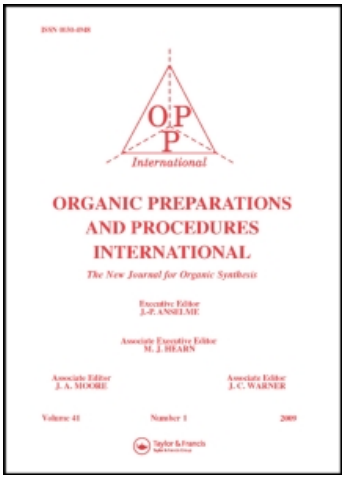

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SYNTHESIS OF 3-AZABICYCLO[3.1.0]HEXANES. A REVIEW

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SYNTHESIS OF 3-AZABICYCLO[3.1.0]HEXANES. A REVIEW

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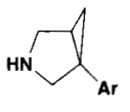
INTRODUCTION

The 3-azabicyclo[3.1.0]hexane ring system is common to a number of bioactive molecules. For example, bicifadine (**1**) shows analgetic and antidepressant activity. Methanoproline (**2**) has gametocidic activity in cereals; structure **3** has antitumor activity; procymidone (**4**) has fungicidic activity, and imide **5** is an aromatase inhibitor.[1] The bioengineered antibiotic indolizomycin (**6**) contains the 3-azabicyclo[3.1.0]hexane moiety by virtue of an equilibrium preference for a hemi-aminal linkage.[2] Trovafloxacin (**7**), a potent Gyrase inhibitor, has shown strong activity against Gram-positive and Gram-negative bacteria, anaerobes, and penicillin-resistant Streptococcus pneumoniae pathogens.[3]



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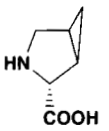

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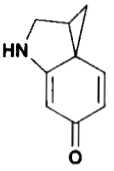

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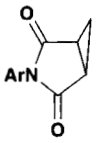

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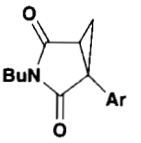
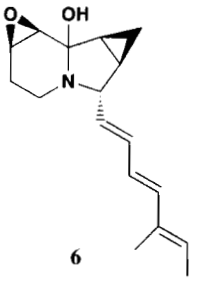


5 Ar = $C_6H_4NH_2$



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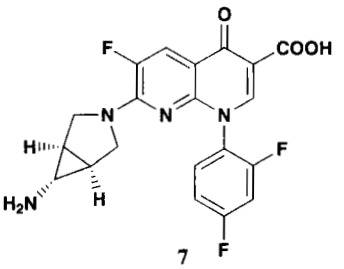


7

I. SYNTHESIS OF 3-AZABICYCLO[3.1.0]HEXANES FROM SUBSTITUTED CYCLOPROPANES

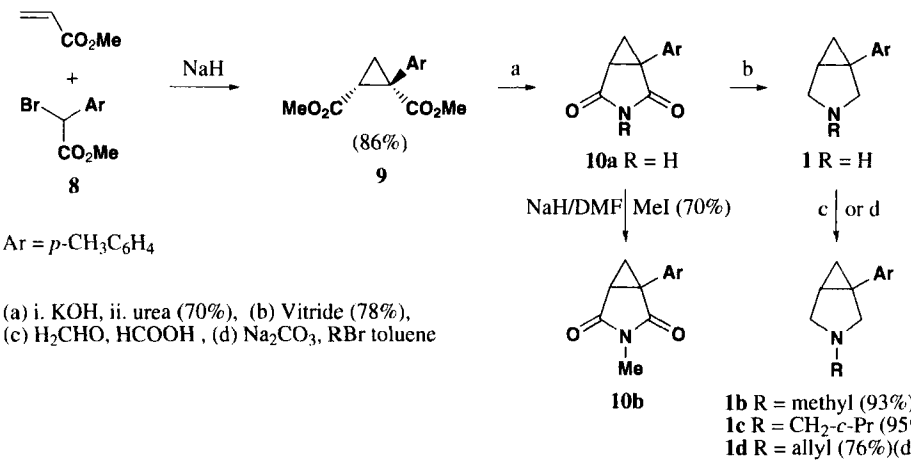
The five-membered pyrrolidine ring can be annulated to a preexisting *cis*-1,2-disubstituted cyclopropane, in which the substituents are a diester,[4,5] its related diacid or anhydride,[6-8] or perhaps

aminomethyl[9,10] or halomethyl[11] groups. Although some target molecules contain the 2,4-dione structure, *e. g.* **4** and **5,** efforts have focused upon the conversion of the imide functionality to synthetically useful intermediates for the synthesis of target molecules, such as bicifadine (**1**) and indolizomycin (**6**).

A variety of cyclopropanation routes are available, including annulation of α,β-unsaturated esters by reaction with anions of α-haloesters,[4,5] catalyzed additions of diazoalkenes[12] and diazoacetate esters to alkenes,[10] dihalocarbene additions,[11] and sulfur ylide additions to conjugated alkenes.[13-15] The method of choice will depend upon the N-substitution desired as well as the functionality desired in the remainder of the molecule. Use of the cyclopropane synthetic methods will be shown in the sections which follow.

A. Synthesis by Ring Annulation of Cyclopropane-*cis*-1,2-dicarboxylic Acids. Maleimides

Cyclopropane1,2-dicarboxylic acids[4-6] or anhydrides[7] can be readily synthesized by annulation of α,β-unsaturated esters with α-haloester anions. Use of this method to synthesize 1-aryl-cyclopropane-1,2-dicarboxylic acid esters gave >9:1 *cis/trans* ratio of isomers for those isomers studied by GLC analysis.[4] An example, shown in Scheme 1, is the formation of 1-aryl-diester **9** from methyl acrylate and the α-bromoester **8**. The diester **9** could be hydrolyzed to a diacid, which upon condensation with urea in refluxing xylene afforded the cyclopropanated maleimide **10a**, a 3-azabicyclo[3.1.0]hexan-2,4-dione. The N-H imide could be readily methylated to give **10b** (70%) by reaction with NaH/DMF followed by addition of methyl iodide. Resolutions could be effected at the diacid stage.[4]



Scheme 1

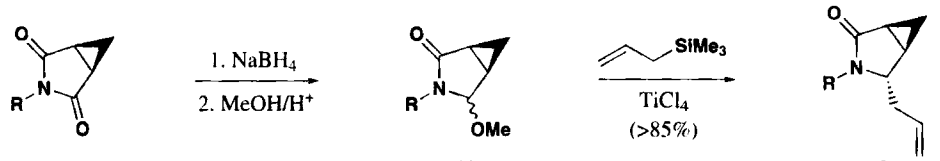
a. Reduction of Cyclopropanemaleimides to Amines

Bicifadine (**1**) has been prepared by borane or *bis*-(2-methoxyethoxy)aluminum hydride (Vitride) reduction of the maleimide **10a** (*Scheme 1*).[4] The N-methyl analog **1b** was prepared in 93%

by reaction of **1** with formaldehyde/formic acid, but direct alkylation of **1** with allyl bromide or cyclopropyl bromide was possible to give tertiary amines **1c** and **1d**. Numerous 1-aryl and N-alkyl analogues of bicifadine (**1**) have been prepared by the methods in Scheme 1.

b. Partial Conversions of Cyclopropanemaleimides to Lactams

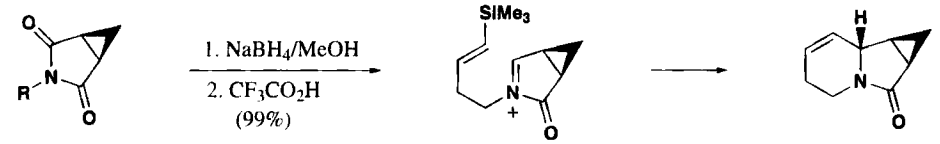
As part of the Danishefsky synthesis of indolizomycin (**6**), the cyclopropyl maleimide **11**, prepared by reaction of cyclopropyl maleic anhydride with 3-azidopropionic acid ethyl ester/PPh_3, was reduced with sodium borohydride and then reacted with methanol gave the methoxyaminal **12**, which reacted with allyltrimethylsilane/$TiCl_4$ to give the substituted lactam **13** (>85%) as the *trans* stereoisomer (*Scheme 2*).[2]



11 R = $(CH_2)_2COOEt$ **12** **13**

Scheme 2

The Danishefsky group also prepared lactam **15**. N-Alkylation of cyclopropyl maleimide (**14a**) gave imide **14b**, which was reduced to a carbinol amide with sodium borohydride/methanol followed by treatment with trifluoroacetic acid to effect trimethylsilyl directed ring closure (*Scheme 3*).[2a] The authors proposed that the β-face is blocked by the cyclopropane ring during cyclization of the acyliminium species derived from the carbinol amide. Attack from the α-face produced the single stereoisomer **15**.



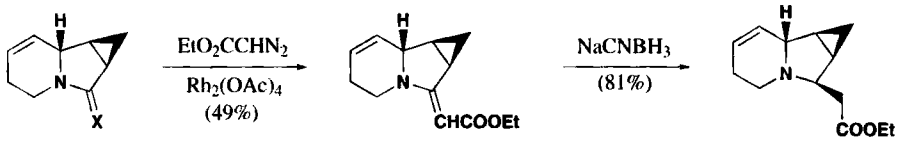
14a R = H
14b R = $(CH_2)_2CH{=}CHSiMe_3$-Z

15

Scheme 3

c. Conversion of 3-Azabicyclo[3.1.0]hexan-2-ones (Lactams) to Amines and Aminols

In a preliminary approach to indolizomycin (**6**), attempts to add Grignard reagents or to reduce the lactam carbonyl of **16a** or its thiocarbonyl analog **16b** were unsuccessful. However, reaction of the thiocarbonyl compound **16b** with ethyl diazoacetate/$Rh_2(OAc)_4$ was accompanied by sulfur extrusion to give the enamine **17** (*Scheme 4*). Sodium cyanoborohydride reduction of enamide **17** afforded a single *exo*-stereoisomer **18**.[2a]



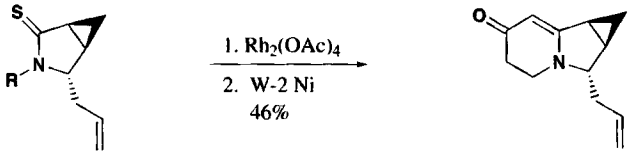
16a X = O
16b X = S

17

18

Scheme 4

In the successful approach to indolizomycin (**6**) the Danishefsky group converted the lactam **13** to the thiolactam **19** with Lawesson's reagent and chain-extended the ester function to give the α-diazoketone **20** (*Scheme 5*). Aza-Robinson annulation was effected by treatment with rhodium acetate in benzene followed by reductive desulfurization with W-2 Raney nickel to give a key intermediate **21** for the preparation of **6**.[2]

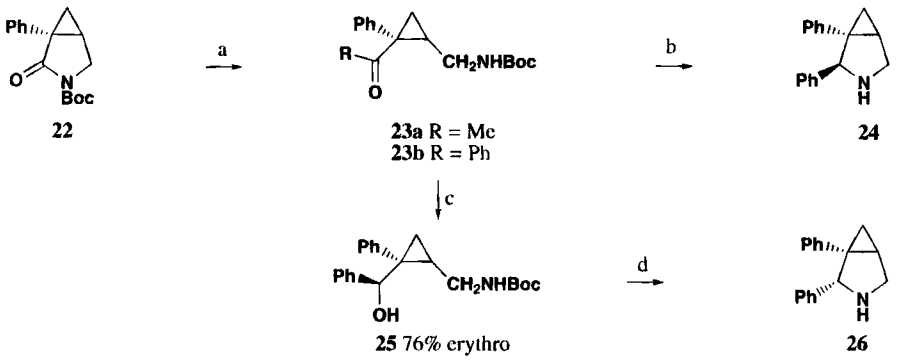


19 R = $(CH_2)_2CO_2Et$
20 R = $(CH_2)_2COCHN2$

21

Scheme 5

Introduction of a substituent in place of carbonyl oxygen at the C-2 position has been accomplished by activation of the lactam carbonyl group with an N-*t*-butyloxycarbonyl or N-trimethylsilyl group. For example, reaction of lactam **22** with MeLi or PhMgBr afforded ring opened ketones **23** (*Scheme 6*). Acid removal of the Boc group of ketone **23b** provided a cyclic imine, which upon reduction with sodium cyanoborohydride gave the 2-*endo*-phenyl isomer of amine **24** (75%).[9] The stereoisomeric amine **26** could be prepared by reduction of the ketone **23b** with potassium borohydride, separation of the major *erythro* isomer **25**, subsequent ring closure with inversion, and final N-deprotection.



22

23a R = Me
23b R = Ph

24

25 76% erythro

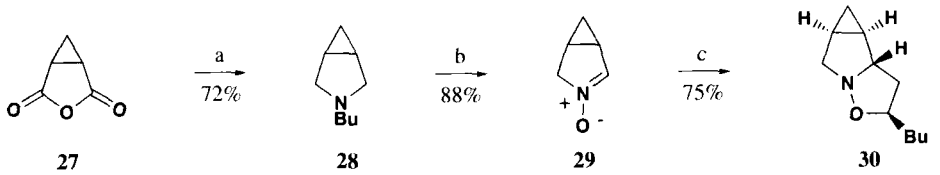
26

(a) MeLi or PhMgBr; (b) i. TFA, ii. $NaCNBH_3$; (c) KBH_4; (d) i. $MeSO_2Cl/Et_3N$, ii. TFA

Scheme 6

d. Introduction and Modification of Substituents at C-2 of 3-Azabicyclo[3.1.0]hexanes

The amine **28** was prepared from cyclopropane maleic anhydride **27**. The α-position of amine **28** was functionalized *via* the derived nitrone **29**. Subsequent 1,3-dipolar cycloaddition yielded adduct **30** possessing a C_2 substituent (*Scheme 7*).[7]

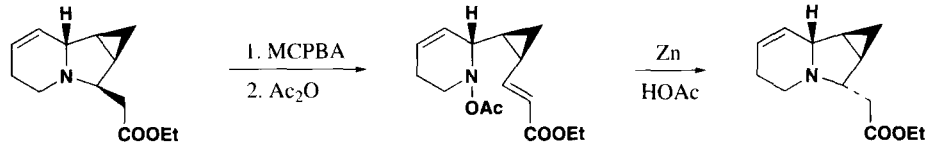


27 **28** **29** **30**

(a) i. $BuNH_2$, ii. Ac_2O, iii. $LiAlH_4$; (b) i. MCPBA, ii. heat, iii. HgO; (c) $BuCH{=}CH_2$

Scheme 7

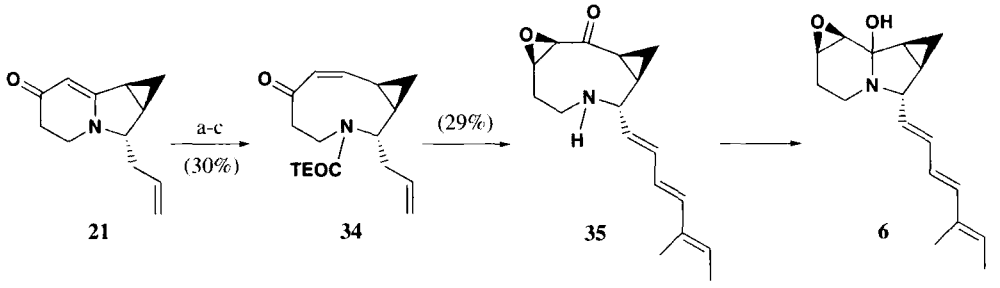
Partial stereochemical inversion of the side-chain substituent of putative indolizomycin intermediate **31** was effected in several steps (*Scheme 8*). N-Oxidation of **31** followed by treatment with acetic anhydride led to ring opened alkene **32**. Subsequent reduction with Zn/HOAc afforded a 3:1 mixture of starting **31** and its *endo* stereoisomer **33** in an unspecified yield.[2a] The low selectivity for the desired *endo* isomer **33** made this route unfeasible for the synthesis of indolizomycin **6** and it was abandoned.



31 **32** **33** + **31** (1:3)

Scheme 8

In the concluding steps of the Danishefsky synthesis of indolizomycin (**6**), the azoninone **34** was formed by O-alkylation of the ketone **21**, reduction of the iminium ion formed, and fragmentation of the ring upon N-acylation with 2-(trimethylsilyl)ethyl chloroformate (*Scheme 9*). Subsequent transformations of ketone **34** led to aminoketone **35**, which spontaneously and quantitatively cyclized to give indolizomycin (**6**).[2]



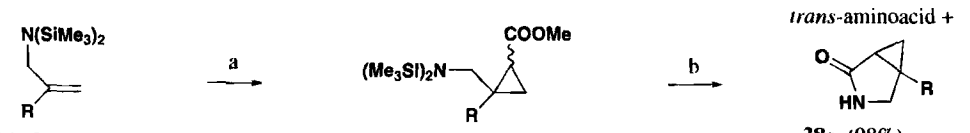
21 **34** **35** **6**

(a) $Me_3O^+ BF_4^-$ (b) $NaBH_4$ (c) TEOCCl

Scheme 9

B. Synthesis by Ring closure of *cis*-(1-Aminomethyl)cyclopropane-2-carboxylic Acids. Lactams

Rhodium acetate catalyzed addition of methyl diazoacetate to allylic amines **36** afforded *cis/trans* mixtures of aminomethylcyclopropane carboxylates **37** (*Scheme 10*). Substitution had little effect on the cyclopropanation stereoselectivity. Upon N-deprotection and heating of the free amines, the *cis* isomers of **37** ring closed to form the lactams **38**.[10a,b] The *trans* isomers of **37** did not cyclize and were isolated as γ-amino acid analogues.



36a R = H
36b R = Me

37a cis/trans 34:66
37b cis/trans 40:60

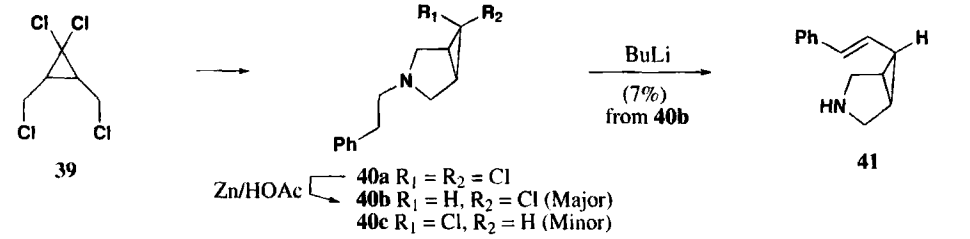
38a (98%)
38b (80%)
(Yields based on *cis*-isomers)

(a) $N_2CHCOOMe$, $Rh_2(OAc)_4$, CH_2Cl_2
(b) EtOH, HCl (c) NaOH, MeOH, heat

Scheme 10

C. Synthesis by ring closure of *cis*-1,2-Di-(halomethyl)cyclopropanes

The *bis*-chloromethylcyclopropane **39** can be N-alkylated to afford a pyrrolidine ring.[11] For example **39** reacted with 2-phenylethylamine to afford the 6,6-dichloro-3-azabicyclo[3.1.0]hexane **40a** (*Scheme 11*).[11a] Zinc/acetic acid reduction of **40a** afforded mainly the 6-*exo*-chloride **40b** (63%). Reaction of amine **40b** with BuLi afforded rearranged structure **41**.

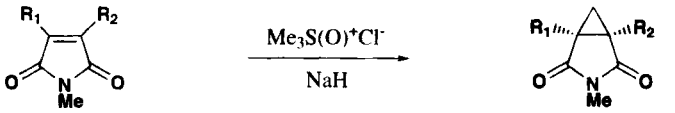


Scheme 11

II. SYNTHESIS BY INTERMOLECULAR CYCLOPROPANATION

Cyclopropanations of N-methyl-2-arylmaleimides **42**[12] (*Scheme 12*) and the lactams **44** and **45**[13,14] have been effected with dimethylsulfoxonium methylide. The lactams **44** and **45**, derived from pyroglutamic acid, also were reacted with a variety of sulfur ylides (*Scheme 13*). Reactions gave cyclopropanes **46** and **47** derived by attack at the less hindered *exo* face in modest to good yields with

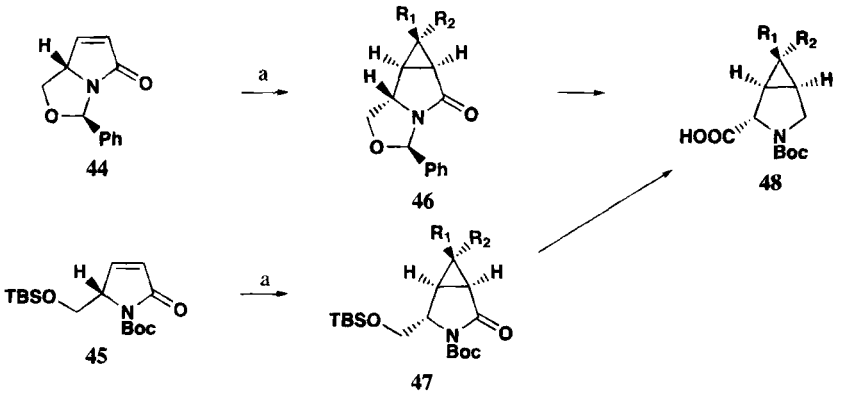
varying *syn:anti* ratios of the C-6 substituents.[13a] Functional group manipulation of the adducts **46** and **47** afforded desired 6-substituted structures **48**, which were utilized as proline analog amino acids for the synthesis of oligopeptides.[13,14a]



42a R_1 = Ph, R_2 = H
42b R_1 = Ph, R_2 = Et
42c R_1 = 3,4,5-$(OMe)_3$Ph, R_2 = H

43a (21%)
43b (81%)
43c (21%)

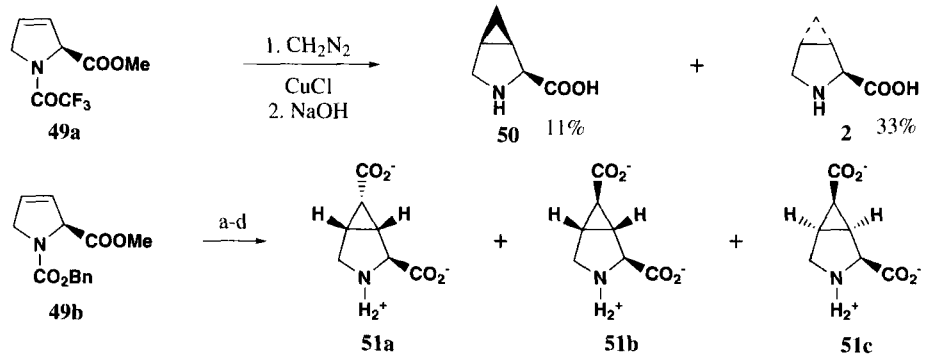
Scheme 12



(a) $Ph_2S^+C^-R_1R_2$; (b) $Me_2S^+C^-R_1R_2$	*anti/syn* (yield) **46**	*anti/syn* (yield) **47**
$R_1 = R_2$ = Me	(89%)	(79%)
R_1 = H, R_2 = Et	1.3/1 (82%)	3/1 (62%)
R_1 = H, R_2 = Me	2.5/1 (84%)	4/1 (54%)
R_1 = H, R_2 = COOMe (Path b)	1/1 (78%)	1/1 (82%)
R_1 = H, R_2 = $CH{=}CH_2$	1/5 (60%)	1/1 (68%)

Scheme 13

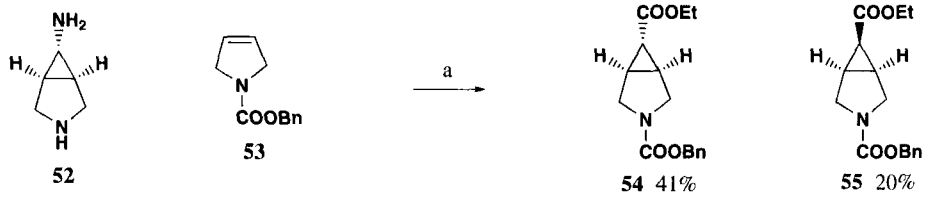
Both *cis* and *trans*-3,4-methylene-L-proline (**50**) and (**2**), respectively, have been synthesized by addition of diazomethane to 3,4-L-dehydroproline **49a** (*Scheme 14*).[15] The cyclopropanation method has been extended to a great variety of structures using diazomethane, phenyldiazomethane, alkyldiazomethanes,[16] and alkyl diazoacetates.[17,18] Bridges and coworkers[18b] synthesized the three diastereoisomers of L-3,4-methanopyrrolidine dicarboxylate **51a-c** (yield unspecified) by addition of ethyldiazoacetate to the neat methyl ester of CBZ-L-dehydroproline **49b** (*Scheme 14*). The L-*anti-endo*-diacid **51a** is a potent competitive inhibitor of the high affinity sodium-dependent glutamate transporter in rat forebrain synaptosomes.



(a) 6 eq. $EtO_2CCHN_2/Rh(OAc)_2$, 90 °C, (b) $H_2/Pd/C$, (c) $Bu_4N^+OH^-/THF/H_2O$, (d) Ion exchange

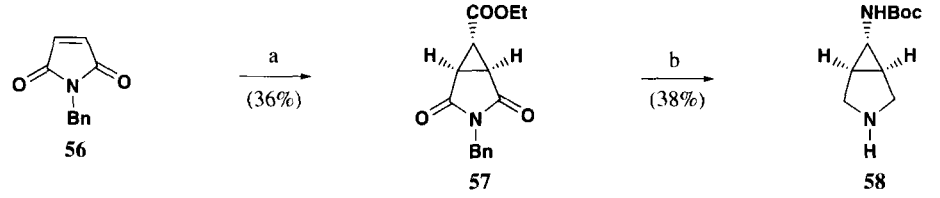
Scheme 14

Trovafloxacin (**7**), a potent gyrase inhibitor,[3] has the 6-amino-3-azabicyclohexane moiety **52**. In an initial approach to **52,** the precursor **54**, formed by rhodium acetate catalyzed ethyl diazoacetate addition to the N-protected pyrroline **53**, afforded a 2:1 mixture of adducts **54** and **55** whose separation was tedious (*Scheme 15*). However, uncatalyzed addition of ethyl diazoacetate to the maleimide **56** afforded only the desired stereoisomer **57** (*Scheme 16*).[18] The amine **58**, a protected form of amine **52**, was prepared from imide **57** by a sequence of steps in which a modified Curtius rearrangement was applied to yield the N-BOC protected amine. Though not the most direct route to amine **58**, the N-benzylmaleimide sequence was pursued by the authors because it offered a sequence which provided a single *exo*-substituted cyclopropane isomer and required only one trivial chromatographic purification.



(a) $EtO_2CCHN_2/Rh(OAc)_2$

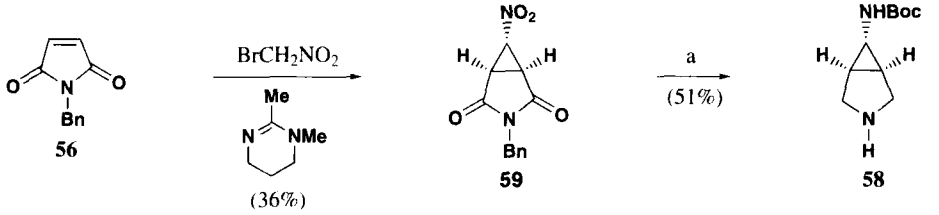
Scheme 15



(a) i. $EtOOCCHN_2$, ii. heat; (b) i. $LiAlH_4$, ii. H_2/Pd, iii. CBzCl, iv. CrO_3, v. $(PhO)_2PON_3/t$-BuOH, vi. H_2/Pd

Scheme 16

An alternative preparation of the protected amine **58** avoided the use of ethyl diazoacetate and DPPA and was amenable to scale-up. Bromonitromethane in the presence of the amidine base dimethyl-1,3,4,5-tetrahydropyrimidine (DMTHP) added to N-benzylmaleimide **56** to give the desired 6-*exo*-nitrocyclopropane **59** (*Scheme 17*).[19] Cyclopropanation yields depended heavily on the base used. Many common bases failed to yield significant amounts of **59**. Dimethyl-1,3,4,5-tetrahydropyrimidine provided the best yield, while use of DBU and tetramethylguanidine provided significantly lower yields (15-22%). It was necessary to reduce the imide functionality of **59** prior to selective reduction of the nitro group. Otherwise, opening of the cyclopropyl ring was observed.

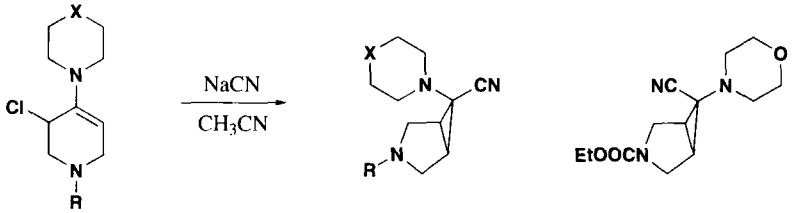


(a) i. BH_3, ii. H_2/Pt, iii. $(t\text{-BuOCO})_2O$, iv. H_2/Pd

Scheme 17

III. SYNTHESIS FROM 4-PIPERIDONE ENAMINES

The N-alkylchloropiperidone enamines **60a-d**, prepared by N-chlorosuccinimide chlorination of the corresponding piperidone enamines, underwent a 1,3-ring closure reaction upon treatment with sodium cyanide in a one-pot procedure to afford the 3-azabicyclo[3.1.0]hexane ring systems as stereochemically pure 6-*exo*-nitriles **61** (*Scheme 18*). If the substituent on nitrogen was ethoxycarbonyl as in **60e**, a mixture of C-6 stereoisomers **61e** and **62** was isolated.[1] The dichloropiperidone enamines **63a,b** afforded stereochemically pure 6-*endo*-cyano-1-chloro analogs **64a** and **64b** (58% and 53%, respectively) (*Scheme 19*). Variations upon this synthetic approach provide 3-azabicyclo[3.1.0]hexane imides fused to carbocyclic rings (*Scheme 20*).[20]

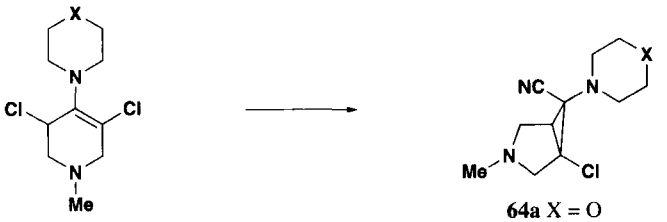


60a X = O, R = Me
60b X = CH_2, R = Me
60c X = NMe, R = Me
60d X = O, R = Bn
60e X = O, R = CO_2Et

61a (75%)
-
-
61d (77%)
61e (31%)

62 (38%)

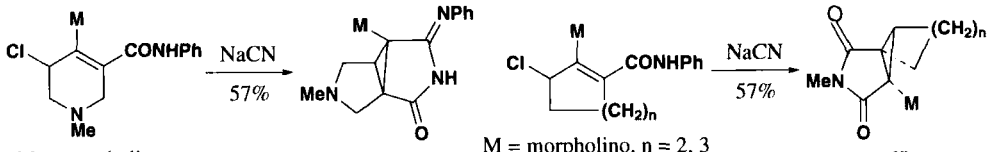
Scheme 18



63a X = O
63b X = NMe

64a X = O
64b X = NMe

Scheme 19



M = morpholino
65

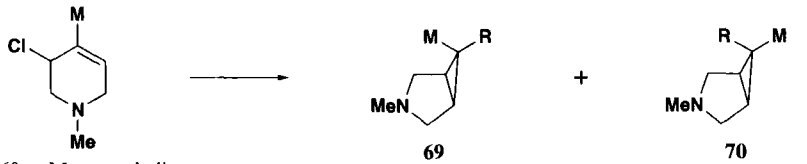
66

M = morpholino, n = 2, 3
67

68

Scheme 20

The chloroenamine **60a** can also be reacted with organolithium reagents or Grignard reagents (Table 1) in the presence of tetramethylethylenediamine (TMEDA) to provide stereochemically pure 6-*endo*-morpholino-3-azabicyclo[3.1.0]hexanes **69** (*Scheme 21*).[21] Organomagnesium reagents afforded stereochemical mixtures of **69** and **70** in the absence of TMEDA as a complexing agent. However, the N-benzylamine **60d** afforded pure *endo* isomer **71** with methylmagnesium bromide in the absence of TMEDA (*Scheme 22*).

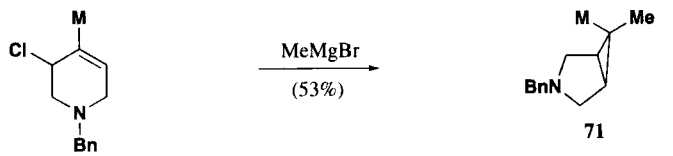


60a M = morpholino

69

70

Scheme 21



60d M = morpholino

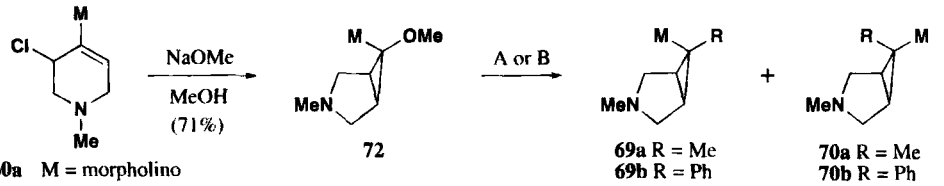
71

Scheme 22

Table 1. Synthesis of 6-substituted 3-Azabicyclo[3.1.0[hexanes **69/70** from Enamine **60a**

Entry	Reagent (RM)		Structure	Yield	Structure	Yield
	R	M		(%)		(%)
1	Me	Li	**69a**	55	**70a**	0
2	Me	MgBr (TMEDA)	**69a**	68	**70a**	0
3	Me	MgBr	**69a**	37	**70a**	31
4	Ph	Li	**69b**	46	**70b**	0
5	Ph	MgBr (TMEDA)	**69b**	38	**70b**	0
6	Ph	MgBr	**69b**	28	**70b**	19
7	Bu	Li	**69c**	46	**70c**	0
8	Bu	MgBr (TMEDA)	**69c**	32	**70c**	0
9	Bu	MgBr	**69c**	14	**70c**	44

If the chloroenamine **60a** was first reacted with sodium methoxide, the 3-azabicyclo[3.1.0]hexane ring **72** was formed (*Scheme 23*). Reaction of **72** with MeMgBr gave a mixture of a small amount of *endo*-methyl adduct **69a** (5%) and mainly the *exo*-methyl adduct **70a** (54%). PhMgBr and adduct **72** gave the *exo*-phenyl adduct **70b** stereoselectively (81%), while PhMgBr/TMEDA gave the *endo*-phenyl adduct **69b** (73%).[21] The selective formation of **70b** was speculated to be due to complexation of the 3-amino group on the *endo* face. It is purported that a cyclic iminium ion derived by loss of methanol from **72** is the intermediate which is attacked by the organometallic reagent. Attack from the *exo* face is normally expected based upon steric considerations and this is observed in Grignard/TMEDA reactions. However, in the absence of TMEDA the magnesium complexes to the 3-amino group and morpholine of the *endo* face, thus directing attack from this face as methanol is lost from the *exo* face.



60a M = morpholino

72

69a R = Me
69b R = Ph

70a R = Me
70b R = Ph

(A) MeMgBr; (B) PhMgBr

Scheme 23

A variety of NH building blocks for trovafloxacin (**7**) analog preparation have been synthesized by stereoselective reductive removal of the 6-methoxy or 6-cyano moieties of benzyl protected structures followed by regioselective removal of the benzyl protecting groups (*Scheme 24*). A key finding was that while sodium/ammonia reduction of nitrile **73a** afforded the *endo*-amino isomer **74a**, Li/ammonia/ethylamine reduction of nitrile **73a** afforded a 4:1 *exo/endo* ratio of amine isomers **74a/75a** (89%). Recrystallization gave *exo* amine isomer **75a** (56%).[22a] The methoxy group of **76** was reductively removed using lithium aluminum hydride or DIBAL to give only 6-*endo*-amino isomer **77** (*Scheme 25*).[22b] Selective removal of the protecting groups was described.

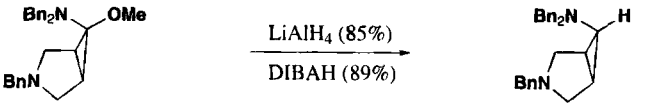
73a R = H
73b R = Bn

74a R = H 60%
74b R = Bn 94%

75a (4:1 *exo/endo*)

(a) Na/NH_3, (b) $Li/NH_3/EtNH_2$ (89%)

Scheme 24



76 **77**

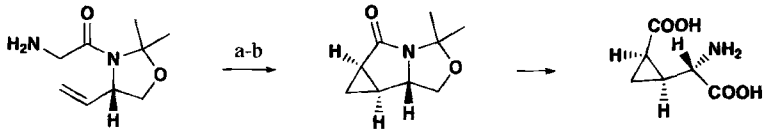
Scheme 25

IV. SYNTHESIS BY INTRAMOLECULAR CYCLOPROPANATION

One approach to intramolecular formation of the fused cyclopropyl and pyrrolidine rings in 3-azabicyclo[3.1.0]hexanes is by internal carbene addition to an alkene. A second intramolecular approach requires that an alkene be activated in such a way that the pyrrolidine and cyclopropane rings might be generated in a two-step process. Examples of both these approaches are shown in the sections which follow.

A. Synthesis by Transition Metal Catalyzed Addition of Amidocarbenes to Alkenes

Ohfune and coworkers[23] have used an intramolecular cyclopropanation reaction to prepare the naturally occurring α-(carboxycyclopropyl)-glycine **80** (*Scheme 26*). Ring closure of an α-diazoamide formed from amine **78** afforded a mixture of cycloadduct **79** (37%) and its C_3C_4 stereoisomer (6%). The major isomer **79** upon modification of protecting groups and oxidation afforded the natural product **80**. The same method was used to prepare 3'-methoxymethyl analogs of L-2(carboxycyclopropyl)glycines (MCG) from D-serinal derivatives (*Scheme 27*).[24] The E-isomer **81a** afforded a 3.3:1 mixture favoring the *exo*-adduct **82a**. The Z-isomer **81b** afforded only exo-adduct **82b**. Removal of protecting groups, methylation, and oxidation of **82a** afforded the *trans*-MCG **83**.

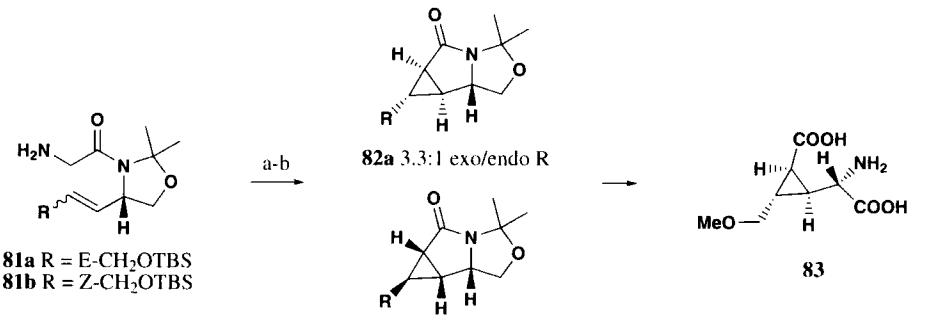


78 **79** (37%) **80**

(a) $NaNO_2$/citric acid
(b) $Pd(OAc)_2$/80°C/toluene

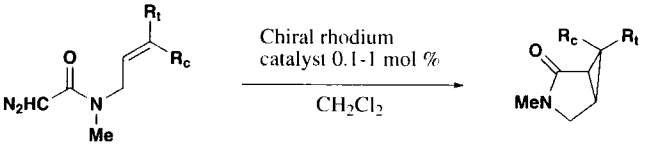
+ C_3C_4 isomer (6%)

Scheme 26



Scheme 27

A highly enantioselective intramolecular rhodium-catalyzed procedure for formation of lactams **85** from N-allylic-N-methyldiazoacetates **84** has been described (*Scheme 28*).[25] Several chiral dirhodium carboxamidate catalysts gave >90% ee in the formation of lactams **85**. However, the %ee observed was <50% if the nitrogen was substituted with a 2-methyl-2-propenyl substituent.



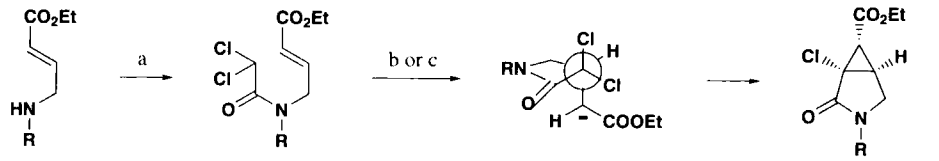
84a R_t = Me, R_c = Me
84b R_t = n-Pr, R_c = H
84c R_t = H, R_c = n-Pr
84d R_t = $(CH_2)_2CH{=}CMe_2$, R_c = H

85a 91%, 94% ee
85b 93%, 92% ee
85c 88%, 95% ee
85d 94%, 94% ee

Scheme 28

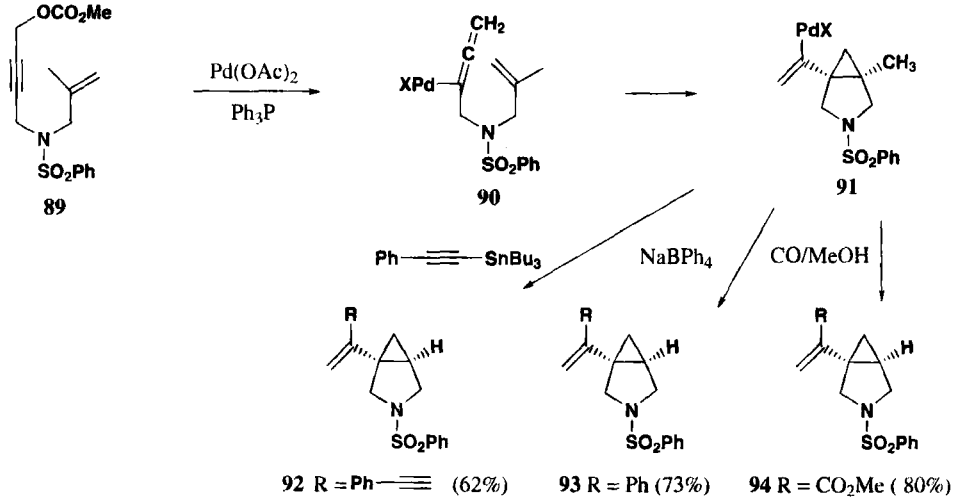
B. Synthesis by Cascade Cyclization and Anion Capture

Complementary to the electrophilic addition of carbenes to alkenes is the tandem nucleophilic Michael-S_N2 process of dichloroamides **86** for the synthesis of lactams **88** (*Scheme 29*).[26] The stereochemistry of the reactions has been rationalized as involving a reversible Michael addition of the conjugate base of **86** to give a five-membered ring intermediate **87** in which the ester group is *anti* to the lactam carbonyl. Cyclization of this intermediate affords what are the thermodynamically preferred products **88**. The cyclization procedure has been extended to the synthesis of larger fused cyclopropyl ring systems.



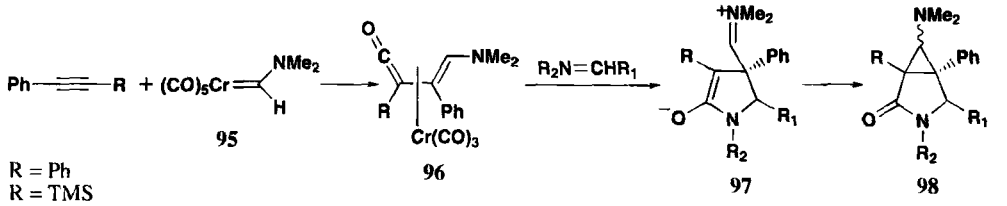
Scheme 29

A palladium catalyzed cascade *bis*-cyclization-anion capture process has been used to prepare 1-vinyl-3-azabicyclo[3.1.0]hexanes (*Scheme 30*).[27] Reaction of the propargyl carbonate **89** with a Pd(0) species generates an allenylpalladium(II) moiety **90**, which upon consecutive olefin insertions yields the ring closure product **91**. Selectivity in the carbocyclizations (5-*exo*-trig and 3-*exo*-trig) are dictated by geometrical constraints leading to a preference for 5- vs 6- and 3- vs 4-membered rings. Generation of the palladium-vinyl species **91** permits further functionalization through well known palladium mediated reactions, such as Stille coupling to give **92**, Suzuki coupling to give **93** and CO insertion/elimination to afford **94**.



Scheme 30

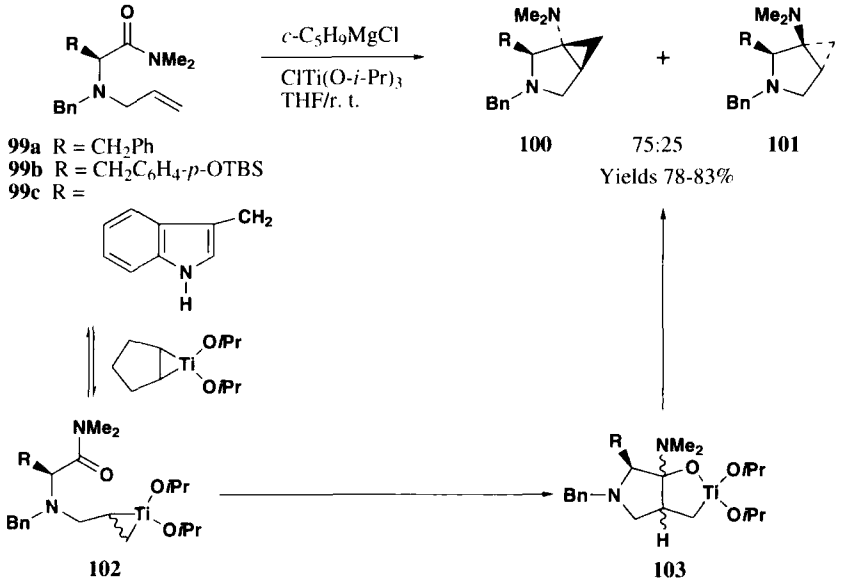
Chromium dimethylaminocarbene complex **95** underwent thermal reaction with internal alkynes to give coordinated enaminoketenes **96** (*Scheme 31*).[28] These reacted with N-substituted aldimines or iminoether to give 6-*endo*-amino-4-*exo*-alkyl lactams **98a-e**. The reaction mechanism likely involves cyclopropane formation by reaction of the imine nitrogen with the ketene carbonyl and ring closure to afford an iminium ion-amide enolate species **97**, which upon further closure gives amines **98**.



98a R= Ph, R_1 = H, R_2 = *t*-Bu (75%)
98b R = R_1 = Ph, R_2 = Me (77%)
98c R = Ph, R_1 = R_2 = $(CH_2)_3O$ (20%)
98d R = TMS, R_1 = Ph, R_2 = Me (-)
98e R = Ph, R_1 = OMe, R_2 = Bn (49%)

Scheme 31

Joullie and coworkers[29] have recently shown that Ti(II) mediates the intramolecular coupling of the terminal alkene function in the N,N-dimethylcarboxamides **99** to give a diastereomeric mixture of the N,N-dimethylcyclopropylamines **100** and **101** (*Scheme 32*). The amides **99** are available from the corresponding amino acids phenylalanine, tyrosine, and tryptophan. Diastereomeric ratios of 3:1 were observed in all cases. The alkenes **99** are converted to diastereomeric titanacyclopropane intermediates **102**. The amide carbonyl next inserts between the titanium and the more substituted carbon to give a pair of *cis*-fused titanaoxacyclopentane intermediates **103**, which rearrange with loss of $(O\text{-}i\text{Pr})_2Ti(=O)$ to give cyclopropanes **100** and **101**.

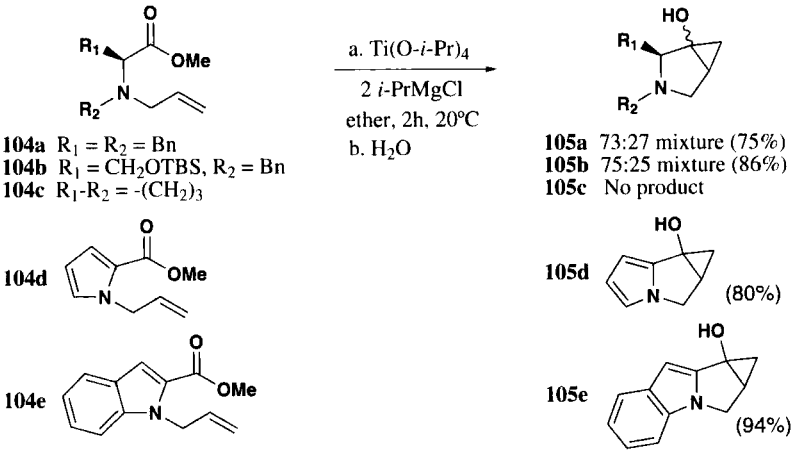


Scheme 32

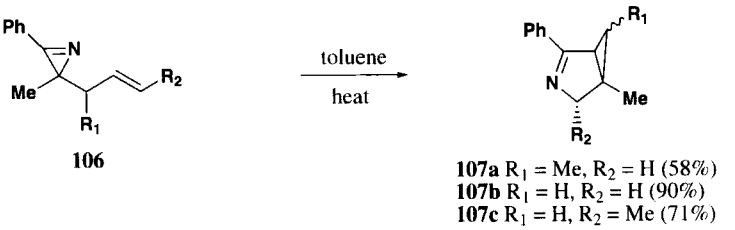
Sato[30] has reported an efficient and practical method for the preparation of 1-hydroxy-3-azabicyclo[3.1.0]hexanes **105** based upon the treatment of N-(2-alkenyl)amino esters **104** with $Ti(O\text{-}i\text{-}Pr)_4/2i\text{-}PrMgX$ reagent (*Scheme 33*). By a mechanism conceptually similar to that shown in Scheme 32, an initially formed Ti(II) alkene complex carries out an intramolecular nucleophilic displacement at the ester and this is followed by intramolecular attack at carbonyl to provide cyclopropanol derivatives **105**. The metallic starting materials are nontoxic and inexpensive. Azabicycles **105a-b** were derived from chiral L-amino acids **104a-b**. Failure of the proline derivative **104c** to react was attributed to a disfavoring of the transition state for ring closure because of a preference for the ester and N-allyl groups to be *trans*. This is not the case for the formation of the [1,2-a]pyrrole **105d** or the [1,2-a]indole **105e**.

V. SYNTHESIS BY INTRAMOLECULAR REARRANGEMENT

Thermal rearrangement of the allyl azirine **106** afforded the 3-azabicyclo[3.1.0]hex-2-enes **107** (*Scheme 34*).[31] Related imines have been reduced with sodium cyanoborohydride.[9]



Scheme 33



Scheme 34

VI. CONCLUSION

The 3-azabicyclo[3.1.0]hexane ring system can be synthesized by a variety of ring closure methods, depending upon the auxiliary functionality desired. Stereocontrol in synthetic transformations on this ring system have been highlighted in this review, particularly in the synthesis of bioactive molecules. Routes to chiral structures have been described based upon resolution,[4] diastereoselective reactions with chiral substrates,[12,15,24] and chiral catalyst mediated enantioselective carbene additions.[25] The authors believe that interest in synthetic methods leading to this ring system will continue to develop as the bioactivity related to this ring system becomes better understood.

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