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AZABICYCLO[2.1.1]HEXANES. A REVIEW

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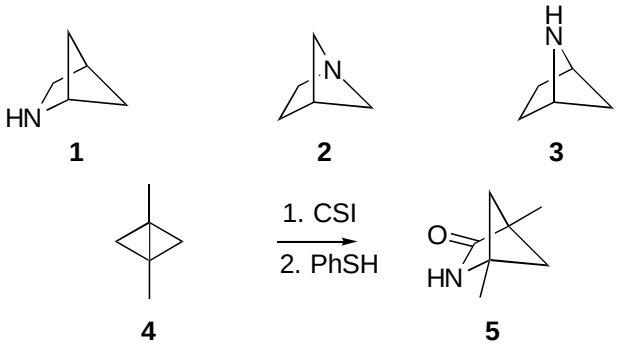
Abstract – The synthesis and reactions of 1-, 2-, and 5-azabicyclo[2.1.1]hexanes are reviewed.

CONTENTS

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.

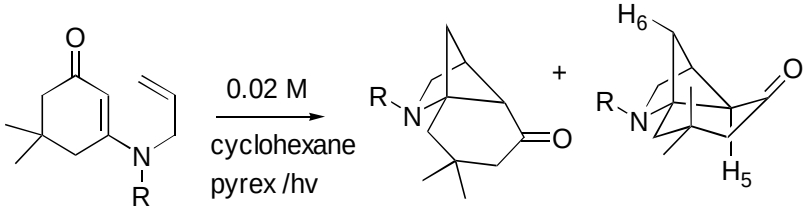


Scheme 1

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]

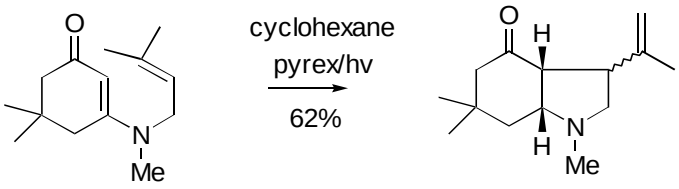


6a R = Me
6b R = $CH_2CH{=}CH_2$
6c R = Ph
6d R = COMe

7a 50-60%
7b 60%
7c 39%
7d 31%

8d 25%

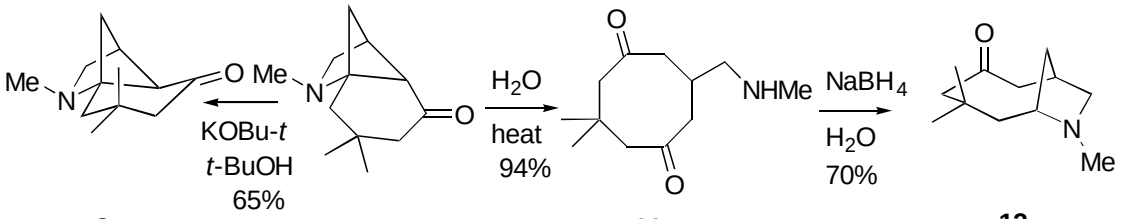
Scheme 2



9 **10**

Scheme 3

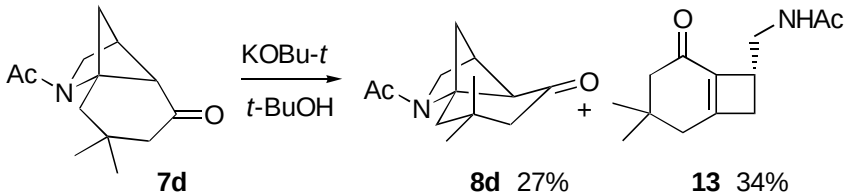
The *N*-Me-5-*syn*-ketone (**7a**), upon brief heating with potassium *t*-butoxide/*t*-BuOH, epimerizes to the 5-*anti*-ketone (**8a**) (Scheme 4). The 5-*syn*-ketone (**7a**) is stable to refluxing toluene, but ring opens in refluxing water to give diketone (**11**). Interestingly, reduction of **11**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



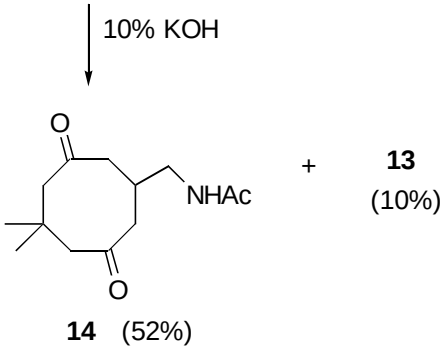
8a **7a** **11** **12**

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.



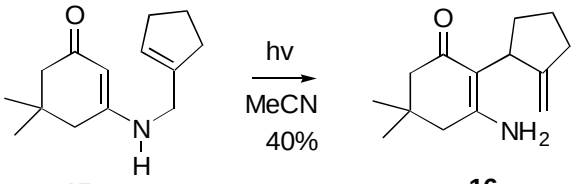
7d **8d** 27% **13** 34%



14 (52%)

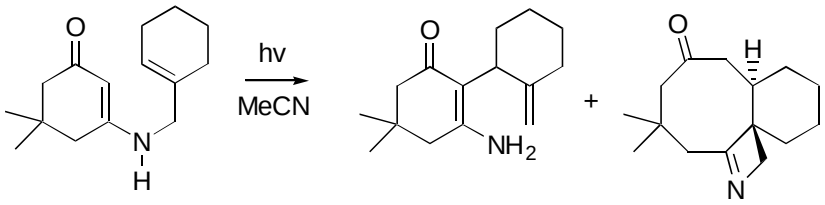
Scheme 5

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 presumedly is a De Mayo reaction in which a "straight" [2 + 2] photoadduct from **17** undergoes a retro-Mannich fragmentation.[10]



15 **16**

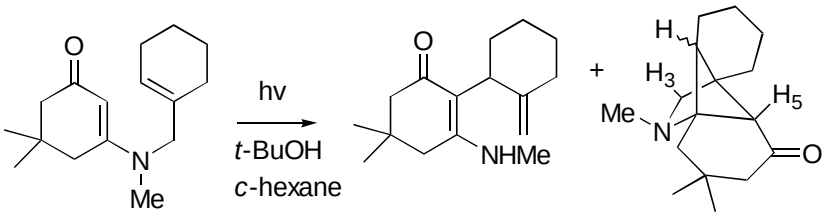
Scheme 6



17 **18** 3% **19** 3.5%

Scheme 7

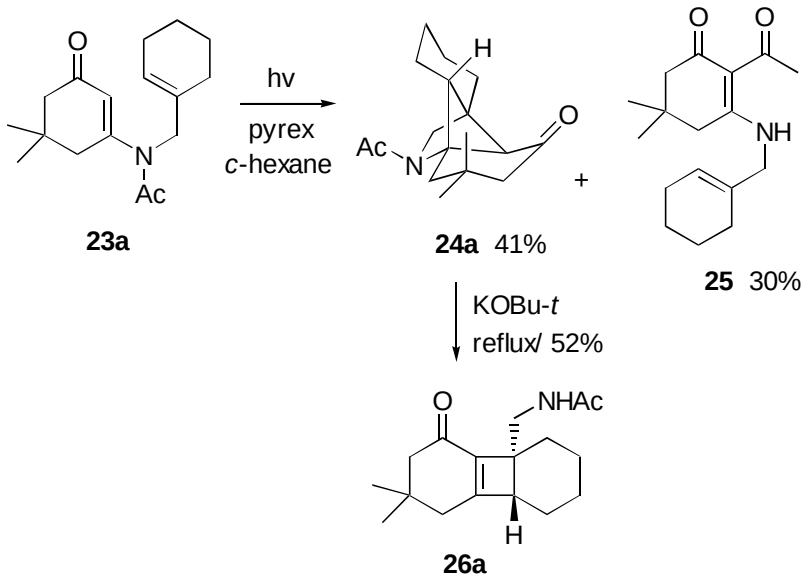
Introduction of an *N*-methyl substituent in enamide (**20**) alters the photochemical outcome (Scheme 8). The photo-aza-Claisen product (**21**) is formed in trace amounts, but a "crossed" [2 + 2] photoproduct (**22**) with a 2-azabicyclo[2.1.1]hexane structure is obtained as well.[10] The *cis* fusion for the cyclohexanone ring of **22** was assigned on the basis of W-plan coupling between H_3 and H_5.



20 **21** 1.5% **22** 9%

Scheme 8

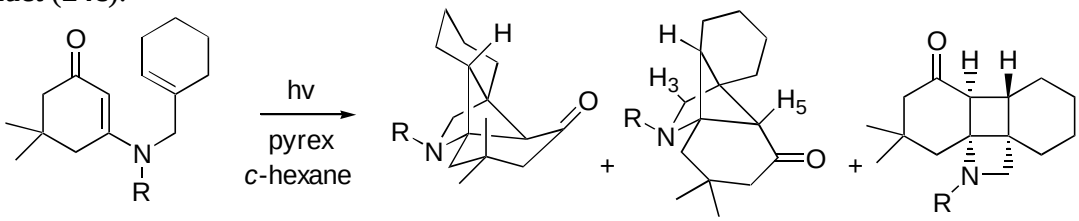
The yields of photoproduct improve upon acylation of the amine nitrogen (Scheme 9). It was discovered by Schell and coworkers that moderate yields of *N*-acetyl-2-azabicyclo[2.1.1]hexane photoproduct (**24a**) are obtained from *N*-acetylamide (**23a**).[11] The structure (**24a**) was confirmed by X-Ray 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]



23a **24a** 41% **25** 30% **26a**

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**).

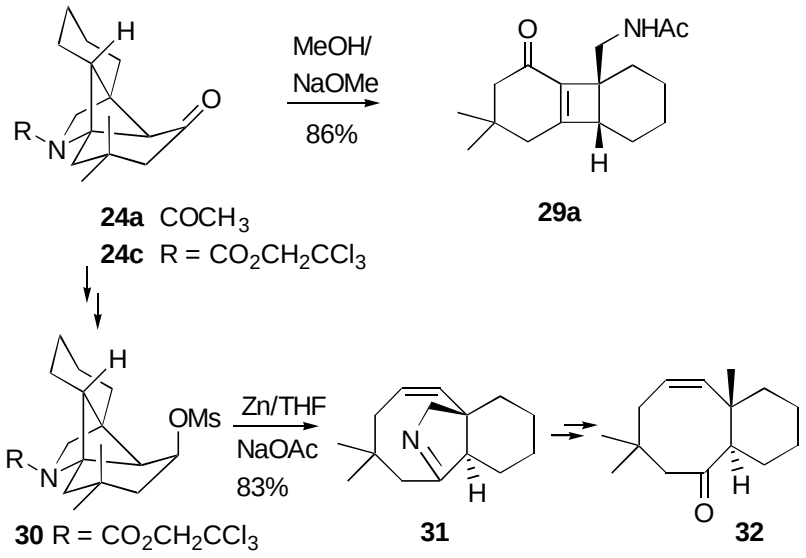


23a R = COMe	**24a** 61%	**27a** 7%	**28a** 2%
23b R = CHO	**24b** 60%	**27b** 9%	**28b** 14%
23c R = $CO_2CH_2CCl_3$	**24c** 71%	-	-

Scheme 10

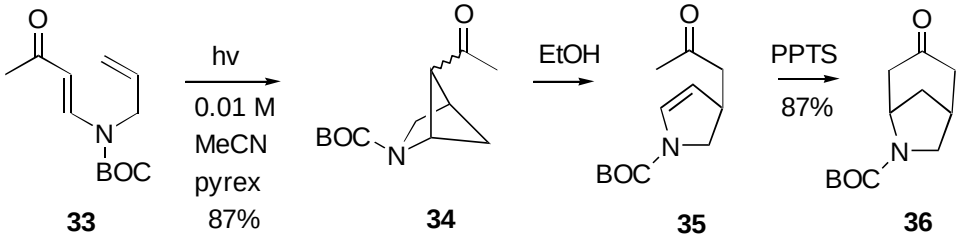
Upon treatment with base, ketone (**24a**) ring opens to cyclobutene (**29a**), which is assigned *cis* geometry on the basis of NOE evidence (Scheme 11).[12] Swindell did prepare the desired *trans* fused taxane BC ring substructure (**32**)**.** Ketone (**24c**) was converted in a straightforward manner 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**).

Winkler[13] prepared the vinylogous amide (**33**) by reaction of di-*t*-butyl carbonate with the adduct of allylamine and 3-butynone (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

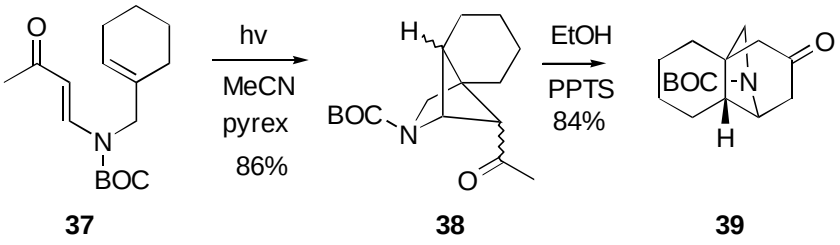


Scheme 11

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

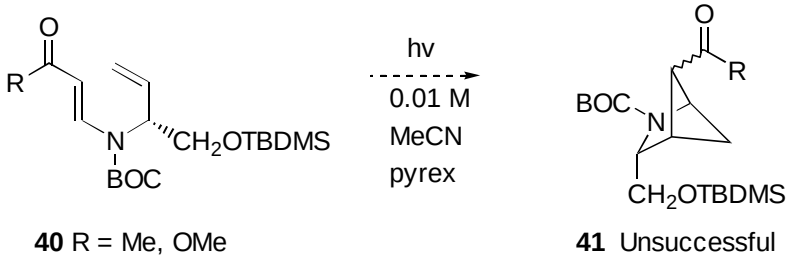


Scheme 12



Scheme 13

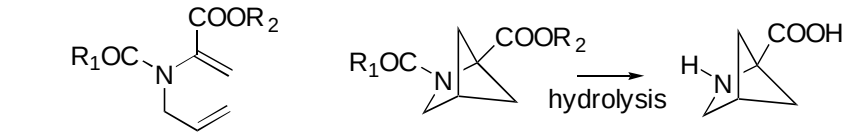
In an attempt to prepare 3-substituted 2-azabicyclo[2.1.1]hexanes using this photochemical approach Lin irradiated the chiral substrates (**40**) (Scheme 13).[14] The desired [2 + 2] photoadducts (**41**) could not be isolated in either case.



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.



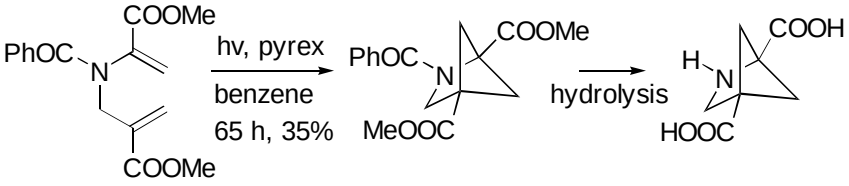
42a R_1 = Me, R_2 = Ph → **43a** 87%

42b R_1 = Et, R_2 = Me → **43b** 55%

44

(a) hv, benzene, acetophenone, pyrex, (b) hv, acetone, 300 nm

Scheme 15

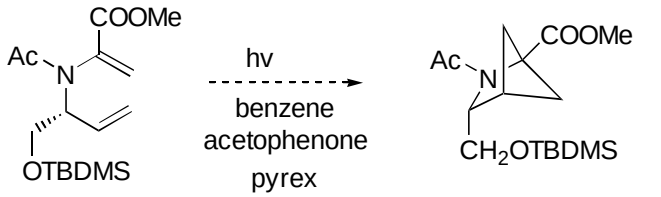


45 **46** **47**

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]

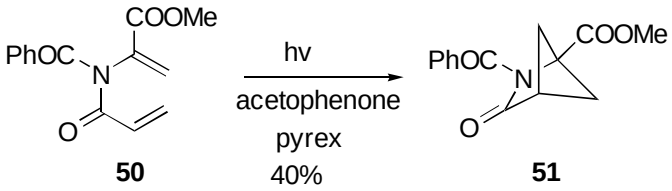
In the hope of obtaining a 3-substituted 2-azabicyclo[2.1.1]hexane (**49**) using this photochemical approach Lin irradiated the chiral substrate (**48**) (Scheme 17).[14] Only starting material (**48**) was recovered.



48 **49** Unsuccessful

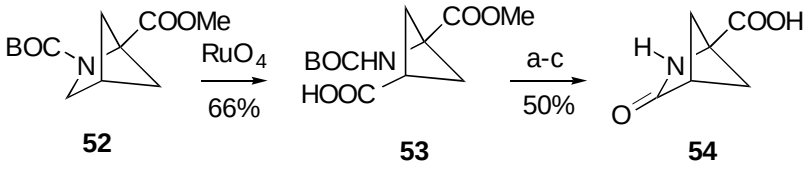
Scheme 17

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]



50 **51**

Scheme 18

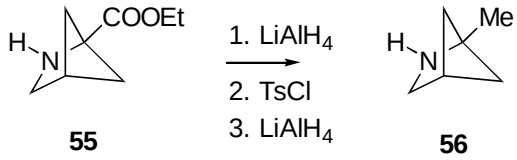


52 **53** **54**

(a) $SOCl_2$, (b) Et_3N, (c) K_2CO_3/MeOH/H_2O

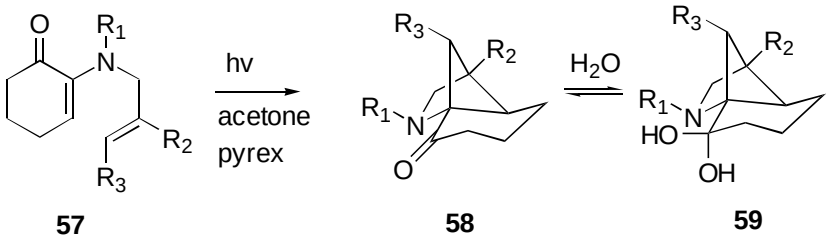
Scheme 19

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]

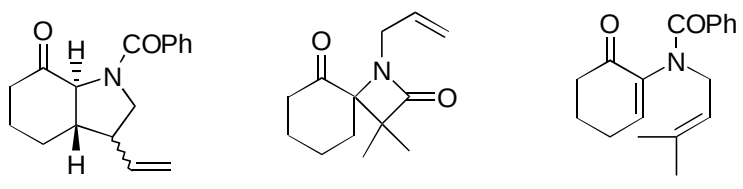


55 **56**

Scheme 20



57 **58** **59**



60 **61** **62**

Scheme 21

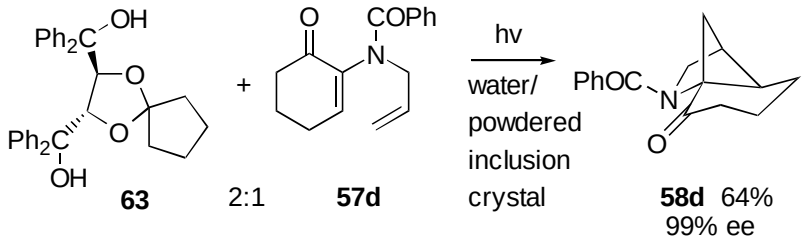
Ikeda and coworkers in 1982 reported photocyclizations of *N*-acyl cross-conjugated amides (**57**) (Scheme

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

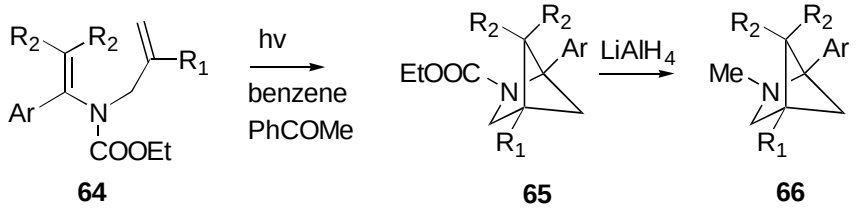
Toda and coworkers have reported an efficient enantioselective photocyclization (Scheme 22).[29] Photoirradiation of a 2:1 inclusion crystal of **57d** with the optically active host crystal (*R,R*)-(-)-*trans*-4,5-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (**63**) in water containing sodium 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.



Scheme 22

Piotrowski has applied the photochemical route from *N*-vinyl-*N*-allylamides (**64**) to the synthesis of 1-aryl- and 1-pyridyl-2-azabicyclo[2.1.1]hexanes (**65**) (Scheme 23).[30] Representative examples are shown in Table 2. Cycloadditions were conducted in benzene using acetophenone as sensitizer. The reactions can be carried out on a preparative scale (0.01-0.38 mol), unless both R_1 and R_2 are methyl in which case only unreacted starting material is recovered. Reduction of adducts (**65d-f**) afforded the

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



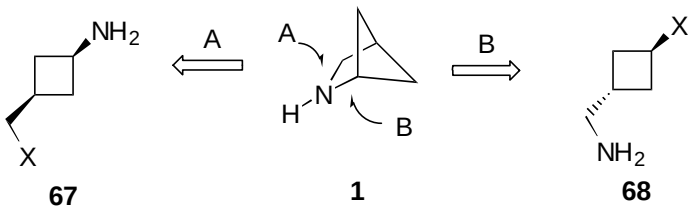
Scheme 23

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**	*p*-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.

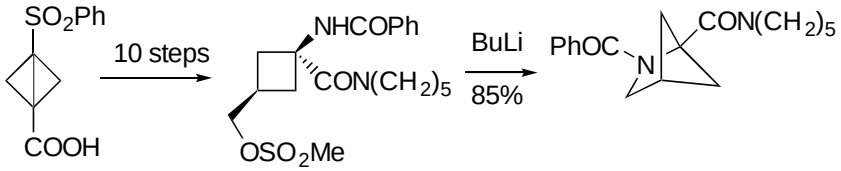
Disconnection of the 2-azabicyclo[2.1.1]hexane skeleton (**1**) at bond A suggests a *cis*-1-amino-3-X-methylcyclobutane (**67**); breaking of bond B suggests a *trans*-1-X-3-aminomethylcyclobutane (**68**) (Scheme 24). Strategies to prepare azabicyclo[2.1.1]hexanes (**1**) by the ring closures of substrates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



Scheme 24

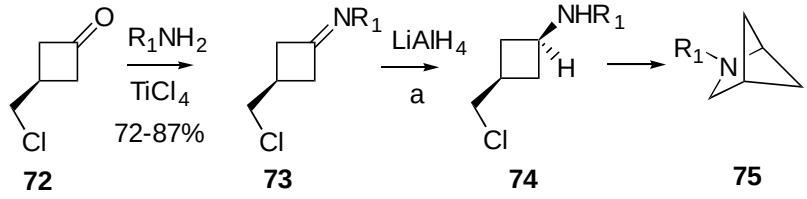
1. Bond A disconnections. The aminocyclobutane route.

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

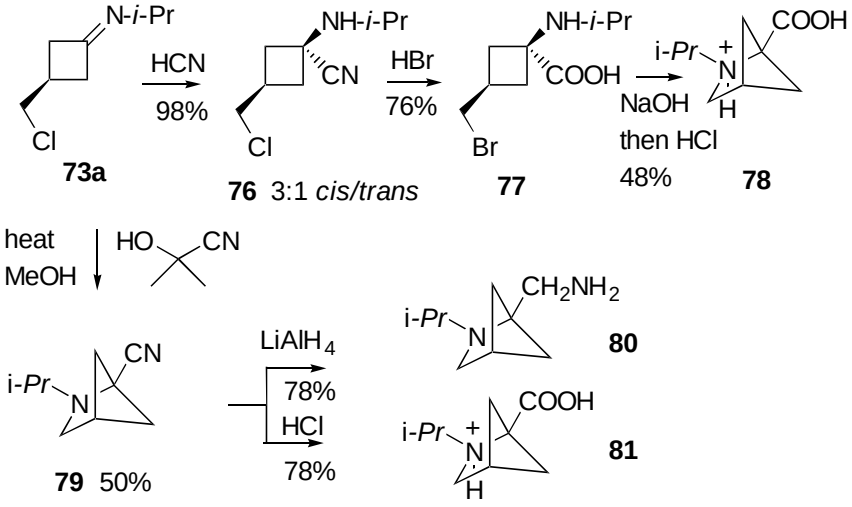
De Kimpe and coworkers reported a more efficient route to 2-azabicyclo[2.1.1]hexanes (**75**) from the cyclobutanone (**72**), prepared in 31% yield in two steps from allyl chloride and dichloroketene (Scheme 26).[31] Conversion of the cyclobutanone (**72**) to the imine (**73**), and subsequent reduction 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**, R_1 = *tert*-butyl.[32]



R_1 = *i*-Pr (80%), Et (18%), *c*-Hex (26%), *s*-Bu (50%), *t*-Bu (0%)

Scheme 26

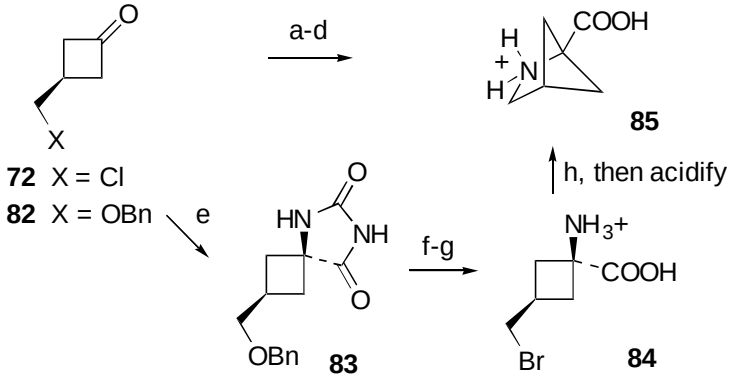
Substituents can be introduced at C_1 by taking advantage of the chemistry of cyclobutanimines (Scheme 27).[31] When *N*-isopropylimine (**73a**) is reacted with cyanide, a mixture is obtained favoring the desired *cis* stereoisomer (**76**). The amino nitrile (**76**) is unstable to base, but is converted 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]

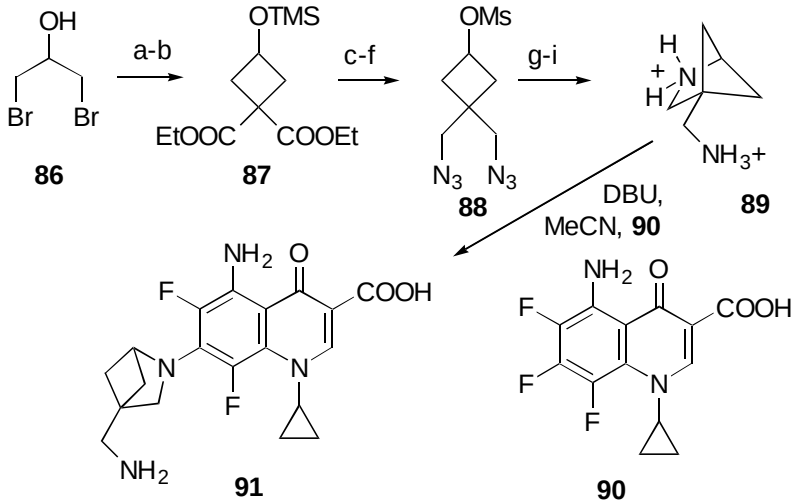


(a) $BnNH_2$, (b) acetone cyanohydrin (73%), (c) HCl (88%),
(d) H_2/Pd/C (99%), (e) $(NH_4)_2CO_3$, KCN (20%) (f) NaOH (100%),
(g) HBr (73%), (h) NaOH 91%

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 C_4 of the 2-azabicycle 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**).

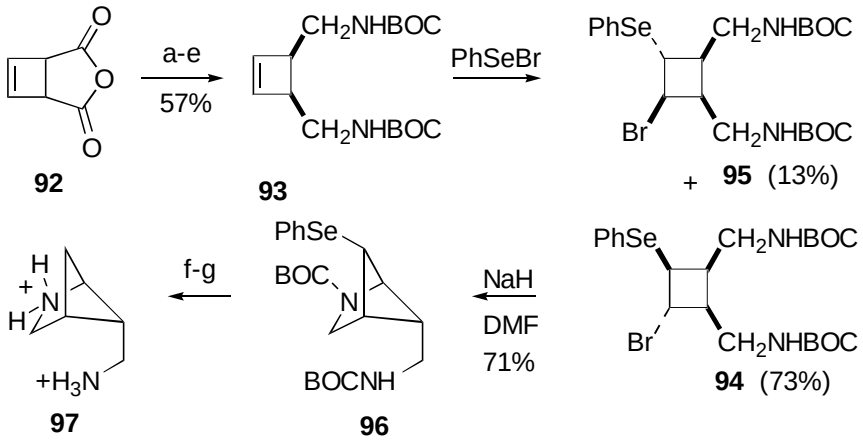


(a) TMSCl, (b) $CH_2(COOEt)_2$/base, (c) reduction, (d) TsCl, (e) sodium azide, (e) Deprotection, (f) MsCl, (g) hydrogenation, (h) BOCX, (i) HCl

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*.

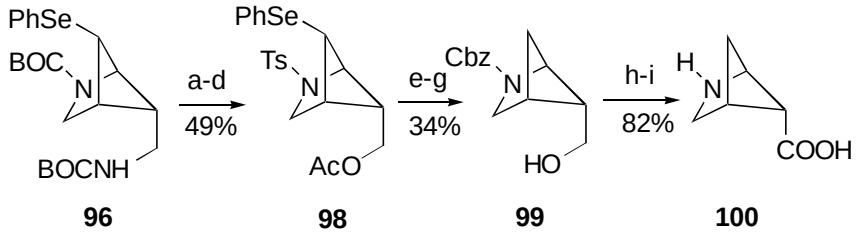
Huet has recently reported application of the Bond B disconnection route to the preparation of 5-*syn*-substituted 2-azabicyclo[2.1.1]hexanes (Scheme 30).[35] The cyclobutene anhydride (**92**), prepared in two steps from maleic anhydride and *trans*-1,2-dichloroethene, is converted in five steps to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



(a) $LiAlH_4$, (b) MsCl, (c) NaN_3, (d) $LiAlH_4$, (e) BOC_2O, (f) Bu_3SnH, AIBN, (g)HCl

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]

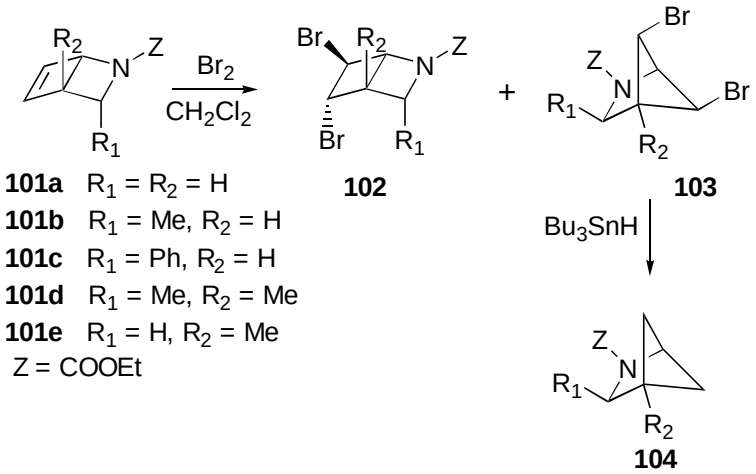


(a) CF_3COOH, (b) $TsCl,Et_3N$, (c) TsCl, NaH, DMF, (d) KOAc, KI, heat,
(e) Bu_3SnH, AIBN, (f) HBr, (g)CbzCl, (h) CrO_3, (i) H_2/Pd/C, MeOH

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 CH_2Cl_2 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

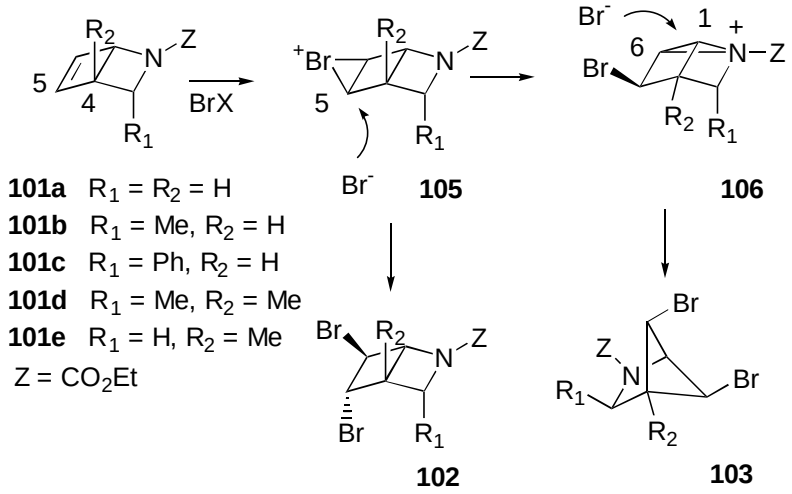
Table 3. Formation of 2-Azabicyclo[2.1.1]hexanes by Reaction of 2-Azabicyclo[2.2.0]hex-5-enes (**101**) with Bromine in Methylene Chloride.

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

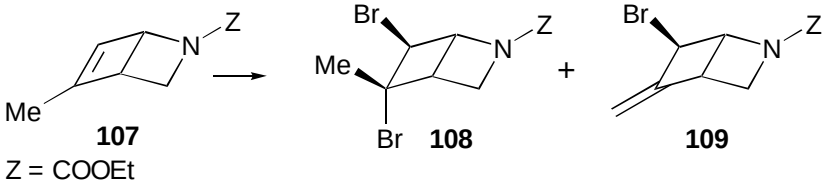
[a]Accompanied by 34-43% of dibromide (**102a**). [b]Accompanied by 20% of dibromide (**102e**).

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*-R_1 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).

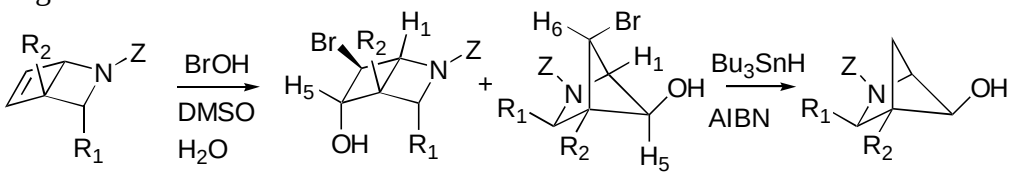


Scheme 33



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**.

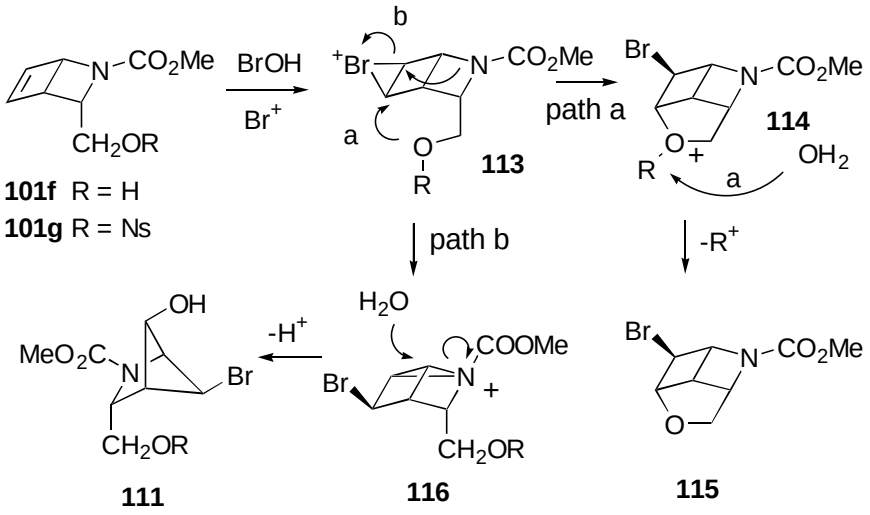


101a $R_1 = R_2 = H$ **110** **111** **112**
101b R_1 = Me, R_2 = H
101c R_1 = Ph, R_2 = H
101e R_1 = H, R_2 = Me
$Z = CO_2Et$

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.



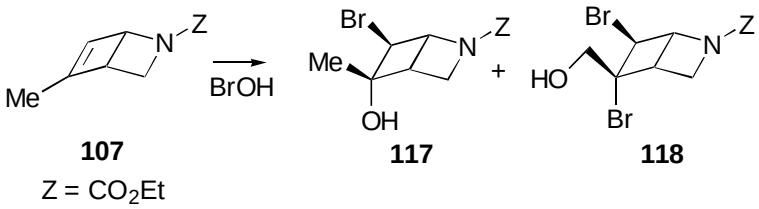
Scheme 36

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_2OH	H	**111f**	0	39
6	**101g**	Me	CH_2ONs	H	**111g**	16	39
7	**101g**	Me	CH_2ONs	H	**111g**	60[c]	39

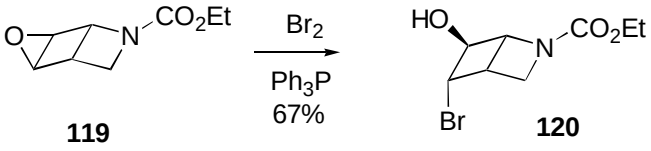
[a] Also, 49-56% of bromohydrin (**110a**). [b]Also, 11% of bromohydrin (**110e**). [c]Solvent 2:1 THF/water.

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



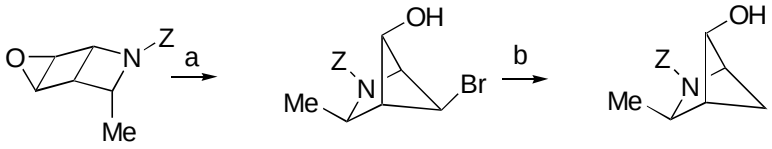
Scheme 37

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 C_3 with bromohydrin (**112b**) (R_1 = Me, R_2 = H) obtained by addition of hypobromous acid to 3-*endo*-methyl-2-azabicyclo[2.2.0]hex-5-ene (**101b**).



119 **120**

Scheme 38



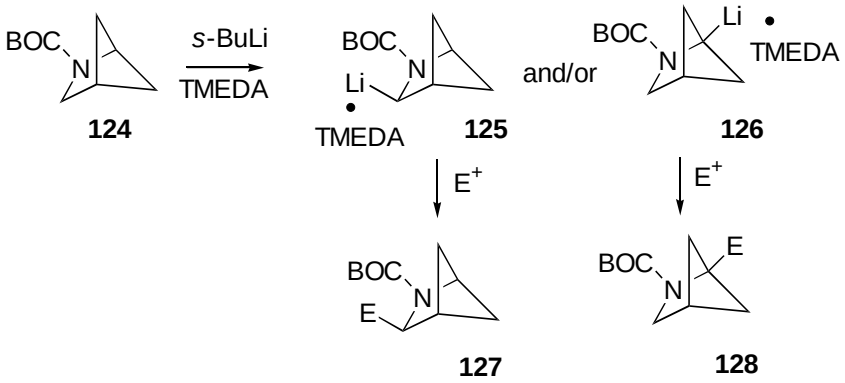
121 **122** **123**

Z = COOEt (a) Br_2/Ph_3P (65%), (b) Bu_3SnH/AIBN/heat (91%)

Scheme 39

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

The protocol of Beak was applied to *N*-BOC azabicycle (**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.



124 **125** **126** **127** **128**

a E = COOH, **b** E = COOMe, **c** E = CHO

Scheme 40

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

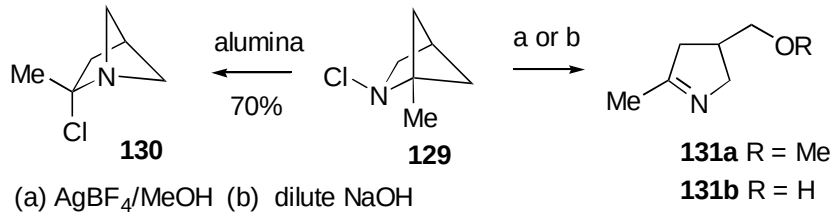
Entry	Reagent[a]	T (°C)[b]	E	Product	Ratio of **127**:**128**	Isolated yield
1	CO_2	0	COOH	**128b**		98
2	CO_2	-78	COOMe	**127b**/**128b**	43:57	76
3	ClCOOMe	0	COOMe	**128b**		70
4	ClCOOMe	-78	COOMe	**127b**/**128b**	50:50	81
5	DMF	0	CHO	**128c**		38
6	DMF	-78	CHO	**127c**/**128c**	49:51	71

[a]Lithium anions were generated from **124** in ether using *s*-BuLi in the presence of TMEDA. [b]Temperature 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 CH_2Cl_2/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 $AgBF_4$/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 $AgBF_4$/methanol, but to be a precursor of alcohol (**131b**) in dilute aqueous base.



130 **129** **131a** R = Me **131b** R = H

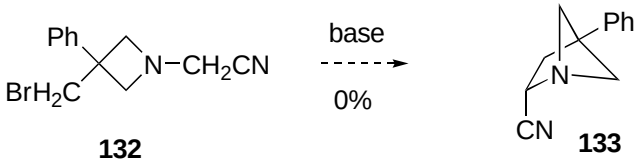
(a) $AgBF_4$/MeOH (b) dilute NaOH

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]

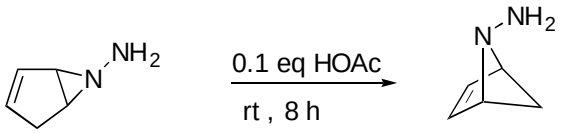


132 **133**

Scheme 42

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

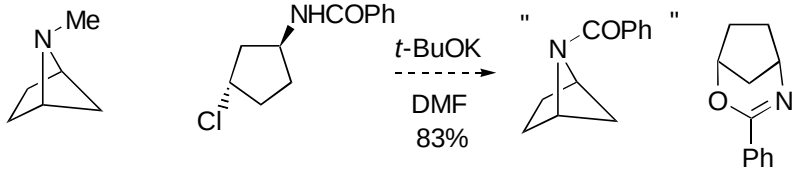
Hoesch and Dreiding have proposed that *N*-amino-6-azabicyclo[3.1.0]hex-2-ene (**134**) undergoes a rearrangement in $CDCl_3$ solution containing 0.1 molar equivalent of acetic acid to give after 8 h an 8:3:3 mixture of unreacted **134** + cyclopentene: cyclopentadiene: *N*-amino-5-azabicyclo[2.1.1]hex-2-ene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



134 **135**

Scheme 43

MM3 calculations predict a high inversion barrier (15.3 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]



136 **137** **138** **139**

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]

ACKNOWLEDGEMENTS

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REFERENCES

1. L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *J. Am. Chem. Soc.*, 1971, **93**, 4503.
2. Y. Tamura, Y. Kita, H. Ishibashi, and M. Ikeda, *Chem. Commun.*, 1971, 1167.
3. P. Hughes and J. Clardy, *J. Org. Chem.*, 1988, **53**, 4793.
4. (a) Y. Gaoni, *Org. Prep. Proced. Int*., 1995, **27**, 185. (b) Y. Gaoni, A. G. Chapman, N. Parvez, P. C.-K. Pook, and D. E. Jane, *J. Med. Chem.*, 1994, **37**, 4288.
5. G. R. Krow, Y. B. Lee, W. S. Lester, H. Christian, D. A. Shaw, and J. Yuan, *J. Org. Chem.*, 1998, **63**, 8558.
6. G. R. Krow, S. B. Herzon, G. Lin, F. Qiu, and P. E. Sonnet, *Org. Lett.*, 2002, **4**, 3151.
7. Y. Tamura, H. Ishibashi, M. Hirai, Y. Kita, and M. Ikeda, *J. Org. Chem.*, 1975, **40**, 2702.
8. Y. Tamura, H. Ishibashi, and M. Ikeda, *J. Org. Chem.*, 1976, **41**, 1277.
9. Y. Tamura, Y. Kita, H. Ishibashi, and M. Ikeda, *Tetrahedron Lett*., 1972, **13**, 1977.
10. B. Vogler, R. Bayer, M. Meller, W. Kraus, and F. M. Schell, *J. Org. Chem.*, 1989, **54**, 4165.
11. F. M. Schell, P. M. Cook, S. W. Hawkinson, R. E. Cassady, and W. E. Thiessen, *J. Org. Chem.*, 1979, **44**, 1380.
12. C. S. Swindell, B. P. Patel, S. J. deSolms, and J. P. Springer, *J. Org. Chem.*, 1987, **52**, 2346.
13. Y.-S. Kwak and J. D. Winkler, *J. Am. Chem. Soc.*, 2001, **123**, 7249.
14. G. Lin and G. Krow, unpublished observation.
15. E. A. Bell, M. Y. Qureshi, R. J. Pryce, D. H. Janzen, P. Lemke, and J. Clardy, *J. Am. Chem. Soc.*, 1980, **102**, 1409.
16. G. C. Kite and H. Ireland, *Phytochemistry*, 2002, **59**, 163.
17. M. C. Pirrung, *Tetrahedron Lett.*, 1980, **21**, 4577.
18. P. Hughes, M. Martin, and J. Clardy, *Tetrahedron Lett.*, 1980, **21**, 4579.
19. G. T. Montelione, P. Hughes, J. Clardy, and H. A. Scheraga, *J. Am. Chem. Soc.*, 1986, **108**, 6765.

20. S. Talluri, G. T. Montelione, G. van Duyne, L. Piela, J. Clardy, and H. A. Scheraga, *J. Am. Chem. Soc.*, 1987, **109**, 4473.
21. L. Piela, G. Memethy, and H. A. Scheraga, *J. Am. Chem. Soc*., 1987, **109**, 4477.
22. C. Mapelli, H. van Halbeek, and C. H. Stammer, *Biopolymers*, 1990, **29**, 407.
23. P. Juvvadi, D. J. Dooley, C. C. Humblet, G. H. Lu, E. A. Lunney, R. L. Panek, R. Skeean, and G. R. Marshall, *Int. J. of Peptide Protein Res.*, 1992, **40**, 163.
24. C. S. Esslinger, H. P. Koch, M. P. Kavanaugh, D. P. Philips, A. R. Chamberlin, C. M. Thompson, and R. J. Bridges, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3101.
25. H. P. Koch, M. P. Kavanaugh, C. S. Esslinger, N. Zerangue, J. M. Humphrey, S. G. Amara, A. R. Chamberlin, and R. Bridges, *Mol. Pharmacol.*, 1999, **56**, 1095.
26. J. W. Davies, J. R. Malpass, and M. P. Walker, *J. Chem. Soc., Chem. Commun*., 1985, 686.
27. M. Ikeda, M. Takahashi, K. Ohno, Y. Tamura, and M. Kido, *Chem. Pharm. Bull.*, 1982, **30**, 2269.
28. M. Ikeda, T. Uchno, M. Takahashi, H. Ishibashi, Y. Tamura, and M. Kido, *Chem. Pharm. Bull*., 1985, **33**, 3279.
29. F. Toda, H. Miyamoto, K. Takeda, R. Matsugawa, and N. Maruyama, *J. Org. Chem*., 1993, **58**, 6208.
30. D. W. Piotrowski, *Synlett.*, 1999, 1091.
31. T. Rammeloo, C. V. Stevens, and N. De Kimpe, *J. Org. Chem.*, 2002, **67**, 6509.
32. C. Stevens and N. De Kimpe, *J. Org. Chem.*, 1996, **61**, 2174.
33. T. Rammeloo and C. V. Stevens, *Chem. Commun*., 2002, 250.
34. T. H. Park, Y. H. Ha, and D. Y. Jeong, Patent application WO 98-KR246 19989898. (*Chem. Abstr*., 1999, **130**, 182388).
35. C. Lescop, L. Mevellec, and F. Huet, *J. Org. Chem.*, 2001, **66**, 4187.
36. (a) P. Beeken, J. N. Bonfiglio, I. Hasan, J. J. Piwinski, B. Weinstein, I. A. Zollo, and F. W. Fowler, *J. Am. Chem. Soc.*, 1979, **101**, 6677. (b) J. Kurita, K. Iwata, H. Sakai, and T. Tsuchiya, *Chem. Pharm. Bull.*, 1985, **33**, 4572.
37. G. R. Krow, Y. B. Lee, W. S. Lester, N. Liu, J. Yuan, J. Duo, S. B. Herzon, Y. Nguyen, and D. Zacharias, *J. Org. Chem.*, 2001, **66**, 1805.
38. G. R. Krow, W. S. Lester, N. Liu, J. Yuan, A. Hiller, J. Duo, S. B. Herzon, N. Nguyen, and K. C. Cannon, *J. Org. Chem.*, 2001, **66**, 1811.
39. G. R. Krow, J. Yuan, G. Lin, and P. Sonnett, *Org. Lett.*, 2002, **4**, 1259.
40. (a) P. Beak and W. K. Lee, *J. Org. Chem.*, 1993, **58**, 1109. (b) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552.
41. A. G. Anderson, Jr. and R. A. Jewell, *Gazz. Chim. Ital*., 1989, **119**, 81.
42. L. Hoesch and A. S. Dreiding, *Chimia*, 1972, **26**, 629.

43. A. M. Belostotskii, P. Aped, and A. Hassner, *Theochem*, 1998, **429**, 265.
44. H. F. Olivo, M. S. Hemenway, and M. H. Gezginci, *Tetrahedron Lett.*, 1998, **39**, 1309.
45. H. F. Olivo, personal communication.
46. G. R. Krow, G. Lin, S. B. Herzon, A. M. Thomas, K. P. Moore, Q. Huang, and P. J. Carroll, *J. Org. Chem.*, 2003, **68**, 7562.
47. T. Rammelooo and C. C. Stevens, *New. J. Chem.*, 2003, **27**, 668.
48. T. J. Katz and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1972, **96**, 1948.
49. G. R. Krow, G. Lin, D. Rapolu, Y. Fang, W. S. Lester, S. B. Herzon, and P. E. Sonnet, *J. Org. Chem.*, 2003, **68**, 5292.
50. G. R. Krow, G. Lin, F. Yu, and P. E. Sonnet, *Org. Lett.*, 2003, **5**, 2739.