SYNTHETIC STRATEGIES FOR THE CONSTRUCTION OF 3-PYRROLIDINOL, A VERSATILE NITROGEN HETEROCYCLE

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Abstract - The biological and/or commercial importance of molecules containing the 3-pyrrolidinol nucleus are presented. Synthetic strategies for preparing both racemic and chiral 3-pyrrolidinols and their N-substituted derivatives are described. A comparison of the yields and optical purities of the chiral products is also given.

CONTENTS

INTRODUCTION

Current interest in both the synthesis and biological activity of compounds containing the 3-pyrrolidinol nucleus has led us to review the different synthetic strategies used to prepare this interesting heterocycle and its N-substituted derivatives. 3-Pyrrolidinol (1) is the precursor to a wide variety of natural products such as prolyl depsipeptides (2) and

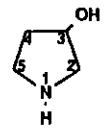
cyclopeptide alkaloids of the amphibine-B family (3). Various other substituted 3-pyrrolidinols (4-11) are also noted for their biological or commercial importance. Compounds (2-11) were chosen for discussion in order to illustrate the diversity both in structure and activity of molecules having a 3-pyrrolidinol moiety incorporated in their skeleton (Figure 1).

The detoxin complex (2) is a selective antagonist against the antibiotic blasticidin S and is of interest for its detoxification effect against this antibiotic both in animal and plant cells[1]. The cyclopeptide alkaloids mauritine-A and nummularine-F are ionophores that show a selectivity for larger ions such as K^+ or Rb^+ and transport them across the mitochondrial membrane[2]. Compounds (4-6) have demonstrated potent antibacterial activity and are of commercial importance as bacteriocidal agents[3-5]. The 3-pyrrolidinol nucleus is also present in compounds of potential medicinal value such as (7) and some of its derivatives which appear to function as central nervous system depressants and have been shown to block agressive behavior in male albino mice[6]. At certain concentrations, compound (8) was found to be a bronchodilator[7]. The substituted 3-pyrrolidinol (9) is an analgetic whose activity seems to approximate that of codeine[8,38]. Finally, salts of substituted 3-pyrrolidinols such as (10) and (11) are useful as antiarrythmic agents[9].

The importance of 3-pyrrolidinol as a key intermediate in the synthesis of compounds (4-8) is evident in Figure II. The coupling of (1) with the appropriate aromatic precursors, effected under various conditions, has led to the formation of the desired targets either directly or upon simple hydrolysis[3-7]. Similarly, as illustrated in Figure III, the reaction of 1-methyl- and 1,2-dimethyl-3-pyrrolidinol with benzyl bromide in the presence of acetic anhydride has been used to generate the antiarrhythmic agents (10) and (11), respectively[9].

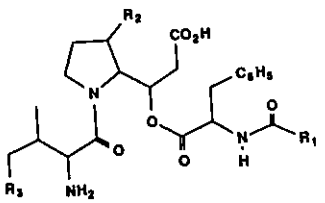
The vast array of compounds containing the 3-pyrrolidinol unit has stimulated many investigations directed toward the synthesis of (1) both in racemic and optically active forms. Section I of this review is a brief survey of the methods leading to racemic (1) while section II describes in detail and compares the methods currently employed to generate chiral 3-pyrrolidinols.

Figure 1



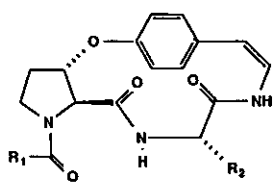
1

3-pyrrolidinol



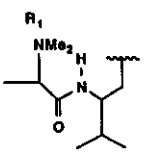
2

		R_1	R_2	R_3
Detoxin	E_1	$CH(CH_3)CH_2CH_3$	$OCOCH_3$	CH_3
	D_1	$CH(CH_3)CH_2CH_3$	$OCOCH_3$	H
	C_1	CH_3	$OCOCH_3$	H
	C_1'	CH_3CH_3	$OCOCH_3$	H
	C_2	$CH(CH_3)_2$	$OCOCH_3$	H
	B_3	CH_3	H	H
	B_1	$CH(CH_3)_2$	H	H



3

Mauritine-A



Nummularine-F

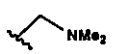
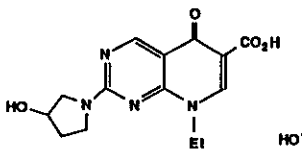


Figure I (continued)



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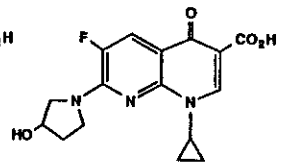

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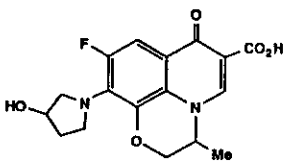

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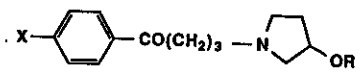
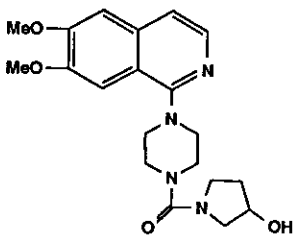


7

X = F; R = H

X = F; R =



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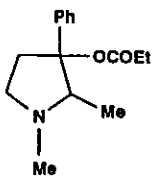
X = F; R =



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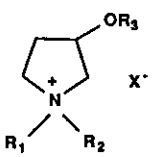

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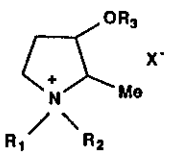


11

R_1 = Me

R_2 = CH_2Ph

R_3 = Ac

X = Br

Figure II

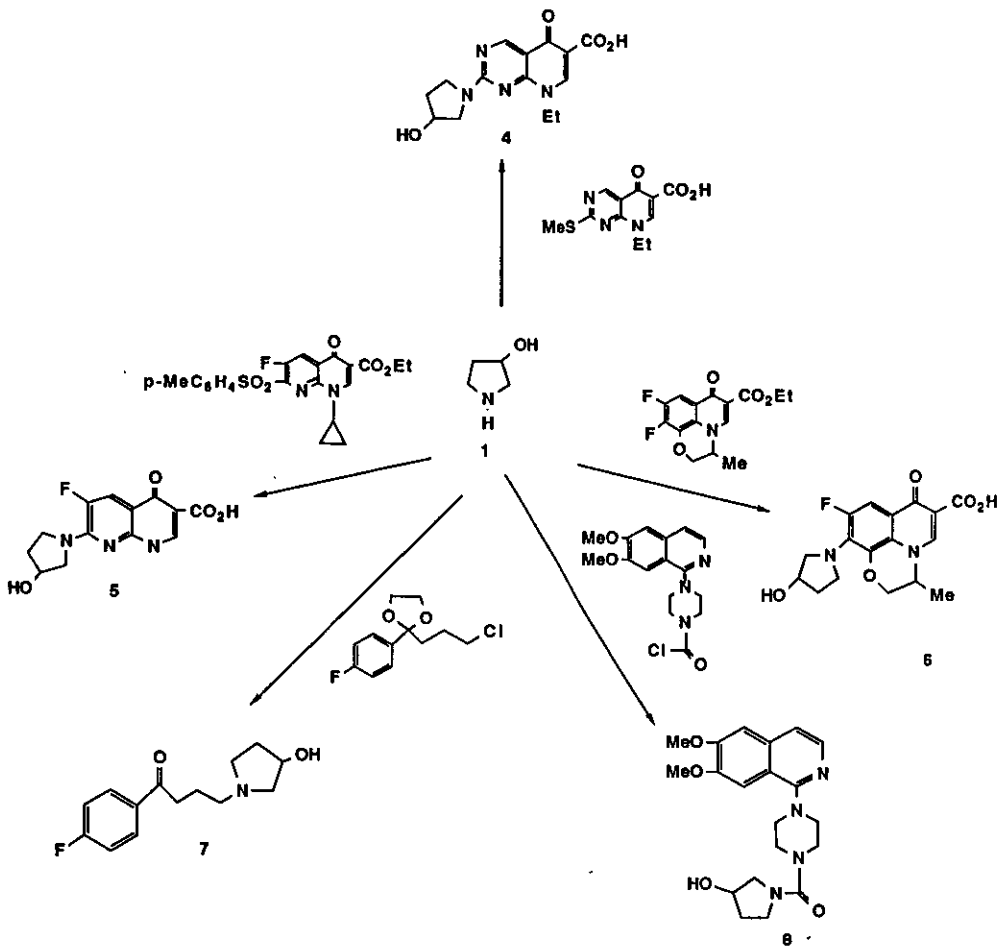
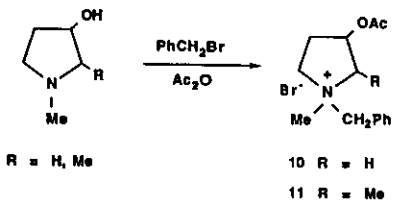


Figure III



R = H, Me

10 R = H

11 R = Me

I. SYNTHETIC ROUTES TO RACEMIC 3-PYRROLIDINOLS

A number of methods have been presented in the literature for the synthesis of racemic 3-pyrrolidinols[10-19]. Although some interesting procedures will be omitted from the present review, the selected routes should provide an overview of the diversity of approaches used to generate the desired heterocycle (1). Table I summarizes the different strategies (methods A-G) employed in the synthesis of N-substituted 3-pyrrolidinols outlining the reaction sequences and the overall yields.

1. From 1,2,4-butanetriol[10].

Method A employed 1,2,4-butanetriol (12) as its starting material. Compound (12) was converted to 1,4-dibromo-2-butanol (13) with an excess of hydrogen bromide at 140°C. Condensation of (13) with benzylamine at the same temperature afforded the N-benzyl derivative (14). Hydrogenation with palladium on carbon as the catalyst afforded (1) in 31% overall yield.

2. From ethyl N-benzylglycinate[12]

Method B utilized the reaction of ethyl N-benzylglycinate (15) and ethyl acrylate (16) in the presence of catalytic amount of Triton B to generate ethyl N-benzyl-N-(β-carboethoxyethyl) glycinate (17). Reaction of compound (17) with potassium tert-butoxide in dry toluene afforded the β-keto ester (18). Decarboxylation under acidic conditions (concentrated hydrochloric acid) produced N-benzyl-3-pyrrolidinone (19) which was subsequently reduced with sodium borohydride in methanol at room temperature to give (14). The overall yield for this sequence was 17%.

3. From 3-buten-1-ol[13,14]

The use of N-chloroamines for cyclizing aliphatic precursors to pyrrolidines is well documented. Method C utilized this reaction in such a way that the β-functionality was also generated. The N-chloroamine (23) was prepared by converting 3-buten-1-ol (20) with phosphorous tribromide to give the corresponding bromide (21) which, in turn, was treated with 1-aminopropane in ethanol. Reaction of 1-propylamine-3-butene (22) with sodium hypochlorite yielded the desired N-chloro derivative (23). Cyclization was achieved by addition of the N-chloroamine to a solution of acetic acid and sulfuric acid (4M). Sodium hydroxide was then added, and the resulting mixture was dissolved in ethanolic sodium hydroxide and heated to 50°C. Workup and purification afforded N-propyl-3-pyrrolidinol (24) in 16% yield from (21).

4. From pyrrolidine[15,16]

Method D employed eneamides and enecarbamates as precursors to pyrrolidinols in an electro-organic synthesis followed by a hydroboration-oxidation sequence. Pyrrolidine (25) was first protected as its N-acyl or N-(carbomethoxy) derivative under standard conditions. The resulting urethane was then subjected to an anodic methoxylation, via a literature procedure[20] to yield 1-(carbomethoxy)-2-methoxypyrrolidine (26). A solution of (26) containing ammonium chloride was refluxed to afford N-(carbomethoxy)-2-pyrroline (27). Hydroboration using sodium borohydride and boron trifluoride etherate in tetrahydrofuran, followed by oxidation with sodium hydroxide and hydrogen peroxide gave N-(carbomethoxy)-3-pyrrolidinol (28) in 40% yield from (25).

5. From 1,4-dichloro-2-butene[21]

Method E, a modification of method A, was used to prepare N-benzyl-3-pyrrolidinol (14). Commercially available 1,4-dichloro-2-butene (29) was condensed with benzylamine in ethanol to afford N-benzyl-3-pyrroline (30). Hydroboration-oxidation of (30) using diborane followed by oxidation with alkaline hydrogen peroxide yielded N-benzyl-3-pyrrolidinol (14). Catalytic hydrogenation of the acetate salt of this compound with palladium on carbon gave 3-pyrrolidinol in approximately 50% overall yield.

6. From (±)-malic acid[21]

Although the previous routes were adequate to prepare racemic 3-pyrrolidinols, not all of these could be utilized in the synthesis of chiral 3-pyrrolidinols. A method that appeared well suited for this purpose, method F, was first developed using racemic malic acid. (±)-Malic acid (31) was heated with benzylamine in ethanol to give N-benzyl-3-hydroxysuccinimide (32). Lithium aluminum hydride reduction of this compound afforded compound (14) which was subsequently debenzylated by catalytic hydrogenation using palladium on carbon to produce (1). The overall yield for this sequence was approximately 53%.

7. From N-substituted pyrrolines[22]

Brown and co-workers investigated the hydroboration-oxidation of several N-alkyl-3-pyrrolines using a variety of hydroborating agents such as borane-methyl sulfide (BMS), 9-borabicyclo[3.3.1]nonane (9-BBN), dicyclohexylborane (Chx_2BH) and disiamylborane (Sia_2BH). A typical procedure (method G) involved addition of hexadecane to a tetrahydrofuran solution of N-benzyl-3-pyrroline (30) followed by treatment with BMS at 0°C. The mixture was kept at room temperature and then oxidized with sodium hydroxide and hydrogen peroxide. The

yields were dependent on the ratio of olefin to hydroborating agent. In the example shown, a ratio of 1 to 1.66 afforded a 97% yield of (14). Several N-alkyl substituents such as methyl and n-butyl, as well as the benzyloxycarbonyl group were examined.

TABLE I RACEMIC 3-PYRROLIDINOLS. SYNTHETIC STRATEGIES

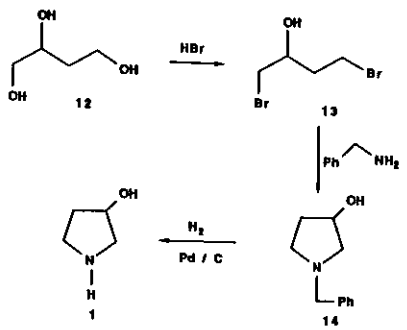
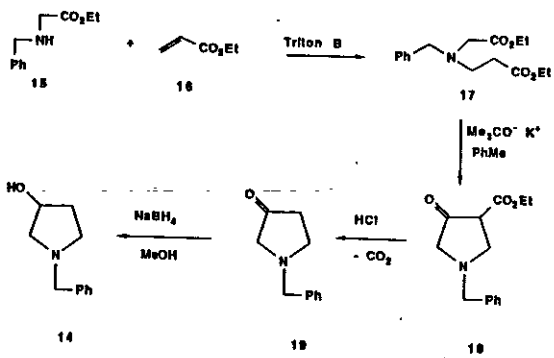
Method	Reaction Sequence	Overall % Yield	Ref.
A		31	10
B		17	12

TABLE I (Cont'd)

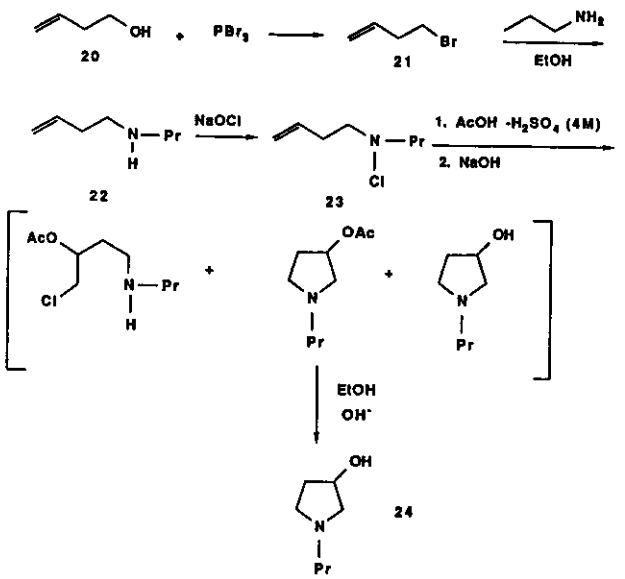
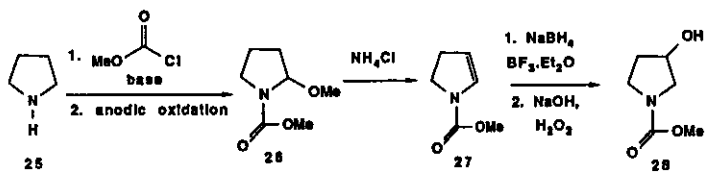
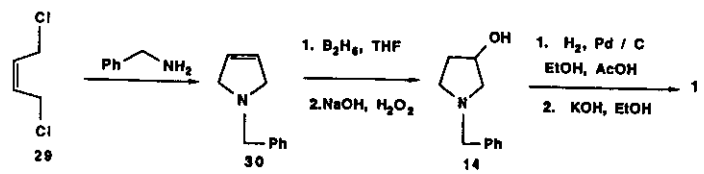
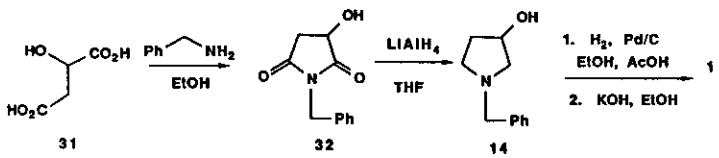
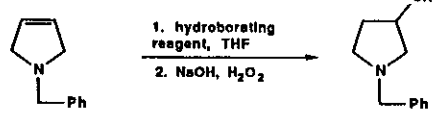
Method	Reaction Sequence	Overall % Yield	Ref.
C		16	13,14
D		40	15,16
E		48	21

TABLE I (Cont'd)

Method	Reaction Sequence	Overall % Yield	Ref.
F	 31 32 14	53	21
G	 30 14	Hydroborating Reagent $BH_3 \cdot SMe_2$ 9 BBN Sia_2BH	97 98 100	22

II. SYNTHETIC ROUTES TO CHIRAL 3-PYRROLIDINOLS

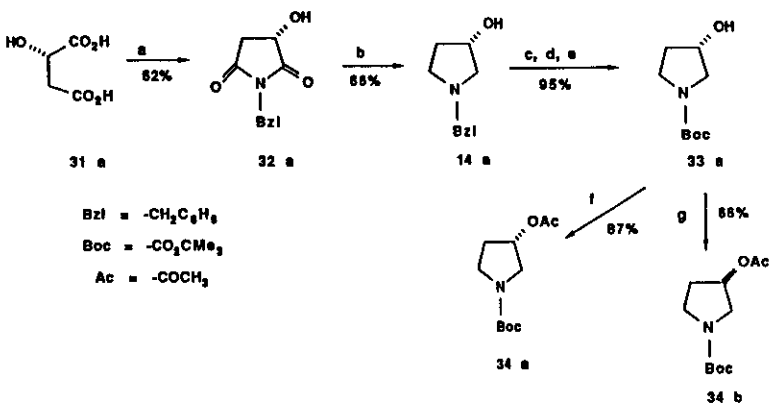
During the last five years several efficient yet facile syntheses of chiral 3-pyrrolidinols and their N-substituted derivatives have been reported[23-28]. The synthetic approaches utilized in these investigations are shown in Schemes I-VI. Table II summarizes and compares the strategies presented with respect to reaction conditions, overall yields, optical rotations of the products, and enantiomeric excesses when available. In addition to the methods described, two additional routes to chiral 3-pyrrolidinols have appeared in the patent literature[29,30].

1. From L-malic acid[23]

A synthesis of chiral 3(S)-pyrrolidinol was based on the sequence described in Section I.6., but using L-malic acid as the chirality source. As seen in Scheme I, the acid (31a) was treated with benzylamine in ethanol at 165-170°C to give N-benzyl-3(S)-hydroxysuccinimide (32a) in 62% yield. Lithium aluminum hydride reduction of (32a) afforded N-benzyl-3(S)-pyrrolidinol (14a) in 66% yield. The optical purity of the product was determined to be 84% by Mosher's

ester method[31,32]. The N-benzyl group was removed by catalytic hydrogenation (Pd/C) and the product treated with di-tert-butyldicarbonate in dichloromethane containing triethylamine to afford N-tert-butyloxycarbonyl-3(S)-pyrrolidinol (33a). The yield for this two step sequence was 95% $[\alpha]_D^{24}$ +13.06° (c 0.49, $CHCl_3$). A simple route to the enantiomeric 3(R)-pyrrolidinol was the inversion of the stereogenic center under Mitsunobu conditions[33]. Treatment of N-tert-butyloxycarbonyl-3(S)-pyrrolidinol or N-Boc-3(S)-pyrrolidinol with diethyl azodicarboxylate and triphenylphosphine, in the presence of acetic acid, gave 3(R)-acetoxy-N-Boc-3-pyrrolidinol (34b) in 66% yield. This product was identical in all respects, except for its optical rotation, to compound (34a) obtained from (33a) by treatment with acetic anhydride in dichloromethane containing dimethylaminopyridine.

Scheme I



[a] $C_6H_5CH_2NH_2$, 165-170°; [b] $LiAlH_4$, THF; [c] H_2, Pd/C, AcOH; [d] KOH, EtOH; [e] $(Boc)_2O$, Et_3N, CH_2Cl_2

[f] Ac_2O ; [g] TPP, DEAD, AcOH.

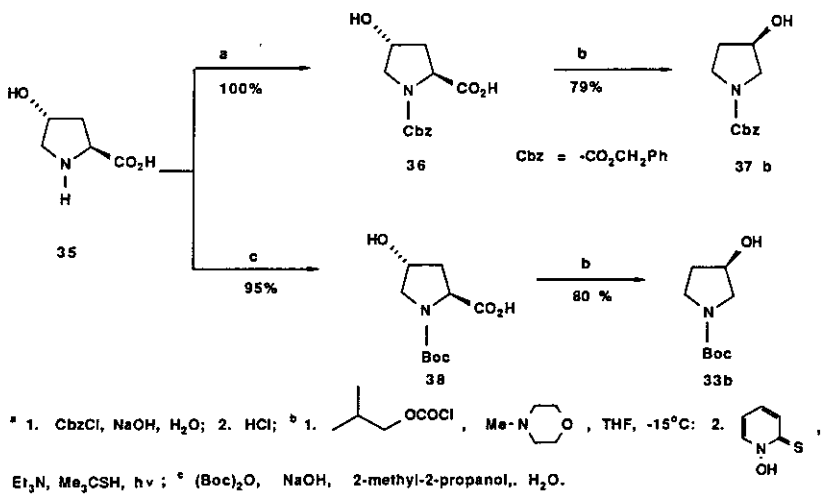
2. From trans-4(R)-hydroxy-L-proline[24,25]

The decarboxylation of α-amino acids has been shown to be an efficient and convenient method for obtaining 3(R)-pyrrolidinols. The two different procedures that utilized this approach are superior to the L-malic acid route (Section II.1.) with respect to both overall yield and optical purity of the product.

In a procedure developed by Barton and co-workers[24], N-benzyloxycarbonyl-trans-4(R)-hydroxy-L-proline or N-Cbz-trans-4(R)-hydroxy-L-proline (36), obtained from trans-4(R)-hydroxy-L-proline (35) using a standard method, were made to undergo reductive radical decarboxylation using esters of N-hydroxypyridine-2-thione as a controlled source of carbon radicals and 2-methyl-2-propanethiol as the hydrogen atom transfer reagent (Scheme II).

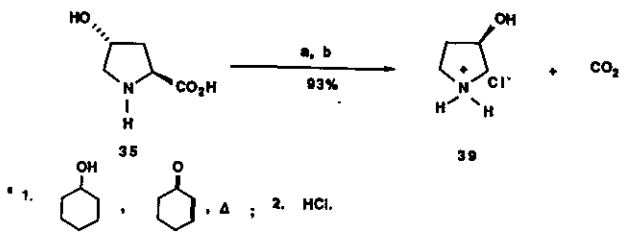
In a typical procedure, the N-protected amino acid was treated with isobutyl chloroformate and N-methylmorpholine in tetrahydrofuran at -15°C. The mixed anhydride thus formed was treated immediately with N-hydroxypyridine-2-thione and triethylamine. After the addition of the thiol, the solution was irradiated with two 100W tungsten lamps until the intermediate ester could no longer be detected. Workup and purification by either column chromatography or recrystallization afforded the N-Cbz-3(R)-pyrrolidinol (37b) in 79% yield; $[\alpha]_D^{23}$ -15.0° (c 0.5, MeOH). This procedure has been repeated several times in our laboratory, by several people, and in each case a comparable yield and optical rotation of the product was obtained. We have also applied this method to N-Boc-trans-4(R)-hydroxy-L-proline (38) and obtained N-Boc-3(R)-pyrrolidinol (33b) in 75% yield; $[\alpha]_D^{23}$ -22.2° (c 1.2, MeOH)[34].

Scheme II



An alternative approach for effecting the decarboxylation of α-amino acids was recently reported by Hashimoto[25]. In a typical procedure, (Scheme III), trans-4(R)-hydroxy-L-proline (35) is refluxed in cyclohexanol containing 1% 2-cyclohexen-1-one for 2h. The product was isolated as its hydrochloride salt (39) in 93% yield; $[\alpha]_D^{20}$ -7.6 (c 3.45 MeOH). We have repeated this reaction and for comparative purposes have converted the product to its N-Boc derivative (33b) by the usual method (di-tert-butyldicarbonate, triethylamine, dichloromethane)[35]. The yield for the decarboxylation and subsequent protection of the nitrogen was 75%, $[\alpha]_D^{20}$ -21.0° (c 1.01, $CHCl_3$). This decarboxylation procedure is simpler than the previous one and obviates the use of 2-methyl-2-propanethiol.

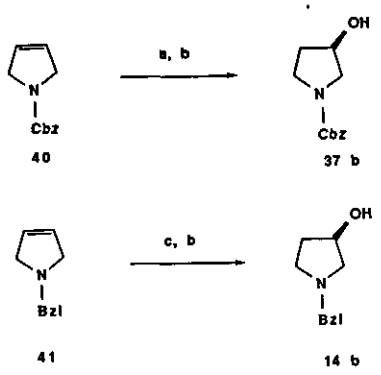
Scheme III



3. From 3-pyrroline[22,26]

A versatile procedure for obtaining either (R) or (S)-N-substituted pyrrolidinols was recently reported by Brown and co-workers. Asymmetric hydroboration of N-Cbz- and N-benzyl-3-pyrrolines (40 and 41, respectively) using either (+) or (-)-diisopinocampheylborane (Ipc_2BH) resulted in the formation of either 3(R)- or 3(S)-pyrrolidinols in good yields and high optical purities. As shown in Scheme IV, N-Cbz-3-pyrroline (40) was added at 0°C to a suspension of (+)-Ipc_2BH in tetrahydrofuran. The trialkylborane was oxidized using 3N sodium hydroxide and 30% hydrogen peroxide at 25°C. Upon completion of the reaction, workup, and purification by chromatography, N-Cbz-3(R)-pyrrolidinol (37b) was obtained in 85% yield; $[\alpha]_D^{23}$ -20.5° (c 3.7, MeOH); 89% e.e. When N-benzyl-3-pyrroline (41) was treated with (-)-Ipc_2BH under similar conditions, N-benzyl-3(R)-pyrrolidinol (14b) was obtained in 89% yield, $[\alpha]_D^{23}$ -3.14° (c 1.2, $CHCl_3$), 100% e.e.[26].

Scheme IV

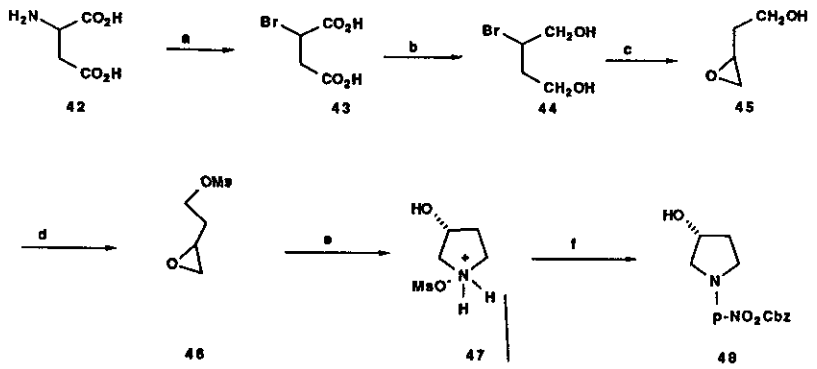


[a] (+)-Ipc_2BH, THF, 0°C; [b] NaOH, H_2O_2; [c] (-)-Ipc_2BH, THF, -25°C.

4. From L-aspartic acid[27]

The conversion of L-aspartic acid (42) to N-p-nitrobenzyloxycarbonyl-3(R)-pyrrolidinol (48) was recently reported by Sugimura (Scheme V). Typically, compound (42) was converted to α-bromosuccinic acid (43) via a literature procedure[36] using sodium nitrite and potassium bromide. A borane-tetrahydrofuran complex in tetrahydrofuran was used to reduce both carboxylic acid groups, at 0°C. The resulting 2-bromo-1,4-butanediol (44) was treated with sodium hydroxide and the product then heated at reflux to form the corresponding epoxide (45). Conversion of the free hydroxyl group into a mesyl group with methanesulfonyl chloride and triethylamine afforded key intermediate (46) in 93% yield from (43) after workup and purification by column chromatography. Addition of alumina B to (46), followed by bubbling of ammonia gas through the solution gave the cyclized product (47). Filtration and concentration of the solvent under reduced pressure and treatment of the residue with p-nitrobenzyloxy-carbonyl chloride and triethylamine at 0°C gave N-p-nitrobenzyloxycarbonyl-3(R)-pyrrolidinol (48) in 28% yield from (46), after workup and purification by column chromatography.

Scheme V



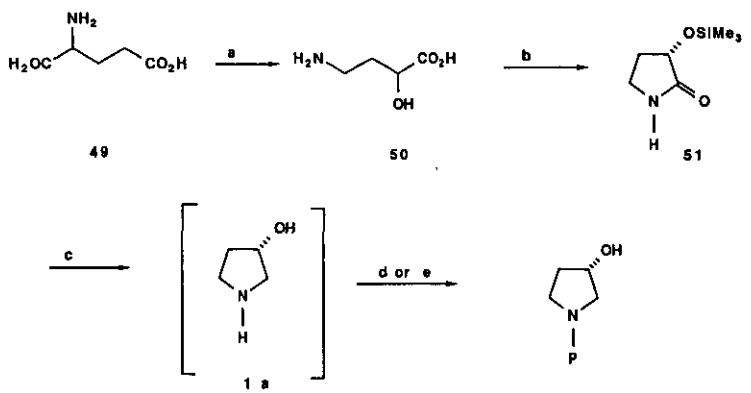
[a] $NaNO_2$, KBr; [b] B_2H_6.THF, 0°C; [c] aq. NaOH; [d] MsCl, Et_3N, CH_2Cl_2; [e] NH_3(g), MeOH; [f] p-nitroCbz, Et_3N, CH_2Cl_2.

5. From L-glutamic acid[28]

A convenient procedure for the syntheses of N-Boc- and N-Cbz-3(S)-pyrrolidinols from L-glutamic acid (49) was recently reported by Joullie' and co-workers (Scheme VI). In a typical preparation, L-(+)-glutamic acid (49), a naturally occurring amino acid, was converted to γ-amino-α-hydroxybutyric acid (50) by a literature procedure[37]. Compound (50) was dissolved in xylene and refluxed with 1,1,1,3,3,3-hexamethyldisilazane to achieve cyclization to

(51) in 81% yield. Compound (51) was then reduced with lithium aluminum hydride in tetrahydrofuran. Workup afforded a crude residue which was dissolved in dichloromethane and treated with triethylamine and benzyl chloroformate at 0°C. Purification gave (37a) in 60% yield from (51); $[\alpha]_D^{28}$ +23.85° (c 0.65, MeOH). The same procedure was followed to prepare (33a). The residue obtained after lithium aluminum hydride reduction was diluted with dioxane, and treated with 1N-sodium hydroxide and di-tert-butyldicarbonate. Workup and purification afforded (33a) in 68% yield from (51); $[\alpha]_D^{27}$ +22.75° (c 1.02, $CHCl_3$).

Scheme VI



[a] reference 37; [b] 1,1,1,3,3,3-hexamethyldisilazane, xylene, TMSCl ; [c] $LiAlH_4$, THF; [d] $(Boc)_2O$, 1 N NaOH, dioxane-water; [e] $ClCO_2CH_2C_6H_5$, Et_3N, CH_2Cl_2.

As mentioned previously, several reports have appeared in the patent literature disclosing the synthesis of racemic and chiral 3-pyrrolidinols. The preparation of 3-(S)-pyrrolidinol methanesulfonate salt has been described in a Japanese patent[29]. Treatment of (S)-$MeSO_3CH_2CH(OH)CH_2SO_3Me$ with ammonia at room temperature for two days afforded the desired compound. Another Japanese patent described the synthesis of 1-benzyl-3(S)-pyrrolidinol by resolution of (±)-1-benzyl-3-pyrrolidinol with optically active mandelic acid[30].

TABLE II CHIRAL 3-PYRROLIDINOLS. COMPARISON OF SYNTHETIC APPROACHES

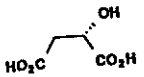
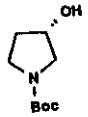
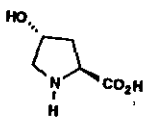
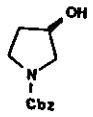
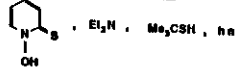
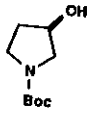
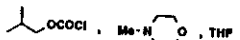
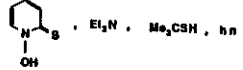
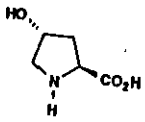
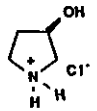
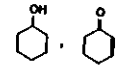
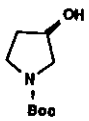
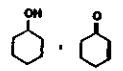
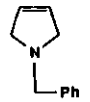
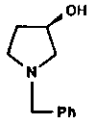
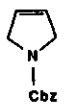
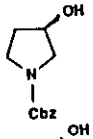
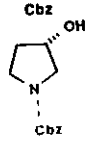
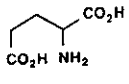
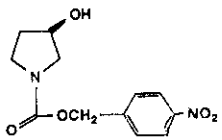
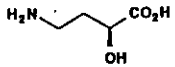
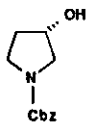
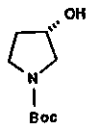
Starting Material	Product	Reagents	Reaction Time	Overall % Yield	$[\alpha]_D$	% ee	Ref.
Scheme I							
		1. $PhCH_2NH_2$, CH_3CH_2OH 2. $LiAlH_4$, THF 3. H_2, Pd/C, CH_3CH_2OH 4. $(BOC)_2O$, $(CH_3)_3COH$, NaOH	1. 3h 2. 2h 3. 16h 4. 12h	39	$[\alpha]_D^{24}$ +13.06° [c 0.49, $CHCl_3$)	84	23
Scheme II							
		1. $PhCH_2OCOCl$, NaOH 2. a)  , THF b)  , Et_3N , Me_3CSH , hn	1. 12h 2. 20 min per mmol	79	$[\alpha]_D^{23}$ -15.0° (c 0.50, MeOH)		24
		1. $(BOC)_2O$, NaOH, $(CH_3)_3COH$ 2. a)  , THF b)  , Et_3N , Me_3CSH , hn	1. 12h 2. 20 min per mmol	76	$[\alpha]_D^{23}$ -22.2° (c 0.54, $CHCl_3$)		34
Scheme III							
		1. a)  b) HCl (g)	3h	93	$[\alpha]_D^{20}$ -7.6° (c 3.45, MeOH)		25
		1. a)  b) $(Boc)_2O$, Et_3N, CH_2Cl_2	2. a) 3h b) 12h	64	$[\alpha]_D^{20}$ -21.0° (c 1.2, MeOH)		35

TABLE II (Cont'd)

Starting Material	Product	Reagents	Reaction Time	Overall % Yield	$[\alpha]_D$	% ee	Ref.
Scheme IV							
		1. a) (-)-IpC_2BH b) NaOH, H_2O_2	4h	89	$[\alpha]_D^{23}$ -3.145° (c 1.2, $CHCl_3$)	100	26
		1. a) (+)-IpC_2BH b) NaOH, H_2O_2	4h	85	$[\alpha]_D^{23}$ -20.5° (c 3.7, MeOH)	89	22
		1. a) (-)-IpC_2BH b) NaOH, H_2O_2	4h	92	$[\alpha]_D^{23}$ +20.5° (c 3.7, MeOH)	89	22
Scheme V							
		1. $NaNO_2$, KBr 2. B_2H_6, THF 3. NaOH 4. MsCl, CH_2Cl_2 5. NH_3, MeOH 6. P-NO_2-(C_6H_4) CH_2OCOCl	2. 5h 3. 3h 4. 30 min 5. 5h 6. 30 min	20.1	$[\alpha]_D$ -18.15° [c 1, $CHCl_3$]		27
Scheme VI							
		1. 1,1,1,3,3,3 hexamethyl-disilazane, TMSCl, CH_2Cl_2 2. $LiAlH_4$, THF 3. $PhCH_2OCOCl$, Et_3N	1. 4h 2. 3h 3. 12h	48.6	$[\alpha]_D^{28}$ +23.85° (c 0.65, MeOH)		28
		1. 1,1,1,3,3,3 hexamethyl-disilazane, TMSCl, CH_2Cl_2 2. $LiAlH_4$, THF 3. $(BOC)_2O$, NaOH, dioxane H_2O	1. 4h 2,3. 36h	55	$[\alpha]_D^{27}$ +22.75° (c 1.02, $CHCl_3$)		28

In conclusion, it is clear from a review of the literature that there exists a growing interest in the synthesis of 3-pyrrolidinols. It is hoped that this account will provide useful synthetic strategies for investigators seeking to incorporate the 3-pyrrolidinol nucleus into other target molecules.

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