# 12.27
# Nine-Membered Rings

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## 12.27.1 Introduction

### 12.27.1.1 Scope of the Chapter

Nine-membered rings were reviewed in CHEC(1984), where they were treated in the single chapter with other heterocycles with ring systems larger than eight membered. CHEC-II(1996) covered the developments of this class of heterocycles up to 1994, and included data on nitrogen, sulfur, and/or oxygen heterocycles, as well as particular examples of fused and bridged ring systems. Synthesis of nine-membered hetarenes and heteroannulenes was a part of a review published recently <2004SOS(17)979> (Chapters 12.18–12.26).

Numerous reviews cover the synthesis, structures, reactivity, and applications of nine-membered heterocycles as a part of the general medium-size ring discussion <2005PHC(17)418, 2004PHC(16)451, 2003PHC(15)431, 2002PHC(14)356, 2001PHC(13)378, 2000PHC(12)352, 1999PHC(11)338, 1998PHC(10)335, 1996PHC(8)320>. Metal-mediated synthesis of medium-sized rings <2000CRV2963>, synthesis of oxygen- and nitrogen-containing

heterocycles by ring-closing metathesis (RCM) <2004CRV2199>, and synthesis of sulfur and phosphorus heterocycles via ring-closing olefin metathesis <2004CRV2239> were reviewed. Synthetic aspects of various nine-membered heterocyclic systems were surveyed as related to total synthesis of natural products <2004CRV3371, 2005CRV4314, 2005CRV4379, 2006CRV911> (see other chapters in Volume 12). Conformational studies of saturated nine-membered rings and nine-membered rings containing one torsional constraint were the subject of the review <1999MI(5)89>.

Syntheses and macrocyclic complexes of 1,4,7-triazacyclononane and related crown-type systems were reviewed <B-2005MI67, 2001ARA331, 2002ARA321>.

### 12.27.1.2 Structural Types

A large number of nine-membered heterocyclic systems are known. Only those rings with nitrogen, oxygen, and/or sulfur heteroatoms, and their fused derivatives are covered in this chapter. Ring systems with phosphorus, boron, and other heteroatoms, as well as bridged systems, are discussed in the corresponding chapters of this volume. Structural types and nomenclature of nine-membered heterocycles were outlined in CHEC-II(1996). Particular types of rings and their fused derivatives are reviewed in this chapter in the order of nitrogen-, oxygen-, and sulfur-containing heterocycles, beginning with rings containing one heteroatom, that is, azonines, oxonines, and thionines. Systems with two heteroatoms are discussed in the order diazonines, dioxonines, and dithionines, followed by oxazonines, thiazonines, and oxathionines.

The number of possible nine-membered rings with three or more heteroatoms is enormous, and the reviewed structures are listed in **Table 1** and surveyed in the heteroatom order of mono- and diheteronines.

**Table 1** Structural types of heteronines and their nomenclature

| | | *Number of heteroatoms* | | |
|---|---|---|---|---|
| *Name* | *Total number of heteroatoms* | *N* | *O* | *S* |
| Triazonine | 3 | 3 | 0 | 0 |
| Trioxonine | 3 | 0 | 3 | 0 |
| Trithionine | 3 | 0 | 0 | 3 |
| Oxadiazonine | 3 | 2 | 1 | 0 |
| Dioxazonine | 3 | 1 | 2 | 0 |
| Thiadiazonine | 3 | 2 | 0 | 1 |
| Dithiazonine | 3 | 1 | 0 | 2 |
| Oxadithionine | 3 | 0 | 1 | 2 |
| Oxathiazonine | 3 | 1 | 1 | 1 |
| Tetraoxonane | 4 | 0 | 4 | 0 |
| Dioxadiazonine | 4 | 2 | 2 | 0 |
| Hexaoxonane | 6 | 0 | 6 | 0 |
| Octathionane | 8 | 0 | 0 | 8 |

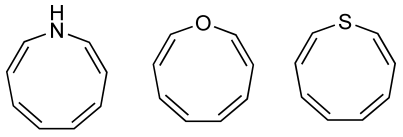
## 12.27.2 Theoretical Methods

*Ab initio*, semi-empirical, and molecular mechanics calculations have been used extensively in the study of nine-membered heterocycles. Theoretical studies of heteronines have centered on the question of their aromaticity, which was surveyed as a part of general heterocycles aromaticity study <2004CRV2777>. Another important aspect is the conformation of the nonconjugated compounds (see Section 12.27.4.3). Computational aspects of conformational behavior of saturated nine-membered rings and nine-membered rings containing one torsional constraint were the part of the review <1999MI(5)89>.

### 12.27.2.1 *Ab Initio* and Semi-Empirical Methods

Full geometry optimization for 1*H*-azonine **1**, oxonine **2**, and thionine **3** was carried out at the B3LYP/6-311G(2d,p) level without symmetry constraints using the Gaussian 94 code <2001T8759>. Azonine has planar aromatic structure, while electronegativity of the oxygen atom in oxonine leads to localized electron pairs and distorted

nonplanar polyenic structure. Thionine, in spite of having the same number of valence electrons as oxonine, is partially aromatic, as sulfur atom is less electronegative than oxygen, and sulfur π-electrons are more delocalized.

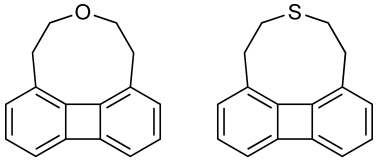


**1** **2** **3**

The aromaticity of heteronines was quantified with the help of nucleus-independent chemical shifts (NICSs) criteria <2005PCA11870>. NICS(0) values, which are defined as the amount of absolute magnetic shielding calculated at the ring center, for azonine, thionine, and oxonine were −13.6, −0.5, and 4.2 ppm, respectively, thus confirming fully aromatic structure of **1** and antiaromatic character of **2**. A set of N-substituted azonines with Me, Et, CHO, COMe, COOMe, COOEt, CN, $CONMe_2$, and $SO_2Ph$ substituents was studied. With the exception of *N*-Et and *N*-Me, the lone pair on nitrogen atom in these structures is not completely available for the cyclic delocalization. As a result, the optimized molecular structures show that planarity is lost in all the molecules and the NICS(0) value for all these species indicated that they are all nonaromatic.

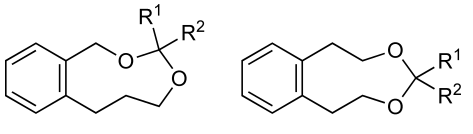
The *ab initio* study showed that the interaction of azonine with surrounding $H_2O$ molecules, with alkali ions in *N*-azonides and substitution of the azonine *N*-H hydrogen, distorts the planarity of the ring <2004PCA4059>. This distortion is such that the aromaticity remains, and the global minimum structures of the alkali salts have the metal residing on top of the distorted ring (cation–π-interaction). These findings explain the experimental $^1H$ nuclear magnetic resonance (NMR) spectra, ultraviolet–visible (UV–Vis) spectra, and thermal stability results.

The conformational properties of bridged biphenylenes, 1,2,4,5-tetrahydrobiphenyleno[1,8-*def*]oxonine **4** and 1-thionine **5**, were studied using *ab initio* molecular orbital and density functional theory (DFT) methods. Studies on the Hartree–Fock (HF)/6-31G* level of theory revealed that for **5**, a plane symmetrical boat conformation was of the lowest energy. The twist, twist-boat, and chair conformations are less stable by 2.41, 5.02, and 2.62 kcal $mol^{-1}$, respectively. Contrary, the twist conformation was found to be the most stable form for **4** <2003JMT(637)115>.



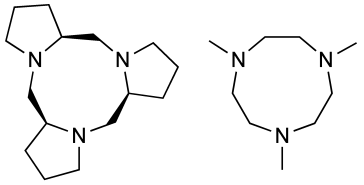
**4** **5**

Conformations of the 2,4- and 3,5-benzodioxonine derivatives **6** and **7** ($R^1$, $R^2$ = H or/and alkyl) were examined using DFT calculations <2006JOC5498>. The most stable conformations were TBC and TCB type 1 for the 2,4- and 3,5-benzodioxonine derivatives, respectively. In both of these conformations, the acetal moiety adopts the $g\pm g\pm$geometry. The natural bond orbital analysis yielded values of the stabilization energy associated with the stereoelectronic $n_O \rightarrow \sigma_{C-O^*}$ interactions that were highest for conformations other than the global minima. Conformers displaying the strongest interactions followed different patterns of atom arrangement within the acetal moiety, namely $g+g-$, and those in which one or both of the torsion angles within the C–O–C–O–C segment were close to 90°. Steric repulsion caused by alkyl substituents at the anomeric carbon was found to influence the strength of the $n_O \rightarrow \sigma_{C-O^*}$ stabilization through modification of bond lengths and torsion angles. The adopted ground-state conformations result from accommodation of steric repulsions and stabilizing stereoelectronic interactions.



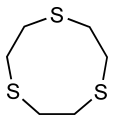
**6** **7**

Quantum-chemical *ab initio* calculations have been conducted to determine the proton affinities of tripyrrolidinyl- and 1,4,7-trimethyl-1,4,7-triazacyclononane (**8** and **9**, respectively). Their proton affinities have been found to be up to 20 kcal mol$^{-1}$ higher than the values of noncyclic tertiary aliphatic amines due to an effective stabilization of the ammonium cations <2005T12371>.



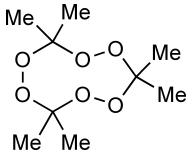
**8** **9**

Complete energy calculations using the AM1 method have been performed for three possible conformers of 1,4,7-trithionane **10** <1995JST(355)169>. The calculations indicated that the most stable conformer is that with $D_3$ symmetry, total energy of which is 24.2 kJ mol$^{-1}$ lower than that of $C_3$-symmetry crystalline structure and 5.2 kJ mol$^{-1}$ lower than the $C_2$-symmetry confomer predicted by molecular mechanics calculations. Calculated forms of the normal modes of vibration of the molecule allowed a complete assignment of the observed bands in the Raman and infrared (IR) spectra (see Section 12.27.3.5).



**10**

The calculations of geometry, binding energies, and vibrational frequencies of triacetone triperoxide **11** were conducted using the DFT-based method as implemented in the Gaussian 98 code package with an appropriate basis set. The geometry of **11** in the ground state obtained was compared to the X-ray crystallographic data (Section 12.27.3.1). A good agreement between the calculated and experimental results was observed, suggesting that the intermolecular forces in the solid phase are too weak to cause any significant alteration of the molecular geometry <2005JA1146>.



**11**

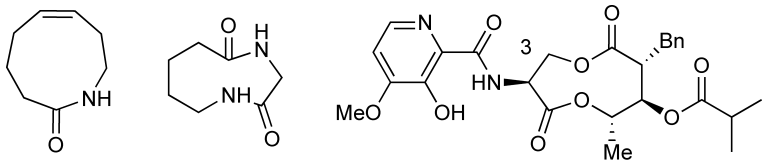
## 12.27.2.2 Molecular Mechanics

Conformational analysis of the *cis*-tetrahydroazoninone **12**, performed using MM2 method, revealed two pairs of major confomers with a comparable energy, which differs by position of NH group against double bond <2005OBC97>. The results obtained for this model structure were further used in the conformational analysis of azoninone amino acid derivatives (Section 12.27.4.3).

Steric energies for the three possible conformations of the two amide systems in macrocycle **13** were determined by MM+ method <2002J(P2)2078>. Depicted *trans–trans*-configuration with total force field energy 8.1–12.3 kcal mol$^{-1}$ is less stable when compared to *trans–cis*-and *cis–cis*-conformations (2.9–6.3 and 6.3 kcal mol$^{-1}$, respectively).

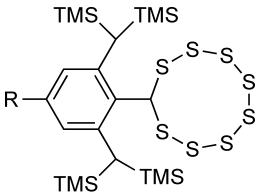
The conformations of substituted (3*S*,7*R*,8*R*,9*S*)-3-amino-7-benzyl-8-hydroxy-9-methyl-1,5-dioxonane-2,6-dione **14**, its (3*R*,7*R*,8*R*,9*S*)-isomer, and their common enol tautomer at the C-3 position were studied by molecular mechanics method. The enol form was supposed to be the initial transition state during the course of the

epimerization. The conformation of 3(*S*)-isomer is similar to that of the enol, which explains its tendency to rapid epimerization. 3(*R*)-Isomer with an axial array of the side chain at the C-3 position is an energetically unfavorable conformation, and it does not undergo epimerization even under harsh reaction conditions <1998T12745>.




**12** **13** **14**

Calculations of substituted octathionane **15a** using MMP2 force field were performed by replacement of one of sulfur atoms of cyclonanosulfur $C_9$ with 2,6-disubstituted phenyl substituent <1995BCJ2757>. Ground-state geometry of **15a** was almost identical with the crystal structure of **15b** and its differences with cycloninosulfur were explained by steric repulsion of bulky aryl group and the polysulfur linkage.



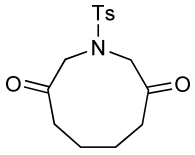

**15a**: R = H
**15b**: R = $CHTMS_2$

## 12.27.3 Experimental Structural Methods

### 12.27.3.1 X-Ray Crystallography

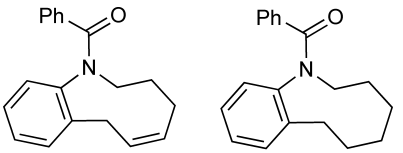
Conformational families of saturated nine-membered rings and nine-membered rings containing one torsional constraint were illustrated by examples from Cambridge Crystallographic Data Base as the part of the review <1999MI(5)89>. In general, the structures of nine-membered heterocycles, as determined by X-ray crystallography, showed predictable bond lengths or angles when compared to acyclic analogues. Considerable deviations from the planarity are characteristic for systems with endocyclic *trans* C═C bonds, ester bonds, or amide bonds.

The structure of *N*-tosyl azonane-3,8-dione **16** was determined using X-ray crystallography <1995J(P1)1137>. The ring adopts conformation with *cis*-orientation of carbonyls.



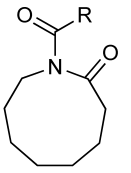

**16**

Conformational features, transannular distances, and dynamic behavior of benzazonines **17** and **18** were studied using X-ray crystallography and variable-temperature NMR spectroscopy <2005JOC1552>. Both benzazonines **17** and **18** adopt boat-chair conformations in the solid state. Amide group distortion revealed ring strain of these medium-sized heterocyclic rings and led to a more stable structure. Thus, the unsaturated heterocycle **17** has an amide bond more distorted than that of **18**, displaying substantial *N*-pyramidization. This is accompanied by a lengthening of the amide bond (1.373(2) Å). Notably, there is a very close transannular distance in **17** between H-4$\alpha$ and H-7$\alpha$ of 2.07 Å, which could suggest the presence of a small repulsive interaction. When the endocyclic double bond is reduced, the transannular distance between H-4$\alpha$ and H-7$\alpha$ in **18** becomes greater (2.15 Å). The C–N bond length returns to a more expected value (1.354(2) Å), as the amide moiety becomes essentially planar.



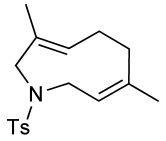
**17** **18**

The most remarkable geometrical feature of *N*-acylcaprylolactams is that the amide linkage of *N*-Cbz lactam **19d** is *trans*, while *N*-acyl derivatives **19a–c** have a *cis* amide linkage in the lactam ring with a similar conformation <2002CC2656>. Compared with the geometry of nonsubstituted caprylolactam, which is *trans* in the crystalline state due to intermolecular hydrogen bonding, *N*-acyl compounds **19a–d** have much larger twist angles, longer N–C(2) bonds, and smaller nitrogen atom pyramidization. These results clearly showed that the *N*-acyl and *N*-Cbz substituents are responsible for the ring conformation by reducing the double-bond character of the endocyclic amide linkage. It results in lengthening of the N–C(2) bond and twisting of the amide bond to diminish the ring strain originated from the planarity of the amide linkage. The conformational differences in *N*-acyl- or *N*-Cbz-substituted compounds are attributable to the differences in the electronic properties of the N-substituents. Due to electronic repulsion between the *N*-benzyloxycarbonyl group and the lactam carbonyl, *trans*-conformation is preferable for **19d**.



**19a**: R = Me
**19b**: R = *i*-Pr
**19c**: R = *t*-Bu
**19d**: R = OBn

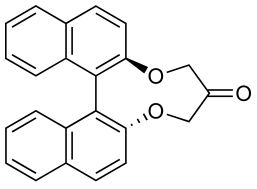
Structure of tosyl derivative **20** was determined by X-ray crystallography and revealed that the sum of the nitrogen's bond angles is 348.2°. This means that the nitrogen center of **20** is chiral and C(3)–C(4) and C(7)–C(8) olefinic moieties form chiral planes in the solid state <2006OL963>.



**20**

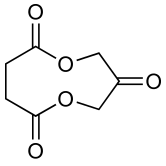
X-Ray crystallography was extensively used for experimental proof of absolute configuration of natural product-like nine-membered lactones <2000CC567> and ethers <2005T7456>.

The structure of dioxonine **21** was confirmed by single crystal X-ray structure analysis. Ketone **21** has a $C_2$-symmetric structure with the keto group, which lies on $C_2$-axis of the molecule and the dihedral angle of the two naphthalene rings is 71° <1997TA2921>. Later, another solid-state non-$C_2$-symmetric conformation for **21** was reported by Yang *et al.* <1998JA5943>.



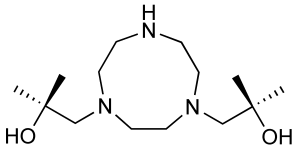
**21**

The X-ray structure of keto diester **22** has twofold symmetry with the keto group lying on the twofold axis and two ester groups with *s-trans*-geometry. The dihedral angle of the ester group (C–O–CO–C, 158°) deviated from its ideal 180° plane. The extent of ester bending, indicating ring strain in **22** and similar cyclic ketones, was attempted to correlate with the activity in catalyzing *in situ* epoxidation <1998JOC9888>.

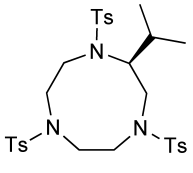


**22**

The single crystal X-ray structure of **23** confirmed that the macrocyclic ring adopts a [333] conformation <1994CC2467>. The solid-state structure of tritosyl derivative **24** <2003OBC2357> indicated that the isopropyl group adopts a pseudoequatorial position on the ring. The ring puckering is dominated by the three $sp^2$ N-centers. Two of them have the same directionality and hold their substituent tosyl groups on the face of the nine-membered ring opposite the isopropyl group. The third tosyl group, furthest from the isopropyl, is on the same face with it. All three N-centers showed considerable deviations from planarity (N-1, N-2, and N-3 lie −0.320, 0.211, and −0.104 Å, respectively, from the planes). The tosyl on the nitrogen adjacent to isopropyl is twisted so that the phenyl ring lies over one face of the nine-membered ring while the other tosyl groups point away from the main body of the molecule. The crystalline nature of hydrobromide salt of triazonine **25** allowed both the stereochemistry and absolute structure to be confirmed unequivocally by single crystal diffraction <2003OBC4408>. X-Ray analysis of cyclic tripeptide **26** confirmed its crown conformation <2004TL1091>.



**23**



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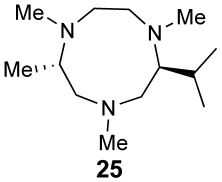

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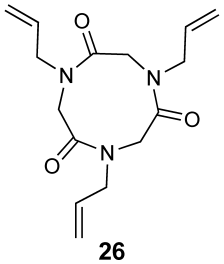
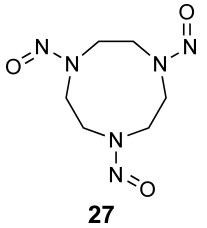


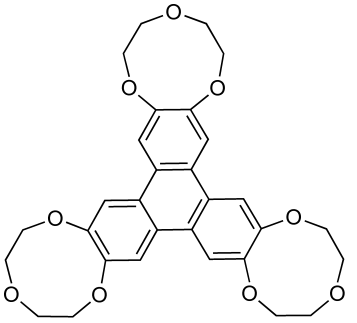
**26**

The ring conformation of trinitroso derivative **27** is very similar to that found in formyl and benzoyl 1,4,7-triazonanes <1996JCD31>. Among the three NO groups, one lies above and two below the average ring plane leading to minimal C–H bond eclipsing. All C–C–N–N–O moieties are essentially planar with maximum deviation of 0.090 Å. The N–N and N–O distances (1.318 and 1.239 Å, respectively) are all equal within experimental error and are typical for *N*-nitroso amines with partial π-electron delocalization over the N–NO fragments <2002TL771>.

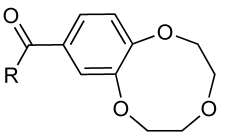


**27**

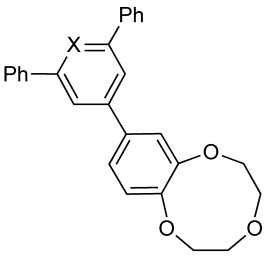
Tris-(9-crown-3)-triphenylene **28**, the product of trimerization of benzo-9-crown-3 ether, crystallized in the monoclinic $P2_{1/c}$ space group: $a = 13.759(2)$ Å, $b = 13.318(2)$ Å, $c = 13.399(2)$ Å, $\beta = 96.883(2)°$, with $Z = 4$. The three 9-crown-3 ether units of the trimer possess different geometries and there is substantial deviation from coplanarity in the three aromatic rings <2001CJC195>. The X-ray crystal structures for the 4-acetyl-, formyl-, and carboxy-benzo-9-crown-3 ethers **29a–c** showed remarkably similar geometries with *gauche* O–C–C–O networks normal for crown ethers <2001JST(561)43>. 9-Crown-3 ethers **30a–c** containing pyrilium, thiopyrilium, and pyridinium subunits were reported. The solid-phase structures of **30a** and **30c** showed small deviation from planarity for the four aromatic rings, whereas two phenyl rings in **30b** are out of heteroaromatic ring <2002JOC2065>.



**28**

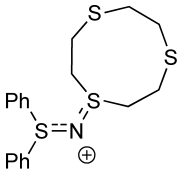


**29a**: R = Me
**29b**: R = H
**29c**: R = OH

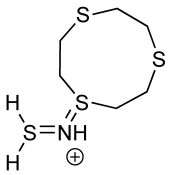


**30a**: X = $O^+$
**30b**: X = $S^+$
**30c**: X = $NH^+$

The X-ray crystal structure of diphenyl *N*-sulfoniosulfimidium **31**, crystallized as tetraphenylborate salt, exhibited an S–N–S angle of 108.55° and S–N distances of 1.6433 Å and N–S (crown) 1.6559 Å <2004NJC959>. Interestingly, the latter distance is almost identical to the S–N distance in the unsubstituted cation **32** <2002CJC1410>.

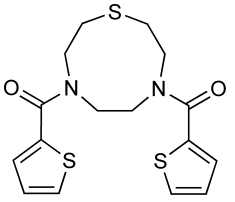


**31**

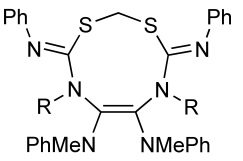


**32**

The torsion angles C(ring)–N–C(carbonyl)-C($\alpha$-thiophene) of 7.2° and 9.8° for disubstituted 1,4,7-thiadiazonane **33** indicated that the amide units are almost planar due to the partial double-bond character of amide C–N. The (CO)–N and C═O bond lengths of 1.348/1.344 Å and 1.236/1.236 Å, respectively, are typical for tertiary amides. Two rotational isomers were observed in the solid state: the major conformation (83%) is related to the minor (17%) by a rotation of 180° about the C(carbonyl)–C($\alpha$-thiophene) <1996AXC3062>. X-Ray analysis for dithiadiazonine **34** (R = 4-Me$C_6H_4$) was reported <1998EJO1803>.



**33**



**34**

Solid-state structure of hexaoxonane **11** can be studied by X-ray crystallography only at low temperatures, as crystals are unstable at room temperature under X-ray irradiation. The crystals of **11** are monoclinic with cell parameters *a* 13.788(6) Å, *b* 10.664(5) Å, *c* 7.894(4) Å, $\beta$ 91.77(5)°, *V* 1160.1(9) $Å^3$, with four molecules in the unit cell and space group $P2_1/c$. The molecules have approximately $D_3$ symmetry with the nine-membered ring adopting a

twisted boat-chair conformation. The crystal packing consisted of stacks around the molecular threefold axis with no apparent C–H···O interactions <2005JA1146>.

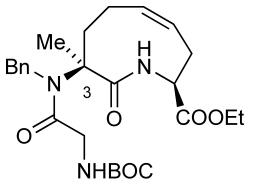
The octathionane ring of **15b** was of $C_1$ symmetry in contrast to cyclonanosulfur $C_9$, which was concluded to be of $C_1$ or $C_2$ symmetry from Raman spectral data and $C_2$ symmetry in the ground state from theoretical calculations <1995BCJ2757>. The crystal structure of 3,3,6,6,9,9-hexamethyl-[1,2,4,5]-tetraoxonane has been reported <1995RCB105>.

### 12.27.3.2 NMR Spectroscopy

NMR spectroscopy has been used extensively for structure elucidation of nine-membered rings and their conformations. The latter is discussed further in Section 12.27.4.3.

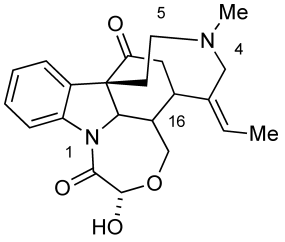
Nuclear Overhauser effect (NOE) experiments clarified the preference of the *cis–trans*-geometry in solution for cyclic lactams **19**. For **19a–c**, X-ray geometries (Section 12.27.3.1) retain in solution, and NOEs were observed between the methylene protons next to the ring carbonyl and the $NCH_2$ protons, whereas no such NOE was observed in **19d** <2002CC2656>.

The double-bond configuration in azoninone **35** was demonstrated to be (*Z*) by the CH═CH vicinal coupling constants of 9–10 Hz <2005OBC97>. Only one set of signals was detected by NMR at room temperature, meaning that only one of the two possible rotamers around the ring amide bond is present. This rotamer in the case of (*S*)-**35** is the *anti* one, as demonstrated by the presence of a strong NOE between the NH and the *ortho*-hydrogens of the benzyl group. A very strong NOE between the NH and the $CH_3$ bonded at C-3 in was observed for (*R*)-counterpart of **35**, which also exists as *anti*-rotamer.




**35**

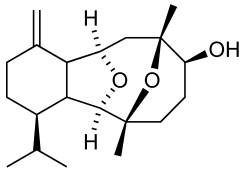
Structure of *Strychnos* alkaloid holstiine **36**, which contains a nine-membered azonine ring, was studied using long-range $^1H$–$^{15}N$ heteronuclear shift correlation technique <2000JNP543>. The structural changes in holstiine relative to its congeners strychnine and brucine are not so large that the nitrogen chemical shifts would be substantially affected. Indeed, the N-1 and N-4 of holstiine resonate at 146.5 and 39.5 ppm, respectively, which compares very favorably with both strychnine and brucine. The sole coupling observed to N-1 in the long-range $^1H$–$^{15}N$ spectrum of **36** is the coupling from H-16$\alpha$. The smaller number of long-range couplings to N-4 can likely be attributed to the greater flexibility of the aliphatic segment of the molecule in which N-4 is contained. Proton H-5β strongly couples to N-4 when the C-5/H-5β bond vector is oriented synclinally to the N-4 lone pair.



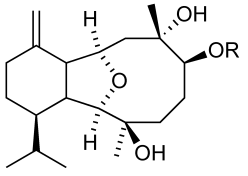

**36**

The structural connectivity derived from examination of the $^1H$, $^{13}C$/DEPT, DQF-COSY, HMQC, and HMBC data (DEPT = distortionless enhancement by polarization transfer; DQF = double quantum filtering; COSY = correlation spectroscopy; HMQC = heteronuclear multiple quantum correlation; HMBC = heteronuclear multiple bond correlation) resulted in global reevaluation of sclerophytin B structure and demonstrated that this compound and the related alcohol are not composed of two ether bridges as in the originally formulated structure **37**, but share the structural features depicted as **38** <2000OL1879>. Comparison of $^{13}C$ and $^1H$ NMR data of Norte's

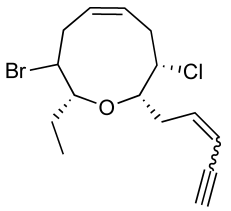
obtusenynes isolated from *Laurencia pinnatifida* with that of two stereoselectively synthesized analogues confirmed their (12*R*,13*R*)-(−)-structure **39** <1999CL461>.




**37**

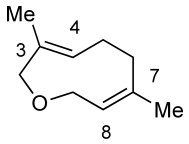



**38**



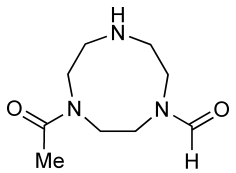

**39**

An NOE experiment of cyclic ether **40** with irradiation at the methyl group on C-3 showed 3% enhancement in the signal of the vinyl proton at C-8. This result along with the molecular modeling suggests that the C(3)–C(4) and C(7)–C(8) olefinic moieties of **40** form stereogenic planes in the most stable conformation, and proves its planar chiral nature <2005JA12182>.



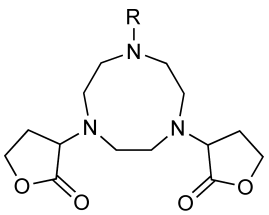

**40**

$^{13}C$ and $^{1}H$ NMR spectra of disubstituted triazonane **41** revealed a mixture of isomeric forms <1999J(P1)1211>. The $^{13}C$ NMR spectrum in $CDCl_3$ showed 21 aliphatic resonances (3 methyl and 18 ring), three formyl C═O resonances, and three acetamide C═O resonances as the major spectral components. Similarly, the $^{1}H$ NMR spectrum showed three major methyl singlets and three major formyl singlets. An additional fourth methyl and fourth formyl singlet were also observable, but they are considerably lower in intensity, suggesting a fourth less stable isomer. This number of observed resonances is consistent with **41** existing in three major and one minor isomeric forms which interconvert slowly on the NMR timescale due to restricted rotation about the C–N amide bonds.




**41**

Structural properties of two macrocyclic derivatives **42** (R = H, Ts) have been studied by molecular mechanics and $^{1}H$ NMR spectroscopy, and new sets of Karplus parameters for calculation of the vicinal coupling constants of the butyrolactone moieties have been determined <2002EJO351>.

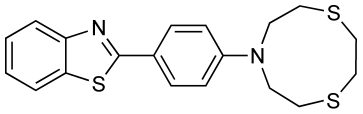



**42**

Solid-phase $^{13}C$ NMR chemical shift differences of ca. 8.5 ppm were observed between the two aryl–O–C carbons of benzo-9-crown-3 derivatives **29a–c**. This was explained using results of *ab initio* calculations performed on anisole,

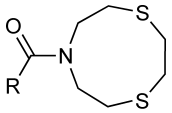
which demonstrated dependence of the total shielding of the methyl group as a function of Ph–O–Me torsion angle <2001JST(561)43>. The recognition of $Li^+$ by the chiral diaza-9-crown-3 derivatives was investigated by $^1H$ NMR in $CD_3CN$ <2004T5799>. The resonances for the crown ether moiety and $\alpha$-methyl protons adjacent to the ring were shifted upfield and broadened upon $Li^+$ recognition.

Complexation of $Ag^+$ ion with benzothiazole dithiazonine derivative **43** was examined by $^1H$ NMR titration <1999J(P2)1273>. The downfield shifts in the proton signals of the methylenes adjacent to the sulfur atoms were caused by the strong interaction of $Ag^+$ ion with the sulfur atoms of the polythiazaalkane moiety. On the other hand, the decrease in $\pi$-electron density of the aromatic group caused by the interaction between the nitrogen atom and the complexed $Ag^+$ ion results in a downfield shift in the chemical shifts of the aromatic signals.



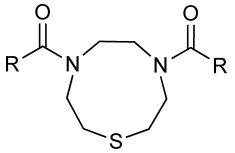
**43**

In $^1H$ NMR spectra of acyl dithiazonines **44**, each of the methylene groups of the ring gives rise to a fairly broad multiplet due to the low symmetry of the molecule imposed by the amide group <2001JMC1011>. Analysis of the COSY $^1H$ NMR spectrum allowed the assignment of each methylene group to individual multiplets. The macrocyclic methylene group closest in space to the amide carbonyl is shifted toward higher frequency and appears at 3.98 ppm. This resonance couples to the adjacent macrocyclic methylene group, which appeared at 3.18 ppm. A second pair of $NCH_2CH_2$ protons can be assigned to the signals at 3.71 and 3.43 ppm, while resonances at 3.06 and 2.95 ppm are due to the protons of the methylene groups situated between sulfur atoms. The $^{13}C$ NMR spectrum of **44** revealed six signals corresponding to the methylene carbon atoms of the macrocyclic ring.



**44**

$^1H$ NMR spectrum of diacyl thiadiazonine **45** showed three resonances at 3.93, 3.80, and 2.88 ppm corresponding to the protons of three distinct sets of macrocyclic methylene groups with an integration ratio of 4:4:4. The $^{13}C$ NMR spectrum of **45** showed the expected three signals for macrocyclic ring <2001JMC1011>.



**45**

$^1H$ NMR spectra of 1,3,5,7-tetraoxonane <1998CC1809> demonstrated the 1:2:2 ratio of $H_a$ (proton of formal linkage, $\delta$ 5.05 ppm) to $H_b$ (proton of formal linkage, $\delta$ 4.93 ppm) and $H_c$ (proton of ether linkage, $\delta$ 3.85 ppm). The $^{13}C$ NMR pattern of this compound showed three different types of carbon: $C_a$ (formal carbon, $\delta$ 96.9 ppm), $C_b$ (formal carbon, $\delta$ 97.1 ppm), and $C_c$ (ether carbon, $\delta$ 70.5 ppm).

### 12.27.3.3 Mass Spectrometry

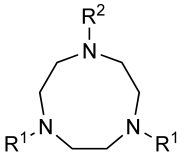
Mass spectrometric techniques are very important in gaining structural information on heterocyclic medium-sized rings. Most of the systems described in this chapter have been subjected to mass spectral analysis and the reader is referred to the individual references for this information. Selected data on published mass spectra of different classes of heteronines and ionization methods are summarized in **Table 2**.

**Table 2** Mass spectrometry of heteronines

| *Name* | *Ionization method* | *References* |
|---|---|---|
| Azonines | CI | 1996J(P1)123, 1997J(P1)447, 2002EJM379, 2001J(P1)2161 |
| | EI | 1996CEJ894, 1997JOC2544, 2003M1241, 2005JOC1552 |
| | FAB | 1997J(P1)447 |
| Oxonines | EI | 1999T7471, 2004JA12432 |
| Oxazonines | N/A | 2003SL1043 |
| Thiazonines | N/A | 1995JOC2597 |
| Oxathionines | N/A | 2004S1696 |
| Triazonine | EI | 1996JA11555, 2002TL771 |
| | FAB | 2001EJO4233, 2004OBC2664 |
| Tetraoxonane | EI | 1998CC1809 |
| Hexaoxonane | CI | 2002AN1627 |

## 12.27.3.4 UV Spectroscopy

The nonaromatic nine-membered rings absorb little in accessible regions of the UV spectrum. **Figure 1** represents structures and data on reported spectra of trisubstituted 1,4,7-triazonanes whose absorptions are due to fused aromatic rings, aromatic substituents, or carbonyl groups. UV absorption data in dioxane–water for hydrazone derivative of 1,4,7-dithiazonane were published <1995BCJ3071>.



**46a–d**

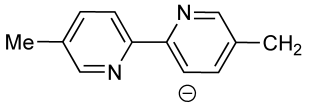
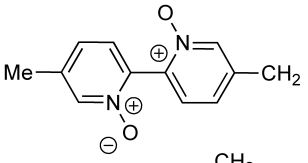
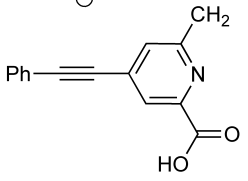
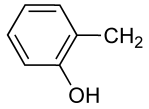
| | | $\lambda_{max}$, *nm* (*log* $\varepsilon$) | *Reference* |
|---|---|---|---|
| **46a** | $R^1 = R^2 =$  | 217 (4.35)<br>239 (4.62)<br>285 (4.75)<br>in $CH_2Cl_2$ | 1998S1339 |
| **46b** | $R^1 = R^2 =$  | 220 (4.94)<br>260 (4.73)<br>in MeOH | 1998S1339 |
| **46c** | $R^1 = R^2 =$  | 288<br>303<br>in $H_2O$ | 1996HCA789 |
| **46d** | $R^1 = CH_2CH_2COOH$; $R^2 =$  | 240 (3.88)<br>292 (3.53)<br>in acetonitrile | 1996JCD4409 |

**Figure 1**

### 12.27.3.5 IR and Raman Spectroscopy

In general, the IR absorption frequencies for nine-membered heterocycles are ill defined, and detailed listings of the vibrational frequencies were reported only for few cyclic systems.

Fleming *et al.* reported a Fourier transform infrared (FTIR) study of 1,4,7-triaza- and 1,4,7-trithia-cyclononanes and their copper(II) complexes in the 120–4000 $cm^{-1}$ region <1999SAA1827>. Raman and IR spectra of 1,4,7-trithiacyclononane **10** in both the pure solid and liquid form, and its IR spectra in $CCl_4$, have been studied. The IR spectrum of liquid **10** is very similar to that of the solution, but both the Raman and IR spectra of the liquid differ from the solid-state spectra. Changes in the spectra on heating through the melting point of the solid near 350 K are attributed to a change from the molecular conformation of symmetry $C_3$ in the solid state to $D_3$ structure in the liquid phase or in solution <1995JST(355)169, 1996JST(378)165>. As the temperature is lowered from room temperature to 10 K, splitting of many bands in the Raman and IR spectra of **10** is observed. This indicates that a further lowering of symmetry occurs at low temperatures. It is suggested that a structural phase change occurs in the crystalline solid near 225 K <1996JST(378)165>.

1,4,7-Triazonane N-trisubstituted with $d_7$-benzyl chloride was characterized <1996JA11555> using IR spectroscopy (KBr, 2277 $cm^{-1}$ (C–D), 2165 $cm^{-1}$ (C–D), and 2045 $cm^{-1}$ (C–D)).

### 12.27.3.6 Other Spectroscopic Methods

Two chiral diaza-9-crown-3 derivatives with naphthalene moieties attached to macrocycle with $CH(Me)NHCOCH_2$ linker were designed as luminescent chemosensors for lithium. The fluorescence emission from the naphthalene moieties was 'switched on' upon $Li^+$ recognition by the crown ether moiety in organic solvents, showing excellent selectivity over other group I and II cations. Even though the recognition of $Li^+$ was not achieved in water (pH 7.4) or aqueous alcohol solution, the fluorescence (which was switched on at pH 7.4) was substantially modulated by spherical anions, where the fluorescence emission was quenched in the presence of $Br^-$ and $I^-$, but less by $Cl^-$ and not by acetate <2004T5799>.

In the photoelectron spectrum of 1,4,7-trithiacyclononane **10**, the ionizations in the region from 8 to 10 eV arise from ejection of an electron from sulfur 3p lone-pair orbitals, while those from about 10 to 12 eV corresponds to removal of an electron from S–C σ-bonding orbitals. Ionizations observed at lower energies correspond to removal of electrons from the C–C σ- and C–H σ-bonding orbitals <1997PCA9180>.

## 12.27.4 Thermodynamic Aspects

### 12.27.4.1 Intermolecular Forces

Heteronines are solids with variable melting points. Their saturated counterparts, heteronanes, are as a rule relatively low-melting solids. For example, unsubstituted 1,5-dithionane, 1,4,7-trithionane, and dithiazonane melt at 57, 81, and 71 °C, respectively, indicating the absence of significant intermolecular interactions <1996JST(378)165, 2003PS1295>. 1,4,7-Heteronanes with *C*- or *N*-phenyl substitution do not have considerably increased melting points <1995JOC3980, 1995BCJ2831>. N-Substitution with thiazole and benzoxazole increased intermolecular interactions and melting points <1995H(41)237>. Heterocycles bearing groups capable of H-bonding are high melting <2002S1398, 2005JOC3838>.

### 12.27.4.2 Protonation, Basicity, and Complexation

Thermodynamic properties of polyazacycloalkanes, including octahydro heteronines, have been carefully studied in regard of their protonation and complexation (usually with transition metals) reactions. This topic rapidly advances, for example, in areas of ternary complexes <2003JA3889> and relationships between changing of macrocycle basicity and increasing ligand denticity <2003AJC61>. It was extensively reviewed <B-2005MI67, 2001ARA331, 2002ARA321> and, hence, only a few points are discussed here.

[$^6Li$,$^{15}N$]-Lithium hexamethyldisilazide ([$^6Li$,$^{15}N$]-LiHMDS) coordination by 1,4,7-trimethyl azononane **9**, along with other polyamines and polyethers, was studied by $^6$Li, $^{15}$N, and $^{13}$C NMR spectroscopy <1996JA10707>. Samples of [$^6Li$,$^{15}N$]-LiHMDS with 1–10 equiv of **9** display exclusively $^6$Li doublets and $^{15}$N triplets characteristic of solvated monomers. The low-temperature $^{13}$C NMR spectra recorded for the monomer complex of [$^6$Li,$^{15}$N]-LiHMDS

and **9** showed numerous broad $^{13}C$ resonances. It was suggested that this behavior of macrocycle-bound LiHMDS is the result of the restricted rotation about Li–N bond.

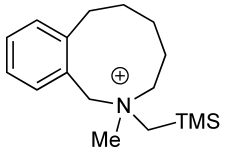
Coordination of [$^{6}$Li]-$\alpha$-(phenylthio)benzyllithium with **9** was studied by $^{1}H$,$^{6}Li$-HOESY NMR technique (HOESY = heteronuclear Overhauser effect spectroscopy) <1998JOM(550)359>. This interaction results in the formation of contact ion pair and ligand and tetrahydrofuran (THF) solvent molecules compete for three coordination sites. The fourth site is occupied by the anionic benzylic carbon atom in an $\eta^1$-like manner.

The charge-transfer complex of 1,4,7-trithiacyclononane **10** and $I_2$ has been prepared by slow evaporation of solutions containing $I_2$ and thioether macrocycle in $CH_2Cl_2$. The structure of the complex showed two independent macrocycles in the asymmetric unit which are linked by a diiodine bridge. Asymmetric units are linked by iodine–iodine and sulfur–iodine interactions to form an extended array of linked macrocycles. The formation enthalpy ($\Delta H = 35.0\,kJ\,mol^{-1}$) and formation constant ($K = 169\,dm^3\,mol^{-1}$) of 1:1 adduct have been determined by electronic spectroscopy and compared to other polythia macrocycles of different sizes <1997JCD1337>.

### 12.27.4.3 Conformational Studies

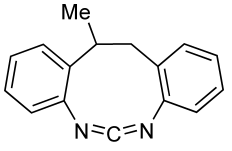
Nine-membered rings are strained in all of their conformations. Conformational studies of saturated heteronines and heteronines containing torsional constraint caused by double bonds, three-membered and benzo-annulated rings, lactams and lactones were the part of the survey <1999MI(5)89>.

The signals in the $^{1}H$ NMR spectra of 2-methyl-2-[(trimethylsilyl)methyl]-2,3,4,5,6,7-hexahydro-1*H*-2-benzazoninium iodide **47** were observed as doubled patterns of the expected proton signals <1997JOC2544>. This result suggested that it exists in solution as a mixture of two stable conformational isomers in the ratio 31:69 and with characteristic signals at 0.27 and 0.33 ppm ($Me_3Si$), 3.34 and 3.09 ppm (N–Me), and 2.64, 3.39 and 3.27, 3.40 ppm ($NCH_2Si$), respectively. The chemical shifts of the (trimethylsilyl)methyl groups at a higher field and of N–Me group at the lower field are assigned to the isomer with a methylene group located around phenyl ring due to the diamagnetic anisotropy effect of the benzene ring (trimethylsilyl = TMS).




**47**

Cyclic carbodiimide **48** theoretically exists as two conformational isomers. Comparison of the coupling constant values, calculated using AM1 Hamiltonian and Karplus relationship, with the experimental vicinal coupling constants of 8.33 and 1.05 Hz, undoubtedly prove its 'methyl-out' structure **48** <1996JOC4289>.




**48**

Analysis of the $^{1}H$ NMR coupling constants and NOEDIFF experiments gave an accurate idea of the preferred conformation of the nine-membered ring in (3*S*)-azoninone **35** and its (3*R*)-isomer <2005OBC97>; see also Sections 12.27.2.2 and 12.27.3.2. An examination of the NMR data indicated that for both isomers a conformation with COOEt in pseudoequatorial ($\beta$-) position is preferred. For (3*S*)-isomer **35**, there is a high coupling constant $J_{1-9}$ of 9.3 Hz, which excludes conformation with the COOEt in pseudoaxial position. The $J_{8-9}$ (3.9 and 7.2 Hz) and $J_{7-8}$ (6.7 and 9.0 Hz) are perfectly compatible with conformations where amide NH is on the opposite side of double bond. Moreover, NOEs detected between the ring NH and one of the H-8 and one of the H-5, and an NOE between H-9 and H-7, are in agreement with the proposed conformation. Similar observations were made for (3*R*)-isomer.

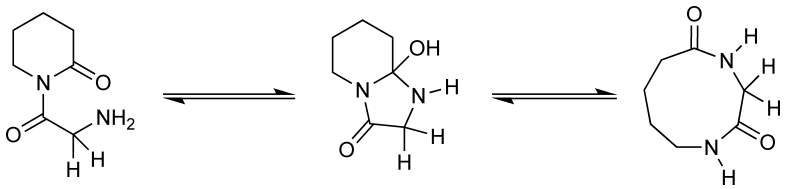
The solid-phase $^{13}C$ cross-polarization/magic angle spinning (CP/MAS) NMR, as a tool for conformation prediction, revealed that the solid-phase conformation of the nine-membered ring crown cavity in naphtho-9-crown-3 is different from benzo-9-crown-3. The two key C–O–$CH_2$ units are predicted to be out of naphthalene plane, and the two C–C–O–$CH_2$ torsion angle values are close to each other <2000JST(526)185>.

Conformational analysis of 1,4,7-trithiacyclononane **10** in the gas phase was done using *ab initio* molecular orbital calculations at the HF and MP2 levels as well as microwave and photoelectron spectroscopies. The photoelectron spectroscopic data showed evidence for at least two conformations with different ionization energies. Using the calculated photoelectron spectra, the observed sulfur 3p-ionization peaks can be assigned to $C_1$ and $C_2$ conformations. Forty of the observed microwave transitions can be assigned to a $C_1$ symmetry, while additional microwave lines are believed to be due to a nonrigid $C_2$-symmetry conformation <1997PCA9180>.

### 12.27.4.4 Kinetics

The thermal decomposition reaction of cyclic triacetone triperoxide **11** in the temperature range of 130.0–166.0 °C and an initial concentration of 0.021 M has been studied in toluene solution. The thermolysis follows first-order kinetic laws up to at least ca. 78% acetone triperoxide conversion. The activation parameters corresponding to the unimolecular thermal decomposition reaction of the molecule ($\Delta H^{\neq} = 41.8 \pm 1.6$ kcal mol$^{-1}$, $\Delta S^{\neq} = 18.5 \pm 3.8$ cal mol$^{-1}$ K$^{-1}$) were determined <2000JOC2319>. Similarly, thermal decomposition reaction of hexaethyl analogue of **11** in chlorobenzene solution follows a first-order kinetic law. The activation parameter values for the initial O–O bond rupture in chlorobenzene ($\Delta H^{\neq} = 134.6 \pm 1.7$ kJ mol$^{-1}$, $\Delta S^{\neq} = 4.2 \pm 3.8$ J mol$^{-1}$ K$^{-1}$) and the observed reaction products supported a stepwise reaction mechanism. It includes as a first step the unimolecular homolytic cleavage of one peroxidic bond of the molecule giving rise to a biradical as intermediate. Additionally, the results obtained were compared with those obtained in toluene, toluene–styrene, and chlorobenzene–styrene solution, showing that the decomposition reaction is strongly solvent dependent <2004JPO215>. Three pathways for the decomposition of **11** were proposed based on theoretical studies <2005JA1146>.

When *N*-(2-aminoacetyl)-2-piperidone **49** was dissolved in aprotic or protic solvents, a fast equilibrium, ca. 1:1, between the cyclol form (tetrahedral intermediate) **50** and the bislactam **51** is established (**Scheme 1**). Dynamic $^1H$ NMR has been used to evaluate the exchange between the two forms at different pH. The rate law for the proposed exchange mechanism between the cyclol form and macrocycle was proposed. Both the macrocycle formation and cyclol formation constants are specific base catalyzed; however, the equilibrium constant is independent of pH <2002J(P2)2078>.



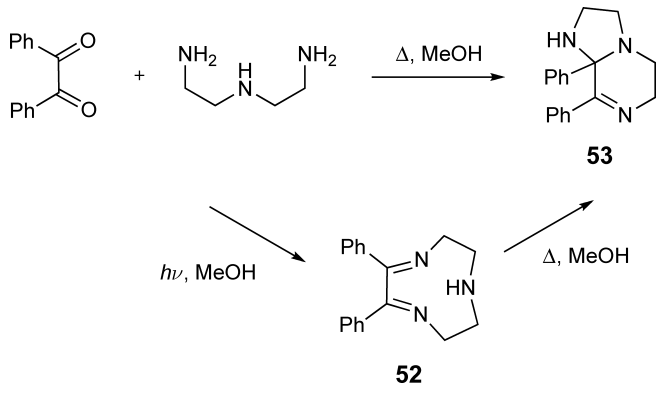

**49** **50** **51**

**Scheme 1**

## 12.27.5 Reactivity of Nonconjugated Rings

### 12.27.5.1 Intramolecular Thermal and Photochemical Reactions

Diphenyl triazonine **52** is a product of UV irradiation of benzyl and diethylenetriamine in the presence of oxygen. It can be thermally converted into bicyclic derivative **53** (**Scheme 2**), which is the major product of the thermal reaction between benzyl and triamine <2000NJC719>.



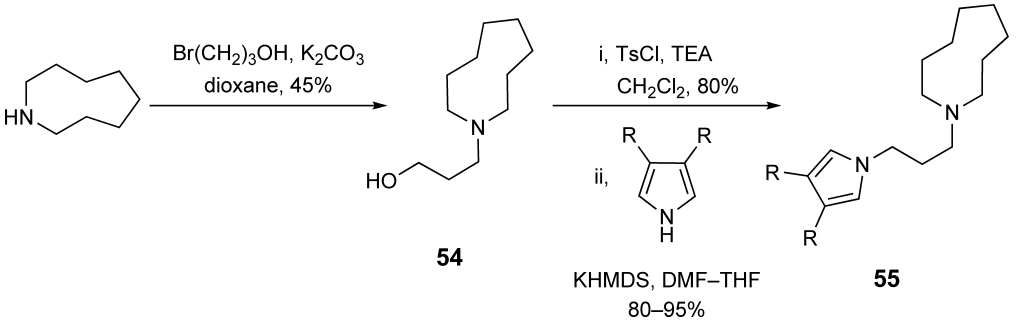

**Scheme 2**

## 12.27.5.2 Electrophilic Attack on Ring Heteroatoms

### 12.27.5.2.1 Electrophilic attack on ring nitrogen

Chapters 5.20.3.3.1 of CHEC(1984) and 9.27.6 of CHEC-II(1996) partially covered this class of transformations. Since that time, numerous syntheses of this type were reported and they have become a major method of synthetic modification of azonines and their poly-heteroatom analogues.

*N*-Ethyl azonan-2-one is readily available by alkylation with the ethyl iodide <1998BML1973>. Similarly, azonane was alkylated with 3-bromopropan-1-ol to afford intermediate alcohol **54** in 45% yield (**Scheme 3**) <2003T9239>.

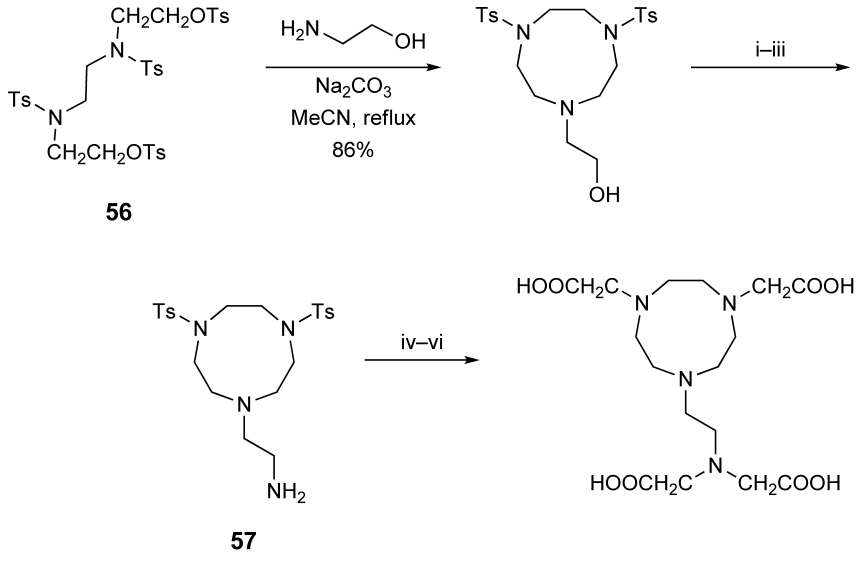



**Scheme 3**

1,4,7-Triazonanes were reacted with various alkylating agents to yield mono-, di-, and trisubstituted products. Expected compounds are often accompanied with by-products of higher degree of substitution. Trisubstitution of this heteronane system with substituted alkyl halides <1995S453, 2000JCD4607, 2000AJC791, 2002AJC655, 2001CJC888, 1997AGE2346, 1999TL4989>, and their activated substituted allyl <2002AJC655>, benzyl <2001CJC888, 2000JA9663, 1997AGE642, 1998CEJ93, 2000CC443, 1996JA11575>, heteroarene methyl <1996HCA789, 1998S1339, 2003JCM704, 2001JA2436, 2002JOC3933, 2000JOM(611)586, 2001PS85, 2001PS325, 2003JCD2428>, or $\alpha$-carbonyl <2002EJO351> analogues are the most common. Selective mono- <1997AGE642> and bis- <1996JA4396> alkylation are quite rare, and protection/deprotection strategies are required if mono- or disubstituted 1,4,7-triazonanes are synthetic targets. Tosyl group is frequently used for monoprotection and sequential dialkylation <1999AGE980, 1996JCD353, 1997ACR227, 2002EJO351, 1995JA10745>. Alkylations of di-BOC <2001JA5030, 2001JA6025, 2003TL535> and di-Cbz <2000JOM(611)586> as well as dialkyl <1996JA10920, 2000JA9663, 2001CC637, 1995JA3983, 1996JA11575> triazonane derivatives are straightforward and high yielding (BOC = *t*-butoxycarbonyl; Cbz = carbobenzyloxy). Triazonane alkylation with tris-(3-chloropropyl)amine leads to 38% yield of a macrocyclic tetramino cage <1999J(P2)2701>. The new bis-triazonane bridged with pyrazole moiety was synthesized from 3,5-dichloromethylpyrazole and ditrityl-protected triazonane <1995HCA693>. Similarly, reactions of 1,4,7-dithiazonane and monoformyl 1,4,7-thiadiazonane afforded corresponding bis-derivatives <1997HCA2315>.

Electrophilic attack on 1,4,7-triazonane with oxiranes <2004JME5683, 2005BMC2389, 1997CC845, 2003AJC61, 1994CC2467, 1999J(P1)1211, 2004CEJ2022>, thiirane <1995JA10745>, and *N*-tosylaziridine <2001CC2582> proceeds smoothly and leads to the corresponding mono- <1999J(P1)1211, 2004CEJ2022, 1994CC2467>, di- <2003AJC61, 1994CC2467, 2001CC2582>, and trisubstituted <2004JME5683, 2005BMC2389, 1997CC845> products.

1,4,7-Oxadiazonane was alkylated with substituted 2-chloroacetamides in acetonitrile to give a mixture of disubstituted (yields of ca. 30%) and monosubstituted derivatives <2002TL4989, 2004T5799>. 2-Aminoethyltriazonane **57** underwent both ring and side-chain alkylations when reacted with *tert*-butyl 2-bromoacetate (**Scheme 4**), <2002JME3458>.

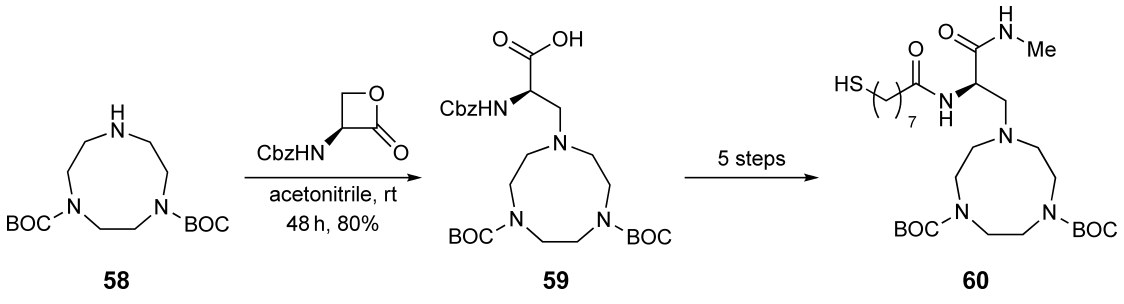



i, $SOCl_2$, benzene, 86%; ii, $NaN_3$, DMSO, 96%; iii, $H_2$, Pd/C, 93%; iv, $H_2SO_4$, 92%; v, *t*-$BuOCOCH_2Br$, 48%; vi, HCl(g), 92%

**Scheme 4**

Michael addition of methyl acrylate to azonane gave methyl 3-(azonan-1-yl)propanoate <2002JOC245>, while addition of acrylonitrile to 1,4-diisopropyl-1,4,7-triazonane resulted in 95% of a heterocyclic nitrile <2000NJC575>.

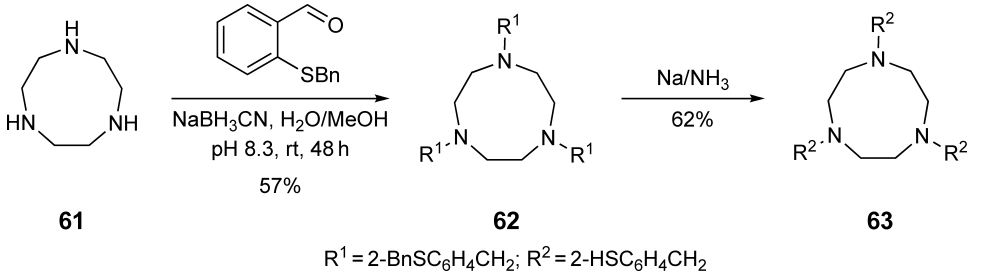
Protected (*S*)-2-amino-3-[1-(1,4,7-triazacyclononane)]propanoic acid **59** (**Scheme 5**) is a valuable building block in peptide synthesis <2002PNA5144> and in the preparation of functionalized amino acid **60** <2004AGE6165>. It was obtained by ring-opening reaction of di-BOC-protected 1,4,7-triazacyolononane **58** with (*S*)-2-Cbz-amino-$\beta$-1actone. This transformation is regiospecific and produces the functionalized amino acid **59**, as a sole product, without any traces of serine amide, an expected by-product corresponding to the attack of the amine on the $\beta$-carbon <1998TL7159, 2000CEJ4498>.




**Scheme 5**

1,4,7-Triazonanes react with formaldehyde or paraformaldehyde and further undergo Mannich reaction with a variety of phenols <1997CEJ308, 1997JA8217, 1997JA8889, 1999CEJ2554>, trialkoxyphosphines <1995S453>, or alkyl dialkoxyphosphines <1995S453, 1996JA4396> to form mono-, di-, and trisubstituted derivatives, which were obtained in good to excellent yields.

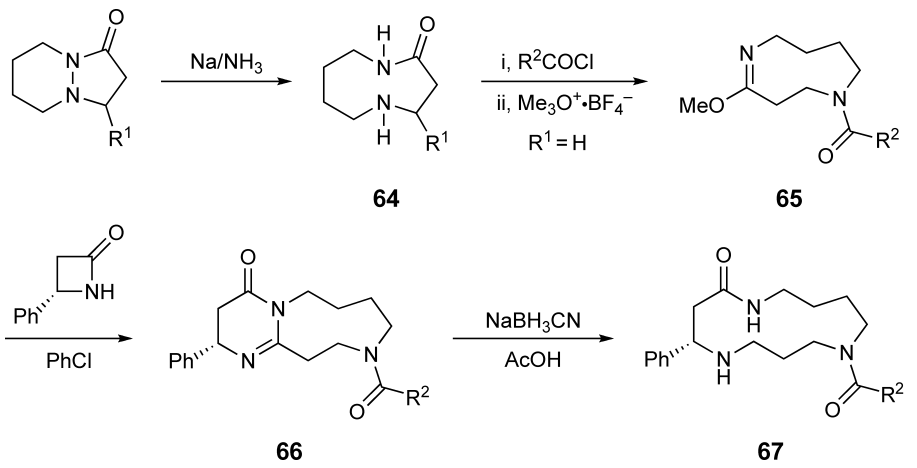
Reductive amination of triazonane **61** requires controlled pH conditions and affords good yield of *ortho-S*-benzyl derivative **62** (**Scheme 6**) <1999T5733>.




**Scheme 6**

1,4-Di-(2-propyl)azonane was successfully transformed into product of reductive amination with *ortho*-diphenylphosphinobenzaldehyde and sodium triacetoxyborohydride <1999JCD1539>.

Acylation of diazoninone **64** and subsequent treatment with Meerwein's reagent ($Me_3O^+BF_4^-$) resulted in the imino ether **65** ($R^2$ = PhCH=CH, **Scheme 7**). It further reacts with $\beta$-lactam to produce the corresponding bicyclic 4-oxotetrahydropyrimidine derivative **66**, as a product of addition–ring-annulation process <2000CL1104>. Analogous sequence was used for the preparation of racemic precursor of dihydroperiphylline <2002T7177>.

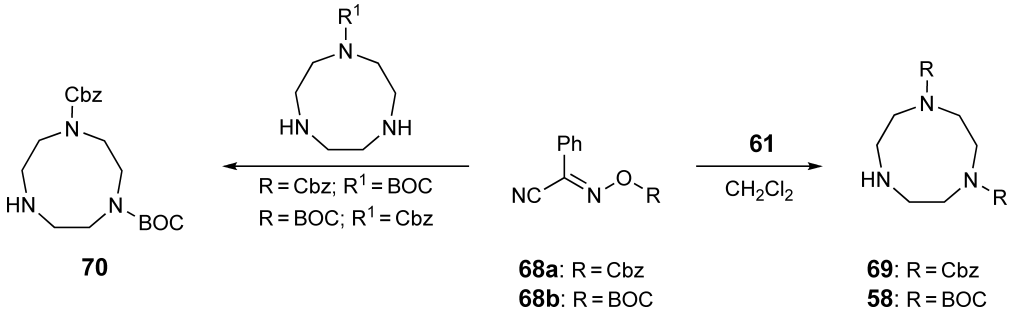



**Scheme 7**

Several acylation transformations of 1,4,7-triazonane were reported. Benzoylation of 1,4,7-triazonane under kinetical control, that is, through formation of dianion with 2 equiv of *n*-BuLi in THF, led to an 85% yield of mono- and disubstituted compounds in 20:1 ratio <1999JOC7661>. Reaction of triazonane with ethyl trifluoroacetate is a facile method of incorporation of two protecting groups and results in 94% yield of the product when reaction is performed in methanol in the presence of triethylamine <2003TL2481>.

1,4,7-Triazonane **61** when reacted with $(BOC)_2O$ yielded di-BOC derivative in 67% yield <2005JOC115>. Noteworthy, reaction with 2 equiv of 2-(benzyloxycarbonyloxyimino)-2-phenylacetonitrile (Z-ON) **68a** or 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON) **68b** in chloroform under anhydrous conditions gave high yields (>90%) of the diprotected derivatives **69** or **58**, respectively (**Scheme 8**) <1995TL9269, 1996BML2673,

2001JA5030, 2001JA6025, 2003TL5699>. The remarkable preference of BOC-ON and Z-ON for disubstitution was demonstrated by the reaction of the monoprotected derivatives with these reagents. Both reactions afforded **70** having two different protecting groups in nearly quantitative yields <1995TL9269>.



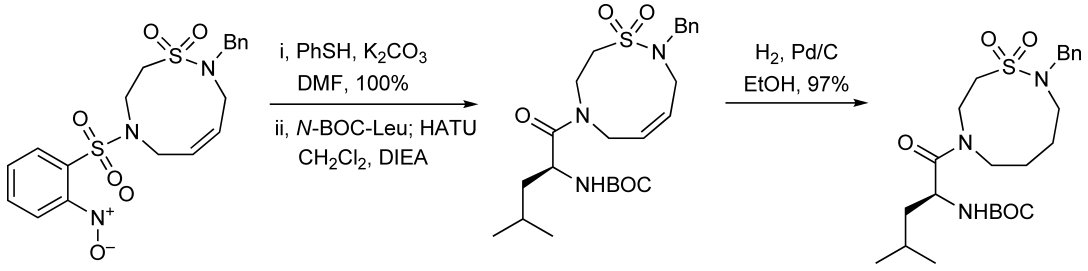

**70** **68a**: R = Cbz; **68b**: R = BOC **69**: R = Cbz; **58**: R = BOC

**Scheme 8**

Other reported examples of triazonane acylations included reactions with succinic anhydride <2002S1398>, carboxymethyl calixarene <1995CC929>, and *N*-BOC-sarcosine <2003TL5699>.

Acylation of 1-thia-4,7-diazonane with 2-chlorocarbonylthiophene in $CH_2Cl_2$ in the presence of triethylamine led to the corresponding bis-amide **33** <1996AXC3062>. 1,4,7-Dithiazonane and 1,4,7-thiadiazonane underwent smooth acylation with substituted benzoyl chlorides to afford correspondent products **44** and **45** <2001JMC1011>.

Synthesis of model cyclic peptidosulfonamides containing 1,2,7-thiadiazonine moiety was performed by the incorporation of an amino acid on the 7-position leading to **71** (**Scheme 9**) <2004JOC3662>.




**71** **72**

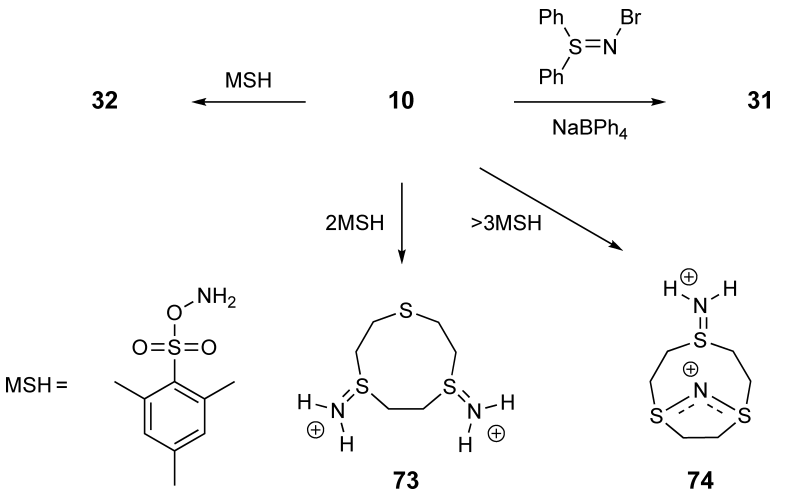
**Scheme 9**

N-Arylation of azonane with 2-chloro-5-nitrobenzoic acid was reported <1998JME5219>. Arylation of anion formed from 1,6-diazonane (PhLi, diethyl ether) with 4-chloropyridine resulted in mixture of mono- (38%) and disubstituted (13%) products <1998CC1625>. A novel 1,4,7-triazonanes bearing thiazol-2-yl and benzoxazol-2-yl substituents were synthesized by high-pressure $S_NAr$ reactions <1995H(41)237>. Arylation of 1,4,7-triazonane with 5 equiv of 4,7-dichloroquinoline in dimethylformamide (DMF) at reflux in the presence of potassium carbonate afforded a mixture of mono- and disubstituted products, while formation of the trisubstituted derivative was not indicated <2001JME1658>.

Triazonane was converted into 1,4,7-trinitroso-1,4,7-triazacyclononane **27** in 84% yield by standard treatment with $NaNO_2$/HCl <2002TL771>.

### 12.27.5.2.2 Electrophilic attack on ring sulfur

Treatment of the 1,4,7-trithionane **10** with 1 equiv of *O*-mesitylsulfonylhydroxylamine (MSH) yielded the water-soluble protonated sulfimide **32** (**Scheme 10**) <2002CJC1410>. Two equivalents of MSH lead to the formation of bis-sulfimide **73**, while excess MSH generated cation **74**. Compounds **32**, **73**, and **74** formed mesitylsulfonate salts, structures of which were assigned based on X-ray crystallography (see Section 12.27.3.1).

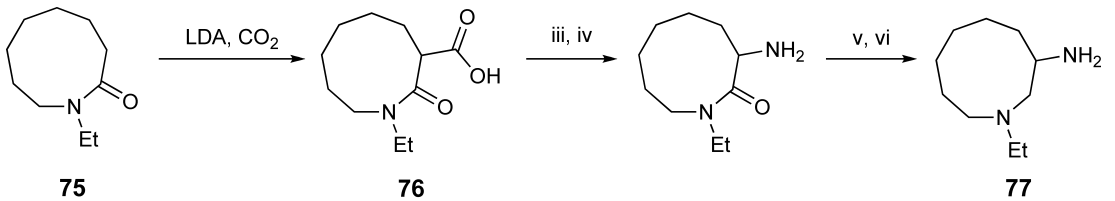



**Scheme 10**

Brominated sulfimide was reacted with trithionane to afford sulfimidium salt **31** <2004NJC959>, which was further crystallized as tetraphenyl borate derivative and studied by $^{1}H$ and $^{13}C$ NMR and X-ray crystallography (Section 12.27.3.1). Contrary to MSH derivatives **73**, and **74**, excess of diphenyl sulfimide did not lead to disubstituted product, which was attributed to bulkiness of phenyl groups.

## 12.27.5.3 Electrophilic Attack on Ring Carbon

*N*-Ethyl azonanone **75** can be lithiated on position 3, and further quenched with carbon dioxide to produce 3-carboxy derivative **76** (**Scheme 11**) <1998BML1973>.




i, ClCOOEt, $NaN_3$, then heat; ii, $Ph_3CCl$, TEA; iii, $NaAlH_2(OCH_2CH_2OMe)_2$; iv, HCl(aq.)

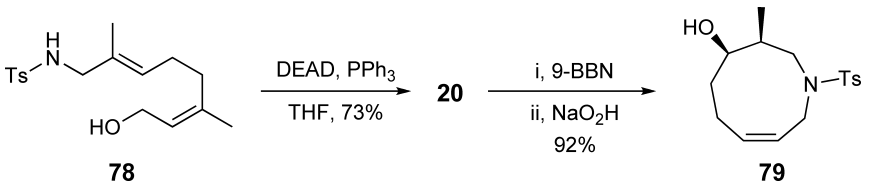
**Scheme 11**

Trinitroso derivative **27** underwent in $CD_3OD/D_2O$ solution fast base-catalyzed H/D exchange on the whole set of methylene hydrogens, and nitroso groups can be subsequently removed by reduction with Ni/Al alloy <2002TL771>.

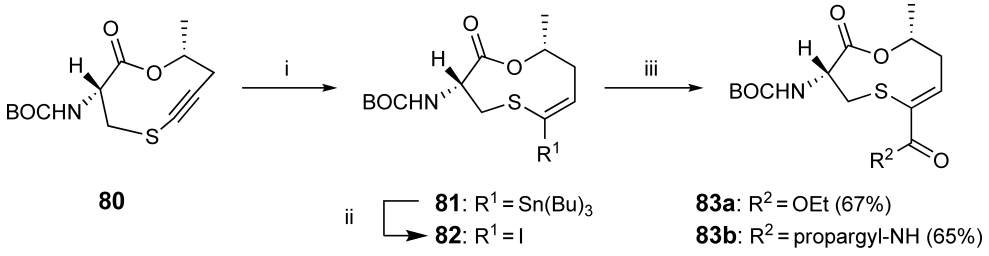
## 12.27.5.4 Reactions with Nucleophiles

Azonine **20** is a representative of cyclic diallylic amides with a remarkably stable planar chirality. When its (*S*)-isomer was hydroborated using 9-borabicyclo[3.3.1]nonane (9-BBN), the reaction went stereospecifically to give exclusively (3*S*,4*R*)-**79** in 92% yield (**Scheme 12**) <2006OL963>.

Oxonane-2,9-dione reacts with amines, producing monoanilide in 94% yield <2001OPP391>. Hydrostannylation of oxathionine **80** gave vinyl tin lactone **81** in 80% yield. Formation of the corresponding iodo lactone **82** was achieved in 87% yield by a Sn/I-exchange (**Scheme 13**) <2002JOC4565>.



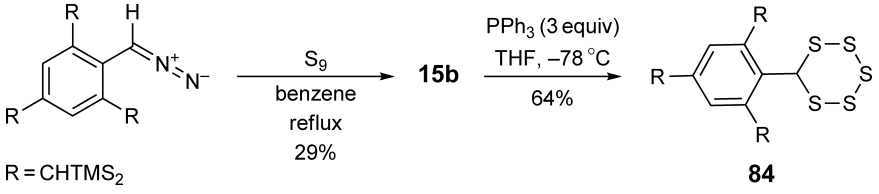

**Scheme 12**




i, $Bu_3SnH$, $Pd(PPh_3)_4$, toluene, 20 °C, 80%; ii, $I_2$, $CH_2Cl_2$, 20 °C, 30 min, 87%; iii, CO (8 bar), $Pd(PPh_3)_2Cl_2$, MeCN, amine or alcohol

**Scheme 13**

*C*-Substituted octathionane **15b**, when reacted with 7 equiv of triphenylphosphine, desulfurized to produce the corresponding 2,4,6-trisubstituted thiobenzaldehyde <1997CEJ62, 1994PS389>. Partial desulfurization to pentathiane **84** occurred when 3 equiv of $PPh_3$ was used (**Scheme 14**) <1994PS389> (Chapter 8.14).




**Scheme 14**

## 12.27.5.5 Oxidation and Reduction

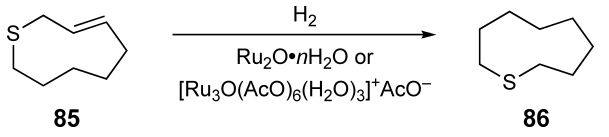
It is convenient to discuss oxidative attack on ring carbon in the same chapter with reduction of heteronines as many reported syntheses involved various oxidative/reductive sequences and reagent combinations. Examples of oxidative transformations involve radical as well as electrophilic oxidizing agents, while reductive syntheses include both chemical reduction and reactions on surfaces via catalytic hydrogenation.

### 12.27.5.5.1 Reactions at surfaces

Catalytic hydrogenation of hexahydroazonines with different substitution patterns afforded almost quantitative yields of azonane racemic amino acids <2002EJM379, 1999SL954, 1997CC637, 1997J(P1)447>. Asymmetric hydrogenation of methyl 4,5,6,7,8,9-hexahydro-1*H*-azonine-2-carboxylate in the presence of a catalytic amount of [Rh(COD)-(2)-(*R*,*R*)-(Et-DuPHOS)]OTf afforded the corresponding saturated cyclic amino acid in excellent yield and with high enantioselectivity (COD = cyclooctadiene) <1998CC1757>.

Hydrogenation of *trans*-isomer of 2,3,4,5,6,9-hexahydrothionine **85** (Equation 1) under heterogeneous $Ru_2O$ catalysis led to only 7% yield of reduction product **86**. A major process is the isomerization into the *cis*-isomer (80% yield), which has a reduced ring strain, and, thus, is inert to reduction under conditions employed

<1996SC899>. Reduction under homogeneous catalysis conditions using $[Ru_3O(AcO)_6(H_2O)_3]AcO$ as a catalyst led to 67% yield of the thionine **86**.




**85** **86** (1)

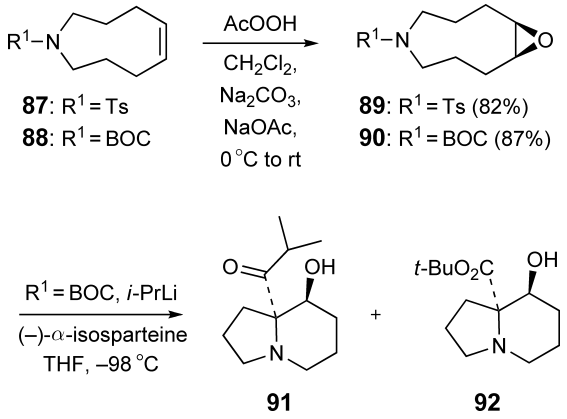
Hydrogenation of **71** led to 1,4,7-thiadiazonane **72** in 97% yield (**Scheme 9**, Section 12.27.5.2.1) <2004JOC3662>.

### 12.27.5.5.2 Chemical reduction

Synthesis of dihydroperiphylline **67** ($R^2$ = PhCH=CH, 81%) was accomplished in one step by treatment of intermediate **66** with sodium cyanoborohydride in acetic acid (**Scheme 7**, Section 12.27.5.2.1). The conditions are mild enough to leave the exocyclic double bond unaffected. The physical, optical, and NMR spectral data of ring expansion product **67**, thus prepared, were consistent with those reported for (+)-(*S*)-dihydroperiphylline <2000CL1104>. Analogous sequence was used for the preparation of racemic dihydroperiphylline <2002T7177>. Borane–THF reduction of 2,3,6,7-tetrahydro-1*H*-benzo[*f*][1,5]diazonin-4(5*H*)-one led to the corresponding hexahydrodiazonine in 88% yield <2004JA3529>. Reduction of substituted 1-acetyl-1,4,7-triazonane with lithium aluminum hydride (LAH) afforded 39% of the corresponding *N*-ethyl derivative <2004OBC2664>.

### 12.27.5.5.3 Oxidations and oxidation/reduction sequences

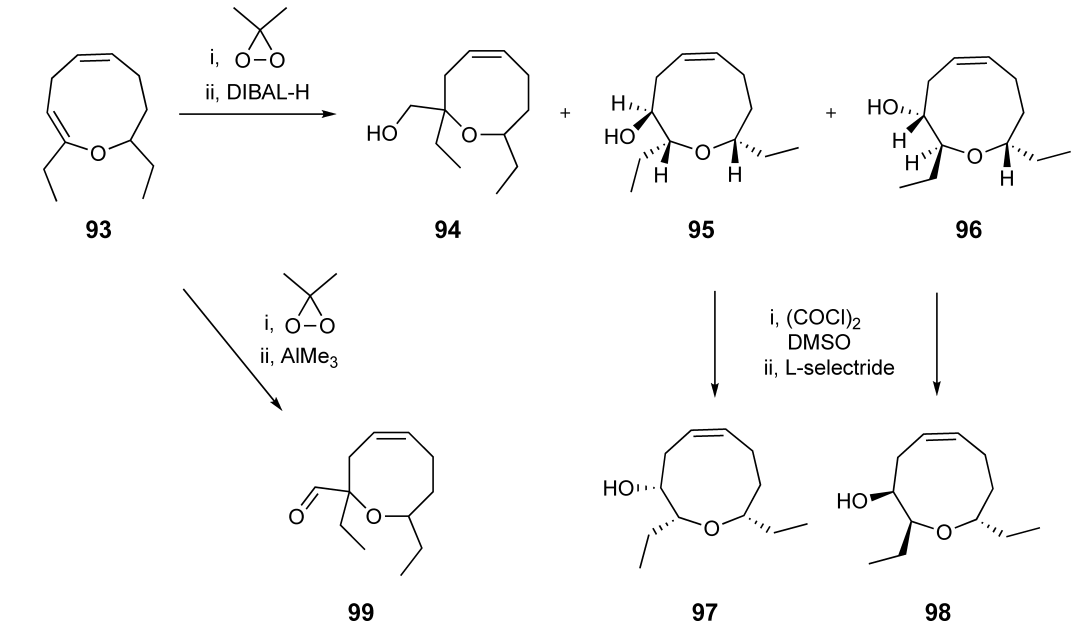
N-Protected azonines **87** and **88** are smoothly transformed into epoxides **89** and **90**, correspondingly, when reacted with peroxyacetic acid (**Scheme 15**) <1999CC309>.



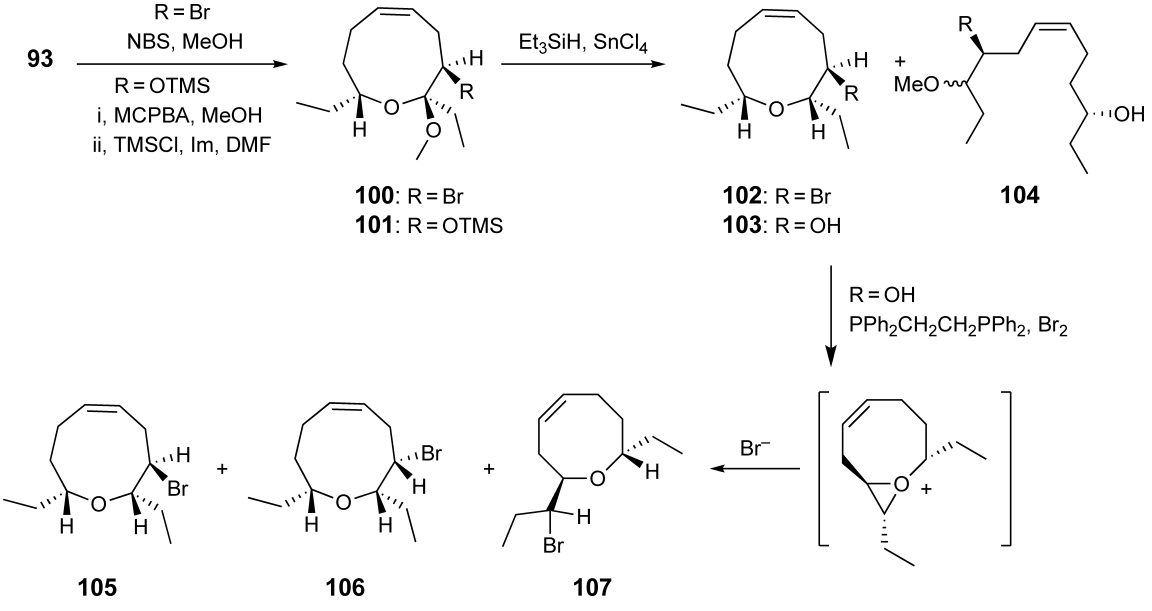

**Scheme 15**

2,3-Epoxidation of oxonine **93** with dimethyldioxirane, followed by reduction with diisobutylaluminum hydride (DIBAL-H), resulted in a separable mixture of alcohols **95** and **96**, and the side product **94** (**Scheme 16**). Each of the isomers was submitted to Swern oxidation and sequential stereoselective reduction with L-selectride to achieve desired stereochemistry of the products **97** and **98**. Formation of the side product **94** was explained by Lewis acidity of DIBAL-H and confirmed by treatment of oxirane derived from **93** with another Lewis acid, $AlMe_3$, to produce oxocine aldehyde **99** in 35% isolated yield <1997CL665>. Similar oxidative synthetic sequence was utilized for the synthesis of functionalized oxonines as precursors of (+)-obtusenyne <1999JOC2616>.

Cyclic diene ether **93** underwent oxidative acetalization to produce corresponding 3-substituted acetals **100** and **101** (**Scheme 17**) <1995TL8263>. Further Lewis acid-catalyzed reduction with triethylsilane afforded corresponding 3-bromo- and 3-hydroxy-oxonenes (**102**: R = Br (68%); **103**: R = OH (49%), respectively) together with 1:1 diastereomeric mixture of acyclic methyl ethers **104** (R = Br (18%); R = OH (13%)).




**Scheme 16**

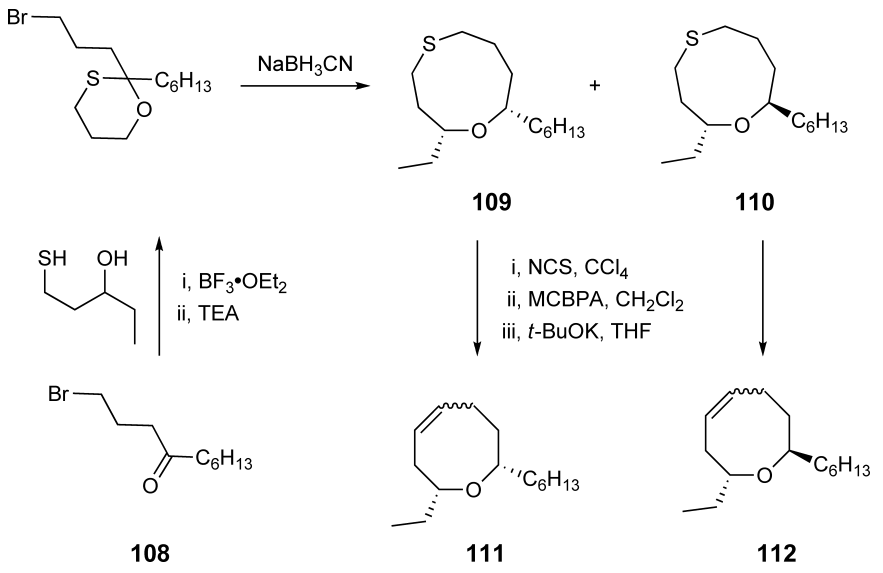



**Scheme 17**

S-Oxidation of oxathionanes is an intermediate step in their transformation into the corresponding oxocines (**Scheme 18**, Section 12.27.5.6.1) <2002OL3047> (Chapter 12.19).

## 12.27.5.6 Intramolecular Ring-Transformation Reactions

Ring strain of heteronines resulted in various ring-contraction reactions to produce more favorable smaller ring systems, or, in some specific cases, bicyclic products of transannular transformations. Heteronines are prone to the formation of bridged systems or ring enlargement when their side chains contain reactive groups. This section covers intramolecular ring-contraction and ring-extension reactions other than photolytic and thermal ones (see Section 12.27.5.1).

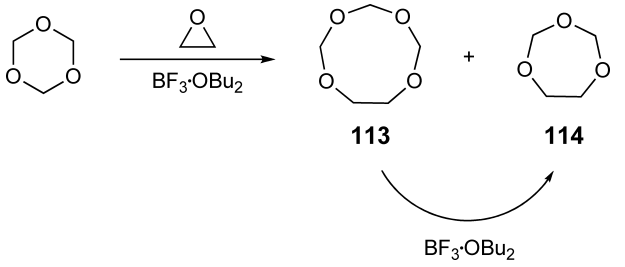



**Scheme 18**

### 12.27.5.6.1 Ring contractions

Oxathionanes **109** and **110** were transformed into the corresponding oxocines using a three-step procedure (**Scheme 18**) <2002OL3047>. Chlorination with *N*-chlorosuccinimide (NCS) followed by oxidation on sulfur with *m*-chloroperbenzoic acid (MCPBA) gave a mixture of four possible $\alpha$-chloro sulfones (not shown in the scheme). Subsequent Ramberg–Bäcklund rearrangement with potassium *tert*-butoxide resulted in oxocines **111** and **112** (56 and 50%, respectively) as ca. 9:1 mixture of *(Z)*- and *(E)*-isomers.

1,3,5,7-Tetraoxonane **113** underwent a ring contraction to afford 1,3,5-trioxepane **114**, which is also observed as the main by-product of the tetraoxonane synthesis (Equation 2) <1998CC1809, 2001TL271> (Chapter 12.16).



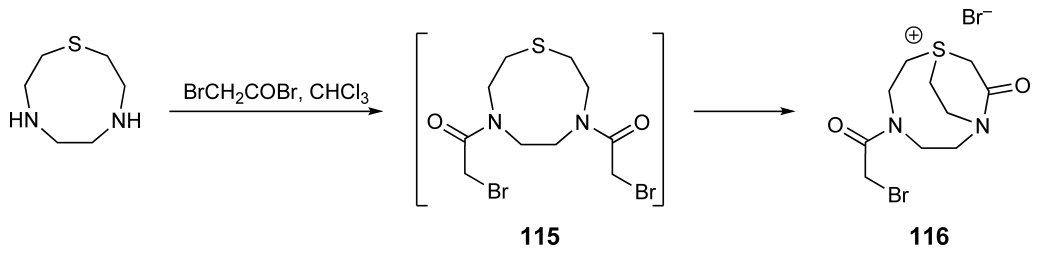

(2)

1,2,4,5,7,8-Hexaoxonane **11** underwent a slow ring narrowing in methylene chloride or chloroform in the presence of *p*-toluenesulfonic acid (PTSA) to yield 60% of diacetone diperoxide <2005JA1146>.

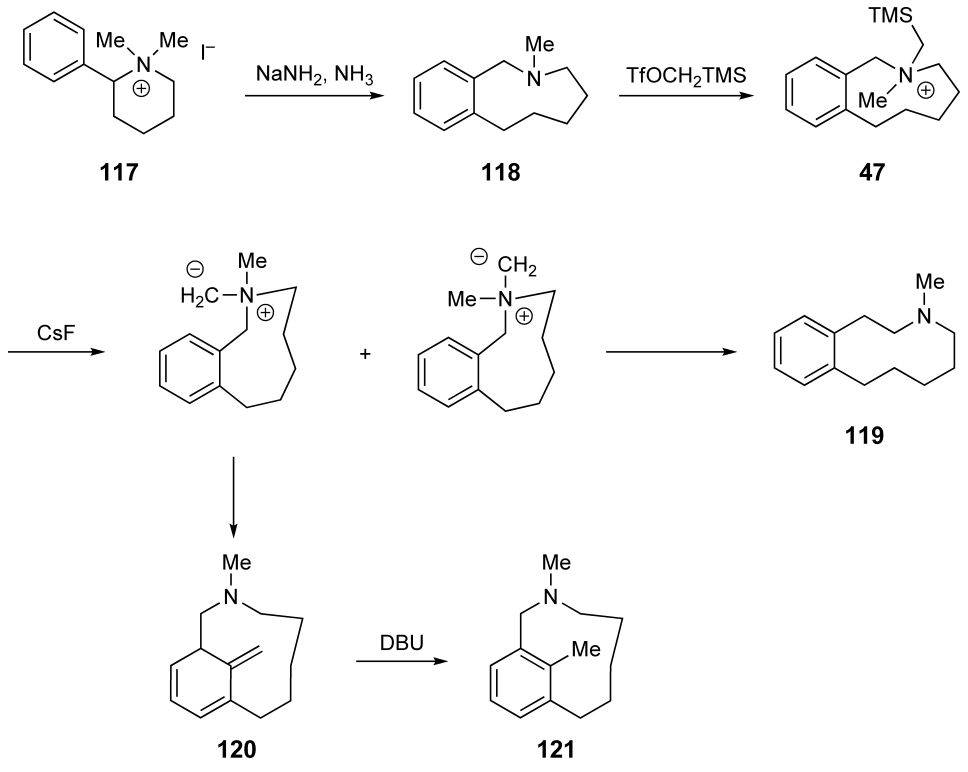
### 12.27.5.6.2 Formation of bridged systems and ring expansions

Reaction of 1,4,7-thiadiazonane with bromoacetyl bromide in $CHCl_3$ afforded, instead of expected 4,7-bis-(2-bromoacetyl)-1-thia-4,7-diazacyclononane **115**, derivative of 1-thionia-4,7-diazabicyclo[5.2.2]undecane **116** as a product of intramolecular cyclization (**Scheme 19**) <2004AXCo100>.

Reaction of 2-methyl-2-[(trimethylsilyl)methyl]-2,3,4,5,6,7-hexahydro-1*H*-2-benzazoninium iodide **47**, with cesium fluoride in DMF for 0.5 h at room temperature, gave a mixture of **119** and product of [2,3]-sigmatropic rearrangement **120** (**Scheme 20**). The structure of **120** was assigned based on a comparison of the $^1$H NMR, $^{13}$C NMR, and UV spectra of the product mixture with those of an authentic sample of **119**. The product ratio **119**:**120** did not change after 24 h. However, when the reaction was repeated in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 2.5 mol equiv), **121** was formed with decreasing yield of **120** <1997JOC2544>.

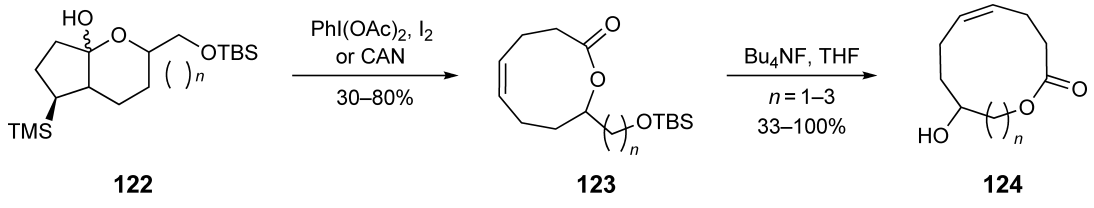



Scheme 19



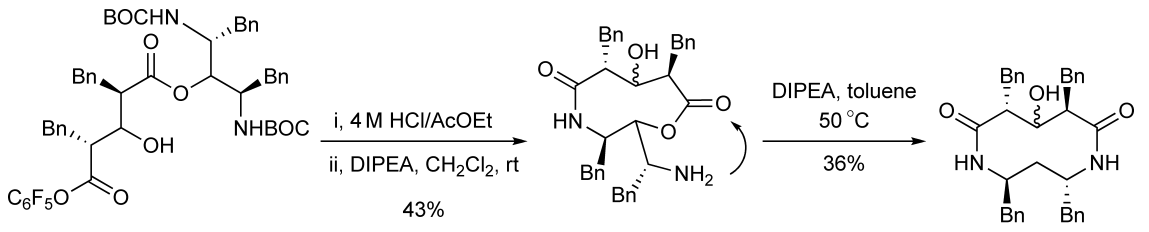

Scheme 20

Nine-membered lactones **123** underwent a ring expansion under mild desilylation conditions to produce 10–12-membered lactones **124** in moderate to excellent yields (**Scheme 21**) <2005OL4301> (Chapter 12.28).




Scheme 21

Ring expansion of oxazonine dione **126** (**Scheme 22**) occurred upon treatment with *N*,*N*-diisopropylethylamine (DIPEA) in toluene at 50 °C to form the corresponding 1,5-diazecane-6,10-dione ring system **127** in 36% yield <2002T2957> (Chapter 12.29).

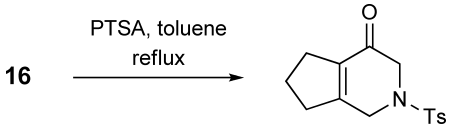



**125** **126** **127**

**Scheme 22**

### 12.27.5.6.3 Transannular transformations

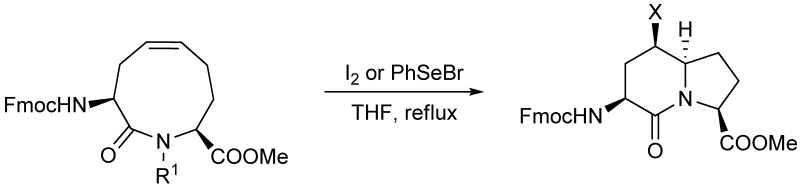
Treatment of *N*-tosyl azonane-3,8-dione **16** with PTSA resulted in an intramolecular aldol reaction giving tetrahydrocyclopenta[*c*]pyridinone ring system **128** (Equation 3) <1995J(P1)1137>.




**128** (3)

Lithiation of epoxide **89** ($R^1$ = Ts; **Scheme 15**, Section 12.27.5.5.3) under standard conditions (*sec*-BuLi in ether at −78 °C for 5 h, followed by warming to 25 °C) led to recovery of the starting material or, in the separate $D_2O$ quench experiment, to *ortho*-deuterium incorporation into tosyl substituent <1999CC309>. Substrate with blocked *ortho*-positions ($R^1$ = 2,4,6-triisopropylbenzenesulfonyl) proved to be unreactive <2001J(P1)2161>. Contrary, BOC-protected **90** underwent a *meso*-epoxide α-deprotonation–transannular N–C-insertion reaction to produce mixture of ketone **91** and ester **92**. The optimized conditions, *i*-PrLi at −98 °C <1999CC309>, or *sec*-BuLi at −90 °C <2003OBC4293> in the presence of (−)-α-isoparteine as an asymmetric inducing agent, resulted in 45–49% isolated yield of **92** with 89% ee and ratio of **91**:**92** = 1:10 <1999CC309>.

Electrophilic transannular cyclization of nine-membered ring lactam **129** led to formation of protected methyl 6-amino-8-iodo-5-oxooctahydroindolizine-3-carboxylates **130a** and **130b** in high yields (Equation 4) <2006OL2851>.



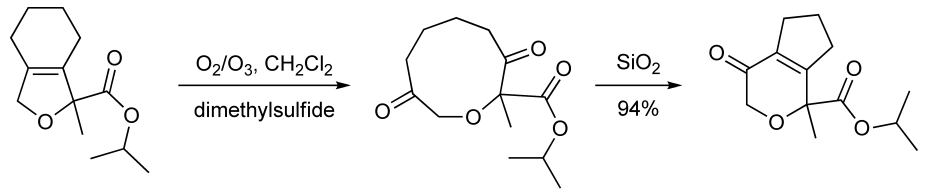

**129**

**130a**: X = I (86%)
**130b**: X = PhSe (79%)

(4)

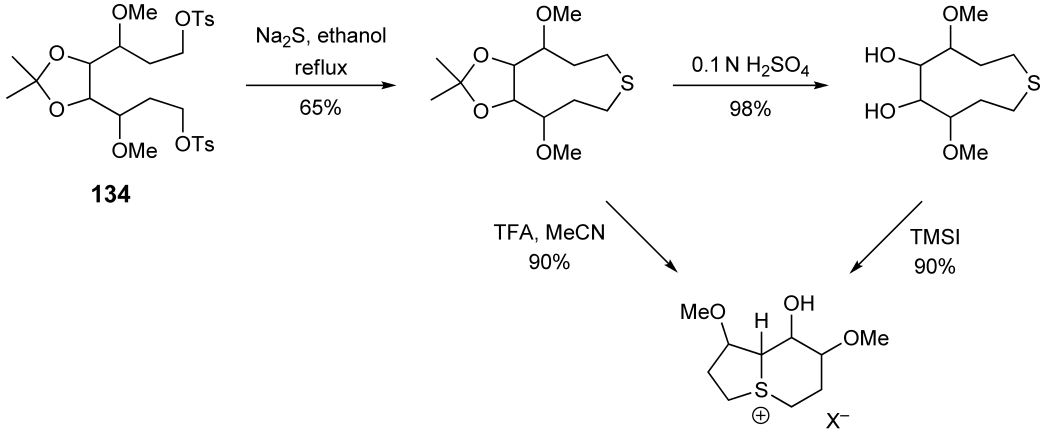
Oxonine diketone **132** (**Scheme 23**) is highly sensitive to acidic conditions and prone to intramolecular aldol condensation. The sole product of the process, 4-oxocyclopenta[*c*]pyran-1-carboxylate **133**, was isolated in 94% yield, and the regiochemistry of the process was assigned by X-ray crystal structure of the related amide aldol adduct <2002OL3059>.

The enantioselective synthesis of bicyclic sulfonium salts **135**, starting from thionane ring system, has been reported <2003JOC3311>. The synthetic strategy is based on a stereo- and regiospecific transannular cyclization of nine-membered cyclic sulfides, mediated by TMSI or carried out under acidic catalysis (**Scheme 24**, stereochemistry omitted). Each compound was prepared in two enantiomerically pure forms starting from the corresponding (*R*,*R*)- and (*S*,*S*)-intermediate.




131 132 133

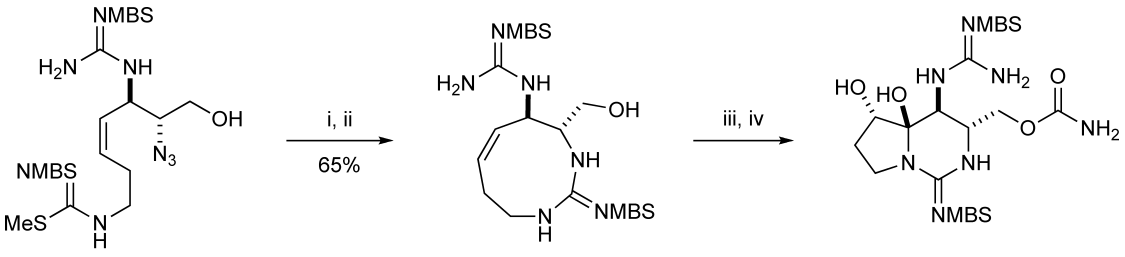
**Scheme 23**




134 135

**Scheme 24**

Nine-membered protected guanidine **137** can be readily transferred into corresponding carbamate, which was further oxidized into intermediate hydroxy ketone, which spontaneously forms the bicyclic dihydroxy compound **138** (**Scheme 25**) <2006JA3926>.



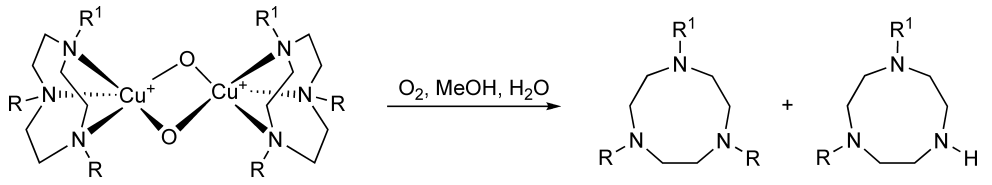

136 137 138

i, $Me_3P$, $THF/H_2O$; ii, $AgNO_3$, TEA, MeCN; iii, $Cl_3C(O)NCO$, 82%; iv,$OsCl_3$, Oxone, $Na_2CO_3$, $EtOAc/MeCN/H_2O$, 57%

**Scheme 25**

## 12.27.5.7 Reactivity of Transition Metal Complexes

Oxidative decomposition of bis(μ-oxo)dicopper complexes of trisubstituted triazonanes **139** resulted in the dealkylation products **141** along with recovered ligand **140** (Equation 5) <1996JA11575>. In the case of tribenzyl-substituted ligand ($R = R^1 = Bn$), equivalent amounts of benzaldehyde were formed and detected as side products of the oxidative process. Ligands with isopropyl moiety ($R = R^1 = i$-Pr; or $R = i$-Pr, $R = Bn$) produced acetone in the similar manner.

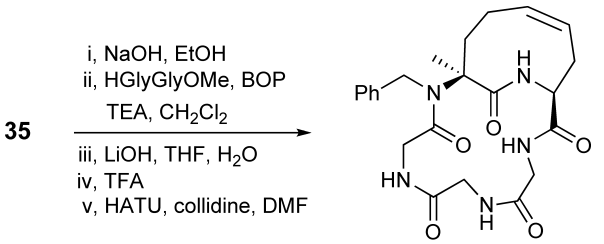



139 140 141 (5)

## 12.27.6 Reactivity of Substituents Attached to Ring Carbon Atoms

### 12.27.6.1 Alkyl Groups and Further Carbon Functional Groups

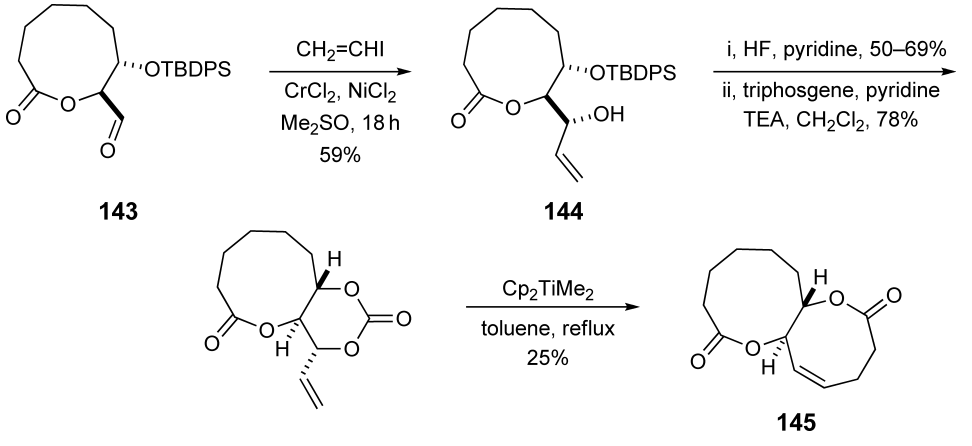
*C*-Carboxy-substituted heteronines and their protected counterparts underwent standard amide bond formation. 2,3,4,5,6,7-Hexahydro-1*H*-benzo[*e*]azonine-3-carboxylic acid underwent two sequential amide bond couplings through BOC-protected intermediate <1997BML1289>. Removal of the terminal protecting groups from *cis*-azoninone **35**, followed by cyclization with *O*-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU)/collidine, afforded the cyclopeptide **142** in 55% yield (Equation 6). Formation of the isomeric adduct (not shown) starting from *trans*-isomer of **35** was much more troublesome, giving only crude 13% yield <2005OBC97>.




142 (6)

Azonanone-3-carboxylic acid **76** was converted into 3-amino-1-ethylazonine **77** by a Curtius rearrangement of intermediate azide, and final protection/reduction sequence (**Scheme 11**, Section 12.27.5.3) <1998BML1973>. Ester group of ethyl 2-oxo-1*H*-azonine-4-carboxylates was selectively reduced with $NaBH_4$ in *tert*-butyl alcohol and methanol to give the corresponding alcohol <1995AGE1026>.

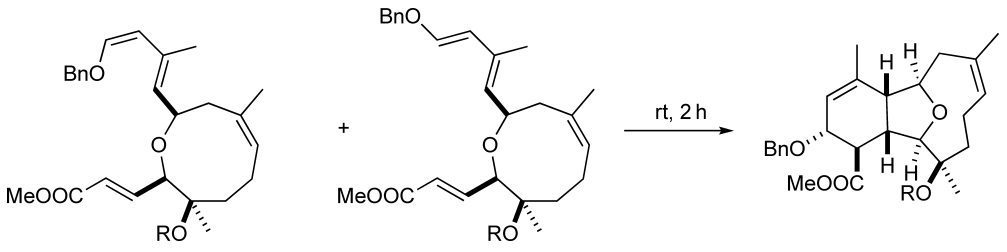
Lactone carbaldehyde **143** was treated with vinyl iodide in the presence of chromium(II) chloride and $Me_2SO$ to provide allyl alcohol **144** in 59% yield as a 2:1 diastereomeric mixture (**Scheme 26**; major isomer shown) <2000CC631>. Further deprotection, conversion into cyclic carbonate, and final treatment with dimethyltitanocene provided *trans*-fused bicyclic lactone **145** in 25% yield.




143 144 145

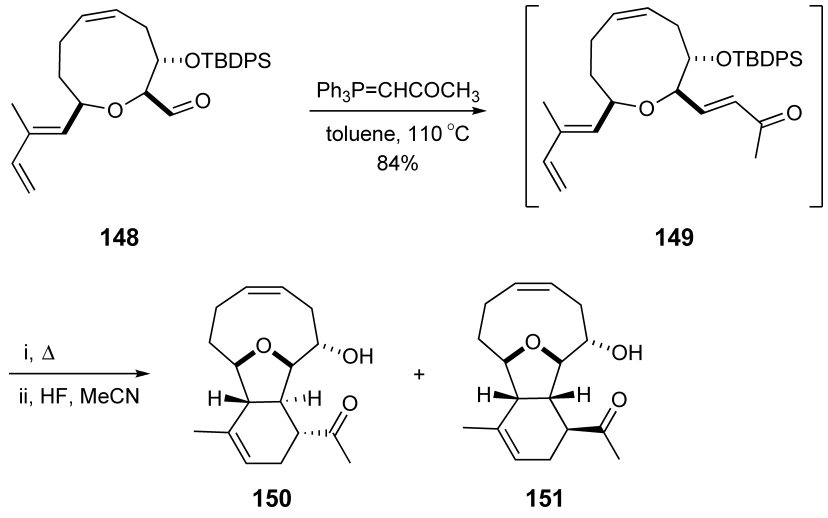
**Scheme 26**

Only diene **147** undergoes *exo*-Diels–Alder reaction when mixture of dienes **146** and **147** was allowed to stand at room temperature (Equation 7) <2004JA10264>. Unreactive isomer **146** was converted into **147** by irradiation, and overall 80% isolated yield was achieved when reaction mixture was submitted to several equilibration cycles.




**146** **147** (7)

Wittig reaction of aldehyde **148**, followed by *in situ* intramolecular Diels–Alder reaction of intermediate **149** and desilylation, afforded eunicellin analogues **150** and **151** as 3:1 mixture (**Scheme 27**) <2004SL1434>.



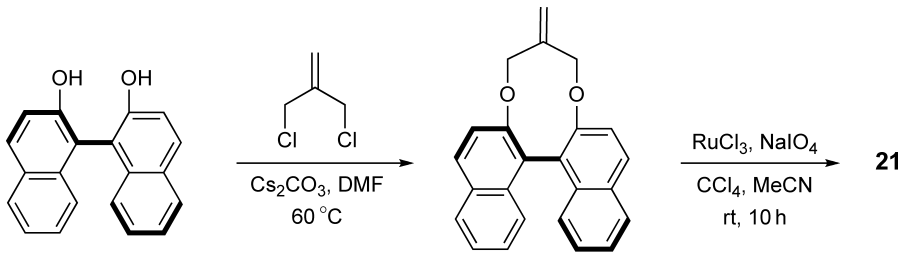

**148** **149** **150** **151**

**Scheme 27**

Many synthetic transformations of carbon functional groups have been reported for a variety of oxonines as directed toward construction of carbon side chains of natural products (cf. Section 12.27.11). They usually involved synthesis of alcohol intermediates by DIBAL-H reduction <2001JA1533, 2004JA10264, 2006JA1371>, *p*-methoxybenzyl (PMB) deprotection <2004JA12432, 2002JA15196> or desilylation <1999JOC2616, 2003JA7592>, their Dess–Martin oxidation <1999JOC2616, 2003JA7592, 2004JA10264, 2004JA12432, 2002JA15196, 2006JA1371> into the corresponding aldehydes followed by Wittig olefination <2003JA7592, 2001JA1533, 2004JA10264, 2004SL1434, 2006JA1371>. Alternatively, aldehyde precursors can be obtained by oxidative cleavage of vicinal diols <2003JA7592, 2001JA1533> or Pummerer rearrangement, followed by cleavage <2004SL1434>. Synthetic pathways involving Peterson olefination <2004JA12432, 2002JA15196> and Sonogashira coupling <2003JA7592, 1999JOC2616> have been reported.

Oxidation of unsaturated intermediate **153** with $RuCl_3/NaIO_4$ <1998JA5943> or its ozonolysis <1997TA2921> resulted in the ketone dioxonine **21** (**Scheme 28**).

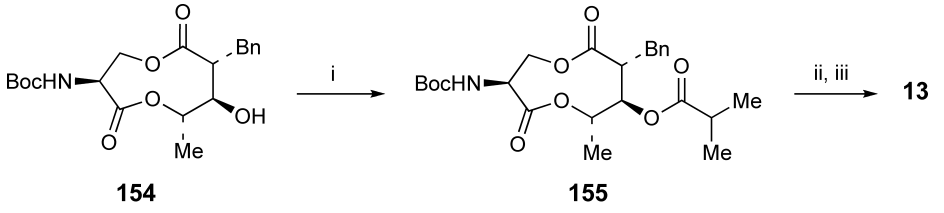
The pyrilium salt **30a** was obtained from benzo-9-crown-3 in 29% yield in two steps by formylation with hexamine in the presence of $CF_3CO_2H$, followed by reaction with 2 equiv of acetophenone in the presence of $POCl_3$ <2002JOC2065>. In the same manner, the Vilsmeier formylation of the *N*-phenyl dithiazonine and the subsequent condensation reaction with 2-aminobenzenethiol resulted in substituted benzothiazole **43** in 38% yield <1999J(P2)1273>. Benzo-9-crown-3 ether trimerizes in the presence of $FeCl_3$ and aqueous sulfuric acid to produce tris-(9-crown-3)-triphenylene **28** in 25% yield <2001CJC195>.




**Scheme 28**

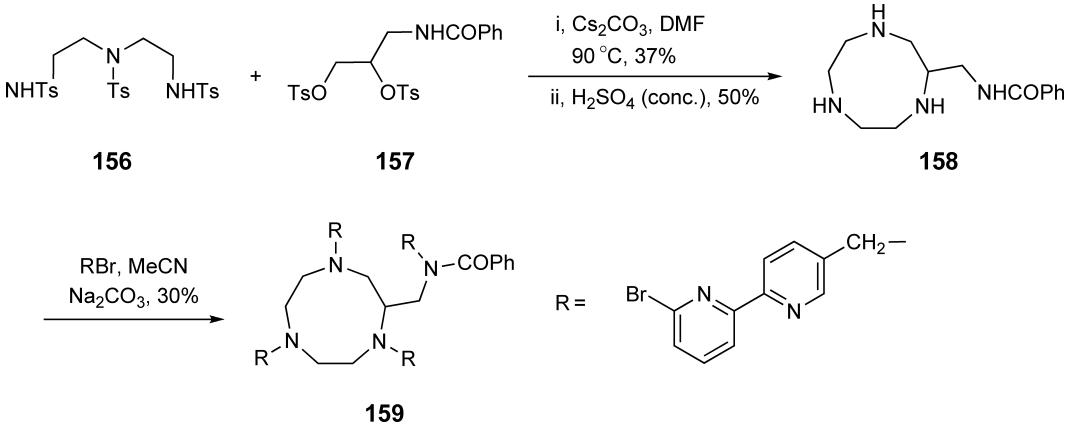
## 12.27.6.2 Amino and Imino Groups

Deprotection of dilactone **155** and sequential coupling with 3-hydroxy-4-methoxypyridine-2-carboxylic acid afforded (*S*)-dioxonine **13** in 51% yield (**Scheme 29**) <1998T12745, 1998TL4363>. Similar reaction sequence performed on (*R*)-isomer (not shown in the scheme) resulted in 61% yield of the product. Several structural analogues of amide **13**, containing heterocyclic moieties other than pyridine, were reported <2005BML2011>.




**Scheme 29**

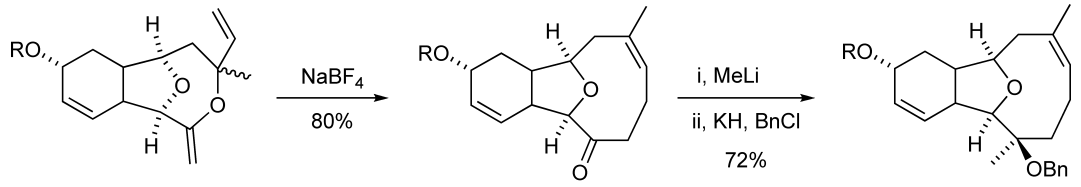
Alkylation of functionalized triazonane **158** involved both ring and side-chain amino groups and afforded tetrasubstituted product **159** in 30% yield (**Scheme 30**) <2002JOC3933>.




**Scheme 30**

### 12.27.6.3 Hydroxy and Oxo Groups

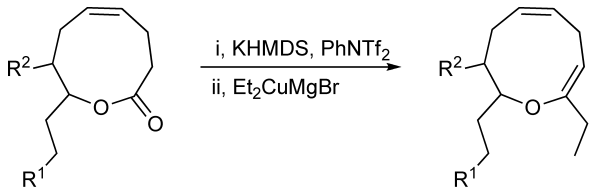
*C*-Hydroxy heteronines underwent standard electrophilic attack to produce O-substituted derivatives. Thus, desilylation and acylation of intermediate cyclic dilactone afforded corresponding ester **155** in 94% yield (**Scheme 29**, Section 12.27.6.2). Similar reaction sequence performed on (*R*)-isomer (not shown in the scheme) resulted in 90% yield of the product <1998T12745, 1998TL4363>. Other examples of reactions with electrophiles include benzylation <2000OL1875, 2001JA9021> and reaction with carbon disulfide <1995J(P1)1137>. Starting hydroxy heteronines are readily available from the corresponding carbonyl compounds via reactions with nucleophiles. 3-Keto oxonine **161** (**Scheme 31**) was reacted with methyllithium to give the corresponding $\alpha$-methyl alcohol, which was further O-alkylated with benzyl chloride to give ether **162** <2000OL1875, 2001JA9021>.




**160** **161** **162**

**Scheme 31**

Cyclic diene ether **93** was prepared in high yield starting from lactone **163** through the corresponding enol triflate (Equation 8) <1995TL8263, 1997CL665>.



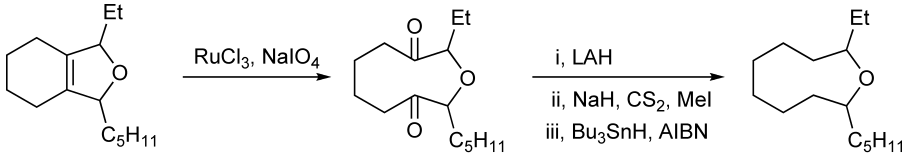

**163**

**93**: $R^1 = R^2 = H$
**164**: $R^1$ = TBDPSO; $R^2$ = Cl

(8)

Similar synthetic strategy was applied for the preparation of functionalized cyclic ether **164** ($R^1$ = TBDPSO, $R^2$ = Cl, 83%) <1999JOC2616> (Chapter 12.19).

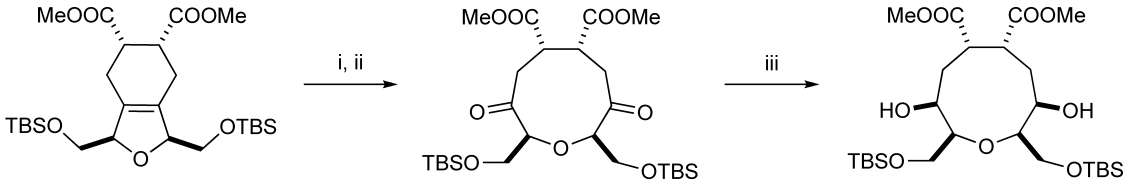
Chemical reductions of carbonyl compounds into hydroxy derivatives are more often and various reducing agents were used. Stepwise deoxygenation of diketone **166** included LAH reduction as a first step toward obtaining structure **167** (**Scheme 32**), which was obtained as a 2.5:1 mixture of *cis*- and *trans*-isomers <1995J(P1)1137>.




**165** **166** **167**

**Scheme 32**

Reduction of diketone **169** with sodium borohydride proceeded stereoselectively to give diol **170**, as a single isomer in 83% yield (**Scheme 33**) <1999T7471>.

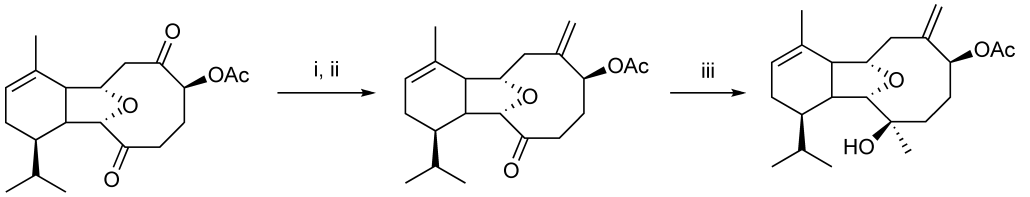



**168** **169** **170**

i, $OsO_4$, *N*-Me-morpholine-*N*-oxide, dioxane, $H_2O$, 75 °C, 94%; ii, $Pb(OAc)_4$, Py, 94%; iii, $NaBH_4$, MeOH, 0 °C, 94%

**Scheme 33**

A keto group was extensively used in olefinations, providing a convenient access to natural-type oxonine products. Chemoselective formation of silyl enol ether of oxonine **171** (**Scheme 34**) followed by Wittig olefination, deprotection, and diastereoselective methylation afforded acetate **172** in good yield <2004JA1642>.

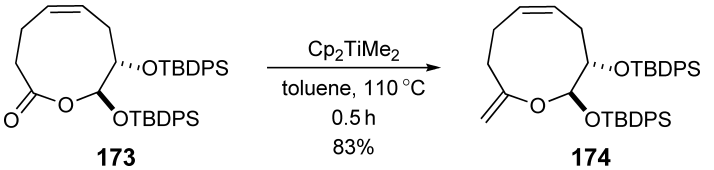



**171** **172**

i, KHMDS, TBSOTf; ii, $PPh_3CH_3Br$, THF, *t*-BuOK, 61%; iii, MeLi, $YbOTf_3$, 66%

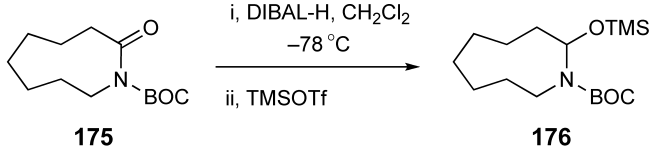
**Scheme 34**

Lactone precursor **173** was converted in 83% yield into enol ether **174** via Petasis methylation (Equation 9) <2004SL1434>.

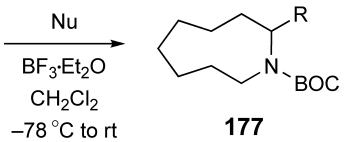



**173** **174** (9)

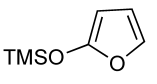
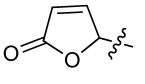
The DIBAL-H reduction of lactam **175** and subsequent etherification of the resulting *N*,*O*-hemiacetal with TMSOTf resulted in **176** (**Scheme 35**). It was further reacted with a variety of nucleophiles in the presence of Lewis acid to afford corresponding α-substituted azonines **177** in high yields <2002TL3165>.




**175** **176**




**177**

| *Nu* | *R* | *Yield* (%) |
|---|---|---|
| TMSCN | CN | 91 |
| AllylTMS | Allyl | 92 |
|  |  | 91 |

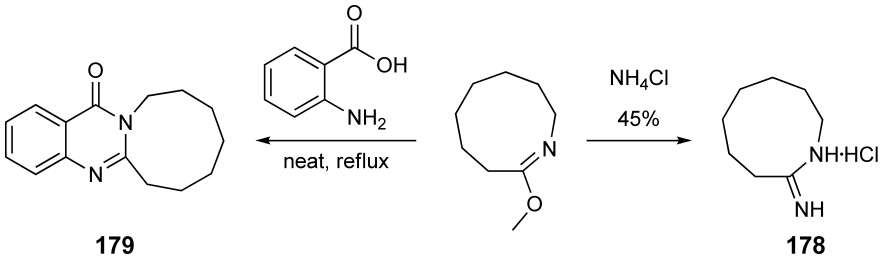
**Scheme 35**

Reduction of nine-membered lactam with $BH_3$–THF afforded the corresponding reduced azonine in moderate yield <1996T8063>.

Reaction of 3-hydroxy-oxonene **103** with the complex of bromine and 1,2-bis(diphenylphosphino)ethane resulted in an expected mixture of brominated compounds **105** and **106**, along with single stereoisomer of oxocene **107**, probably due to the formation of the bridged oxonium cation and its two different directions of the reaction with bromide anion (**Scheme 17**, Section 12.27.5.5.3) <1995TL8263>.

## 12.27.6.4 Other O-Linked Groups

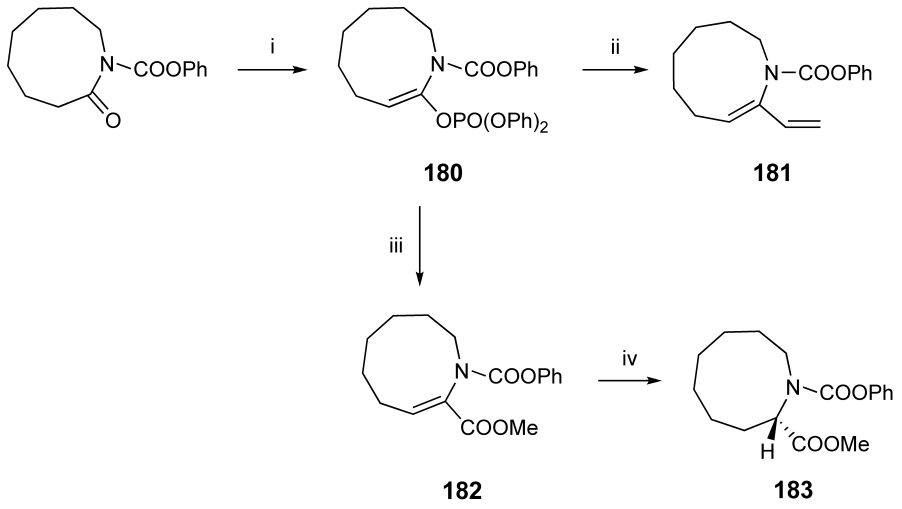
Azonan-2-one easily forms cyclic imidate, which produced azonan-2-imine **178** (**Scheme 36**) <1996JME669>. On the other hand, its reaction with anthranilic acid led to the corresponding quinazolinone-type 6,6,9-ring system **179** <1996BML737>.




**179** **178**

**Scheme 36**

N-Protected 2-oxoazonane formed ketene aminal diphenylphosphate **180** via potassium enolate. It underwent coupling reactions with appropriate partners under palladium(0)-catalyzed conditions (**Scheme 37**). Reactions proceeded smoothly in good to excellent yields furnishing diene **181** and ester **182** <1998CC1757>.




**180** **181**

**182** **183**

i, $(PhO)_2POCl$, KHMDS, THF, –78 °C, 0.5 h, 41%; ii, $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, LiCl, THF, 94%; iii, CO (1 atm), $Pd(OAc)_2$, $PPh_3$, MeOH, $Et_3N$, DMF, 60 °C, 4 h, 74%; iv, $H_2$ (90 psi), cat., MeOH, rt, 97%, 94.5% ee

**Scheme 37**

Oxonine with homoallyl ether side chain was a suitable intermediate for RCM synthesis of oxonines with annulated oxepine ring <2004TL7567>.

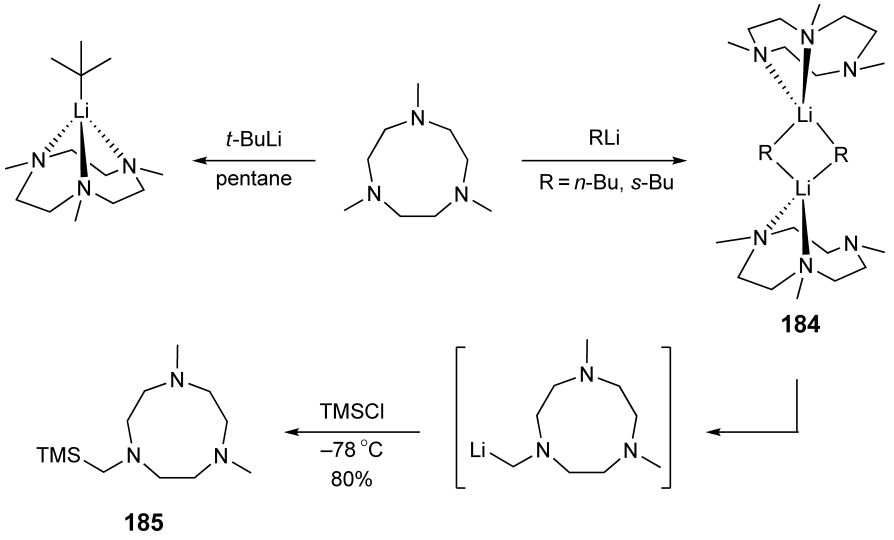
### 12.27.6.5 Halogen Atoms

Synthesis of ester **83a** and amide **83b** was performed by palladium-catalyzed carbonylation starting from iodo lactone **98** to afford products in good yields (**Scheme 13**, Section 12.27.5.4) <2002JOC4565>.

## 12.27.7 Reactivity of Substituents Attached to Ring Heteroatoms

### 12.27.7.1 Alkyl Groups

Monomer complex of *t*-BuLi with 1,4,7-trimethyl-1,4,7-triazacyclononone **9** is identified by $^{13}C$ NMR and it is stable in pentane at temperatures up to 20 °C and (**Scheme 38**) <1997T9977>. Conversely, lithiation of *N*-Me was the exclusive reaction with *n*-BuLi and *s*-BuLi, as indicated by the formation of TMS derivatives **185**, isolated after silylation of the reaction mixture. This result evidenced the existence of uncoordinated *N*-Me groups in complexes with *n*-BuLi and *s*-BuLi. Dimeric structure **184** was suggested based on decreasing tendency to form monomer complexes going from *t*-BuLi via *s*-BuLi to *n*-BuLi.

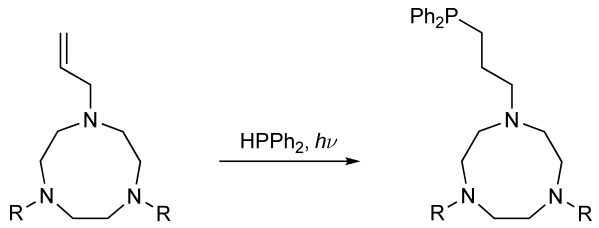



**Scheme 38**

Trityl protecting groups are easily cleaved (MeOH, HCl) from substituted 1,4,7-triazonane <1995HCA693>. Reaction of 2-methyl-2-[(trimethylsilyl)methyl]-2,3,4,5,6,7-hexahydro-1*H*-2-benzazoninium iodide **47** with cesium fluoride in DMF for 0.5 h at room temperature led to formation of ylide, which spontaneously transforms into a mixture of ring-enlargement products **119** and **120** (**Scheme 20**, Section 12.27.5.6.2) <1997JOC2544> (Chapter 12.28).

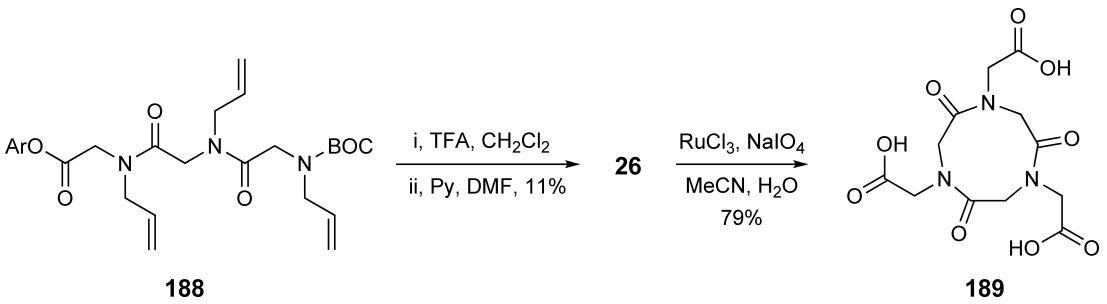
### 12.27.7.2 Further Carbon Functional Groups

The key step in the synthesis of triazonines with pendant diphenylphosphine arms is the free radical addition of $Ph_2PH$ across the alkene double bond (Equation 10) <1996CC1817>. This is accomplished in quantitative yield by photolysis under strictly anaerobic conditions using a mercury lamp. The method was not restricted to allyl substituents; longer-arm alkenes react in an identical manner, although more slowly, yielding phosphines with longer alkyl, for example C-5, chains.




(10)

Oxidative cleavage of triallyl cyclic tripeptide **26** resulted in 79% of tricarboxylic acid **189** (**Scheme 39**) <2004TL1091>.




**Scheme 39**

*N*-Acyl heteronines with more then two nitrogen atoms were of primary interest due to their synthetic utility through protection/deprotection sequences. *N*-Formyl 1,4,7-triazonanes are easy accessible from 1,4,7-triazatricyclo[5.2.1.$0^{4,10}$]-decane (see Section 12.27.9.1). This protecting group was readily cleaved in refluxing 3 M hydrobromic acid as it was demonstrated for 1-formyl-4,7-bis(2-hydroxyethyl)-1,4,7-trazacyclononane <2003AJC61>. Deprotection of 1-formylazonane and 1-formyl-4-benzylazonane was achieved under basic conditions with KOH in ethanol <1994CC2467> or Amberlite IRA400 resin <1999J(P1)1211>. Formyl-protected derivative of the bridged bis-thiadiazonine was successfully deprotected in 3N HCl to afford 46% of the product <1997HCA2315>.

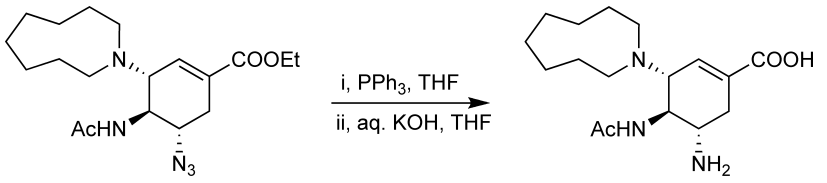
Di-BOC-1,4,7-triazonanes are smoothly deprotected with trifluoroacetic acid (TFA) in dichloromethane <2001JA5030, 2001JA6025>. Triazonines can be selectively cleaved from the trityl-type polymer support with 1% TFA in $CH_2Cl_2$, while BOC-protecting groups are not affected under these conditions <2004SL453>.

Synthesis of 1,4-di-Cbz-protected triazonane and further substitution on the position 7 and 1,4-deprotection were reported <2000JOM(611)586>. Methyl carbonate protecting group is easily removed in *p*-hydroxybenzoyl derivatives of thiadiazonane and dithiazonane by $NH_4OH$ <2001JMC1011>. Their further O-acylation gave a variety of derivatives with ester substituents on benzoyl moiety.

Reduction of *N*-acyl moieties in heteronines proceeded in a regular fashion. Thus, refluxing of quinazolinone **179** (Section 12.27.6.4) with zinc dust in acetic acid/hydrogen chloride afforded the corresponding quinazoline <1996BML737>. Both ring and side-chain BOC protecting groups of 1,4,7-triazonane afforded the corresponding methyl derivatives upon treatment with LAH in refluxing THF <2003TL5699>. Carboxy functional groups attached to heteronine ring with a spacer show usual reactivity, for example, amide coupling through preparation of activated pentafluorophenyl ester <2002S1398>.

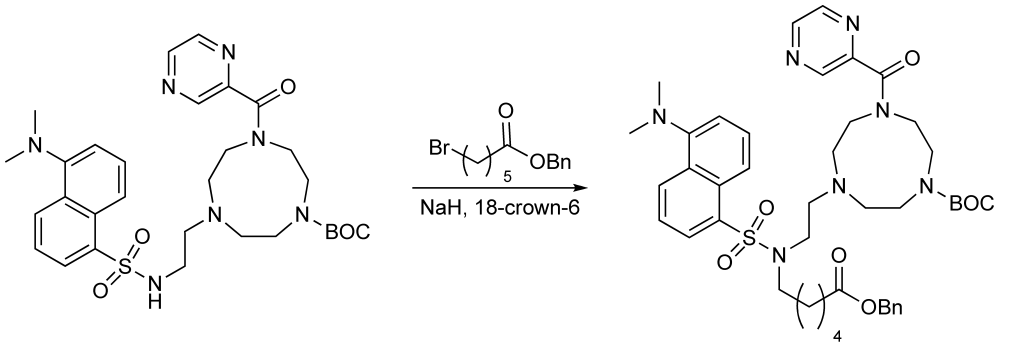
### 12.27.7.3 Amino Groups and Other N-linked Substituents

Azide **190**, available through palladium-catalyzed amination of the corresponding cyclohex-2-enyl acetate with azonane, can be sequentially reduced and hydrolyzed to produce amino acid **191** (Equation 11) <2000BML1257>.




190 191 (11)

N-Alkylation of the sulfonamide **192** with benzyl 6-bromohexanoate yielded the highly functionalized **193** – a valuable synthon for fluorescent sensors synthesis (Equation 12) <2000TL9601>.




192 193 (12)

Amide group reduction of *N*-acyl-1,4,7-triazonanes with LAH proceeded smoothly to afford corresponding saturated alkyl chain derivatives <1995CC929, 2001CC637, 2003TL5699>. Reduction of side-chain nitrile group with borane–THF complex in refluxing THF led to the corresponding amine in 67% yield <2000NJC575>, while hydrogenation of azide affords 93% of amine **57** (**Scheme 4**, Section 12.27.5.2.1) <2002JME3458>.

1-(3,5-Di-*tert*-butyl-2-nitrobenzyl)-4,7-dimethyl-1,4,7-triazacyclononane can be easily reduced with LAH in THF to afford corresponding 2-aminobenzyl derivative <2000JA9663>. Reduction of side-chain aromatic nitro group in trisubstituted triazonanes with Raney-Ni has been reported <2000CC443>.

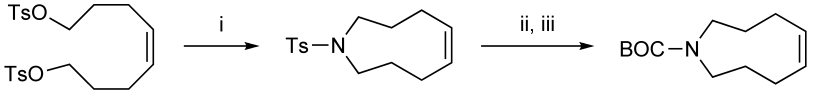
## 12.27.7.4 Hydroxy and Oxo Groups

*N*-2-Hydroxyethyl- and *N*-3-hydroxypropyl-1,4,7-azonanes were smoothly converted into corresponding chlorides with thionyl chloride in high to quantitative yields (**Scheme 4**, Section 12.27.5.2.1) <2002JME3458>; see also <2004JME5683> and <2005BMC2389>. 3-*N*-Hydroxypropylazonane was activated through tosylation and further reacted with 3,4-disubstituted pyrrole to afford derivative **55** in good yield (**Scheme 3**, Section 12.27.5.2.1) <2003T9239>.

## 12.27.7.5 S-Linked Substituents

Developments in the chemistry of *N*-tosyl heteronines and similar sulfonamides are connected with their easy accessibility through Richman–Atkins cyclization (Section 12.27.8.3) and synthetic utility through protection/deprotection sequences. Selective cleavage of sulfonamides was a primary goal of many studies.

Exchange of protecting group for azonine was achieved in two steps (**Scheme 40**), including detosylation of intermediate **87** using sodium naphthalenide and immediate BOC reprotection of the amine hydrochloride salt to give the BOC-azonine **88** in 64% yield <1999CC309>.



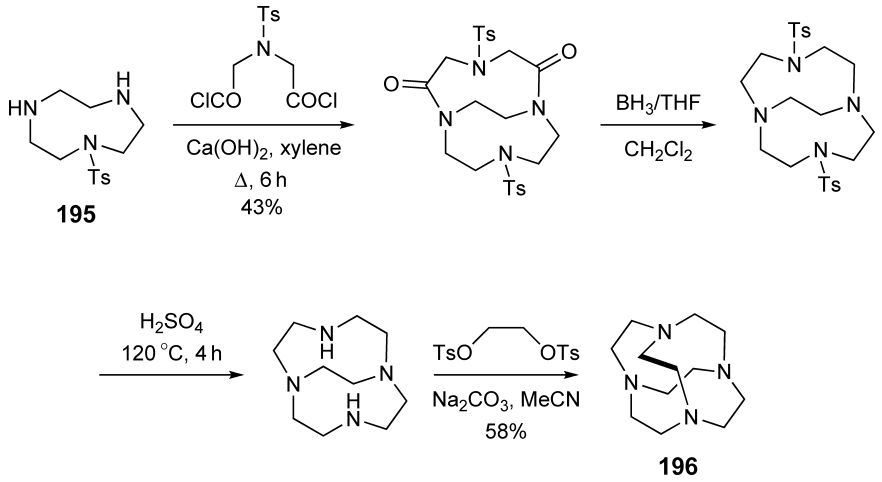

194 87 88

i, $TsNH_2$, NaOH, $Bu_4NI$, toluene–$H_2O$; ii, Na naphthalenide, THF, –78 °C; iii, $BOC_2O$, DMAP, $CH_2Cl_2$, rt

**Scheme 40**

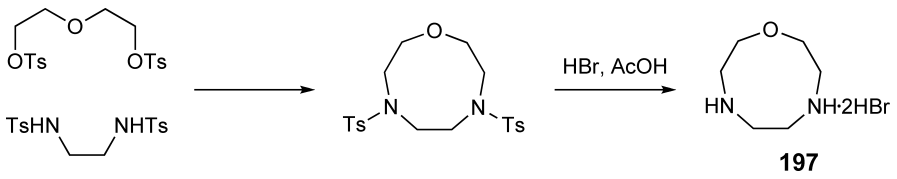
Mono- and ditosylated 1,4,7-triazacyclononanes were synthesized in 30% and 68% yields, correspondingly, by rapid partial deprotection of 1,4,7-tritosyl-1,4,7-triazacyclononane in vigorously stirred refluxing acetic acid–hydrobromic acid mixture <2001SC3141>. Rapid full detosylation of tritosyl 1,4,7-triazonane was achieved in high yield by heating it in a 50% solution in concentrated sulfuric acid at 170–180 °C for 5–8 min <1995SC3181>, or at milder conditions for a prolonged period of time <2004OBC2664>. This process is accelerated by microwave irradiation <2003PJC485>.

Similarly, two tosyl groups were selectively removed by heating under reflux in 47% water HBr solution and acetic acid in 2:1 ratio for 5 h to afford **195**, as a dihydrobromide salt in 69% yield <1999AGE956>. The next sequence of four synthetic steps (**Scheme 41**), including second nine-membered ring annulation, reduction, full detosylation of bicyclic intermediate with sulfuric acid, and bridge formation, resulted in hexaethylene tetramine **196**.



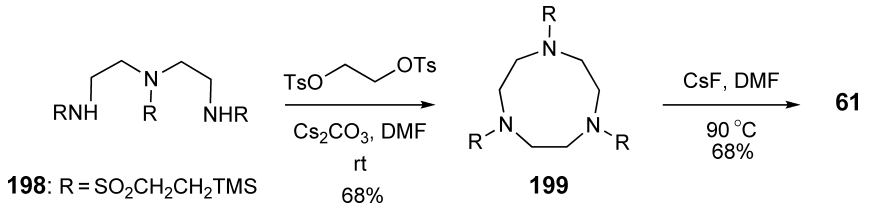

**Scheme 41**

The ditosyl derivative of 1,4,7-oxadiazonane was reacted with HBr in acetic acid to afford the deprotected **197**, as HBr salt in 87% yield (**Scheme 42**) <2004T5799>.




**Scheme 42**

*ortho*-Nitrophenyl sulfonyl protecting group was easily removed from 1,2,7-thiadiazonine using potassium carbonate/thiophenol in DMF (**Scheme 9**, Section 12.27.5.2.1) <2004JOC3662>. Removal of the $\beta$-trimethylsilylethanesulfonamide (SES-sulfonamide) group from triazonane **199** smoothly occurred upon treatment of the macrocyclic tris-sulfonamide with CsF in DMF at 95 °C for 24 h (**Scheme 43**) <2001JOC2722>.

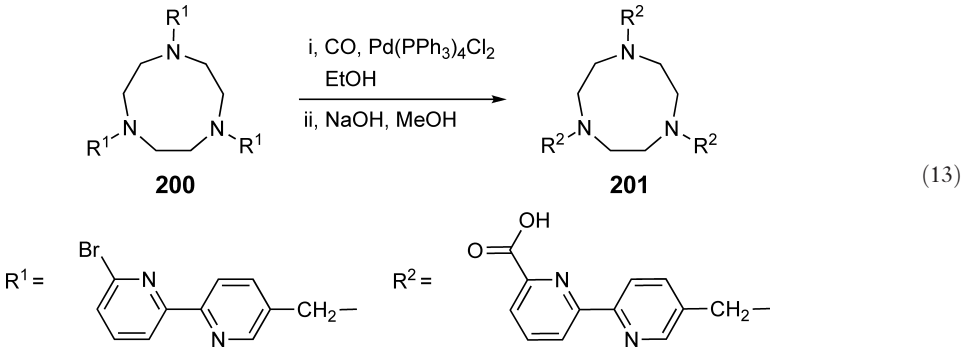



**Scheme 43**

Triazonane thiobenzyl derivative **62** was smoothly transformed into corresponding thiol **63** using sodium in liquid ammonia (**Scheme 6**, Section 12.27.5.2.1) <1999T5733>.

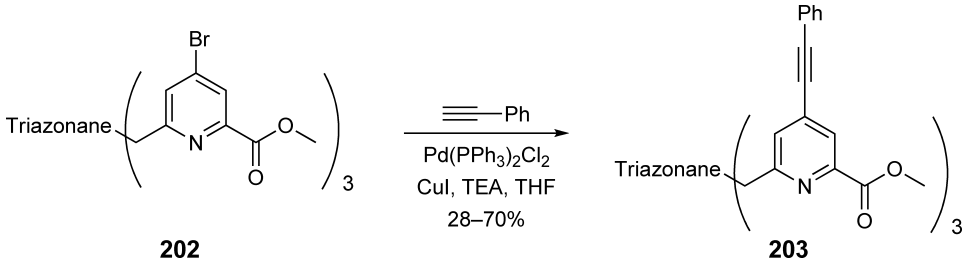
### 12.27.7.6 Halogen Atoms

Triazonane bearing three ethyl carboxylate 2,2′-bipyridine units was synthesized in 83% yield from the corresponding 6-bromo derivative **200** by a carboalkoxylation reaction promoted by a catalytic amount of Pd(0) (Equation 13). Subsequent smooth saponification resulted in the tris-acid **201** in 80% yield <2001JA2436, 2002JOC3933>.




(13)

Trisubstituted 4-bromopyridine **202** was coupled with phenyl acetylene to produce corresponding alkyne **203** in 28–70% yield (Equation 14) <1996HCA789>.




(14)

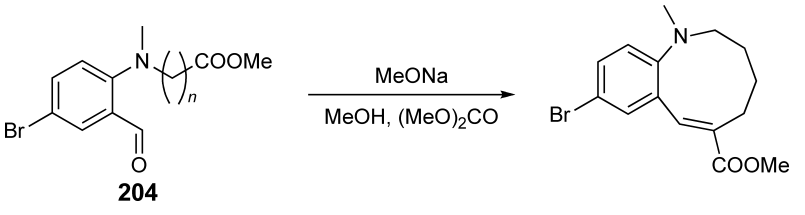
## 12.27.8 Ring Syntheses from Acyclic Compounds

### 12.27.8.1 Bond Formation by Intramolecular Cyclization

Unimolecular cyclization is an important method of heteronine ring system formation. It is reviewed in this section in the order of the bond types formed. Taking into account the synthetic value of the RCM strategy and its extensive development over recent years, it is excluded from general discussion of C–C bond-formation reactions in Section 12.27.8.1.1 and considered separately in Section 12.27.8.6.

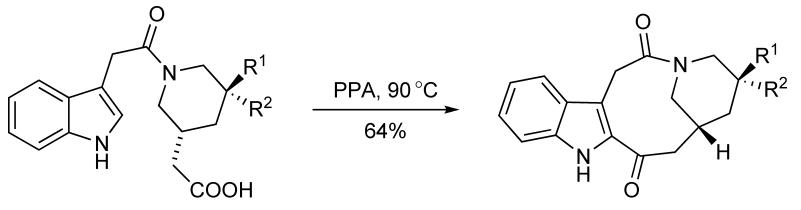
#### 12.27.8.1.1 C–C Bond formation

A convenient synthesis of 1-benzazonine, which can be performed in large scale, involved intramolecular cyclization of formyl derivative **204** to give the product in 18% yield (Equation 15) <2004TL9335>.



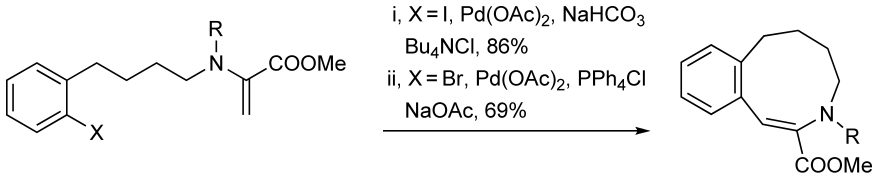

(15)

Closure of the nine-membered ring for the *trans*-isomer of the indole derivative **205** was carried out by heating with PPA for 30 min at 90 °C to give the desired tetracyclic keto lactam **206** in good yield (Equation 16) <2006JOC3804>.



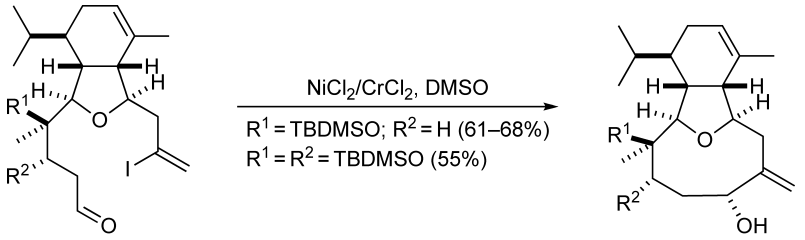

**205** **206** (16)

Heck-type cyclization of iodo ester **207** (X = I) with catalytic amounts of palladium acetate proceeded smoothly to generate **208** in 86% yield (Equation 17) <2002EJM379, 1999SL954, 1995CC1743, 1997CC637, 1997J(P1)447>. A catalytic system utilizing $PPh_4Cl$ permitted the extension of this methodology to the corresponding aryl bromide (X = Br) <1999SL954>.




**207** **208** (17)

The oxonane ring was fashioned by treating aldehydes **209** with $NiCl_2/CrCl_2$ in dimethyl sulfoxide (DMSO) to provide tricyclic ether **210** in 65% yield (Equation 18) <1995JA10391, 2000OL2683, 2001JA9033, 2001OL135, 2003JA6650, 2003OL1543>.




**209** **210** (18)

Reductive coupling of aromatic diimine **211** with zinc in the presence of MsOH in DMF or DMF–THF led to the substituted dioxdiazonane **212** in 43–49% yield (Equation 19) <1995JOC3980>.

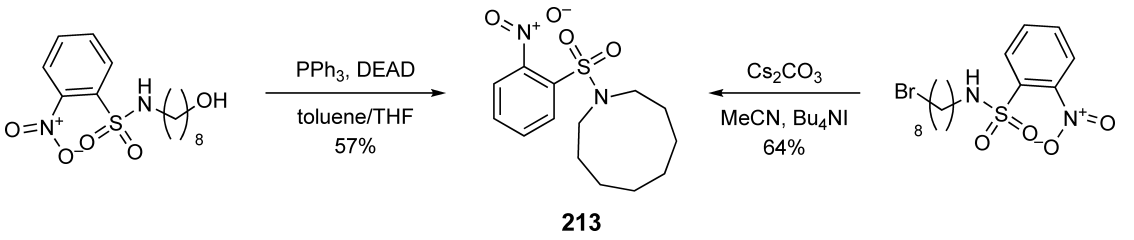

**211** **212** (19)

### 12.27.8.1.2 C–N bond formation

The most general methods of C–N bond formation used for heteronine formation are alkylation or Mitsunobu condensation. Azonine **213** was synthesized starting from 2-nitrobenzenesulfonamides and using conventional alkylation procedures or Mitsunobu conditions (**Scheme 44**) <2002SL697, 2002T6267>.

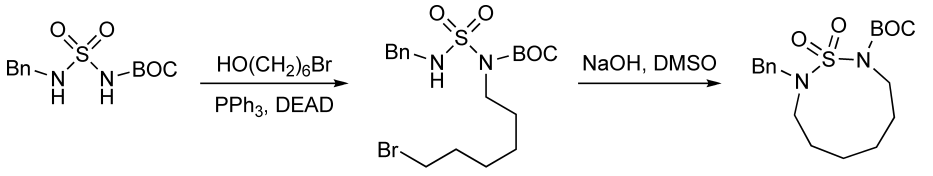
Facile formation of nine-membered N,N′-protected cyclic sulfamide **214** was carried out in two steps by an intermolecular Mitsunobu condensation and subsequent intramolecular N-alkylation (**Scheme 45**) <2003T6051>.

Mitsunobu cyclization of sulfonamides **215** produced substituted heteronines **216** in moderate yield (Equation 20) <1999JME4547>.



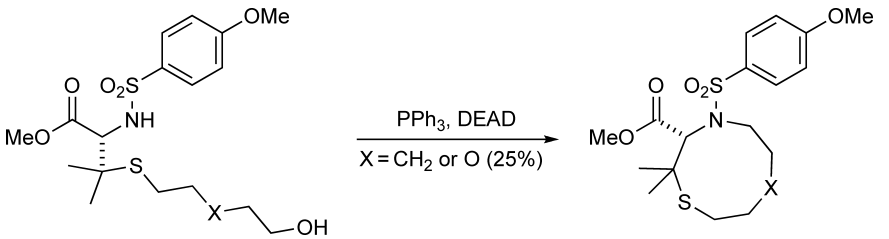

**213**

**Scheme 44**




**214**

**Scheme 45**




(20)

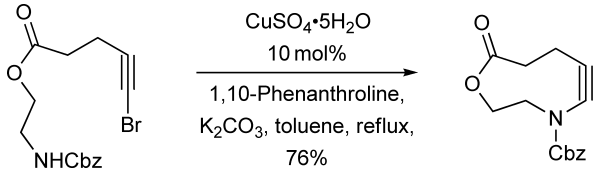
**215** **216**

An intramolecular Mitsunobu reaction of alcohol **78** was performed under high-dilution conditions (0.01 M) providing cyclic tosyl derivative **20** in 73% yield (**Scheme 12**, Section 12.27.5.4) <2006OL963>.

Amide bond-formation cyclizations were reported. Deprotection of di-BOC derivative **125** (**Scheme 22**, Section 12.27.5.6.2) and subsequent treatment with DIPEA led to the oxazonine dione **126** in good yield <2002T2957>. Activated ester **188** after deprotection was converted in the mixture of pyridine and DMF under diluted conditions into cyclic tripeptide **26** in 11% yield along with *22%* of *N*,*N*′-diallyldiketopiperazine (**Scheme 39**, Section 12.27.7.2) <2004TL1091>.

Unusual macrocyclization with the formation of guanidine moiety has been reported (**Scheme 25**, Section 12.27.5..6.3) <2006JA3926>. Reduction of azide **136** with $Me_3P$ was followed by its immediate exposure to $AgNO_3$/TEA. The latter conditions presumably trigger formation of a reactive *N*-sulfonylcarbodiimide, which in turn is intercepted by the pendant C-6-amine to form the nine-membered guanidine **137** in 65% yield.

Copper(II)-catalyzed intramolecular amidation of alkynyl bromide **217** led to macrocyclic ynamide **218** in 76% yield (Equation 21) <2006JOC4170>.



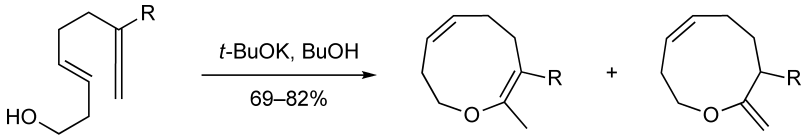

(21)

**217** **218**

### 12.27.8.1.3 C–O bond formation

The most general method of cyclization through C–O bond formation is lactonization, and its synthetic aspects, including alcohol or acid moiety activation, enantio- and diastereoselectivity, were reviewed recently <2006CRV911>.

Synthesis of cyclic ethers is less common. Thus, basic conditions (*t*-BuOK in BuOH at 30 °C) effected the rapid *endo*-mode ring closure of the allene derivatives **219** to furnish 2,3,6,7-tetrahydro-9-methyloxonines **220** in good yields as single isomers (Equation 22) <2004JOC6867>. In the case of sulfonyl derivative **220** (R = $SO_2Ph$), the *endo*-mode reaction proceeded as expected to give the ring-closed products in 66% yield as a mixture of **220** and its isomer **221** with an *exo*-methylene moiety in a ratio of ca. 2:1.

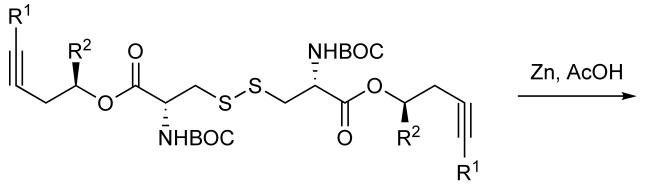



**219** **220** **221** (22)

Oxonan-2-yl methanols are readily available from the corresponding hydroxy epoxides <2003TL2709>. 1,4,7-Oxadithionane was isolated and characterized as a side product of hydrolysis of 1,2-bis(2-chloroethylthio)ethane <2003AJC309>.

### 12.27.8.1.4 C–S bond formation

Treatment of cystine derivatives **222** with Zn/AcOH led to S–S bond cleavage and ring closure of intermediate thiols into lactones **223a–d** in moderate yields (Equation 23) <2004S3029>.

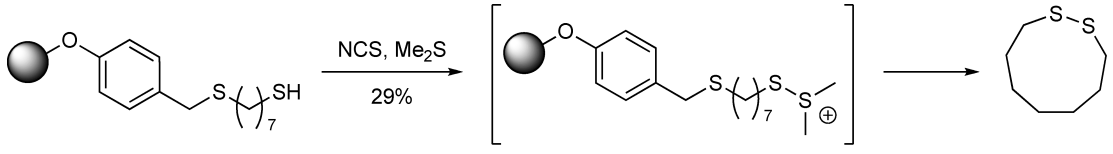



**222** (23)

**223a**: $R^1 = R^2 = H$ (51%)
**223b**: $R^1$ = COOEt; $R^2$ = H (62%)
**223c**: $R^1$ = H; $R^2$ = Me (31%)
**223d**: $R^1$ = COOEt; $R^2$ = Me (12%)

### 12.27.8.1.5 S–S bond formation

Polymer-bound thiol was reacted with the complex of NCS and dimethylsulfide to afford 1,2-dithionane through spontaneous cyclization of the dimethyl(thio)sulfonium intermediate **224** (**Scheme 46**) <2000TL9989>.




**224**

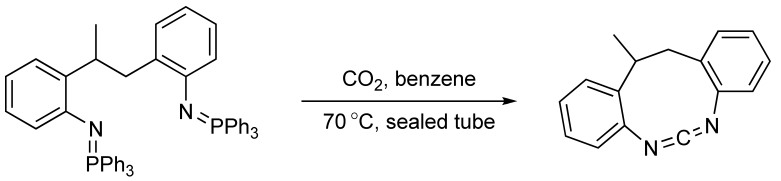
**Scheme 46**

## 12.27.8.2 Ring Formation by [8+1] Cyclization

Cyclization of the ditosylate **194** under dilute conditions gave *N*-tosyl azonine **87** in 62% yield (**Scheme 40**, Section 12.27.7.5) <1999CC309, 2001J(P1)2161>. Similarly, monosubstituted ditosyl 1,4,7-triazonanes are readily available from the corresponding 1,8-ditosylate **56** and amine, for example, **Scheme 4** (Section 12.27.5.2.1) <2002JME3458>;

see also <2003SC1147>, <2001EJO4233>, and <1999TL9363>. Synthesis of thionane ring system from the corresponding 1,8-ditosylate **134** and sodium sulfide in 65% yield has been reported (**Scheme 24**, Section 12.27.5.6.3) <2003JOC3311>.

Bis(iminophosphorane) **225** was reacted with carbon dioxide in dry benzene at 70 °C in a sealed tube to afford the nine-membered cyclic carbodiimide **48** in 98% yield (Equation 24) <1996JOC4289>.




**225** **48** (24)

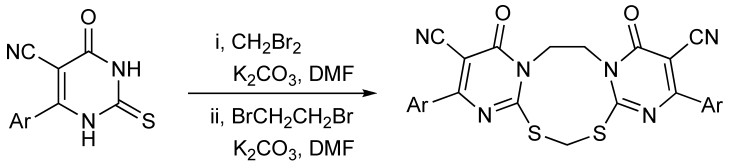
1,3-Dioxonines are readily available from corresponding 1,6-diols and geminal dielectrophiles. Therefore, *trans*-acetalization of substituted acrolein dimethyl acetals with 1,2-phenylenedimethanols has been reported <2004T415>. Reaction of substituted 1,1-difluoro alkene with 1,6-hexanediol led to the formation of dioxonane ring in 2% yield <1995H(41)641>.

### 12.27.8.3 Ring Formation by [7+2] Cyclization

Cyclizations of this type involved suitable 1,7-dinucleophilic species and 1,2-dielectrophile, which is typically a 1,2-dihaloethane or ethylene glycol ditosylate.

The Richman–Atkins cyclization of tritosyl-substituted ethylenetriamine with glycol ditosylate gave tritosyl 1,4,7-triazonane, for example, **Scheme 30** (Section 12.27.6.2) <2002JOC3933>; see also <1998J(P2)83> and <2002IJB372>. Functionalized <2003OBC2357> and chiral <2002TL3795, 2002OL949, 2003OBC4408> derivatives of diethylenetriamine can also be used. Similar reaction of tri-$\beta$-trimethylsilylethanesulfonamide **198** afforded the protected triazonane **199** in 68% yield (**Scheme 43**, Section 12.27.7.5) <2001JOC2722>. Kuksa *et al.* reported Richman–Atkins-type cyclization of bis-hydroxylamine to produce dioxadiazonine ring system <1999S1034>.

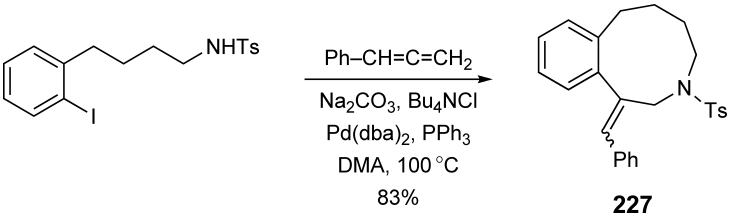
Reaction of 2,2′-thiodiethanethiol with 1,2-dichloroethane yielded 37% of 1,4,7-trithionane <1995T4065>. A convenient synthesis of 2,3-pyrimidinophanes **226** has been described starting from 6-aryl-5-cyano-2-thiouracils (Equation 25) <2003JCM380>. A reaction of 2-thiouracil with dibromomethane and a sequential second S-alkylation with dibromoethane under basic conditions produced 2,3-pyrimidinophane **226** in 11% yield.




**226** (25)

1,2-Diketone, for example, benzyl, can serve as a dielectrophile in its reaction with diethylenetriamine giving triazonine **52** as a product under UV irradiation in the presence of oxygen (**Scheme 2**, Section 12.27.5.1) <2000NJC719>).

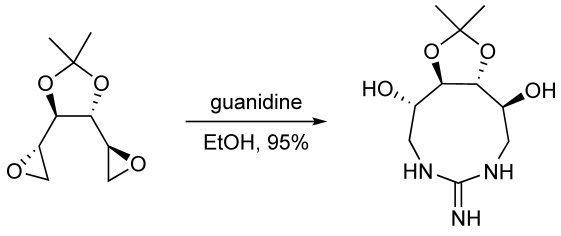
Palladium-catalyzed heteroannulation is illustrated by synthesis of substituted 1*H*-benzo[*d*]azonine **227**, which was prepared from allene and tosylamide-containing aryl halide (Equation 26). The reaction was suggested to proceed by addition of an arylpalladium compound to the allene to generate a π-allylpalladium intermediate, which subsequently undergoes nucleophilic displacement of palladium at the less-hindered end of the π-allyl system <1998JOC6859>.




**227** (26)

### 12.27.8.4 Ring Formation by [6+3] Cyclization

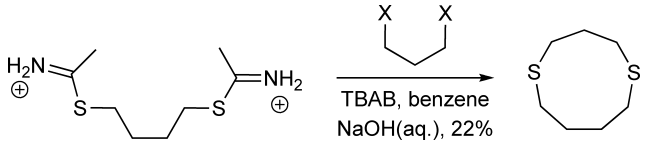
Guanidine serves in a regular manner as a 1,3-dinucleophile when reacted with suitable 1,6-dielectrophile. This approach resulted in an efficient method for the synthesis of symmetrical cyclic guanidino-sugars **229** from 1,2:5,6-dianhydro-3,4-*O*-methylethylidene-L-iditol **228** (Equation 27) <1998SL402, 2000BMC307>.




(27)

**228** **229**

A useful route toward heteronines is an application of 1,3-dielectrophiles when they react with O- and S-nucleophiles. The chiral (*R*)-1,1′-bi-2-naphthol **152** was reacted with 3-chloro-2-(chloromethyl)prop-1-ene to afford dioxonine **153** (**Scheme 28**, Section 12.27.6.1) <1998JA5943, 1997TA2921>. A novel procedure for the preparation of cyclic polythioethers by the reaction of dithioiminium salt with 1,3-dihalopropane using phase-transfer catalyst has been reported (Equation 28) <2003PS1295>. This approach avoided the use of thiols, which are not only hard to handle, but also prone to oxidation.

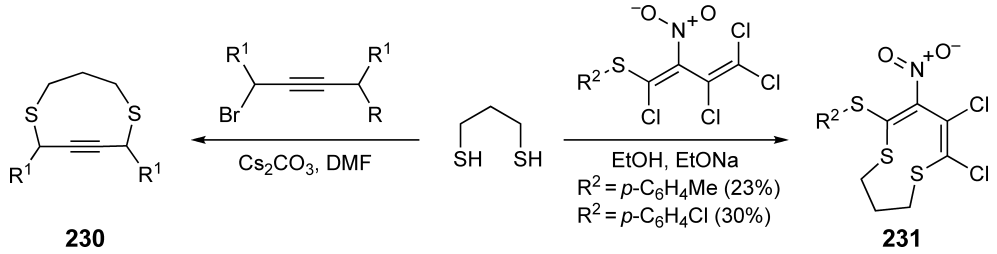



(28)

Reaction of vicinal oximes with 1,3-dibromopropane in THF in the presence of 2 equiv of NaH resulted in 60% of 1,5,6,9-dioxadiazonines <2000H(53)851>.

### 12.27.8.5 Ring Formation by [5+4] Cyclization

1,5-Dinucleophilic reagents have a limited use in heteronine ring assemblies. 1,5-Dioxonane-3,6,9-trione **22** was readily available from succinic anhydride and 1,3-dihydroxy acetone <1998JOC9888>. Dithionine **230** has been prepared by the reaction of 1,4-dibromobut-2-yne ($R^1 = H$) with dithiol in DMF in 75% yield (**Scheme 47**) <1996JOM(519)177>. The more-hindered dibromide ($R^1 = i$-Pr) gave a mixture of the corresponding dithionine and dimeric 18-membered product. Reaction of 2-nitropentachlorobutadiene with 1,3-dithiopropane in ethanol under basic conditions led to dithionines **231** in moderate yields <1996BSB317, 1997PS79>.




**230** **231**

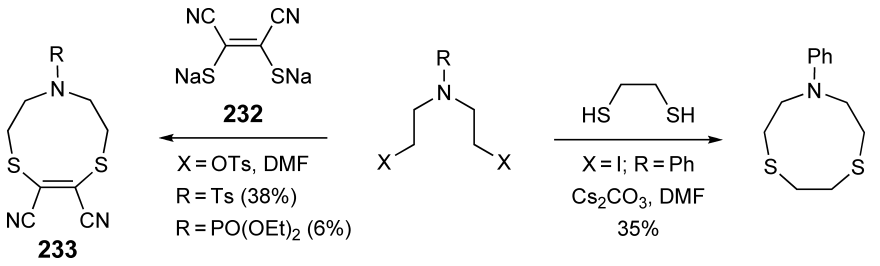
**Scheme 47**

The reaction of benzoin oxime with sodium hydride in propan-2-ol produced a 1,5-dianion which further cyclized with 1,4-dibromobutane into dioxazonine in 75% yield <2004S837>.

The use of 1,4-dinucleophiles is more common due to accessibility of 1,2-dihydroxy compounds, 1,2-diamines, and their derivatives. Benzo-9-crown-3 ether is easily available from pyrocatechol and 1-chloro-2-(2-chloroethoxy)ethane <1998ANC5259, 2002JOC2065>. Similar procedure for 2,3-dihydroxynaphthalene resulted in a 4.5% yield of naphtha-9-crown-3 <2000JST(526)185>.

Ditosyl derivative of 1,4,7-oxadiazonane was synthesized from *N*,*N*′-ditosyl diaminoethane and diethylene glycol ditosylate (see **Scheme 42**, Section 12.27.7.5) <2004T5799> or with 1-chloro-2-(2-chloroethoxy)ethane <1998JRM1448>. Similarly, Richman–Atkins cyclization of ditosyl-substituted ethylenediamine with ditosylate of *N*,*N*-bis(2-hydroxyethyl)-4-methylbenzenesulfonamide gave the functionalized triazonanes <2003OBC2357>.

Bis-heteronucleophilic Michael addition of symmetrical dibenzyl 1,2-diaminoethane to divinyl sulfone resulted in the quantitative yield of *S*,*S*-dioxo-1,4,7-thiadiazonane <2003EJO54>. Disodium derivative **232** gave moderate to poor yields of dithiazonines **233** (**Scheme 48**) <1995T8175>, while a moderate yield of *N*-phenyl dithiazonane was obtained from 1,2-ethanedithiol <1995BCJ2831, 1995BCJ3071>. The latter was used as a 1,4-dithio fragment for functionalized 1,4,7-oxadithionanes synthesis as well <1999SC3939>.




**Scheme 48**

## 12.27.8.6 RCM Syntheses

RCM strategies gained significant value over the last few years and were extensively developed for nine-membered heterocyclic systems. Although formally they belong to unimolecular C–C bond-formation reactions, discussed in Section 12.27.8.1.1, it is more convenient to discuss them separately in this section. This type of heteronines ring construction was reviewed as a part of more general medium-size ring surveys <2000CRV2963, 2004CRV2199, 2004CRV2239> (see other chapters in Volume 12). Usually the formation of medium-size rings, and nine-membered rings in particular, by RCM is a considerable challenge, since their ring strain prompts cyclic systems toward ring-opening metathesis or ring-opening metathesis polymerization.

Azonine **35** was synthesized in 53% yield when RCM is carried out with Grubbs' first-generation catalyst in refluxing $CH_2Cl_2$; while in refluxing benzene, dichloroethane, or THF, the catalyst was rapidly deactivated. When Grubbs' second-generation catalyst was employed the reaction was faster; however, the relative percentage of intermolecular products was increased. The reaction was completely stereoselective with regard to the double bond, giving only (*Z*), and **35** as well as its diastereomer were easily separated from each other <2003TL7655, 2005OBC97>. Further examples of azonine ring systems synthesized by RCM methodology are depicted in **Figure 2** and include 2-trifluoromethylazonine **234** <2003JOC8932>, 1*H*-benzo[*b*]azonine **235** <2005JOC1552>, azonine amino acids **236** <2005JOC3838, 2006OL2851> and **237** <2005JOC3838>, *N*-tosylazonine **238** <2001CEJ4811>, mono- <2005SL631> and di-<2004TL9607> carboxy derivatives, **239** and **240**, respectively.

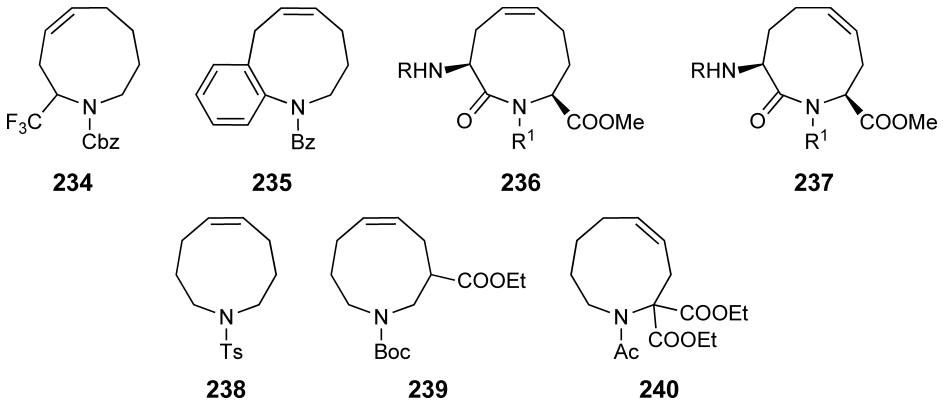



**Figure 2**

The RCM methodology was widely used for oxonine ring construction. Target compounds, which are depicted in **Figure 3**, included oxirane derivative **242** and its unsaturated precursor **241** <2003JA7592>, dibenzyloxy alcohol **243** <2004JA10264, 2006JA1371>, protected trialcohols **244** and **245** ($R^1$ = Bn, $Et_3Si$; $R^2$ = H, TMS, Ac; $R^3$ = Bn, 1,1,3,3-tetraisopropydisiloxane (TIPS)) <2001JA1533, 2002T1817>, and oxirane **246** <2002T1817>. RCM strategy was successfully used for stereoselective synthesis of BCDE fragment of brevetoxin A <2005OL4033>.

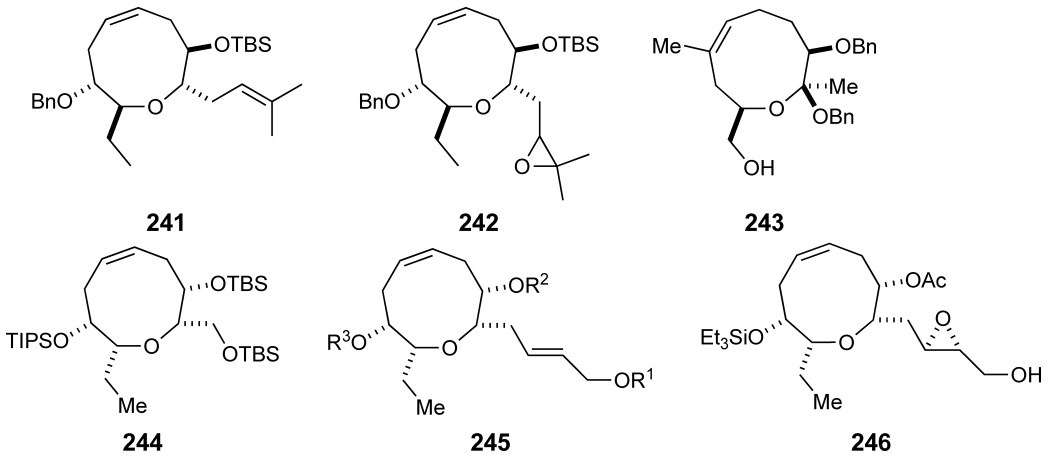
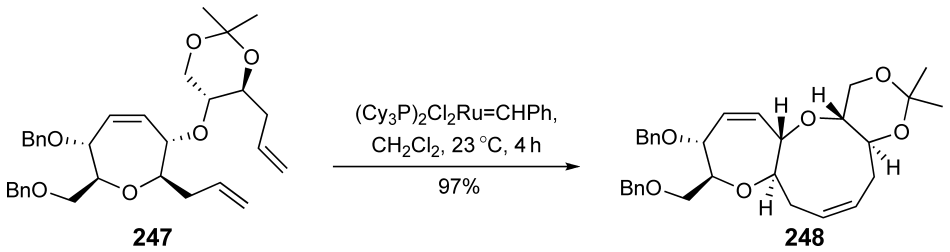



**Figure 3**

Besides oxonine single ring construction, RCM is an efficient tool in oxonine cycle annulation. Thus, intermediate **247** with Grubbs' first-generation catalyst in $CH_2Cl_2$ at room temperature produced annulated oxonine **248** in 97% yield (Equation 29) <2005T7392>.




(29)

The RCM syntheses of diazonine ring system (**Figure 4**) led to 61% of cyclic urea **249**, <2003JOC4876>, hydrazide **250** (42%) <2004OL4351>, ditosyl derivative **251** (85%) <2002TL4207>, diprotected 1,2-diazonine **252** (72%) <2004TL3757>, and [1,4]diazonino[1,2-*a*]indole **253** (62%) <2002T10181>.

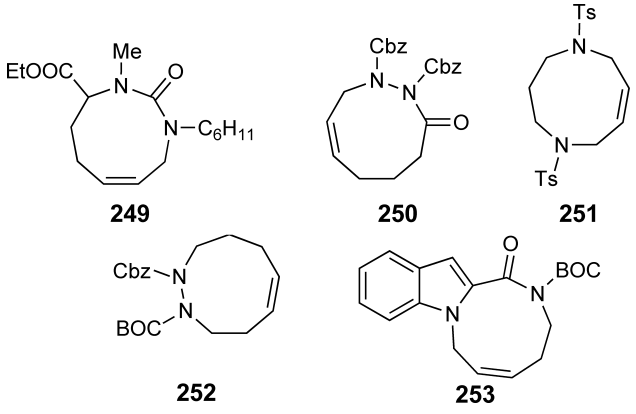
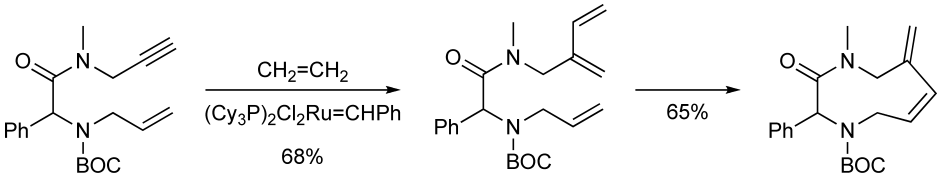


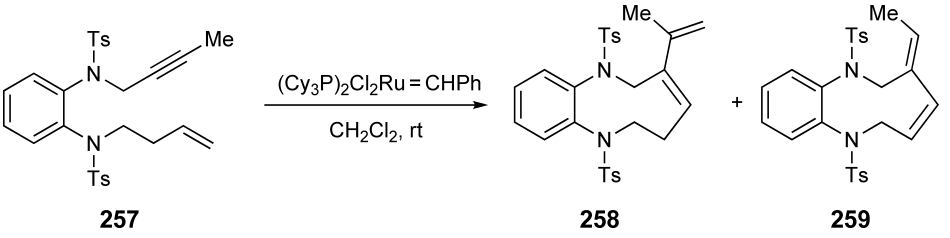

**Figure 4**

Contrary to foregoing examples, acyclic enyne substrate **254** was inert to direct ring-closure enyne metathesis, giving only recovery of the starting material. However, it underwent an efficient cross-metathesis with ethylene to form **255** and afforded **256** upon subsequent RCM in good overall yields (**Scheme 49**) <2004JA15074>. The formation of *endo*-product, observed in this case, is significant as the normal tendency for medium-sized rings is to give *exo*-products via direct enyne metathesis.



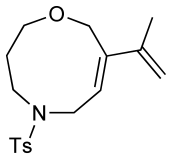

**Scheme 49**

Enyne derived from ditosyl *o*-phenylenediamine **257** formed in the presence of benzylidene ruthenium carbene complex a nine-membered ring **258** in 5% yield (Equation 30) <2000OL543, 2001S654>. Dimerization was a major by-process (22% yield) along with formation of a small amount of **259** (5% yield), which was explained by $\beta$-hydride elimination from the intermediary ruthenacyclobutane.



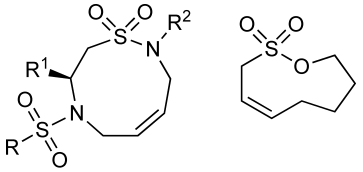

(30)

Ring-closure enyne metathesis was a convenient route toward tosyl oxazonine derivative **260** <2001S654>. Synthesis of 1,2-oxazonines from dienes tethered by hydroxylamine has been reported <2003SL1043>.



**260**

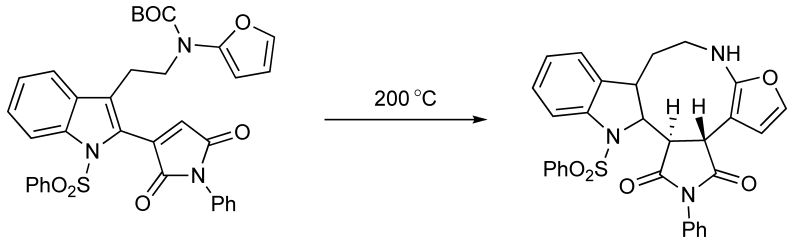
Further examples of RCM in heteronine synthesis include a variety of 1,2,7-thiadiazonines **261**, which can be incorporated into a peptide sequence <2004JOC3662>, and unsaturated nine-membered sultone **262** <2004S1696, 2002SL2019>.



**261** **262**

### 12.27.8.7 Miscellaneous Methods

Thermolysis of indole maleimide derivative **263** led to deprotection and cyclization to form substituted azonine system **264**, as a sole product, in 45% yield (Equation 31) <2005JOC2206>.

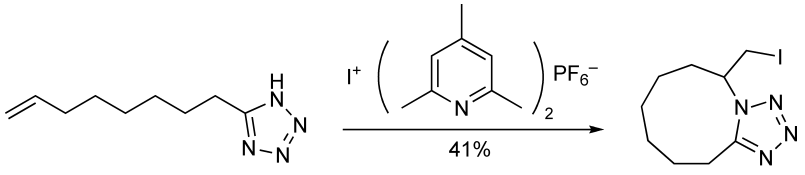



**263** **264** (31)

A convenient regiospecific synthesis of a new conjugated tetrazole derivative **266** was reported via reaction of dienone **265** with the tetrachlorosilane and sodium azide (Equation 32) <2003M1241>. Similar transformation, started form cyclooctanone and $AlCl_3$, instead of tetrachlorosilane, afforded unsubstituted tetrazolo azonine in 75% yield <2005SC1115>.

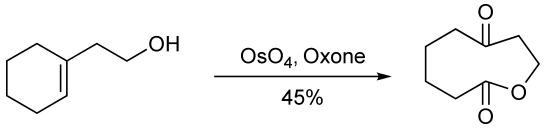

**265** **266** (32)

When unsaturated tetrazole **267** was added as $CH_2Cl_2$ solution using a syringe pump to bis-(collidine)-iodo hexafluorophosphate, iodomethyl derivative **268** was formed in moderate yield (Equation 33) <2003T6759>.



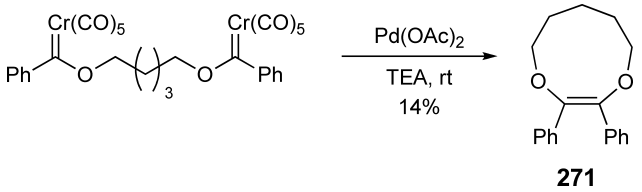

**267** **268** (33)

The tandem $OsO_4$-catalyzed oxidative cleavage of olefin **269** with Oxone® as the co-oxidant and sequential direct oxidation of intermediate aldehyde in alcoholic media led to cyclic keto lactone **270** in 45% yield (Equation 34) <2003OL3089>. Similar oxidative cyclization with $KMnO_4$–$CuSO_4$ resulted in 32% yield of **270** <1994T11709>.




**269** **270** (34)

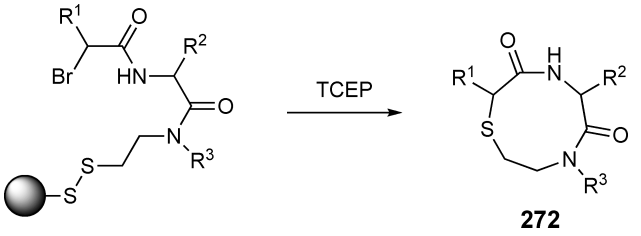
The intramolecular dimerization of chromium bis-carbene complex allowed the preparation of 1,4-dioxonine **271** (Equation 35) <2001JA851>.




**271** (35)

Mono-*O*-allyl derivative of 1,6-hexanediol undergoes $RuCl_2(PPh_3)_3$-catalyzed isomerization to give 2-ethyl 1,3-dioxonane <2004SL1203>.

A library of thiadiazonines **272** were prepared when tris-(2-carboxyethyl)phosphine (TCEP) was used to reduce the disulfide in cleavage–cyclization strategy (Equation 36) <1996TL6961, 1999JA1817, 1999JME4380>. Both an excess of phosphine and phosphine oxide were scavenged by polymer-bound tetramethylguanidine to yield the crude **272** uncontaminated with reagent by-products. A similar synthetic approach was reported for the solution-phase thiadiazonine synthesis <2000BML2731>.




**272** (36)

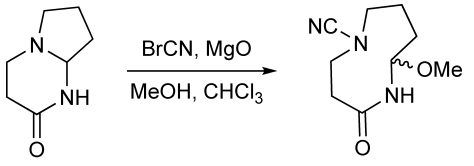
1,4,7-Trithionine was readily available from *cis*-1,2-dichloroethylene and sodium sulfide <2001JA11534>. 1,2,4,5,7,8-Hexaoxonane **11** was accessible in 65% yield by the reaction of acetone and 30% water solution of hydrogen peroxide at 0 °C <2005JA1146>.

## 12.27.9 Ring Syntheses by Transformation of Another Ring

Many heteronines are synthesized using another ring-expansion reactions, while contractions of the larger rings into nine-membered heterocyclic systems are less frequent. General methods for ring expansions were categorized in CHEC-II(1996), and this classification is followed in the current section.

### 12.27.9.1 Ring Expansion by Ionic Ring Openings

Reaction of bicyclic lactam **273** with BrCN and MgO in $MeOH/CHCl_3$ led to formation of the nine-membered amino compound **274** in 47% yield (Equation 37) <1999AJC1131>.

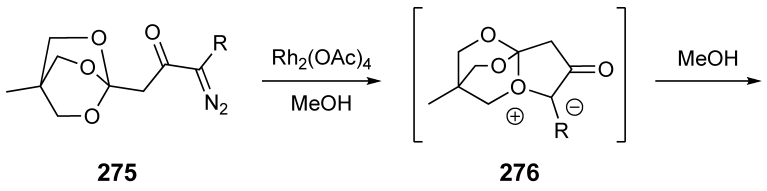


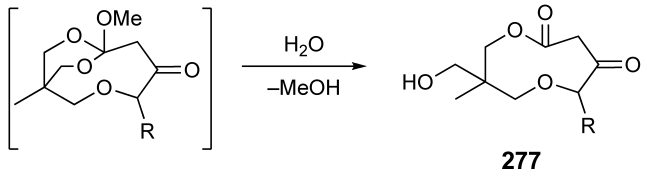

**273** **274** (37)

Bicyclic ortho esters **275**, which are tethered to a diazocarbonyl group by a methylene linkage, were prepared and catalytically decomposed by treatment with $Rh_2(OAc)_4$ either in the presence or absence of a protic nucleophile (MeOH, PhOH, AcOH) to give ring-enlargement, functionalized lactones **277** (**Scheme 50**) <2000JOC1899>. A similar sequence led to unsubstituted rings, when cyclic acetals were used instead of orthoesters <1998J(P1)3623>.

The formation of the products can be explained by an intramolecular reaction between the alkylidenecarbene and a cyclic acetal or cyclic orthoester units and formation of bicyclooxonium ylides **276**. Analogous alkylidenecarbene species were generated using copper catalyst <1996TL5053>.

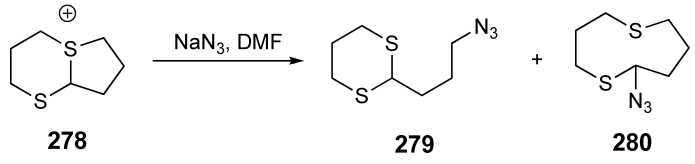
Nucleophilic attack by azide anion on bicyclic sulfonium salt **278** kinetically favors ring opening to give a nine-membered $\alpha$-azidosulfide **280**, while 2-(3′-azidopropyl)-1,3-dithiane **279** is the thermodynamic product (Equation 38) <2003TL2841>.




| *R* | *Yield* (%) |
|---|---|
| H | 73 |
| COOMe | 67 |

**Scheme 50**

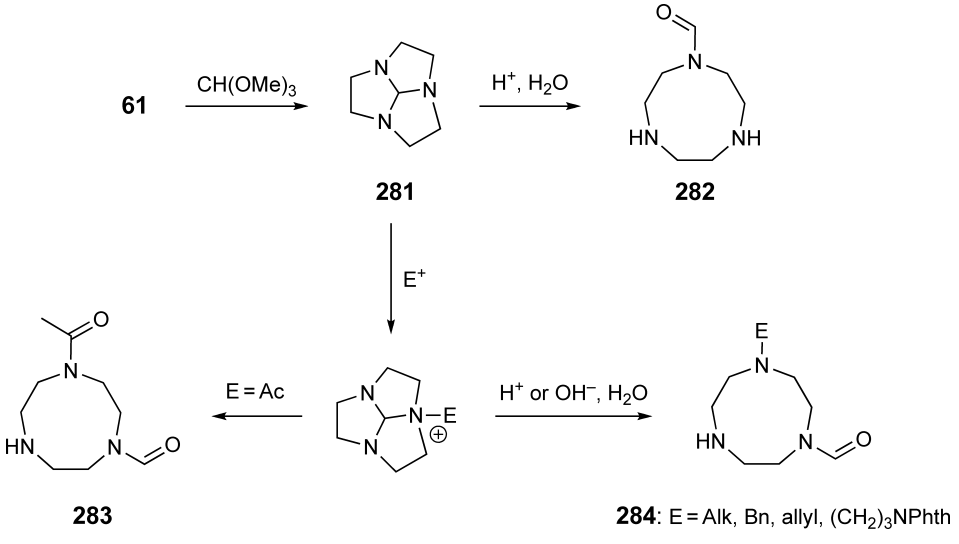



| *Temp.* (°C) | *Ratio* **279**:**280** |
|---|---|
| 0 | 22:78 |
| 25 | 32:68 |
| 70 | 46:54 |

(38)

Ring expansion of $\omega$-bromoalkyl benzothiazolium salt into *N*-formyl derivative of benzo[*b*][1,4]thiazonine has been reported <1995JOC2597>.

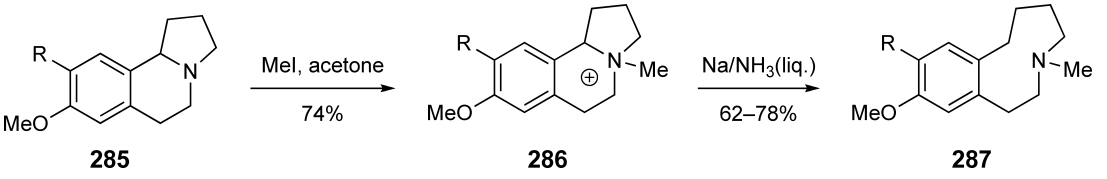
The general method for the synthesis of N-protected triazonines (**Scheme 51**) utilizes the synthesis of the bridged 1,4,7-triazatricyclo[5.2.1.$0^{4,10}$]decane **281**, followed by its acidic hydrolysis to afford *N*-formyl triazonane **282** <2003AJC61>. Similar synthetic routes, which involved intermediate benzylation <1994CC2467, 2001OL2855, 2005T7499>, allylation <1996CC1817>, alkylation <2005T7499>, or acetylation <1999J(P1)1211> steps followed by acidic or basic hydrolysis, were utilized for the synthesis of 1,4-diacyl triazonane **283** and formyl derivatives **284**. Bis-thiadiazonanes were prepared using the same methodology <1997HCA2315>.




**Scheme 51**

### 12.27.9.2 Reductive Ring Openings

Ionic species described in Section 12.27.9.1 can be submitted to reactions with reducing agents rather then solvolysis to produce saturated azonane analogs. Thus, treatment of hexahydropyrrolo[2,1-*a*]isoquinolines **285** with MeI in acetone afforded quarternary salts **286**, which were subjected to ring opening using $Na/NH_3$ to produce hexahydro-1*H*-benzo[*d*]azonines **287** in good yields (**Scheme 52**) <2002AP443>. Similarly, dimethoxy intermediate **286** (R = MeO) was reacted with benzyl chloroformate and sodium cyanoborohydride to give N-unsubstituted analogue through a 3-Cbz benzazonine intermediate.

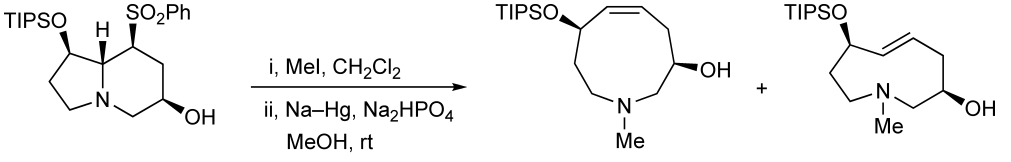



**285** **286** **287**

**Scheme 52**

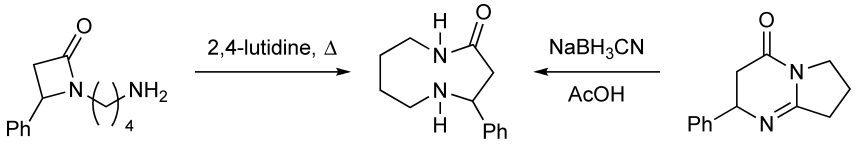
An analogous sequence was used for the synthesis of indole-fused azonanes and benzoazonanes <2006JME760>.

Alkylation–reduction methodology was applied for the synthesis of monosubstituted dihydroxy azonine, which was obtained as a separable mixture of *cis*-**288** and *trans*-**289** isomers (44% and 38%, respectively; Equation 39) <2001OL2957>.




**288** **289** (39)

Diazoninones **64** were synthesized by reduction of hexahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-ones with sodium in liquid ammonia (**Scheme 7**, Section 12.27.5.2.1) <2000CL1104, 2002T7177>. One of the synthetic routes for the preparation of diazoninone **291** includes reduction of dihydropyrimidinone **292** (**Scheme 53**) <2002T7177>.



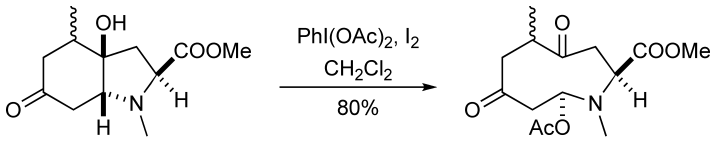

**290** **291** **292**

**Scheme 53**

Synthesis of oxathionanes from ω-bromo ketone **108**, which is formally a [5+4]-type cyclization, requires Lewis acid-catalyzed cyclic acetal intermediate formation. It was further transformed into the corresponding oxathionanes **109** and **110** using a two-step reductive procedure (**Scheme 18**, Section 12.27.5.6.1) <2002OL3047>.

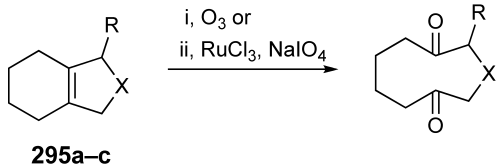
### 12.27.9.3 Oxidative Ring Openings

Tertiary alcohol **293**, when reacted with iodobenzene diacetate and iodine, underwent a formal alkoxy radical fragmentation and provided the nine-membered diketone **294** in 80% yield as a separable 1.2:1 mixture of epimers (Equation 40) <1999JOC4576>.




293 294 (40)

Ozonolysis of tosyl derivative **295a** led to the corresponding protected azonane-3,8-dione in 50% yield (Equation 41). Ruthenium-catalyzed oxidation was found to be more efficient, resulting in an increased 70% yield of the product, which is consistent with the result obtained for dialkyl-substituted systems (**Scheme 32**, Section 12.27.6.3) <1995J(P1)1137>. Similar ozonolysis of pyrrolo ethyl carboxylate **295c** led to 75% of cyclic amino acid derivative <2001OL861>.




**295a–c**

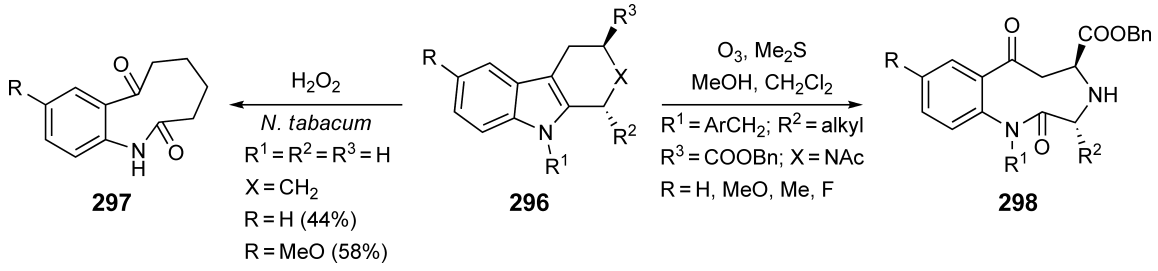
| | Conditions | R | X | Yield (%) |
|---|---|---|---|---|
| **a** | i | H | NTs | 50 |
| **b** | i | H | O | 0 |
| **a** | ii | H | NTs | 70 |
| **b** | ii | H | O | 58 |
| **c** | i | COOEt | NBOC | 75 |

(41)

Oxidative ring expansion of hexahydroisobenzofuran derivatives was less straightforward. Thus, unlike pyrrole derivatives **295a** and **295c**, ozonolysis of **295b** did not lead to the corresponding oxonine-3,8-dione (Equation 41) <1995J(P1)1137>. Ruthenium-catalyzed oxidation was found to be more efficient, resulting in 58% yield of the product. Another example of ruthenium-catalyzed transformation, that is, the catalytic oxidative cleavage of octahydrobenzofuran-3*a*-ols, was reported <2003OL1337>. Catalytic amounts of ruthenium trichloride and an excess of sodium periodate, as a co-oxidant, led to the nine-membered ring keto lactones in moderate to good yields and high purity.

Oxidative cleavage of the double bond in **168** (**Scheme 33**, Section 12.27.6.3) by ozonolysis was unsuccessful, while its dihydroxylation and treatment of resulting diol with lead(IV) acetate gave diketone **169** <1999T7471>. Ozonolysis of isopropyl 1,3,4,5,6,7-hexahydro-1-methylisobenzofuran-1-carboxylate **131** (**Scheme 23**, Section 12.27.5.6.3) proceeded smoothly and led to the corresponding oxonine carboxylate **132** <2002OL3059>.

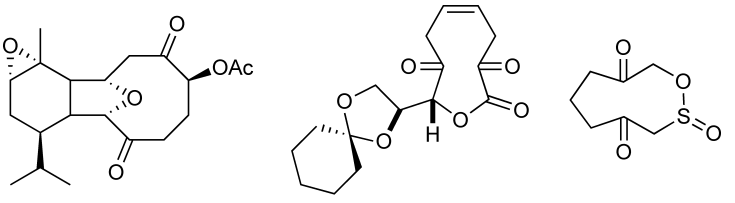
A novel procedure for the oxidative cleavage of indole carbon double bonds in the presence of $H_2O_2$ using plant cell cultures, as a catalytic system, led to benzazonine diones **297** (**Scheme 54**) <2004TL8061>. 1*H*-Benzo[*h*][1,4]diazonines **298** were obtained in a highly substituted form and in high yields by ozonolysis of 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole derivatives **296** (X = NAc) <2000JME3518>.




**297** **296** **298**

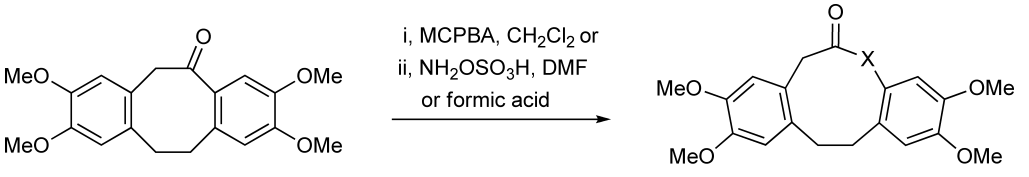
**Scheme 54**

Bicyclic semi-acetals **122**, when reacted with Dess–Martin periodate or ceric ammonium nitrate (CAN), underwent oxidative ring expansion to produce nine-membered unsaturated lactones **123** in moderate to good yields (**Scheme 21**, Section 12.27.5.6.2) <2005OL4301> (Chapters 9.06–9.08). Several other products of oxidative ring-expansion strategy have been reported, including epoxy dione **299** <2004JA1642>, diketo lactone **300** <2000CC567, 2002T1779>, and unstable diketone **301** <2002HCA712>.



299 300 301

Dibenzo[*a*,*e*]cycloocten-5-one **302** was transformed by Baeyer–Villiger oxidation into the substituted 6-oxodibenzo-[*b*,*f*]oxonin **303** (Equation 42) <1996T8063>. The regiochemistry of the process and structure of the product was assigned based on $^1$H NMR data and their comparison to theoretical chemical shifts of the product and of the hypothetic dihydrodibenzo[*c*,*g*]oxonin-5(7*H*)-one isomer.




**302**

**303**: X = O, conditions i
**304**: X = NH, conditions ii

(42)

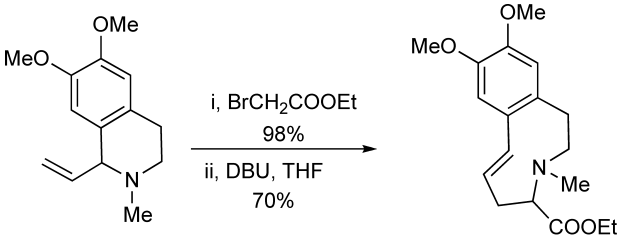
## 12.27.9.4 Beckmann and Related Rearrangements

2,3,8,9-Tetramethoxy-5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-5-one **302** was reacted with hydroxylamine-*O*-sulfonic acid and underwent a one-pot Beckmann (formic acid, reflux) or Schmidt (DMF, reflux) rearrangement to afford the 6-oxodibenzo[*b*,*f*]-azonine **304** (Equation 42). Regioselectivity of the process was assigned based on $^1$H NMR data and on model reactions to prove preferential migration of the 3,4-dimethoxyphenyl over the 3,4-dimethoxybenzyl group <1996T8063>.

## 12.27.9.5 Sigmatropic Rearrangements

Sommelet–Hauser rearrangement of α-phenylcycloammonium *N*-methylides is useful for three-carbon ring enlargement of cyclic amines. Thus, 2-methyl-2,3,4,5,6,7-hexahydro-1*H*-2-benzazonine **118** was obtained in high yield by the reaction of 1,1-dimethyl-2-phenylpiperidinium iodide **117** with sodium amide in liquid ammonia (**Scheme 20**, Section 12.27.5.6.2) <1997JOC2544>. Similar ylides derived from 3-aryl tetrahydroisoquinolines gave a complex mixture of azonine type [2,3]-sigmatropic rearrangement products, accompanied by benzazepine and open-chain products resulting from a Stevens rearrangement and Hofmann degradation, respectively <1995JOC4272>.

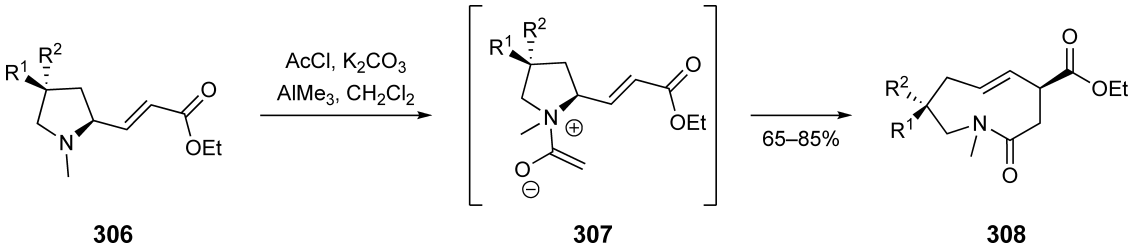
Alkylation of 1-vinyl tetrahydroisoquinoline with ethyl bromoacetate afforded the ammonium salt in high yield (Equation 43). Treatment of this compound with DBU in THF at room temperature gave the [2,3]-sigmatropic rearrangement product **305** in 70% yield. The product consisted of a mixture of isomers in an (*E*)/(*Z*)-ratio of 96:4 <2005JOC5519>.




**305**

(43)

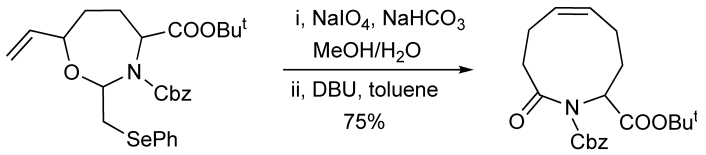
Two-phase conditions were developed for the Claisen rearrangement of amino esters **306** into azonines **308** (**Scheme 55**). A slurry of the amino ester and solid potassium carbonate in anhydrous chloroform at 0 °C was treated with acetyl chloride and trimethylaluminum to produce azoninones **308** in good yields. The reaction mechanism involves formation of zwitterionic intermediate **307** from acyl ammonium salt via deprotonation of the $\alpha$-position of the activated carbonyl group. Further [3,3]-sigmatropic rearrangement resulted in azoninones **308** <1995AGE1026, 1999SL25>.




**306** **307** **308**

**Scheme 55**

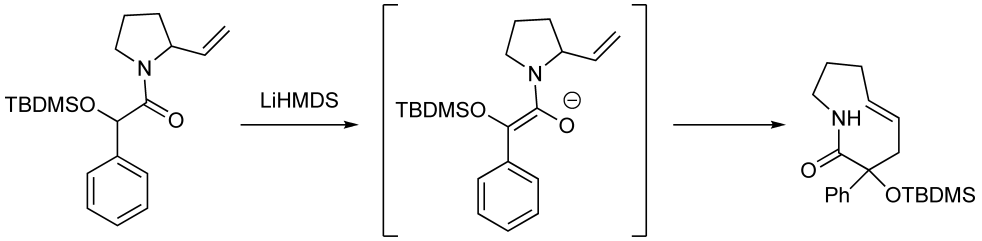
Aminal **309** was oxidized to selenoxide, and then heated in refluxing toluene with DBU to give the protected 9-substituted azoninone **310** in 75% yield as a result of Claisen rearrangement of the vinyl-substituted intermediate (Equation 44) <1996J(P1)123>.




(44)

**309** **310**

The base-induced aza-Claisen rearrangement (**Scheme 56**) of 2-vinylpyrrolidine intermediate **311** proceeded smoothly in refluxing toluene to give the nine-membered lactam **312** in good yield <2005T2659>.

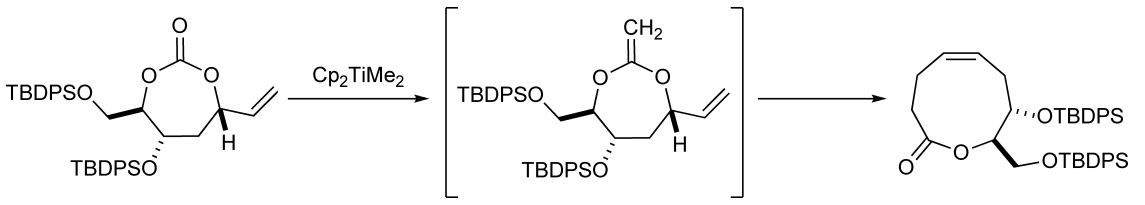



**311** **312**

**Scheme 56**

Substituted 3-keto oxonine **161** was accessible through a thermal Claisen rearrangement of the corresponding 2-methylene-7-vinyl-1,4-dioxepane **160** (**Scheme 31**, Section 12.27.6.3) <2000OL1875, 2001JA9021>. The conversion of vinyl-substituted seven-membered cyclic carbonates into nine-membered ring lactones has been achieved in good yields using dimethyltitanocene in toluene at reflux (**Scheme 57**) <2002T1943>. The reaction proceeds by initial formation of ketene acetal, which undergoes subsequent *in situ* Claisen rearrangement to provide corresponding lactones.

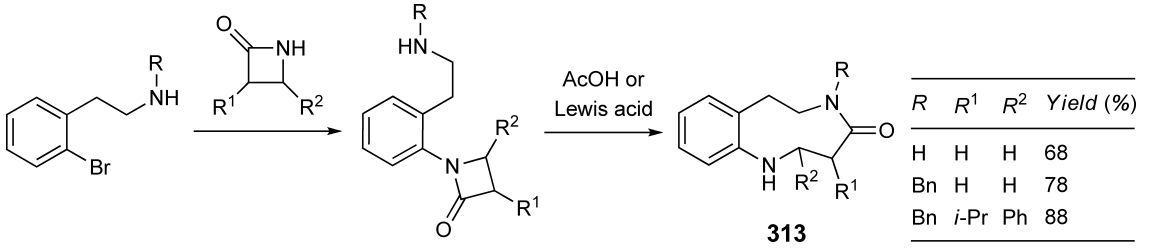
The anionic [3,3] sigmatropic rearrangement of cyclic diacyl pyrazolidines resulted in poor to good yields of 1,5-diazonane-6,9-diones <2000H(53)151>.




**Scheme 57**

## 12.27.9.6 Miscellaneous Ring-Expansion Methods

*N*-(2-Aminoacetyl)-2-valerolactam **49** underwent ring expansion into 1,4-diazonane-2,5-dione **51** in MeOH media (**Scheme 1**, Section 12.27.4.4) <2002J(P2)2078>. An alternative route for the preparation of diazoninones **291** includes thermal ring expansion of $\omega$-aminoalkyl-$\beta$-lactam **290** (**Scheme 53**, Section 12.27.9.2) <2002T7177>. Tandem Cu-catalyzed coupling of a $\beta$-lactam with an aryl bromide followed by intramolecular attack of a pendant amino group led to diazonines **313**. In some instances, the intermediate $\beta$-lactam was observable and can be further converted to the aza-heterocycle by catalysis (**Scheme 58**) <2004JA3529>.



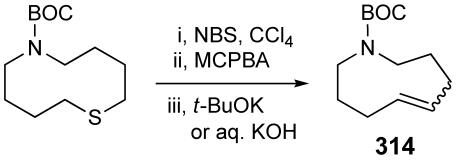

| *R* | $R^1$ | $R^2$ | *Yield* (%) |
|---|---|---|---|
| H | H | H | 68 |
| Bn | H | H | 78 |
| Bn | *i*-Pr | Ph | 88 |

**Scheme 58**

Bicyclic 9-oxabicyclo[6.1.0]nonan-2-ol when treated with diethylaminosulfur trifluoride (DAST) gave a rearranged 2-fluoro-2,3,4,5,6,7-hexahydrooxonine by a ring expansion via C–C bond cleavage of the oxirane ring <2002OL451>. A novel 1,3,5,7-tetraoxonane was synthesized in 33% yield when ethylene oxide was bubbled through melted 1,3,5-trioxane at 70 °C in the presence of $BF_3{\cdot}OBu_2$ (Equation 2, Section 12.27.5.6.1) <1998CC1809, 2001TL271>. Thermal reaction of the *C*-aryl diazomethane with cyclooctasulfur in benzene in the dark led to octathionane **15b** (**Scheme 14**, Section 12.27.5.4) <1995BCJ2757>.

## 12.27.9.7 Ring Contractions

*tert*-Butyl 1,6-thiazecane-6-carboxylate underwent a Ramberg–Bäcklund reaction to produce after treatment with base, the *N*-BOC-azonine **314** (Equation 45) <2000JOC8367>. When the reaction was conducted with potassium *tert*-butoxide, the *trans*-olefin was produced in quantitative yield with high stereoselectivity (96:4), while with aqueous KOH it gave only 59% of the product in a 65:35 *trans*:*cis* ratio.




(45)

## 12.27.10 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

There has been a tremendous increase in the methodology available to assemble nine-membered ring systems during the last decade. Development of efficient routes to prepare various natural products was a primary goal of numerous studies. Synthesis of different saturated structures relative to crown ethers, usually with 1,4,7-heteroatom pattern, were of great importance.

In spite of the apparent problems with cyclizing medium-size ring systems, most classes of heteronines are accessible through flexible synthetic routes. Numerous high-yield processes for heteronines have been developed starting with acyclic precursors. Advances in RCM methodology have had a remarkable impact on nine-membered heterocycles synthesis providing feasible routes toward azonine, oxonine, and diazonine ring systems (see Section 12.27.8.6). The RCM chemistry for other heteronines is less well developed, although it suggests a potentially versatile and general route particularly deserving of further study. Unimolecular cyclizations involving C–N bond formation include intramolecular alkylations and Mitsunobu condensations and were applied for a variety of azonines, while macrocyclic lactonization is the most reliable method for oxonine core synthesis through C–O bond formation. Other types of unimolecular cyclizations are scarce and erratic, and they usually depend on stereochemistry of the open-chain precursors and require tuning of the functional groups involved.

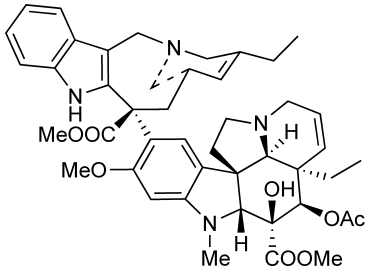
Bimolecular heteronine syntheses remain the most important way of ring assembly. Utility of 1,2- and 1,3-dielectrophilic reagents predominates in [7+2] and [6+3] syntheses, while cyclization of 1,2-diamines (or their protected counterparts), 1,2-diols, or 1,2-thiols with dielectrophiles remains the primary means of entry to the 1,4-diheteronine ring system.

Syntheses from other heterocyclic systems via ring expansion are well developed (Sections 12.17.9.1–12.27.9.6). Each of the approaches reported thus far for this type of ring construction appears rather promising, although ionic, reductive, and oxidative strategies are the most advanced. The ring-contraction approach is applicable, but limited in scope given the challenging accessibility of heterocyclic rings with 10 and more atoms.

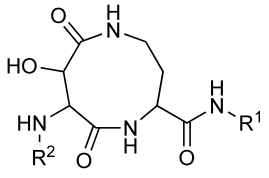
Transformations of side chains are largely explored including both reactivity of substituents attached to ring carbons and heteroatoms. Reactivity of the rings typically includes electrophilic substitution on heteroatoms and oxidative/reductive sequences involving C–C double bonds. Transformations of heteronines into other, usually bicyclic [6,5]-systems, are of significant value.

## 12.27.11 Important Compounds and Applications

Nine-membered heterocyclic rings are structural blocks of valuable natural products and their synthetic analogues. *Strychnos* alkaloid holstiine **36** is structurally related to strychnine and brucine <2000JNP543>. Navelbine **315**, synthetic azonine-bearing analog of natural alkaloids isolated from *Catharanthus roseus* (L.) G. Don (Apocynaceae) or *Vinca rosea* L., is used against non-small-cell lung and advanced breast cancers <2004JNP273>. Cyclic derivative of D-*threo*-$\beta$-OH-Asp and L-diaminobutyric acid **316** is a key structural fragment of marinobactins, a class of newly discovered marine bacterial siderophores, which are responsible for the acquisition of iron by heterotrophic bacteria <2002JA13408>.

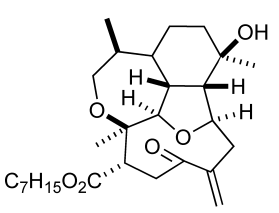



**315**

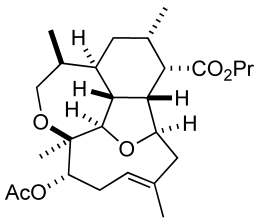



**316**

(−)-7-Deacetoxyalcyonin **210**, which contains oxonine cycle, was obtained as acetate from a *Cladiella* species of soft coral, and belongs to eunicellin diterpenes, a family of marine metabolites <1995JA10391, 2000OL2683, 2001JA9033, 2001OL135>. Other representatives of this diterpene family are briarellins **317** and asbestinins **318**, and they have in common a rare tricyclic oxonine containing ring system <2003JA6650>. Oxonine unit is a structural element of several marine organism metabolites, including brevetoxin A <2005OL4033> and topsentolides <2006JNP567>.



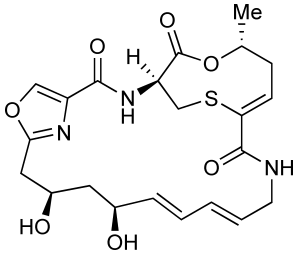

**317**




**318**

The dioxonine subunit is a core of UK-2A, dilactone which was isolated along with the structurally similar congeners, from the mycelial cake of *Streptomyces* sp. 517-02 <1998TL4363, 1998T12745>.

Griseoviridin **319**, a cyclic structure which encompasses the unsaturated sulfur-containing nine-membered lactone, is a representative member of streptogramin group A antibiotics, which was isolated from *Streptomyces griseus* <2002JOC4565, 2000AGE1664, 2000JOC4553, 2003JOC5346>.



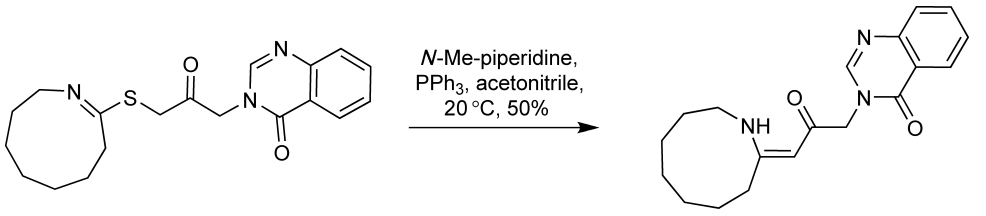

**319**

1,4,7-Triazacyclononane **61** and related crown-type systems are important ligands in inorganic chemistry and they have been extensively reviewed <B-2005MI67, 2001ARA331, 2002ARA321>. Manganese complexes of substituted 1,4,7-triazacyclononanes catalyze the selective epoxidation of a large number of olefins to epoxides with hydrogen peroxide <1996JOM(520)195, 1999T5345>.

1,4,7-Triazacyclononane-capped porphyrin models of myoglobin were synthesized and steric interactions of their gas binding were studied <1997JA3481, 1997JOC2308, 1998JOC8082, 2004OL1033, 2005OL975>. 1,4,7-Triazonane serves as a building block for the synthesis of novel conical peptides from the cyclooligomerization of functionalized thiazole amino acids <2001JA333>.

## 12.27.12 Further Developments

Few novel examples of the mono-heteronines have been reported recently. Azonane analogue **321** of antimalarial alkaloid (±)-deoxyfebrifugine is the product of an Eschenmoser sulfide contraction of intermediate thioimidate **320** (Equation 46, <2006SL383>).

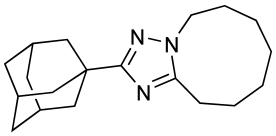



(46)

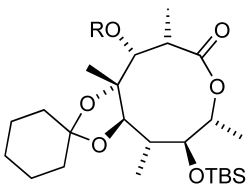
**320** **321**

Synthesis of azonane-2-one from cyclooctanone by a Schmidt reaction <2006JCR(S)218> is advantageous when compared to the Beckmann rearrangement of the corresponding oxime <2005JA11240>, providing 92% and 27% yields of the product, respectively. Further reaction of azonane-2-one with trimethyloxonium tetrafluoroborate produces a cyclic imidate, which can be reacted with hydrazide adamantane-1-carbohydrazide to give triazole **322** <2005BMCL4359>.

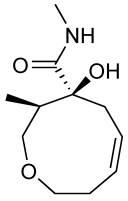
Stereoselective synthesis of the *pseudo* 2-epibotcinolide **323**, which contains a nine-membered lactone has been reported <2006OL5279>. Functionalized oxonine **324** can be synthesized by RCM of the corresponding *spiro* morpholinone precursor <2006OL5897>.



**322**

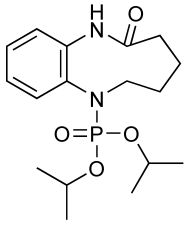


**323**

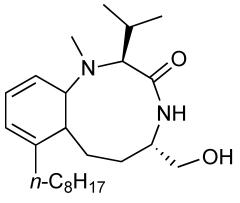


**324**

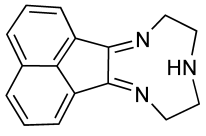
Benzodiazonine **325**, which is readily available by an intramolecular copper-catalyzed *N*-arylation of the corresponding 2-bromoaniline phosphoramidate <2005OL4781>, induces apoptosis of human chronic myelogenous leukemia K562 cells <2006BMC3766>. 8-Octyl-benzolactam **326** has been synthesized by lactam bond formation starting from the corresponding *N*-aryl-valine benzyl ester <2006JMC2681>.



**325**



**326**



**327**

Similar to diphenyl triazonine **52** (**Scheme 2**, Section 12.27.5.1), the fused analog **327** with naphthalene motif has been reported <2005JMC7192>. 1,4,7-Triazonane has been studied as a multivalent scaffold for fully symmetrical functionalization on a solid support <2006T11670>. Its 2-aminomethyl derivative can be synthesized by LAH reduction of the corresponding nitrile <2006TL3673>. *N*-Alkylation of triazacyclononane with ethyl 6-chloromethyl-pyridine-2-carboxylate results in the mixture of mono-, di- and tri-substituted products <2006CEJ7133>. Other types of transformations for 1,4,7-triazonane include Buchwald–Hartwig coupling of di-BOC derivative with aryl bromides <2006MI1823>, coupling to *C*-terminus of glycine <2005JOC115>, and alkylation with tosylates <2006TL3541>, alkyl bromides, and functionalized propiolactone <2007JOC376>.

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## Biographical Sketch

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