174** intermediates. A similar reaction sequence was applied to convert **169** into the pyrrolidine **170**.

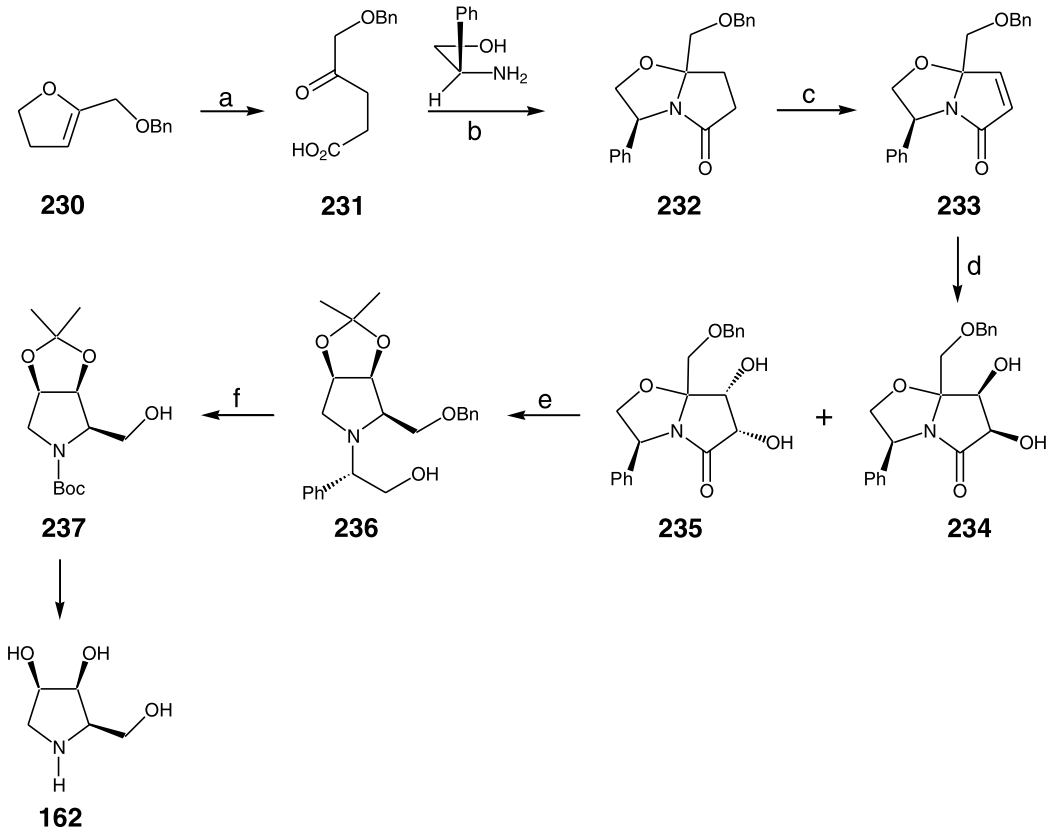
D-Serine has been also used for the synthesis of (2*S*,3*S*,4*S*)- (**11**), (2*S*,3*R*,4*R*)- (**187**), (2*S*,3*S*,4*R*)-



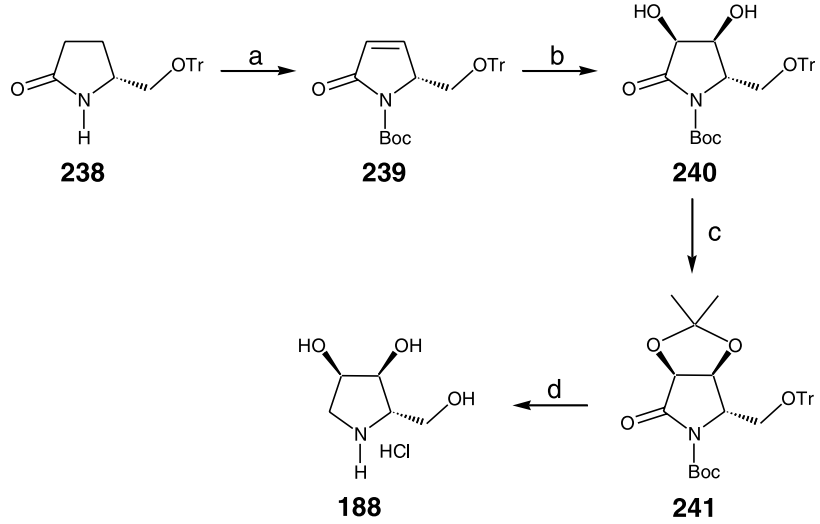
Scheme 33. (a) OsO_4, NMO, acetone, H_2O, 40 °C, 5 h, 69% of 41:9 mixture of **222** and **223**; (b) DMP, Amberlyst-15, rt, 1.5 h, quant.; (c) Na_2CO_3, CH_3OH; (d) H_2, 10% Pd on C, CH_3OH, rt, 2.5 h, 94%; (e) 6N HCl, pH 7, 50 °C, 1.5 day; (f) $LiAlH_4$, Et_2O; (g) 1. $ClCO_2Bn$, $NaHCO_3$, CH_3OH, 94%; 2. $NaBH_4$, *i*-PrOH, 50 °C, 6 h; (h) 1. aqueous NaOH, 2. $ClCO_2Bn$, $NaHCO_3$, *i*-PrOH, 69%; (i) aqueous HCl, 85%; (j) 1. Amberlyst-15, EtOH, 80 °C, 9 h; 2. 10% Pd on C, H_2, EtOH; 3. HCl, CH_3OH, 85%.

(**188**), and (2*S*,3*R*,4*S*)-2-hydroxymethylpyrrolidine-3,4-diols (**189**) (Scheme 28).[86] Methyl L-serinate (**176**) was treated with imido ester **177** in the presence of triethylamine to give 4-(carbomethoxy)-2-phenyl-2-oxazoline (**178**), which was treated with slight excess of DIBAL-H at low temperature followed by condensation with $Ph_3P{=}CHCO_2CH_3$ to give a mixture of alkenes **179** (64%) and **180** (8.4%). Hydroxylation of **180** with OsO_4 afforded the diol **181** (43%) and **182** (27%), which were separated and independently treated with aqueous HCl to give the respective lactams **184** and **183**. These were reduced with B_2H_6 to produce the pyrrolidines **11** and **187**, respectively. A similar reaction sequence was applied to convert **179** into the pyrrolidines **188** via **185**, and **189** via **186**.

The vinyl derivative **190** of glycine methyl ester hydrochloride was used for the synthesis of (2*R*,3*R*,4*R*)- (**10**) and (2*R*,3*R*,4*S*)-2-hydroxymethylpyrrolidine-3,4-diol (**12**) (Scheme 29).[87] Reduction of the *N*-Cbz-vinyl derivative **190** with $LiBH_4$ afforded **191**, which was treated with allyl bromide to afford the *N*-allyl-4-vinyl-oxazolidin-2-one (**192**). This was hydrolyzed with sodium hydroxide followed by treatment with di-*tert*-butyl dicarbonate to give the metathesis precursor **193**, which underwent intramolecular cyclization to afford dehydroprolinol derivative **194**. Subsequent *O*-protection of **194** with trityl chloride afforded trityl ether **195**, which underwent hydroxylation using OsO_4 to give **196** followed by removal of the protecting groups to give **12** in 78% yield. On the other hand,



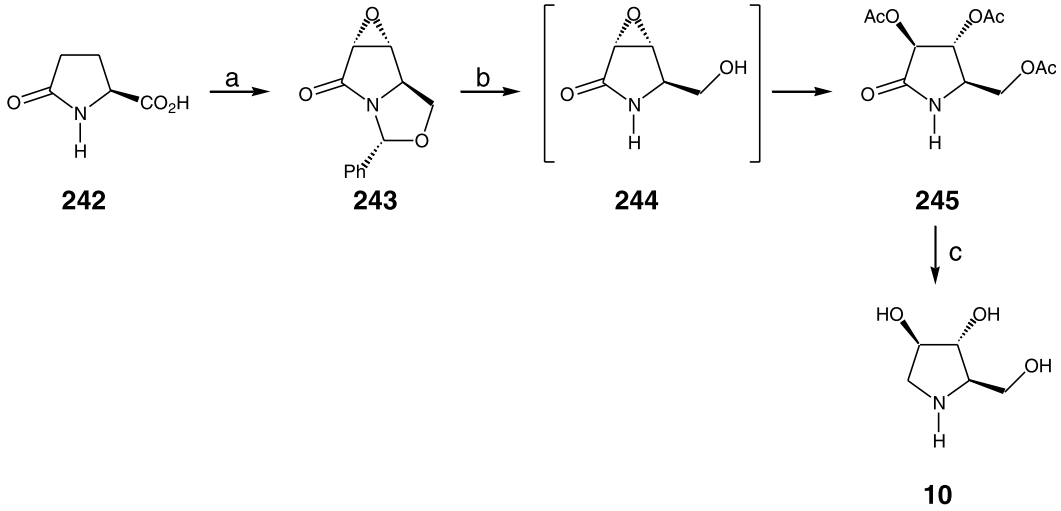
Scheme 34. (a) Jones reagent; (b) toluene, reflux, 38% for two steps; (c) KH, $PhSO_2CH_3$, toluene, reflux, 85%; (d) OsO_4, NMO, acetone, 80%; (e) 1. DMP, *p*-TsOH, 98%; 2. 9-BBN, THF, reflux, 81%; (f) 1. $Pd(OH)_2$, H_2-Boc_2O, 75%.



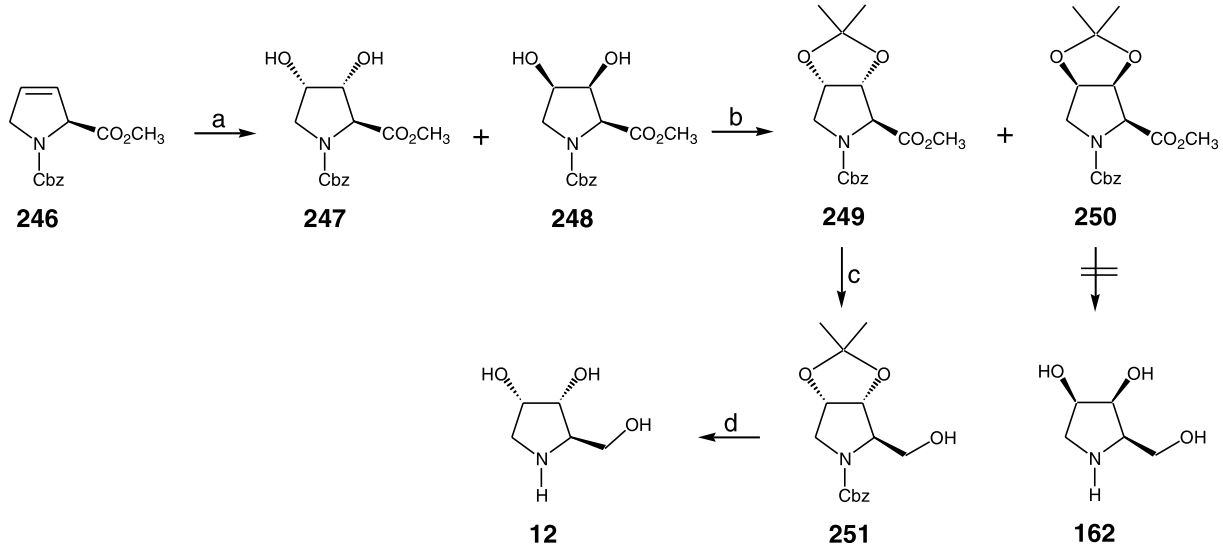
Scheme 35. (a) 1. Boc_2O, Et_3N, CH_2Cl_2, rt, 16 h, 82%; 2. *n*-BuLi, diisopropylamine, THF, −78 °C, 10 min; then PhSeBr, THF, −78 °C; then aqueous NH_4Cl, 79%; (b) OsO_4, NMO, acetone, H_2O, rt, 20 h, 88%; (c) DMP, acetone, *p*-TsOH, rt, 2 h, 88%; (d) BMS, THF, 70 °C; then 5% aqueous HCl, 19%.

epoxidation of **195** with *m*CPBA followed by regioselective epoxide opening with lithium borohydride gave, after removal of the protecting groups, **10**.

Both enantiomers of 1,4-dideoxy-1,4-iminolyxitol (**162** and **209**) and 1,4-dideoxy-1,4-iminoribitol (**12** and **188**) have been synthesized from 2,3-dibromopropanoyl chloride (**197**) (Scheme 30).[88] Reaction of **197** with 4-methoxyphenol and (*S*)-1-methylbenzylamine afforded a mixture of **198** and **199** in 43 and 51% yields, respectively. These were converted into azomethine ylide



Scheme 36. (a) Refs. 68 and 95; (b) 1. TFA, THF, H_2O, 80 °C; 2. Ac_2O, Py, rt, 24 h, 43%; (c) $LiAlH_4$, THF, reflux, 4 h, 74%.

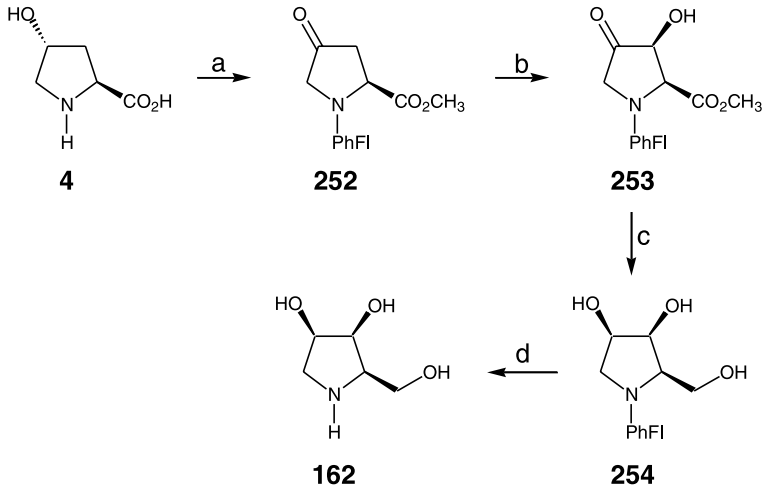


Scheme 37. (a) OsO_4, *t*-BuOH, H_2O_2, NMO, THF, 50 °C, overnight, 97%; (b) DMP, 4M HCl, 1,4-dioxane, rt, 18 h, 92%; (c) $LiBH_4$, THF, rt, 90 min; (d) 1. TFA, H_2O, 35 °C, 15 min, 96%; 2. 10% Pd on C, H_2, EtOH, 18 h, 95%; or **251** and sodium naphthalenide solution in THF, −78 °C, then 0.1 M HCl, 72%.

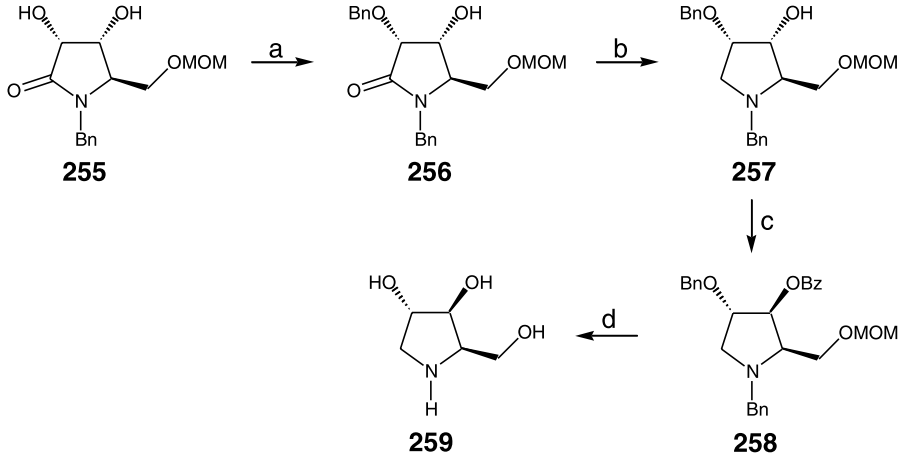
200, which underwent 1,3-dipolar cycloaddition with vinylene carbonate to give four separable compounds **201**, **202**, **203**, and **204**. Reduction of **201** with lithium aluminum hydride gave N-substituted triol **205** in 71% yield, which was subjected to removal of the N-protecting group to give **209** in 83% yield. Similarly **206**–**208** were converted into **162**, **188**, and **12**, respectively.

The (2*R*,3*S*,4*R*)- (**162**) and (2*S*,3*S*,4*R*)- (**188**) 2-hydroxymethylpyrrolidine-3,4-diol have been synthesized from *N*-tosylaziridine **210** (Scheme 31).[89] Thermal treatment of tosylaziridine **210** with vinylene carbonate afforded the 2,3-*syn*-disubstituted pyrrolidine **214** via **211**, which underwent reduction followed by detosylation using sodium in naphthalene to produce pyrrolidine **162**. Alternatively, under photochemical conditions, the aziridine **210** obtained via **212** was coupled with vinylene carbonate to give a mixture of the *anti* isomer **213** and *syn*-isomer **214** in the ratio ~31:19. Lithium borohydride reduction of the pyrrolidine ester **213** and subsequent removal of the protecting groups afforded 1,4-dideoxy-1,4-iminoribitol **188**.

1,4-Dideoxy-1,4-imino-D-ribitol (**12**) was synthesized from the sulfonyl amino alkene **215** (Scheme 32)[90] by monoallylation using allyl bromide in the presence of K_2CO_3 followed by reductive removal of the sulfonyl group with SmI_2 to afford **216**. N-protection with Boc group followed by ring closure using Grubbs catalyst gave the pyrroline derivative **217**. Dihydroxylation of



Scheme 38. (a) 1. CH_3OH, H^+; 2. PhFIBr, Me_2SiCl, $Pb(NO_3)_2$, CH_2Cl_2; 3. $(COCl)_2$, Me_2SO, $-60\ ^\circ C$, 78%; (b) NaHMDS, THF, MoOPH, -78 to $-23\ ^\circ C$, 80%; (c) $LiEt_3BH$, THF, 91%; (d) H_2, 10% Pd on C, 100%.



Scheme 39. (a) Bu_2SnO, toluene, reflux, 2 h; then CeF, P_2O_5, 1 h, BnBr, DMF, rt, 2 h, 74%; (b) BMS, THF, 70 °C, 90 min, rt; then 10% aqueous HCl, 70 °C, 5 min, 80%; (c) Ph_3P, BzOH, DEAD, THF, rt, 14 h, 72%; (d) 1. $NaOCH_3$, CH_3OH, rt, 3 h, 74%; 2. NaH, THF–DMF, rt, 30 min, BnBr, 80%; 3. 10% aqueous HCl, CH_3OH, 70 °C, 1 h, 90%; 4. EtOH, 10% Pd on C, HCl, H_2, 13 h, 81%.

217 using a catalytic amount of OsO_4 and NMO afforded **218** as a single isomer, which was subjected to protection of the diol as its isopropylidene derivative followed by conversion of the 2-furyl group at C-2 into the hydroxymethyl function giving **219** in 82% yield. Reduction of the ester group in **219** using DIBAL-H in ether afforded the alcohol **220**, which was treated at room temperature with 80% aqueous TFA to give **12** as its hydrochloride salt.

The oxazine **221** has been used for the synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol (**162**) and 1,4-dideoxy-1,4-imino-L-ribitol (**188**) (Scheme 33).[91] Catalytic osmylation of **221** gave a mixture of **222** and **223** in 41:9 ratio and 69% overall yield. The diol function in the major isomer **222** was protected with dimethoxypropane as the acetone derivative **224**, which underwent basic rearrangement with sodium carbonate to give **225** as a 3:1 diastereoisomeric mixture. Hydrogenolysis of **225** led to the corresponding isopropylidenated *cis*-dihydroxy-L-proline methyl ester, which was deprotected to give (2*S*,3*S*,4*R*)-3,4-dihydroxy-L-proline (**226**). Catalytic hydrogenation of **225** and subsequent reduction gave **227**, whose deprotection gave **162**. On the other hand, catalytic hydrogenation of **225** and subsequent reaction with benzyl chloroformate gave a mixture of **228** and **229**; the latter could be converted into the former, which upon deprotection gave the salt of **188**.

The dihydrofuran derivative **230** has been used for the synthesis of the 1,4-dideoxy-1,4-imino-D-lyxitol (**162**) (Scheme 34).[92] Simultaneous hydrolysis and oxidation of **230** was achieved by treatment with Jones reagent, furnishing the keto acid **231**, which underwent cyclodehydration with (*S*)-phenylglycinol to give the chiral lactam **232** in 38% overall yield. Treatment of **232** with methyl phenylsulfinate and potassium hydride, followed by thermal elimination of the intermediate sulfoxide in

refluxing toluene, afforded the unsaturated product **233** in 85% yield. Dihydroxylation of **233** with OsO_4 and NMO gave a 87:13 mixture of *endo* **235** (64%) and *exo* diols **234** (16%). The major isomer **235** was acetonated with DMP, followed by reductive cleavage of the oxazolidine C–O bond to afford the pyrrolidine **236**. Hydrogenation of **236** over palladium hydroxide in the presence of Boc_2O gave the protected pyrrolidine **237**. This was deprotected to give 1,4-dideoxy-1,4-imino-D-lyxitol (**162**).

(*R*)-5-Trityloxymethyl-2-pyrrolidinone (**238**) has been used as a starting material for the synthesis of (2*S*,3*S*,4*R*)-2-hydroxymethylpyrrolidine-3,4-diol (**188**) (Scheme 35).[93] N-protection of **238** with the Boc group, followed by formation of an α,β-unsaturated bond using the selenenylation–deselenenylation procedure, has been used to give **239**, which was subjected to *cis* dihydroxylation using a catalytic amount of OsO_4 and NMO to give the lactam **241**. Reduction of **241** with borane–dimethyl sulfide followed by acid hydrolysis afforded (2*S*,3*S*,4*R*)-2-hydroxymethylpyrrolidine-3,4-diol hydrochloride (**188**).

(*S*)-Pyroglutamic acid **242** (Scheme 36)[94] could be converted into the epoxide **243**,[68,95] which upon treatment with TFA followed by acetylation with acetic anhydride in pyridine gave **245** via intermediate **244**. Reaction of **245** with lithium aluminum hydride followed by deacetylation gave (2*R*,3*R*,4*R*)-2-hydroxymethylpyrrolidine-3,4-diol (**10**) in 74% yield.

Dihydroxylation of the (2*S*)-3,4-dehydroproline derivative **246** (Scheme 37)[96] afforded **247** and **248**, which were treated with DMP to give the separable mixture of **249** and **250**. Reduction of the major isomer **249** afforded the protected pyrrolidine **251**, which was deprotected to give (2*R*,3*R*,4*S*)-2-hydroxymethylpyrrolidine-3,4-diol (1,4-dideoxy-1,4-imino-D-ribitol) (**12**). Compound **250** under similar condition failed to give **162**.

A stereoselective synthesis of **162** from proline **4** has been reported (Scheme 38).[97] Regio- and stereoselective introduction of the hydroxyl group at C-3 was achieved by treatment of **252** with NaHMDS followed by oxidation of the corresponding enolate with MoOPH. Reduction of **253** with $LiEt_3BH$ led to triol **254**, which underwent deprotection by hydrogenation to form prolinol **162** in 57% overall yield from **4**.

(*S*)-Pyroglutamic acid has been also used for the synthesis of (2*R*,3*S*,4*S*)-2-methoxymethylpyrrolidine-3,4-diol (**259**) (Scheme 39).[98] Selective benzylation of **255** afforded **256**, which underwent lactam reduction using borane–dimethyl sulfide to give the pyrrolidine **257** in 59% yield from **255**. The Mitsunobu reaction of **257** led to inversion of the stereochemistry of the unprotected secondary hydroxy group to give **258** (72%), which was deprotected to give **259**.

Acknowledgements

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