

AZABICYCLO[2.1.1]HEXANES. A REVIEW

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Abstract – The synthesis and reactions of 1-, 2-, and 5-azabicyclo[2.1.1]hexanes are reviewed.

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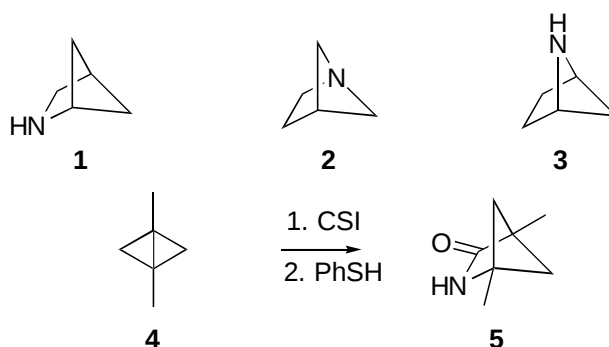
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INTRODUCTION

Of the three possible azabicyclo[2.1.1]hexanes (**1-3**), the 2-aza isomer (**1**) was the first prepared and is the most investigated. The history of the 2-azabicyclo[2.1.1]hexane ring system (**1**) begins with the 1971 report of Paquette that lactam (**5**) is obtained upon reaction of 1,3-dimethylbicyclo[1.1.0]butane (**4**) with

the uniparticulate electrophile chlorosulfonyl isocyanate (CSI) (Scheme 1).¹ Although Paquette's synthesis of the 2-azabicyclo[2.1.1]hexane ring was limited to a single substrate **5**, more general photochemical (1971),² ring closure (1988, 1995),^{3,4} rearrangement (1998),⁵ and α -functionalization (2002)⁶ methods have since been introduced. This review will explore the scope and limitations of these general synthetic methods and will note selective ring opening strategies for variously substituted 2-azabicyclo[2.1.1]hexanes (**1**). A number of biologically interesting molecules in which 2-azabicyclo[2.1.1]hexanes are either targets or synthons will be identified. Subsequently, synthetic approaches to the isomeric 1- and 5-azabicyclo[2.1.1]hexanes (**2**) and (**3**) will be discussed.

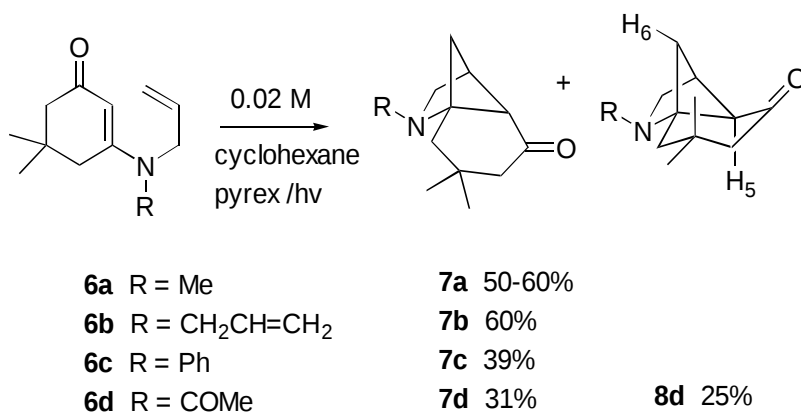


Scheme 1

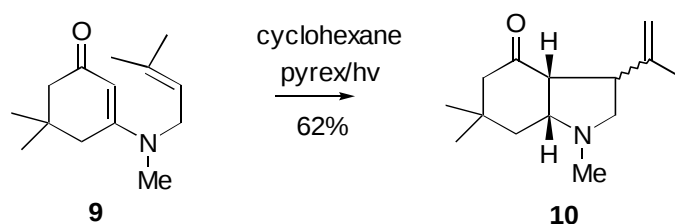
I. SYNTHESIS OF 2-AZABICYCLO[2.1.1]HEXANES

A. Photochemical ring closure of linearly-conjugated *N*-allyl-*N*-vinylamides.

Tamura and coworkers found that intramolecular head to tail [2 + 2] photocycloadditions of *N*-allyl-*N*-vinylamides (**6a-c**) provide mainly azabicyclo[2.1.1]hexanes (**7a-c**) with the six-membered-ring ketone *cis* fused (Scheme 2).^{2,7} The amide (**6d**) provides a mixture of *cis* fused (**7d**) (major) and *trans* fused (**8d**) ketone photoproducts.⁷ The *trans* stereochemistry of **8d** was assigned on the basis of a W-plan coupling ($J_{5,6} = 8.5$ Hz). Irradiation of the dimethylallylamine derivative (**9**), by contrast, gives a product (**10**), obtained by a photochemical intramolecular "ene" reaction (Scheme 3).⁸

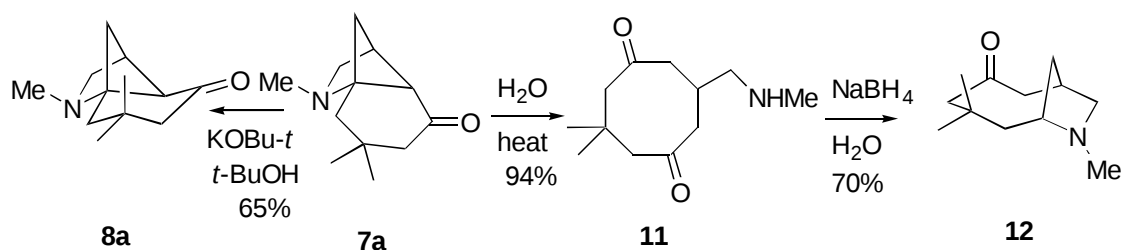


Scheme 2



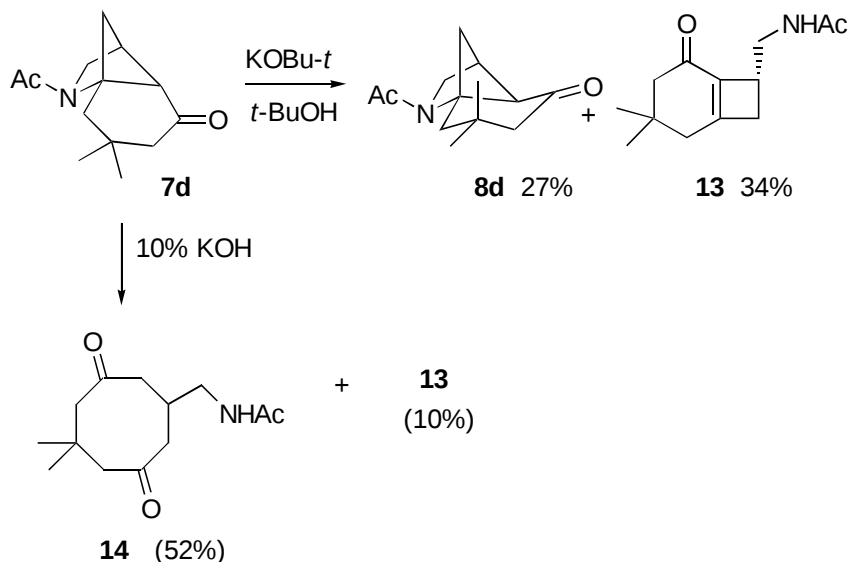
Scheme 3

The *N*-Me-5-*syn*-ketone (**7a**), upon brief heating with potassium *t*-butoxide/*t*-BuOH, epimerizes to the 5-*anti*-ketone (**8a**) (Scheme 4). The 5-*syn*-ketone (**7a**) is stable to refluxing toluene, but ring opens in refluxing water to give diketone (**11**). Interestingly, reduction of **11** with sodium borohydride affords the azabicycle (**12**).⁹



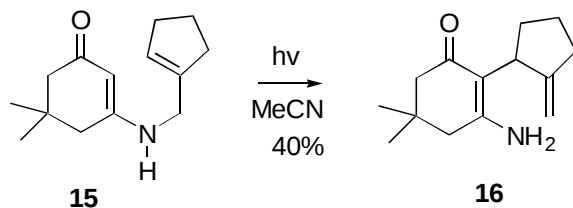
Scheme 4

Base catalyzed epimerization of the *N*-acetyl-5-*syn*-ketone (**7d**) with potassium *t*-butoxide/*t*-BuOH affords the 5-*anti*-ketone (**8d**), but also provides the enone cleavage product (**13**) (Scheme 5).⁷ The 5-*anti*-ketone (**8d**) is recovered unchanged under these reaction conditions. Both ketone isomers (**7d/8d**) react with KOH to give a mixture of diketoacetamide (**14**) and enone (**13**) via a β -elimination pathway.

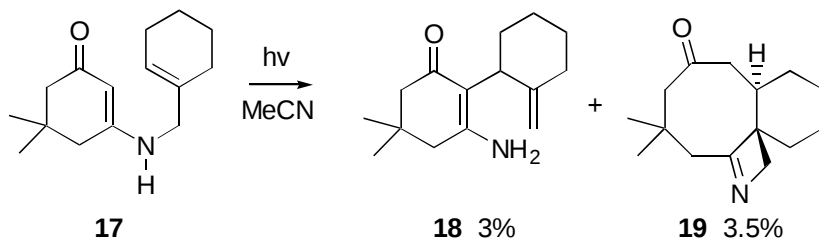


Scheme 5

The presence of an *N*-alkyl or *N*-acyl substituent is important to the outcome of these photochemical reactions. Irradiation of the *N*-(H)-vinylogous amide (**15**) forms the photo-aza-Claisen rearrangement product (**16**) in moderate yield (Scheme 6).¹⁰ The homologous cyclohexeneamide (**17**) under the same conditions affords photo-aza-Claisen product (**18**), *albeit* in very low yield (Scheme 7). The irradiation also yields a second product (**19**), whose origin presumably is a De Mayo reaction in which a "straight" [2 + 2] photoadduct from **17** undergoes a retro-Mannich fragmentation.¹⁰

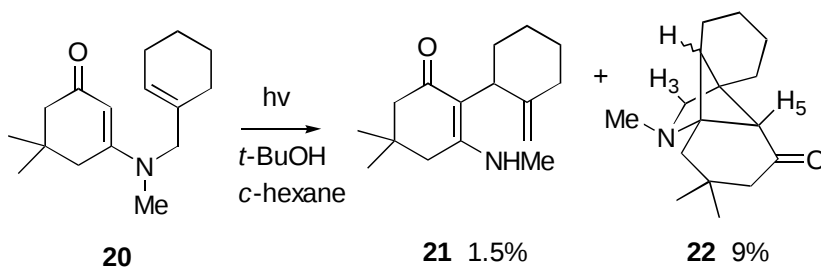


Scheme 6



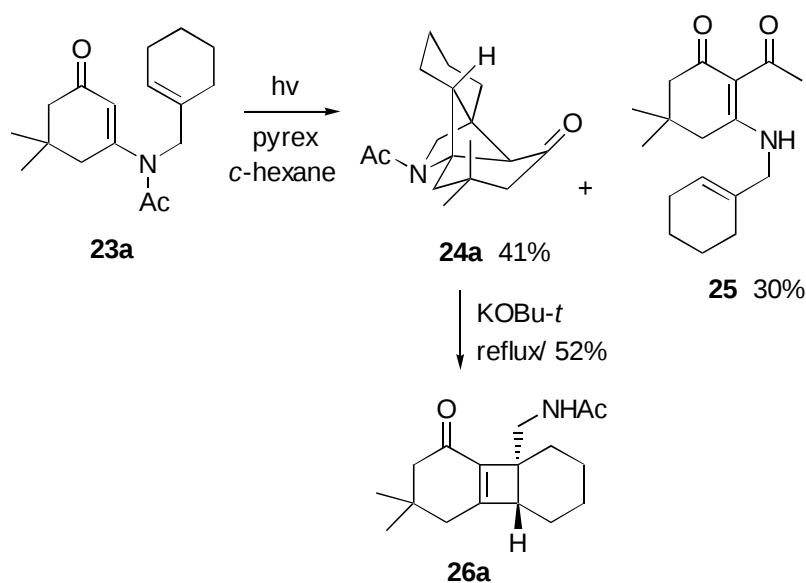
Scheme 7

Introduction of an *N*-methyl substituent in enamide (**20**) alters the photochemical outcome (Scheme 8). The photo-aza-Claisen product (**21**) is formed in trace amounts, but a "crossed" [2 + 2] photoproduct (**22**) with a 2-azabicyclo[2.1.1]hexane structure is obtained as well.¹⁰ The *cis* fusion for the cyclohexanone ring of **22** was assigned on the basis of W-plan coupling between H₃ and H₅.



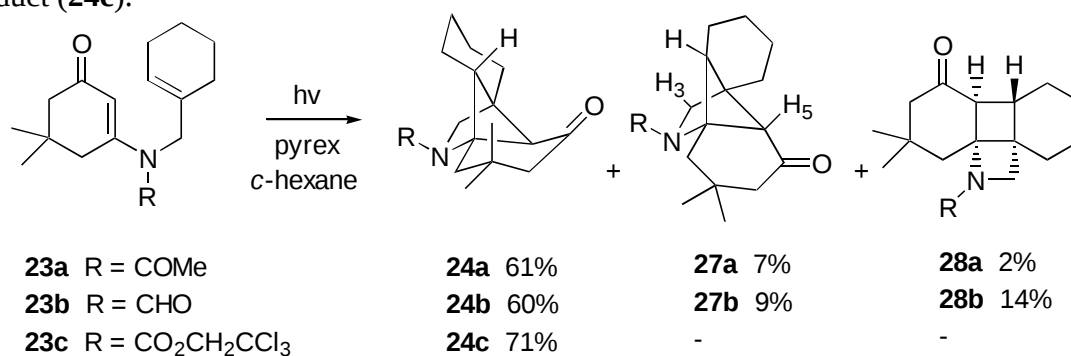
Scheme 8

The yields of photoproduct improve upon acylation of the amine nitrogen (Scheme 9). It was discovered by Schell and coworkers that moderate yields of *N*-acetyl-2-azabicyclo[2.1.1]hexane photoproduct (**24a**) are obtained from *N*-acetylamide (**23a**).¹¹ The structure (**24a**) was confirmed by X-Ray analysis. Also obtained from the irradiation of **23a** is the 1,3-acyl shift product (**25**). Treatment of adduct (**24a**) with potassium *t*-butoxide affords a ring-opened cyclobutene (**26a**), whose substituents were presumed to be *trans* on the basis of the structure of **24a** and mechanistic considerations. The *trans* stereochemical assignment to **26a** was later shown to be incorrect by Swindell.¹²



Scheme 9

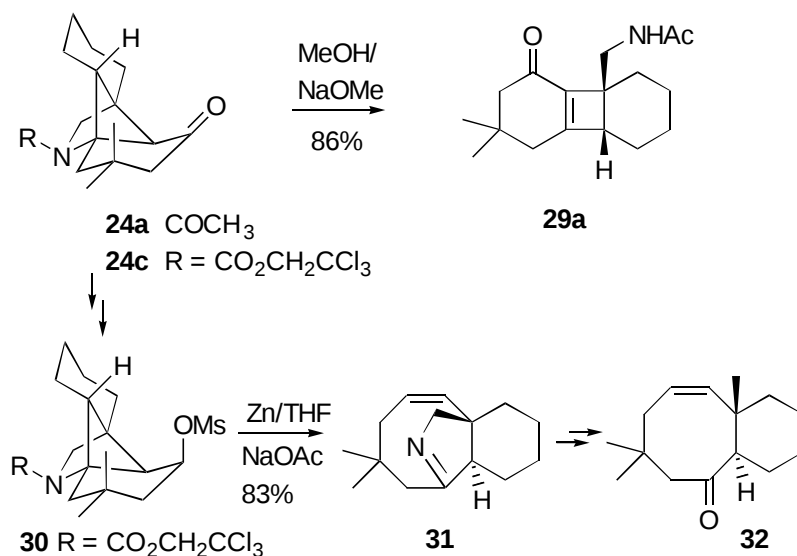
Swindell envisaged using cycloadduct (**24a**) as a taxane BC ring substructure synthon and so repeated Schell's experiment (Scheme 10).¹² Irradiation of **23a** did afford photoproduct (**24a**) as the major product, accompanied by minor amounts of a stereoisomer (**27a**), and a small amount of "straight" [2 + 2] photoadduct (**28a**). It was also reported that the carbamate (**23c**) affords the synthetically more useful photoproduct (**24c**).



Scheme 10

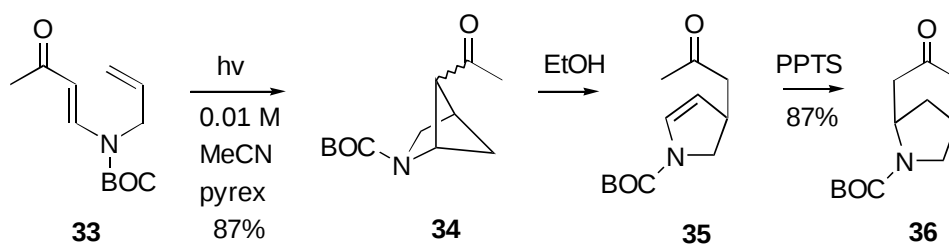
Upon treatment with base, ketone (**24a**) ring opens to cyclobutene (**29a**), which is assigned *cis* geometry on the basis of NOE evidence (Scheme 11).¹² Swindell did prepare the desired *trans* fused taxane BC ring substructure (**32**). Ketone (**24c**) was converted in a straightforward manner to a mesylate (**30**), which after protecting group removal was ring cleaved to give the imine (**31**). Further modifications gave octenone (**32**) in eight overall steps (21%) from photoproduct (**24c**).

Winkler¹³ prepared the vinylogous amide (**33**) by reaction of di-*t*-butyl carbonate with the adduct of allylamine and 3-butyne (Scheme 12). Irradiation leads to 5-acyl-2-azabicyclo[2.1.1]hexane (**34**) as a mixture of stereoisomers. Exposure of **34** to refluxing ethanol causes a retro-Mannich reaction to enamide (**35**), which upon further treatment with PPTS provides the 6-azabicyclo[3.2.1]octanone (**36**). This cleavage-recondensation method was utilized to convert enamide (**37**) to ketone (**38**), and then to the core

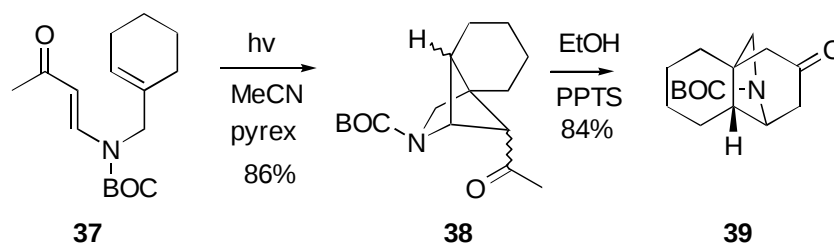


Scheme 11

structure (**39**) found in the azabicyclohetisine alkaloids (Scheme 13).¹³

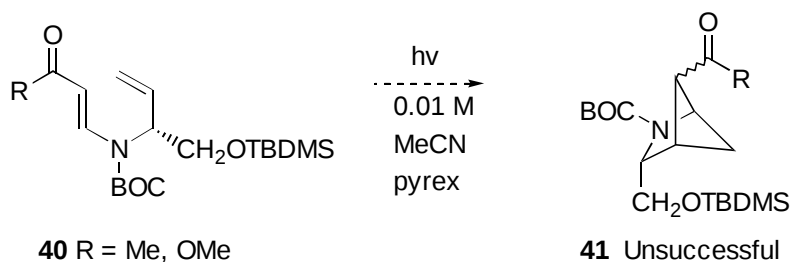


Scheme 12



Scheme 13

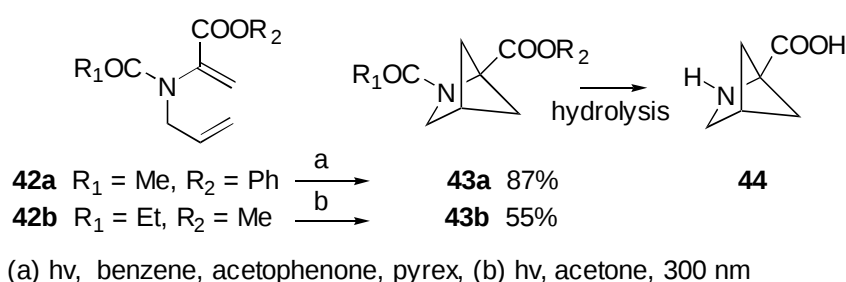
In an attempt to prepare 3-substituted 2-azabicyclo[2.1.1]hexanes using this photochemical approach Lin irradiated the chiral substrates (**40**) (Scheme 13).¹⁴ The desired [2 + 2] photoadducts (**41**) could not be isolated in either case.



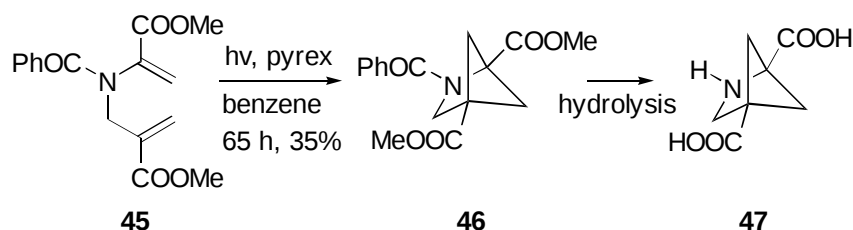
Scheme 14

B. Photochemical ring closure of cross-conjugated 1-acyl- or 1-aryl-*N*-vinyl-*N*-allylamines.

The isolation of 2,4-methanoproline (**44**) from the seeds of *Ateleia herbert smithii* Pittier (Leguminosae) in 1980 provided much of the impetus for development of new synthetic approaches to 2-azabicyclo[2.1.1]hexanes.^{15,16} Shortly thereafter, irradiation of cross-conjugated *N*-vinyl-*N*-allyl substrates (**42**) was exploited for the synthesis of 2,4-methanoproline from the photoproducts (**43**) (Scheme 15).^{3,17,18} The conformationally constrained 2,4-methanoproline (**44**) was incorporated into several proteins in place of proline.¹⁹⁻²³ It was discovered that the more rigid **44** stabilizes the *s-trans* conformation of the amide linkage to the ring *N*-atom.

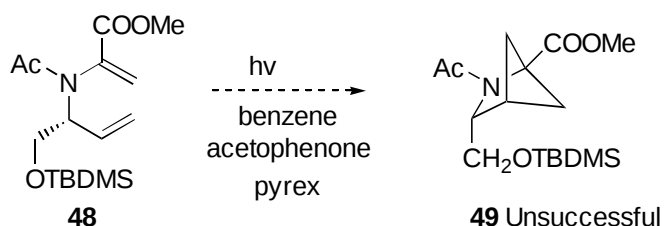


Scheme 15



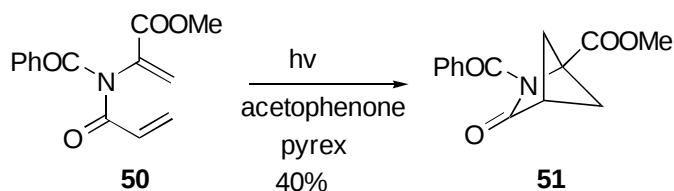
Scheme 16

Other 2-azabicyclo[2.1.1]hexanes, as conformationally constrained pyrrolidines, have generated similar interest. Esslinger and coworkers prepared 2,4-methanopyrrolidine-2,4-dicarboxylic acid (**47**) by irradiation of amide (**45**) and subsequent hydrolysis of the photoproduct (**46**) (Scheme 16).²⁴ The diacid (**47**) was found to act as a substrate for the rat forebrain synaptosomal glutamate uptake system.²⁵ In the hope of obtaining a 3-substituted 2-azabicyclo[2.1.1]hexane (**49**) using this photochemical approach Lin irradiated the chiral substrate (**48**) (Scheme 17).¹⁴ Only starting material (**48**) was recovered.

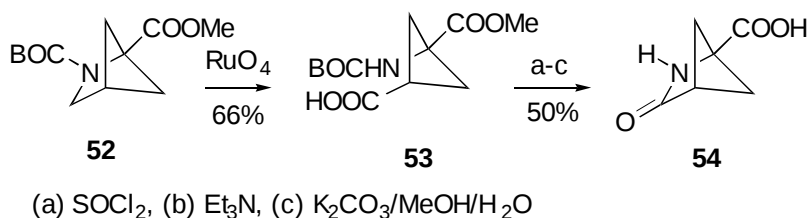


Scheme 17

The photoirradiation method also succeeds for the preparation of the lactam (**51**), but only at high dilution of diene (**50**), so it is impractical for large scale (Scheme 18). An alternative entry to the lactam acid (**54**) is via RuO_4 oxidation of carbamate (**52**) to give the ring-opened acid (**53**), followed by ring closure and selective ester hydrolysis (Scheme 19).³

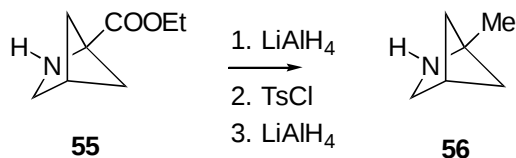


Scheme 18

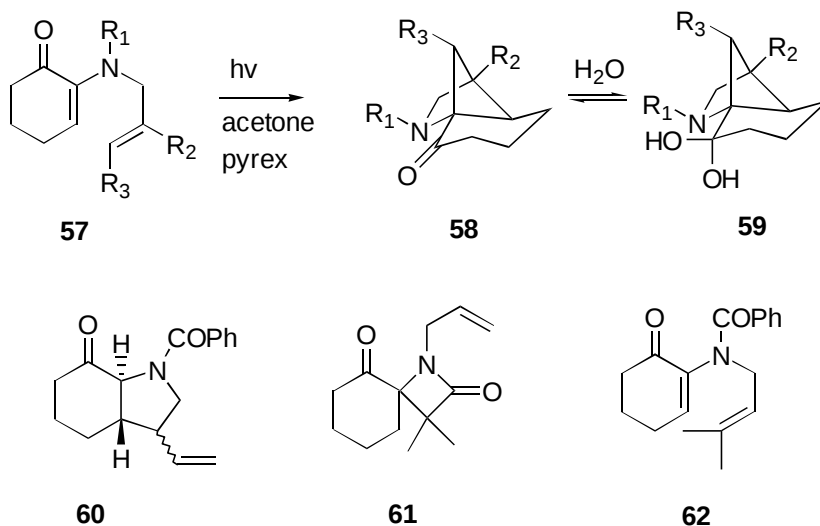


Scheme 19

Photoadduct (**55**) has been modified to prepare other 1-substituted 2-azabicyclo[2.1.1]hexanes (Scheme 20). Malpass used a reductive sequence to convert ester (**55**) to the 1-methyl structure (**56**), utilized in a synthesis of a 1-azabicyclo[2.1.1]hexane (See Section II.)²⁶



Scheme 20



Scheme 21

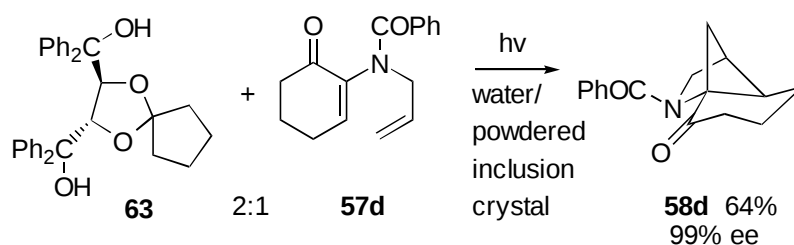
Ikeda and coworkers in 1982 reported photocyclizations of *N*-acyl cross-conjugated amides (**57**) (Scheme

21 and Table 1).²⁷ Amide (**57a**) (Entry 1) gives the *trans*-fused ketone (**58a**) upon irradiation in acetone or acetophenone (Scheme 21). The ketone (**58a**) rapidly absorbed water to form the hydrate (**59**). The photocyclization failed with the *N*-methyl derivative (**58b**) (Entry 2),²⁷ but was successful with other *N*-acyl derivatives shown in Table 1.²⁸ Substrate (**57f**) (Entry 6) afforded minor amounts of an "ene" product (**60**). Substrate (**57g**) (Entry 7) afforded a β -lactam (**61**) by hydrogen abstraction from the acyl group and subsequent ring closure. The irradiation of **62** having geminal methyl groups on the allyl terminus gave only a complex mixture.

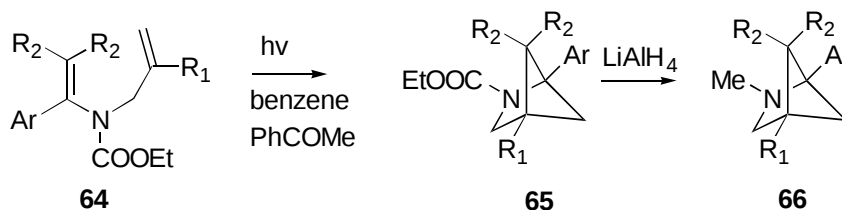
Table 1. Synthesis of 1-Acyl-2-azabicyclo[2.1.1]hexanes by Irradiation of Substrates (**57**).²⁸

Entry	Substrate	R ₁	R ₂	R ₃	Product	Yield (%)	Product	Yield (%)
1	57a	COMe	H	H	58a	52		
2	57b	Me	H	H	58b	0		
3	57c	COOMe	H	H	58c	56		
4	57d	COPh	H	H	58d	61		
5	57e	COPh	Me	H	58e	54		
6	57f	COPh	H	Me	58f	25	60	16
7	57g	COCHMe ₂	H	H	58g	26	61	20

Toda and coworkers have reported an efficient enantioselective photocyclization (Scheme 22).²⁹ Photoirradiation of a 2:1 inclusion crystal of **57d** with the optically active host crystal (*R,R*)-(-)-*trans*-4,5-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (**63**) in water containing sodium alkyl sulfate as a surfactant gave 99% ee of photoproduct (**58d**). The reaction was extended to a similar chiral host and other *N*-acyl substituents with similar outcomes.



chloropyridyl-methanonicotine analogs (**66d-f**) (Table 2). Structure (**66d**) appears to be a nicotinic agonist.



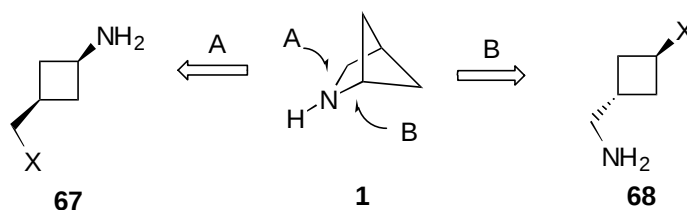
Scheme 23

Table 2. Cycloadditions of Substrates (**64**) to give 1-Aryl-2-Azabicyclo[2.1.1]hexanes (**65**).³⁰

Entry	Substrate	Product	Ar	R ₁	R ₂	Yield
1	64a	65a	<i>p</i> -ClPh	H	H	52
2	64b	65b	Ph	H	Me	55
3	64c	65c	Ph	Me	Me	0
4	64d	65d	4-Cl-3-Pyridyl	H	H	68
5	64e	65e	4-Cl-3-Pyridyl	Me	H	35
6	64f	65f	4-Cl-3-Pyridyl	H	Me	21
7	64g	65g	Pyridyl	H	H	32

C. Synthesis of 2-azabicyclo[2.1.1]hexanes from cyclobutanes.

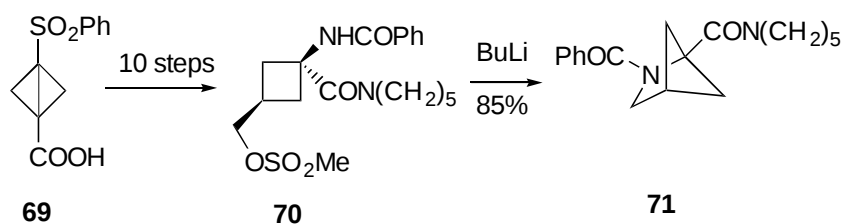
Disconnection of the 2-azabicyclo[2.1.1]hexane skeleton (**1**) at bond A suggests a *cis*-1-amino-3-X-methylcyclobutane (**67**); breaking of bond B suggests a *trans*-1-X-3-aminomethylcyclobutane (**68**) (Scheme 24). Strategies to prepare azabicyclo[2.1.1]hexanes (**1**) by the ring closures of substrates related to either **67** or **68** have met with success.



Scheme 24

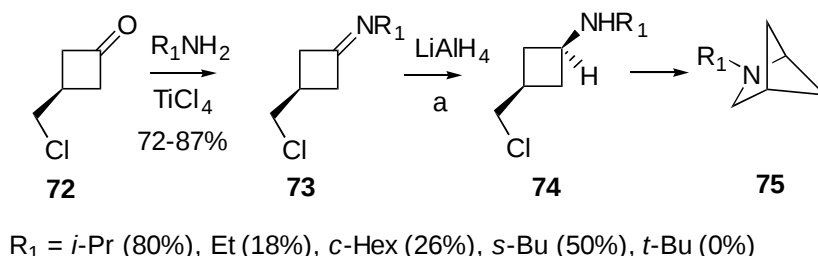
1. Bond A disconnections. The aminocyclobutane route.

Gaoni in 1995 prepared the methanoproline derivative (**71**) by base catalyzed ring closure of the *cis*-1-acylamino-3-hydroxymethyl mesylate (**70**) (Scheme 25).⁴ The method suffers from the many steps involved in preparing **70** from the unusual precursor (**69**).



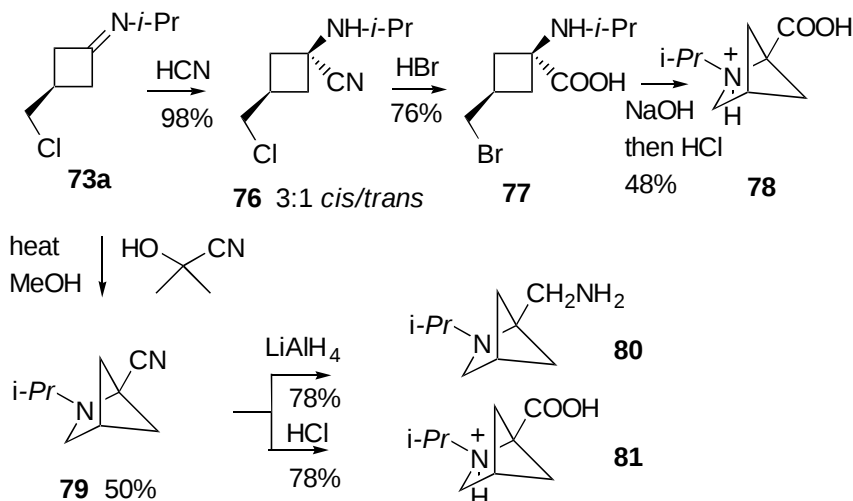
Scheme 25

De Kimpe and coworkers reported a more efficient route to 2-azabicyclo[2.1.1]hexanes (75) from the cyclobutanone (72), prepared in 31% yield in two steps from allyl chloride and dichloroketene (Scheme 26).³¹ Conversion of the cyclobutanone (72) to the imine (73), and subsequent reduction with lithium aluminum hydride *anti* to the chloromethyl substituent, leads directly *via* 74 to the *N*-alkyl-azabicycles (75). The ring closure fails for 74, $\text{R}_1 = \text{tert-butyl}$.³²



Scheme 26

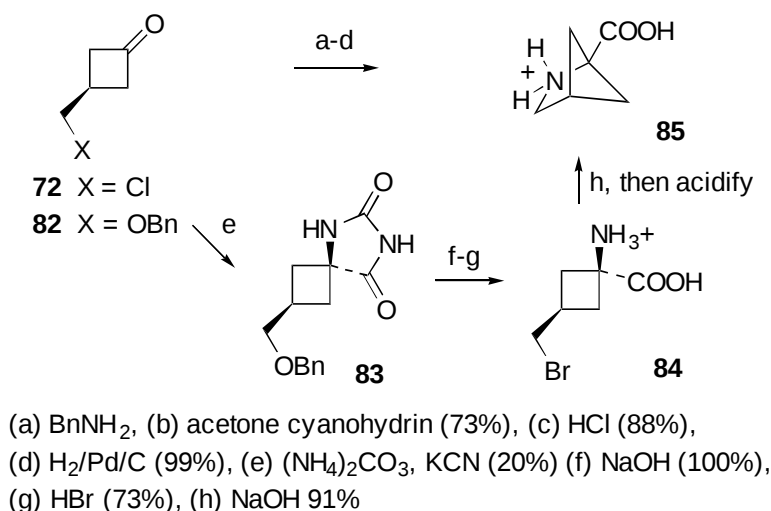
Substituents can be introduced at C_1 by taking advantage of the chemistry of cyclobutanamines (Scheme 27).³¹ When *N*-isopropylimine (73a) is reacted with cyanide, a mixture is obtained favoring the desired *cis* stereoisomer (76). The amino nitrile (76) is unstable to base, but is converted by HBr to the bromo acid (77). Ring closure of 77 to the azabicyclic amino acid (78) occurs upon base treatment. Alternatively, the imine (73a) when heated with acetone cyanohydrin in methanol affords the 1-cyano-2-azabicyclo[2.1.1]hexane (79). Reduction of 79 gives the diamine (80); hydrolysis affords the amino acid (81).



Scheme 27

By using benzylamine in place of isopropylamine in the above sequence, Stevens was able to extend the

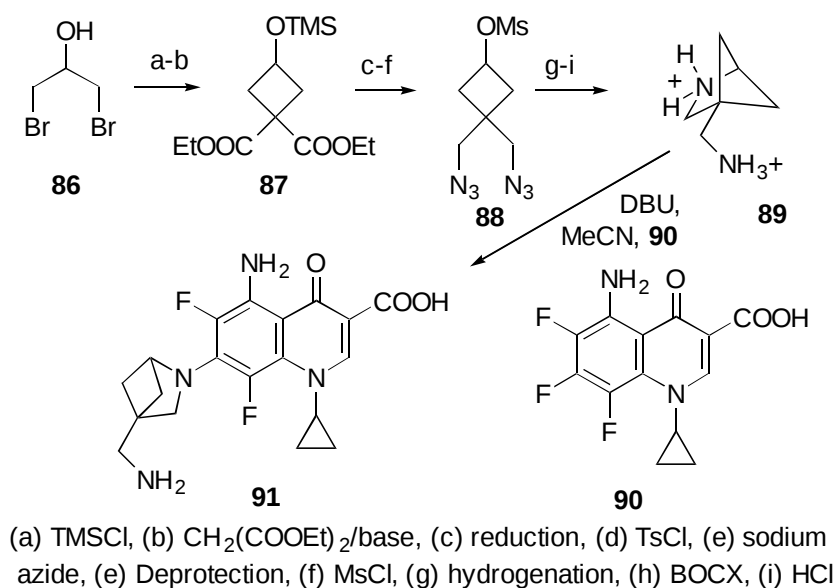
ring closure method to prepare *N*-H derivatives of 2,4-methanoproline from cyclobutanone (**72**) (Scheme 28).³¹ The *N*-benzyl group is removed by catalytic hydrogenation to give the amine salt (**85**). Alternatively the cyclobutanone (**82**) is converted to hydantoin (**83**), isolable by selective crystallization. Hydrolysis and ring closure of **83** affords the 2,4-methanoproline salt (**85**).³³



Scheme 28

2. Bond B disconnections. The aminomethylcyclobutane route.

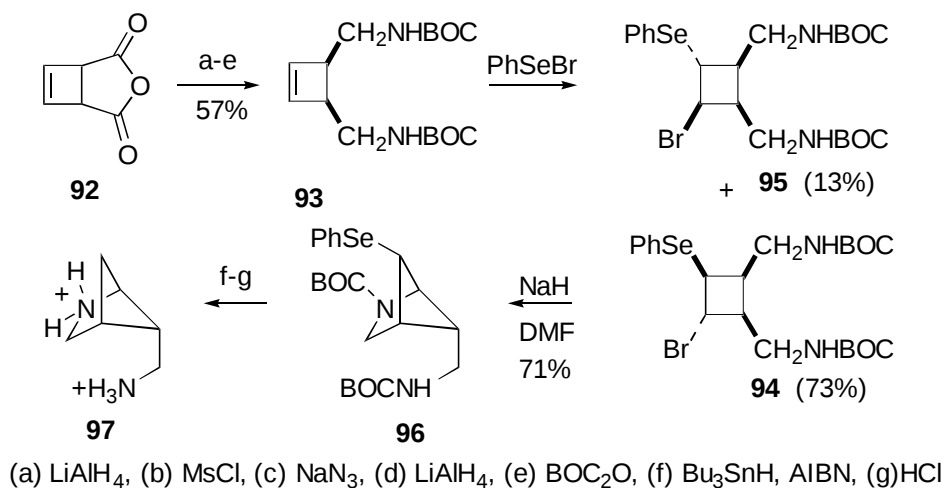
A novel twist on the ring closure route that avoids stereochemical issues and provides a substituent at C₄ of the 2-azabicyclohexyl was reported by Park and coworkers (Scheme 29).³⁴ The diamine salt (**89**) was desired in order to prepare antibacterial azabicyclohexylquinolonecarboxylic acid derivatives. The protected cyclobutanol (**87**) is prepared from 1,3-dibromo-2-propanol (**86**).



Scheme 29

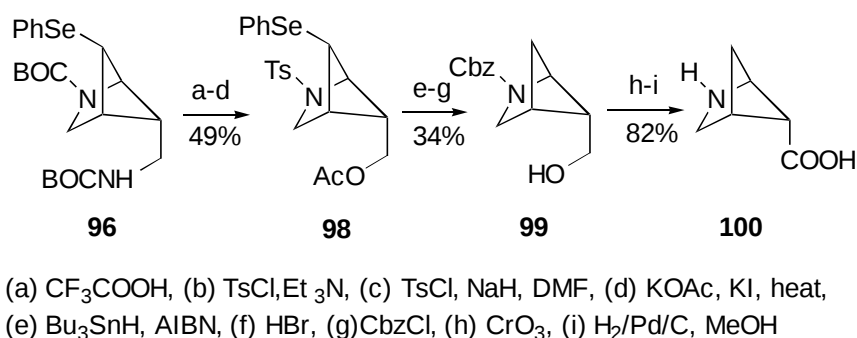
Reduction of the ester groups of **87** gives a pair of hydroxymethyl groups that lead to the diazide (**88**), whose reduction is accompanied by ring closure to give a diamine isolated as salt (**89**). Coupling of 7-fluoro-4-oxoquinolone (**90**) with the diamine from **89** gives adduct (**91**), which is considerably more potent than both ciprofloxacin and sparfloxacin against six gram-positive bacterial strains *in vitro*.

Huet has recently reported application of the Bond B disconnection route to the preparation of 5-*syn*-substituted 2-azabicyclo[2.1.1]hexanes (Scheme 30).³⁵ The cyclobutene anhydride (**92**), prepared in two steps from maleic anhydride and *trans*-1,2-dichloroethene, is converted in five steps to the protected diamine (**93**). Addition of PhSeBr to **93** affords a mixture of isomers (**94/95**) favoring **94** in which the phenylselenenyl group is mainly *syn* to the nitrogen substituents. Ring closure from **95** is effected by sodium hydride to provide the functionalized azabicycle (**96**). Reductive removal of the phenylselenenyl group and nitrogen deprotection gives the diamine salt (**97**).



Scheme 30

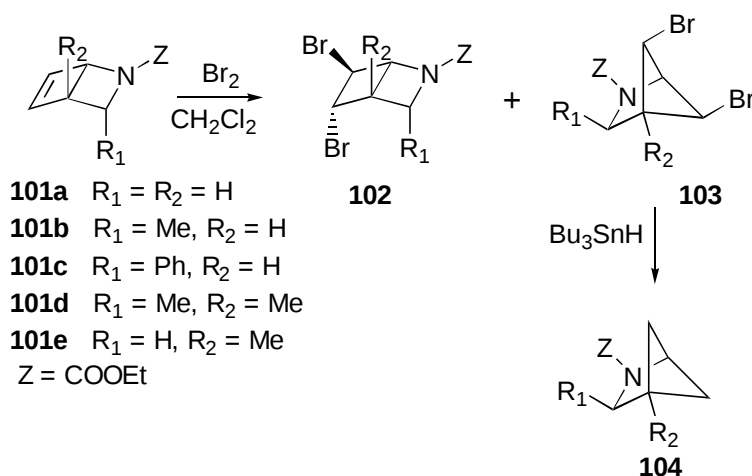
In order to prepare a 5-*syn*-carboxylic acid (**100**), it is necessary to remove the amino group from the aminomethyl side chain of **96** (Scheme 31). This is done by a sequence of steps in which acetate (**98**) is ultimately formed by displacement of an *N,N*-ditosylamide using potassium acetate. Reduction and protecting group modification gives alcohol (**99**), which is oxidized to the novel acid (**100**). Biological evaluations of diamine (**97**), amino alcohol (**99**) and amino acid (**100**) indicate that each show no significant activity for protection of an unspecified crop.³⁵



Scheme 31

D. Synthesis of 2-azabicyclo[2.1.1]hexanes from 2-azabicyclo[2.2.0]hex-5-enes.

N-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hexanes (**101a-e**) can be prepared by irradiation of 1,2-dihydropyridines readily formed from pyridine or an appropriately substituted pyridine.^{36,37} Addition of bromine to **101a** in CH₂Cl₂ results in a 55:45 mixture of *trans*-dibromide (**102a**) and rearranged dibromide (**103a**) (Scheme 32).^{5,37} Reductive debromination of **103a** affords the *N*-protected azabicycle (**104**). As shown in Table 3, effectiveness of the rearrangement increases with the introduction of non-reactive 3-*endo* substituents in substrates (**101b-d**); only the rearranged isomers (**103b-d**) are observed.



Scheme 32

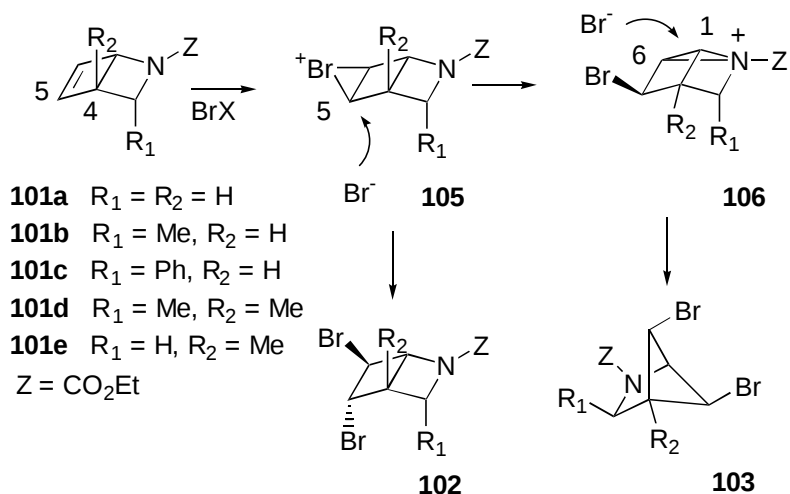
Table 3. Formation of 2-Azabicyclo[2.1.1]hexanes by Reaction of 2-Azabicyclo[2.2.0]hex-5-enes (**101**) with Bromine in Methylene Chloride.

Entry	Substrate	R ₁	R ₂	Product	Yield (%)	Ref.
1	101a	H	H	103a	27-35 ^a	5,37
2	101b	Me	H	103b	99	37
3	101c	Ph	H	103c	80	37
4	101d	Me	Me	103d	89	37
5	101e	H	Me	103e	54 ^b	37

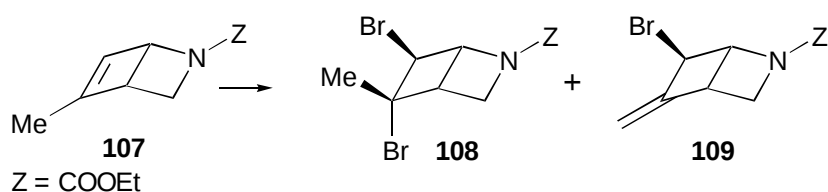
^aAccompanied by 34-43% of dibromide (**102a**). ^bAccompanied by 20% of dibromide (**102e**).

The mechanism shown in Scheme 33 explains these observations. Attack of bromide ion at C5 of bromonium ion (**105**) gives unrearranged dibromide (**102**). If the attack at C5 is blocked by a 3-*endo*-R₁ substituent the intermediate ion (**105**) rearranges preferentially to the aziridinium ion (**106**). This ion then is selectively attacked at C1 to give the rearranged dibromide (**103**). The rearrangement completely fails to occur if a cation stabilizing substituent is introduced onto the alkene 5-position; structure (**107**)

gives a mixture of dibromide (**108**) and allyl bromide (**109**) (Scheme 34).

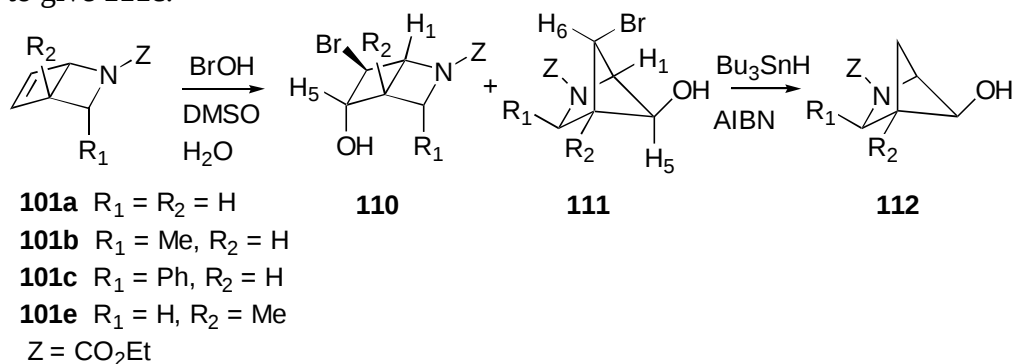


Scheme 33



Scheme 34

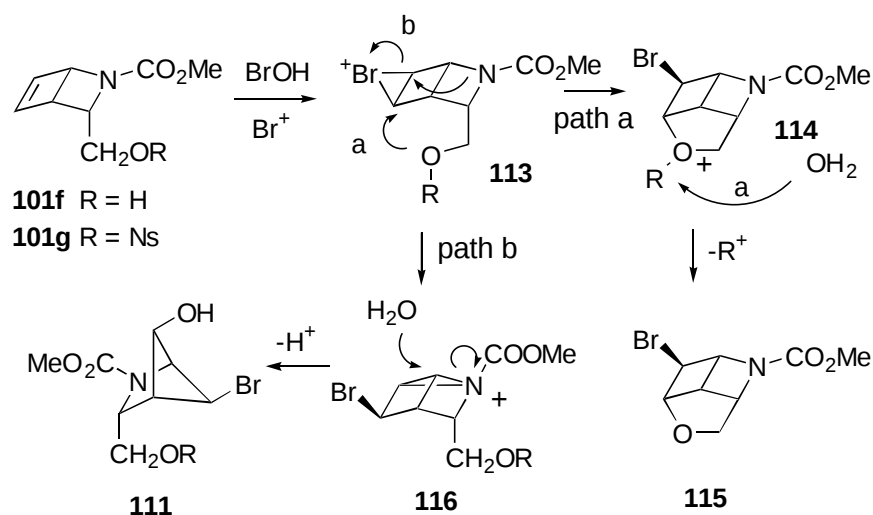
In a similar manner hypobromous acid in DMSO/water reacts with alkenes (**101**) (Table 4).^{5,38} Alkene (**101a**) and HOBr (Entry 1) give 70-80% of a 7:3 mixture of unrearranged bromohydrin (**110a**) and rearranged bromohydrin (**111a**) (Scheme 35). The bromine atom can be reductively removed to afford the parent amino alcohol (**112**). An unreactive 3-*endo* methyl or phenyl substituent in alkenes (**101b-c**) blocks the formation of unrearranged bromohydrins (**110b-c**) and yields the rearranged bromohydrins (**111b-c**) exclusively (Entries 2 and 3).³⁸ The 4-methyl group in **101e** (Entry 4) does not block rearrangement to give **111e**.



Scheme 35

By contrast (Scheme 36), the nucleophilic oxygen of the 3-*endo*-hydroxymethyl substituent of **101f** (Entry 5) attacks the bromonium ion (**113**) to give an oxonium ion (**114**), which deprotonates to give the

tricycle (**115**) (path a).³⁹ The tendency for neighboring group participation by oxygen can be lessened by conversion of the alcohol to the nosylate (**101g**) (Entry 6), and this provides aziridinium ion (**116g**) and subsequently bromohydrin (**111g**) in low yield. Preference for rearranged product (**111g**) is further enhanced in the solvent system THF/water (Entry 7). The multiple functionality of **111g** should allow for numerous additional synthetic manipulations.



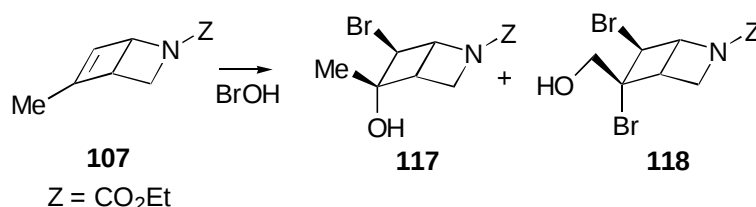
Scheme 36

Table 4. Formation of 2-Azabicyclo[2.1.1]hexanols (**111**) by Reaction of 2-Azobicyclo[2.2.0]hex-5-enes (**101**) with NBS in 2:1 DMSO/water.

Entry	Substrate	R	R ₁	R ₂	Product	Yield (%)	Ref.
1	101a	Et	H	H	111a	21-24 ^a	5
2	101b	Et	Me	H	111b	85	38
3	101c	Et	Ph	H	111c	47	38
4	101e	Et	H	Me	111e	44 ^b	38
5	101f	Me	CH ₂ OH	H	111f	0	39
6	101g	Me	CH ₂ ONs	H	111g	16	39
7	101g	Me	CH ₂ ONs	H	111g	60 ^c	39

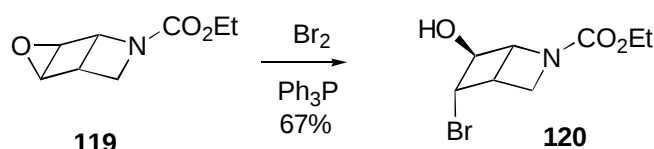
^a Also, 49-56% of bromohydrin (**110a**). ^b Also, 11% of bromohydrin (**110e**). ^c Solvent 2:1 THF/water.

The presence of a cation stabilizing substituent on the alkene blocks the desired rearrangement reaction. Alkene (**107**) affords a mixture of bromohydrin (**117**) and dibromoalcohol (**118**) (Scheme 37).³⁸

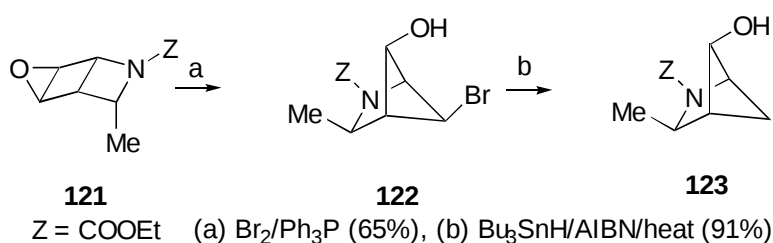


Scheme 37

A variation of the rearrangement approach to 2-azabicyclo[2.1.1]hexanols uses an epoxide. Epoxide (**119**) and bromine/triphenyl phosphine give the unrearranged bromohydrin (**120**) (Scheme 38).³⁸ Epoxide (**121**), which has a 3-*endo*-methyl group, gives bromohydrin (**122**) (Scheme 39). Reductive debromination of **122** affords **123**, which is epimeric at C₃ with bromohydrin (**112b**) (R₁ = Me, R₂ = H) obtained by addition of hypobromous acid to 3-*endo*-methyl-2-azabicyclo[2.2.0]hex-5-ene (**101b**).



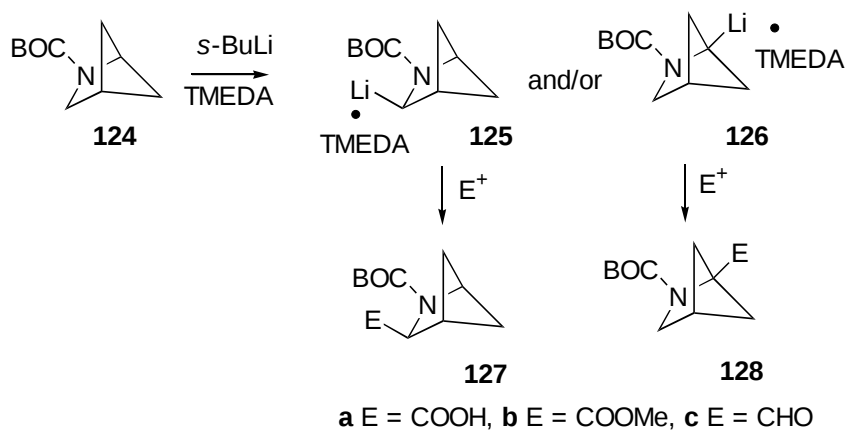
Scheme 38



Scheme 39

E. Synthesis of 2-azabicyclo[2.1.1]hexanes by α -functionalization.

The protocol of Beak was applied to *N*-BOC azabicyclo (**124**) in order to introduce functionalization adjacent to the nitrogen atom.⁴⁰ Krow and coworkers found that at -78°C , *s*-BuLi/TMEDA gives a mixture of regioisomeric α -anions (**125**) and (**126**) (Scheme 40).⁶ Quenching of anions (**125/126**) with carbon dioxide, methyl chloroformate, or DMF provides a mixture of 3- and 1-substituted 2-azabicycles (**127/128**) (Table 5). When anion generation is effected at 0°C , only the 1-substituted azabicycles (**128**) are formed upon electrophilic quenching.



Scheme 40

Table 5. Formation of 1- and 3-Substituted 2-Azabicyclo[2.1.1]hexanes (**127/128**) from Azabicyclo (**124**) by α -Functionalization.⁶

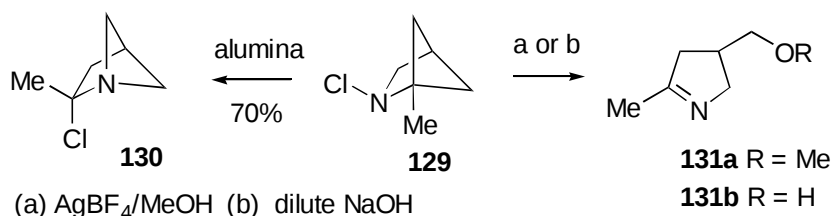
Entry	Reagent ^a	T (°C) ^b	E	Product	Ratio of 127:128	Isolated yield
1	CO ₂	0	COOH	128b		98
2	CO ₂	-78	COOMe	127b/128b	43:57	76
3	ClCOOMe	0	COOMe	128b		70
4	ClCOOMe	-78	COOMe	127b/128b	50:50	81
5	DMF	0	CHO	128c		38
6	DMF	-78	CHO	127c/128c	49:51	71

^aLithium anions were generated from **124** in ether using *s*-BuLi in the presence of TMEDA. ^bTemperature at which the anion was generated.

II. SYNTHESIS OF 1-AZABICYCLO[2.1.1]HEXANES.

A. Synthesis of a 1-azabicyclo[2.1.1]hexane from a 2-azabicyclo[2.1.1]hexane.

Malpass has found that 1-methyl-*N*-chloro-2-azabicyclo[2.1.1]hexane (**129**), when placed on alumina in CH₂Cl₂/petroleum ether, rearranges to the 2-chloro-2-methyl-1-azabicyclo[2.1.1]hexane (**130**) (Scheme 41).²⁶ The retention of chlorine during methanol elution of the product (**130**) from alumina is surprising; the absence of methanol incorporation suggests rearrangement to chloramine (**130**) is complete prior to the methanol elution. By contrast, treatment of the *N*-chloro substrate (**129**) with AgBF₄/methanol affords the ring-opened pyrroline (**131a**) in unspecified yield. The 2-chloro-1-azabicyclohexane (**130**) was shown not to be a precursor of **131a** in AgBF₄/methanol, but to be a precursor of alcohol (**131b**) in dilute aqueous base.

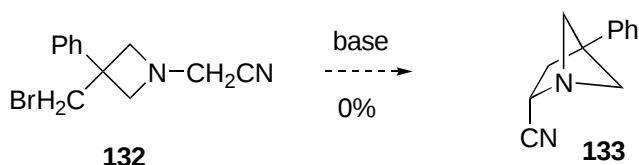


Scheme 41

B. Attempted synthesis of a 1-azabicyclo[2.1.1]hexane from an azetidine.

Attempted ring closures of the bromomethylazetidine (**132**) to give the 1-azabicyclo[2.1.1] structure (**133**) were unsuccessful. Heating of **132** with sodium or lithium hydride resulted primarily in recovery of starting material (Scheme 42). Reaction of potassium *tert*-butoxide or potassium amide in ammonia

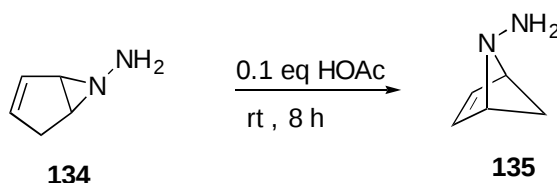
with **132** gave polymeric material.⁴¹



Scheme 42

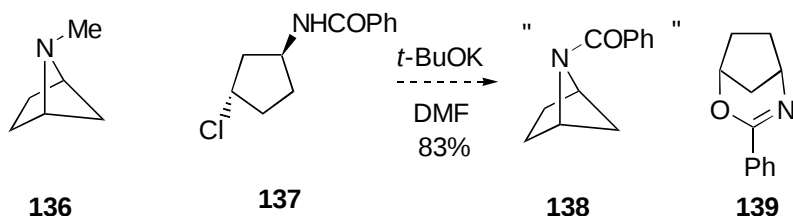
III. SYNTHESIS OF 5-AZABICYCLO[2.1.1]HEXANES.

Hoesch and Dreiding have proposed that *N*-amino-6-azabicyclo[3.1.0]hex-2-ene (**134**) undergoes a rearrangement in CDCl_3 solution containing 0.1 molar equivalent of acetic acid to give after 8 h an 8:3:3 mixture of unreacted **134** + cyclopentene: cyclopentadiene: *N*-amino-5-azabicyclo[2.1.1]hex-2-ene (**135**) (Scheme 43).⁴² The structural assignment to **135** was based solely on 60 MHz ^1H NMR peaks in this mixture, primarily using peaks at δ 6.01 (t or dd, $J = 3\text{--}4$ Hz) for the vinyl hydrogens and δ 4.04 (m) for the bridgehead protons. After 8 d the NMR peaks assigned to **135** had disappeared.



Scheme 43

MM3 calculations predict a high inversion barrier ($15.3 \text{ kcal mol}^{-1}$) for azabicycle (**136**).⁴³ An attempt to synthesize *N*-benzoyl-5-azabicyclo[2.1.1]hexane (**138**) by ring closure of *trans*-1-chloro-3-acylamine (**137**) was reported (Scheme 44).⁴⁴ However, Olivo has since reassigned the ring-closed structure as **139**.⁴⁵



Scheme 44

Additions in proof.

A convenient photochemical ring closure route to 5-*anti*- and 5-*syn*-carboxy-2,4-methanopyrrolidines and their conversion to 2,4-methanopyrrolidine (**124**) has been reported (I. A.).⁴⁶ The

2-azabicyclo[2.1.1]hexane skeleton (**1**) can be found embedded in tricyclic structures (I. C. 1.).^{47,48} The finding that the rearrangement route from 2-azabicyclo[2.2.0]hex-5-ene (**101a**) is solvent and electrophile dependent has led to greater selectivity in the formation of rearranged dibromide (**103a**) and bromoalcohol (**111**) (I. D.).⁴⁹ A second-chance rearrangement route has enabled synthesis of 5(6)-*syn,anti*-difunctional 2-azabicyclo[2.1.1]hexanes (I. D.).⁵⁰

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