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THE MITSUNOBU REACTION IN THE CHEMISTRY OF NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS. THE FORMATION OF HETEROCYCLIC SYSTEMS (REVIEW)

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Methods for the design of nitrogen-containing heterocyclic systems involving the formation of C–N bonds under the conditions of the Mitsunobu reaction are discussed.

Keywords: nitrogen-containing heterocyclic compounds, alkaloids, protecting groups, Mitsunobu reaction.

The Mitsunobu reaction [1-4] is the reaction of compounds containing a mobile hydrogen atom HX with alcohols in the presence of a reagent system consisting of an azodicarboxylic ester and a phosphine PR^1_3. This reaction results in the formation of an alkylation product RX accompanied by oxidation of the phosphine PR^1_3 to phosphine oxide $R^1_3P{=}O$ and reduction of the azodicarboxylic ester to the corresponding hydrazine.

The reaction takes place under very mild conditions and usually at room temperature. If a chiral secondary alcohol ROH is used, the reaction is usually stereospecific and is accompanied by inversion of the configuration at the asymmetric carbon atom of the alcohol [1-3].

From the moment of the first report [5] the Mitsunobu reaction became a powerful tool in synthetic organic chemistry and found widespread use in the synthesis of various heterocyclic compounds, optically active substances, steroids, alkaloids, carbohydrates, and nucleosides [1-4, 6]. In particular, in a number of cases the Mitsunobu reaction has made it possible to synthesize new physiologically active compounds or to put forward new highly effective approaches to synthesis. Several reviews have been devoted to the Mitsunobu reaction [1-4, 6, 7]. Data on the use of the Mitsunobu reaction in the synthesis of alkaloids were reviewed in [6]. Various experimental techniques that make it possible to simplify the isolation of the products of the Mitsunobu reaction RX from the reaction mixture, including the use of reagents attached to a polymer support, were discussed in [7].

* Dedicated to Afanasi Andreevich Akhrem on his 95th birthday.

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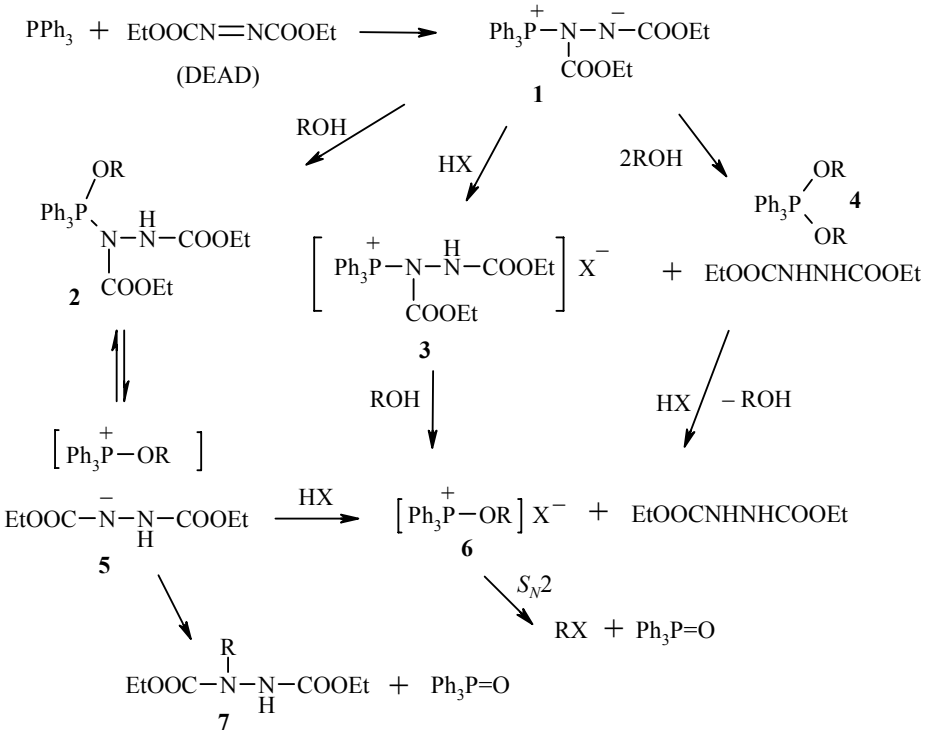
In this review methods published over the last ten years for the synthesis of nitrogen-containing heterocyclic systems based on the use of the Mitsunobu reaction to create an endocyclic C–N bond are summarized. It is most important in our view to dwell on a brief examination of the mechanism of the Mitsunobu reaction.

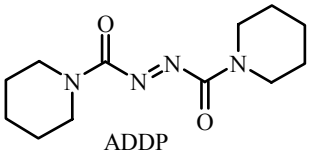
1. THE GENERAL CHARACTERISTICS AND CERTAIN ASPECTS OF THE MECHANISM OF THE MITSUNOBU REACTION

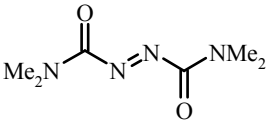
The triphenylphosphine (PPh_3)–diethyl azodicarboxylate (DEAD) oxidation–reduction system is used in the classical version of the Mitsunobu reaction [1]. The possible sequence of reactions can be represented by the following scheme [1-3, 8].

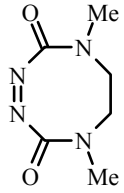


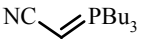
At the first stage the zwitterionic adduct **1** is formed as a result of the reaction of triphenylphosphine and diethyl azodicarboxylate. This is followed by deprotonation of the substrate HX and activation of the alcohol on account of its transformation into the alkoxytriphenylphosphonium salt **6**. The question as to how the betaine **1** is transformed into the phosphonium salt **6** remains open. This may occur through the formation of the intermediate compound **2**, the phosphonium intermediate **3**, or the phosphorane **4**. The concluding stage involves nucleophilic substitution in the alkoxyphosphonium salt **6**, leading to the acylation product RX and triphenylphosphine oxide. As a rule nucleophilic substitution is realized by an S_N2 mechanism with total inversion of the configuration at the asymmetric carbon atom of the alcohol molecule, although there are exceptions [9-11]. Inversion is not observed during anchimeric assistance from neighboring groups [11] or during the realization of a monomolecular nucleophilic substitution mechanism, e.g., during glycosylation [2]. In the absence of other nucleophilic reagents alkylation of the anion of diethyl hydrazinedicarboxylate (**5**) occurs, leading to the formation of the hydrazine **7**.

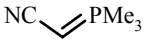
Various OH-, NH-, CH-, and SH-acidic compounds such as carboxylic acids, phenols, imides, hydroxamates, NH-acidic heterocycles, sulfonamides, β-keto esters, and thioamides have been used as substrates for alkylation under the conditions of the Mitsunobu reaction [3]. High yields of the alkylation product with the classical oxidation–reduction system have been recorded for compounds with pK_a < 15 [3]. Other oxidation-reduction systems – combinations of tributylphosphine and amides of azodicarboxylic acid such as azodicarbonyldipiperidine (ADDP) [12], tetramethylazodicarboxamide (TMAD) [13, 14], dimethylhexa-hydrotetrazocinedione (DHTD) [13, 14], phosphoranes (cyanomethylenetributylphosphorane, CMBP) [13, 14], and cyanomethylenetrimethylphosphorane (CMMP) [13, 14] – have been proposed in order to extend the Mitsunobu reaction to substrates with larger pK_a values.


ADDP


TMAD

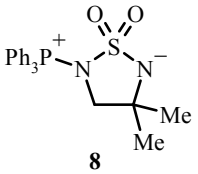

DHTD


CMBP


CMMP

Diisopropyl (DIAD) and di-*tert*-butyl (DBAD) azodicarboxylates are often used in combination with PPh_3 instead of DEAD (see the examples in the main part). In some cases it is possible to use triisopropyl phosphite [15].

The use of the betaine **8**, which is easily obtained in the reaction of the cyclic sulfamide **9** with PPh_3 and DEAD, as an alternative to the classical oxidation–reduction system has been reported [16]. The betaine **8** proved particularly effective for substrates sensitive to phosphines [17, 18].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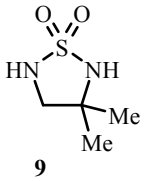

9

A large number of oxidation-reduction systems that facilitate the isolation of the product from the reaction mixture have also been proposed [7, 19].

Primary and secondary alcohols are mainly used as alkylating agents in the Mitsunobu reaction, although there are examples of the use of tertiary alcohols [20]. The Mitsunobu reaction is widely used for the construction of cyclic structures [3, 6].

2. THE FORMATION OF HETEROCYCLIC SYSTEMS UNDER MITSUNOBU CONDITIONS

By using the Mitsunobu reaction to create an endocyclic C–N bond it is possible to obtain a wide range of saturated and partially saturated heterocyclic systems. The ring size varies from small (three- and four-membered) to macrocycles. Substrates containing electron-accepting groups (e.g., acyl, sulfonyl) at a nitrogen atom, which increase the NH acidity, are usually employed for heterocyclization under Mitsunobu conditions, although a number of examples of the cyclization of nonactivated amino alcohols are known [6, 21, 22].

2.1. The Production of Three-Membered Rings

Aziridines are reagents widely used in organic synthesis [22, 23]. They can be produced by cyclization of the corresponding vicinal amino alcohols under Mitsunobu conditions (Table 1). Moderate yields are usually obtained, and this is due to the low acidity of the amino group. The cyclization is conducted by prolonged boiling in toluene or THF [22, 24].

It should be noted that sterically hindered amino alcohols (Table 1, Nos. 3-5) and also *syn*-amino alcohols (Table 1, No. 8) do not form aziridines with DEAD and PPh_3.

The cyclization of vicinal amino alcohols under Mitsunobu conditions was also used successfully for the synthesis of derivatives of adenosine **10** containing an aziridine fragment [25].

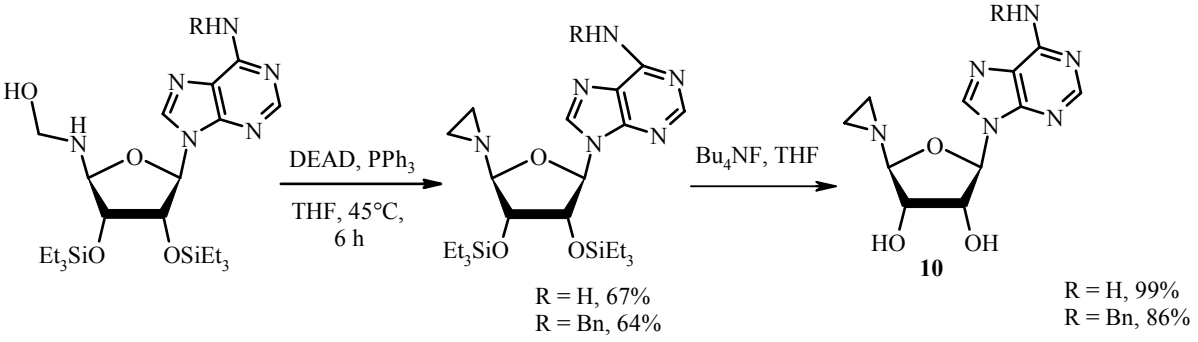


TABLE 1. The Cyclization of Vicinal Amino Alcohols in the Presence of PPh_3 and DEAD

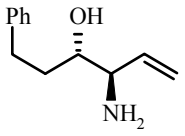
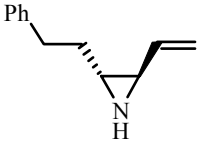
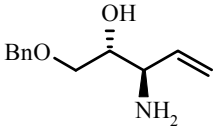
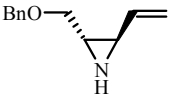
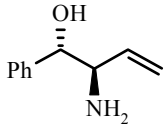
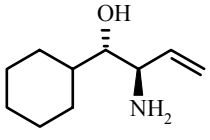
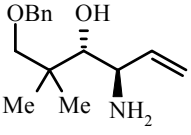
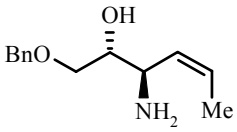
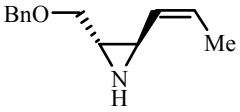
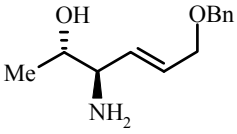
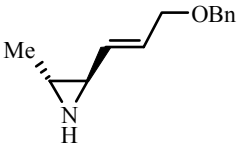
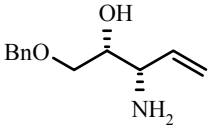
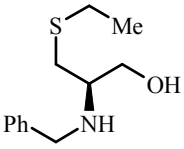
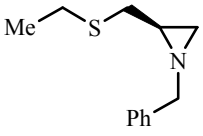
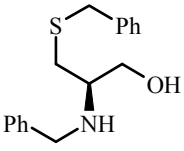
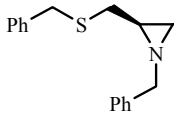
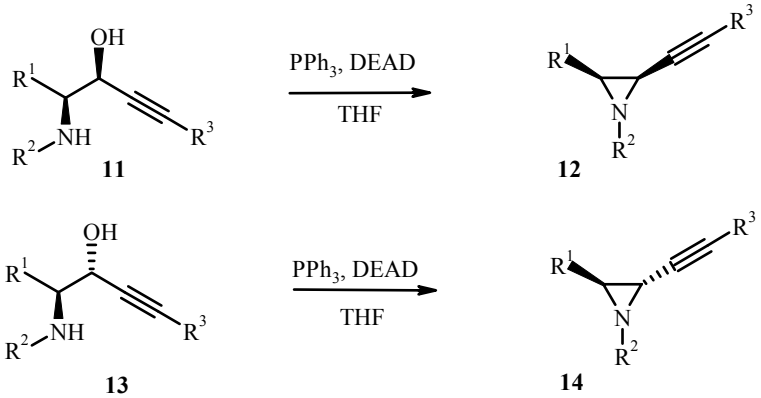
No.*	Amino alcohol	Aziridine	Solvent	Yield, %	Ref.
1	2	3	4	5	6
1			THF PhMe	44 52	[22]
2			PhMe	50	[22]
3		—	PhMe	0	[22]
4		—	PhMe	0	[22]
5		—	PhMe	0	[22]

TABLE 1. (continued)

1	2	3	4	5	6
6			PhMe	54	[22]
7			PhMe	53	[22]
8		—	PhMe	0	[22]
9			THF	69	[24]
10			THF	61	[24]

* Optically active amino alcohols and aziridine (Nos. 1-6 and 9, 10), racemic amino alcohol and aziridine (Nos. 7, 8).

In order to produce optically active 2-ethynylaziridines [23] the cyclization of vicinal amino alcohols, containing electron-accepting activating groups at the nitrogen atom, with the DEAD–PPh_3 oxidation–reduction system was realized at 0-25°C for 0.5-2.5 h. The yields of the cyclization products varied from high to close to quantitative (Table 2).



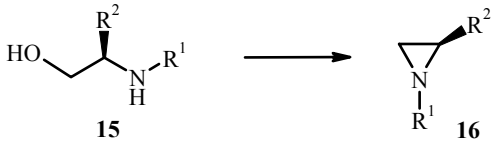
11 **12** **13** **14**

TABLE 2. The Synthesis of 2-Ethynylaziridines under Mitsunobu Conditions*

No	R^1	R^2	R^3	Amino alcohol	Aziridine	*T*, °C	Time, h	Yield, %
1	*i*-Pr	Boc	TMS	**11a**	**12a**	25	0.5	96
2	*i*-Pr	Boc	TMS	**13a**	**14a**	25	2	73
3	*i*-Pr	Mts	H	**11b**	**12b**	0	0.5	97
4	*i*-Pr	Mts	H	**13b**	**14b**	0	0.5	98
5	*i*-Pr	Boc	H	**11c**	**12c**	25	0.5	87
6	*i*-Pr	Boc	H	**13c**	**14c**	25	2	64
7	$TBSOCH_2$	Mts	TMS	**11d**	**12d**	0	0.5	94
8	$TBSOCH_2$	Mts	H	**11e**	**12e**	0	0.5	96
9	$TBSOCH_2$	Mts	TMS	**13d**	**14d**	0	0.5	99
10	$TBSOCH_2$	Mts	H	**13e**	**14e**	0	0.5	95

* TMS = trimethylsilyl; Mts = 2,4,6-trimethylbenzenesulfonyl; TBS = *tert*-butyldimethylsilyl.

The aziridines **16** were obtained with high yields by the cyclization of serine derivatives **15** containing an activating group at the nitrogen atom (Table 3) [19, 26, 27].



15 **16**

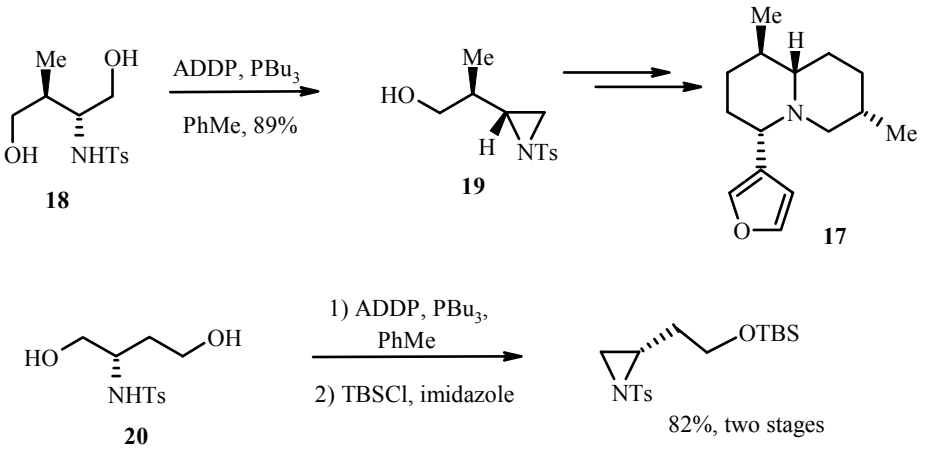
Thus, the formation of the three-membered aziridine ring is easily realized for substrates containing both *tert*-butoxycarbonyl and sulfonyl activating groups.

The selective cyclization of the aminodiol **18** with the formation of the aziridine **19** was used in the synthesis of the alkaloid (−)-deoxynupharidine **17** [28]. This reflects the known higher rate of formation of three-membered rings compared with four-membered rings [29]. At the same time the cyclization of the aminodiol **20** also leads to the corresponding aziridine and not the piperidine [30], although it is known that the formation of six-membered rings as a result of intramolecular nucleophilic substitution occurs more readily [29].

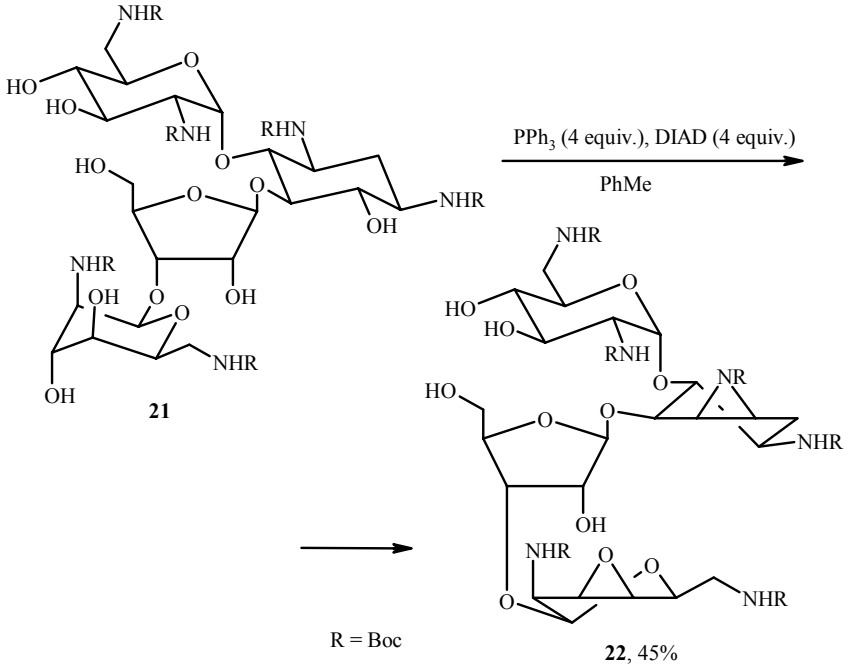
TABLE 3. Cyclization of Serine Derivatives*

No.	R^1	R^2	Conditions	Yield	Ref.
1	Ns	CO_2t-Bu	DEAD, PPh_3, THF	92	[27]
2	Ns	4-Methyl-2,6,7-trioxabicyclo-[2.2.2]octyl	DEAD, PPh_3, THF	98	[26]
3	Boc	CO_2Bn	DEAD, PPh_3, CH_2Cl_2	92	[19]
4	Boc	CO_2Bn	Di-*p*-chlorobenzylazo-dicarboxylate, PPh_3, CH_2Cl_2	88	[19]

*Ns = *o*-nitrophenylsulfonyl



The closure of three-membered rings (aziridine and oxirane) was observed in the reaction of N-Boc neomycin B **21** with an excess of PPh_3 and DIAD in toluene [31]. Apart from the bisanhydrido derivative **22** a monoanhydrido derivative, containing an oxirane ring and not containing an aziridine ring, was isolated with a yield of 33% (not shown in the scheme).

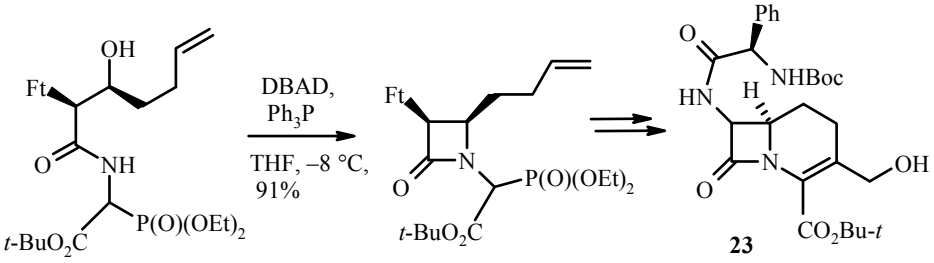


Earlier compound **22**, obtained under analogous conditions, was erroneously assigned a structure containing aziridine and azetidine rings [32].

2.2. The Production of Four-Membered Rings

Among four-membered nitrogen-containing heterocycles a special position is occupied by β-lactams. This heterocyclic fragment enters the structure of a wide range of antibiotics such as penicillins, cephalosporins, carbapenemes, and monobactams [33-35]. The Mitsunobu reaction can serve as a convenient method for the

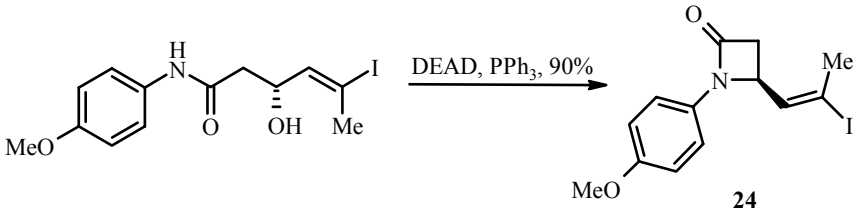
synthesis of β-lactams [33-37]. A significant advantage of amide substrates is their increased NH acidity, and the introduction of additional activating groups is not necessary for successful cyclization under the conditions of the Mitsunobu reaction. Closure of the β-lactam ring under Mitsunobu conditions was used in the synthesis of the carbacephalosporin **23** [33].



23

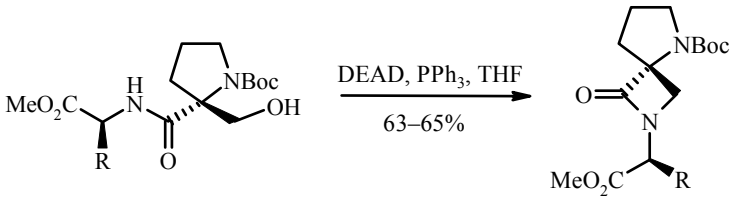
Ft = 1,3-dioxa-1,3-dihydroisoindol-2-yl

The azetidinone **24**, an intermediate compound in the synthesis of the antitumor product lankacidin C isolated from *Streptomyces*, was prepared in a similar way [36].



24

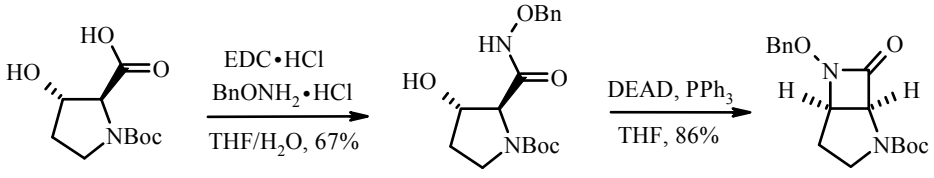
The Mitsunobu reaction was also used for the production of spirocyclic β-lactams **25** [37].



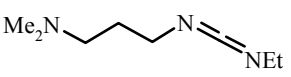
25

R = H, 2,6-dichlorobenzyloxy

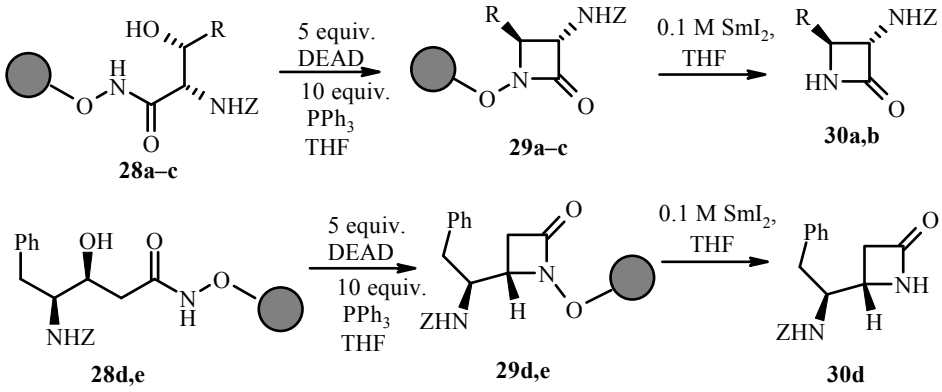
Hydroxamates are suitable subjects for alkylation under the conditions of the Mitsunobu reaction [4]. Thus, the bicyclic compound **27** – the precursor of a series of familiar β-lactamase inhibitors – is formed during the cyclization of the hydroxamate **26**, produced from *trans*-3-hydroxy-L-proline [34].



26 **27**

EDC = 

A solid-phase method was developed for the production of β-lactams based on the Mitsunobu reaction using derivatives of hydroxyamino acids **28** attached to a polymer [35]. In this case a considerable excess of PPh_3 and DEAD is required for more complete conversion.



a R = H, Z = Cbz; **b** R = Me, Z = Boc; **c** R = H, Z = Fmoc; **d** Z = Boc; **e** Z = Fmoc
Cbz – benzyloxycarbonyl; Fmoc – 9-9-fluorenylmethoxycarbonyl

A series of peptidomimetics containing a β-lactam fragment, potential new protease inhibitors, was obtained by cyclization of the hydrazides **31** – derivatives of serine and threonine (Table 4) [38, 39].

As well as diethyl azodicarboxylate, the di-*tert*-butyl ester has also been used as azo component under the conditions of the Mitsunobu reaction (Table 4, Nos. 1, 2, 5, 6). This was due to the fact that the series of β-lactams **32** and the diethyl hydrazinedicarboxylate formed as side product proved difficult to separate by chromatography. The isolation of the reaction products was facilitated by the use of di-*tert*-butyl azodicarboxylate.

A series of N-tosyl-2-arylazetidines was obtained from the tosylimines of aromatic aldehydes [40]. Cyclization of an amino alcohol containing a tosyl activating group at the nitrogen atom under Mitsunobu conditions occurred at the concluding stage of the synthesis.

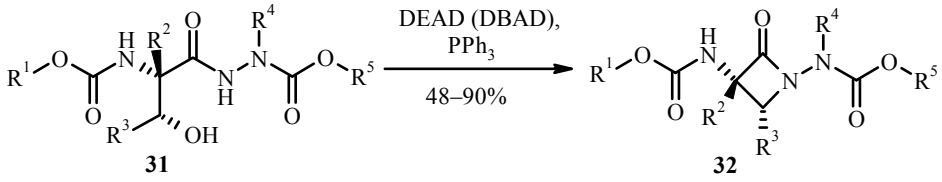
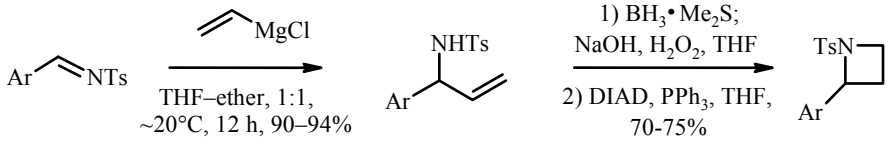


TABLE 4. The Cyclization of Serine and Threonine Derivatives

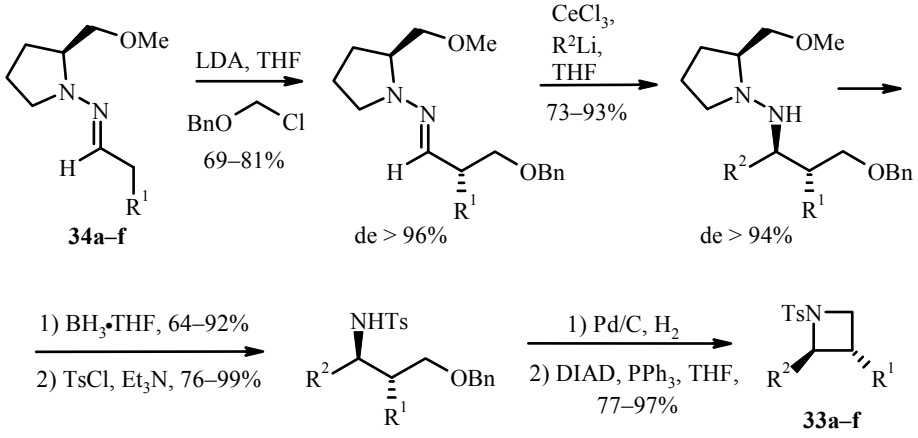
No.	R^1	R^2	R^3	R^4	R^5	Yield **32**, %	Ref.
1	*t*-Bu	H	H	Me	Bn	88	[38]
2	Bn	H	H	Me	*t*-Bu	89	[38]
3	*t*-Bu	H	H	*i*-Pr	Bn	71	[38]
4	*t*-Bu	H	H	*i*-Bu	Bn	79	[38]
5	*t*-Bu	H	H	Bn	Bn	48	[38]
6	*t*-Bu	H	Me	Me	Bn	90	[38]
7*	*t*-Bu	Bn	H	Me	Bn	85	[39]

* Racemic compounds.



Ar = Ph, 3-BrC_6H_4, 4-$MeOC_6H_4$, 2,3-$(MeO)_2C_6H_3$

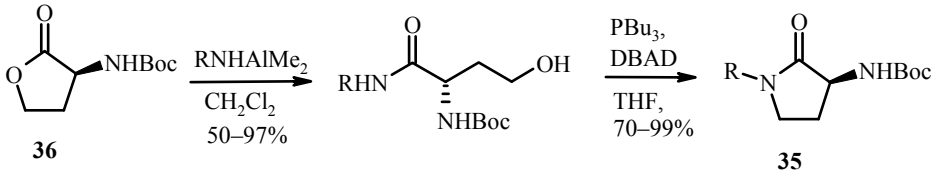
An asymmetric version was proposed for the synthesis of optically pure azetidines **33** [41] from the chiral hydrazone **34** including the cyclization of N-tosylamino alcohols.



a R^1 =Me; **b** R^1 = Et; **c**,**d** R^1 = Bu; **e** R^1 = Ph; **f** R^1 = H; **a**,**b**,**d** R^2 = Bu; **c**,**e**,**f** R^2 = Hex

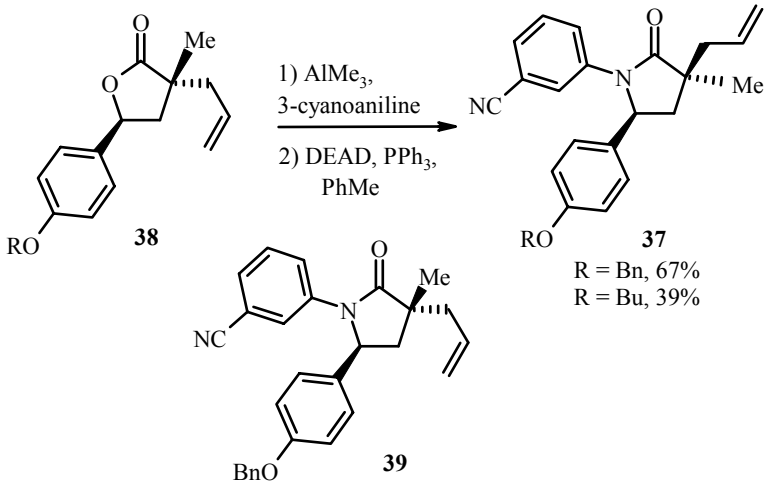
2.3. The Production of Five-Membered Rings

As in the case of β-lactams, a γ-lactam ring is also readily formed under the conditions of the Mitsunobu reaction [42-44]. Thus, a series of enantiomerically pure 3-aminopyrrolidinones **35** was obtained from (*S*)-homoserine lactone **36** [42]. The Mitsunobu reaction was conducted in the presence of the DBAD–PBu_3 system at room temperature. High yields of the cyclization products were observed both for aromatic and for aliphatic amides.

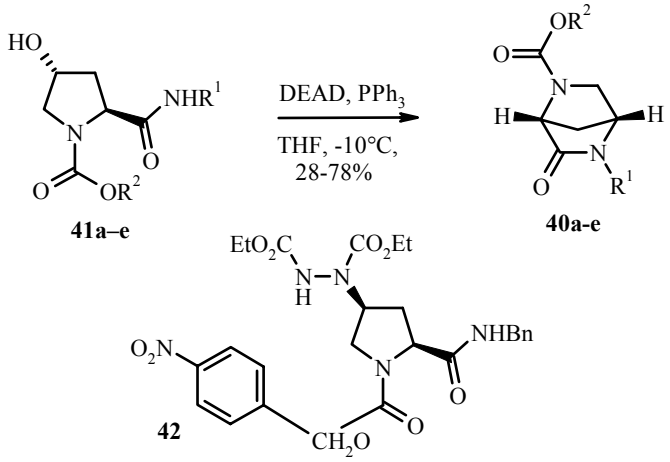


R = 2-Py, 3-Py, 4-Py, pyrazin-2-yl, pyrimidin-4-yl, 4-(morpholin-4-yl)phenyl, isoquinolin-5-yl, quinolin-5-yl, thiazol-2-yl, isoxazol-3-yl, 3-tetrahydrofuryl, 1-benzylpyrrolidin-3-yl, 1-benzylpiperidin-4-yl

The γ-lactams **37** were obtained similarly from the γ-lactones **38** [43]. The acyclic amides formed at the first stage were not isolated. In the case of R = Bn a diastereomer of **39** was also isolated from the reaction mixture with a yield of 10%.

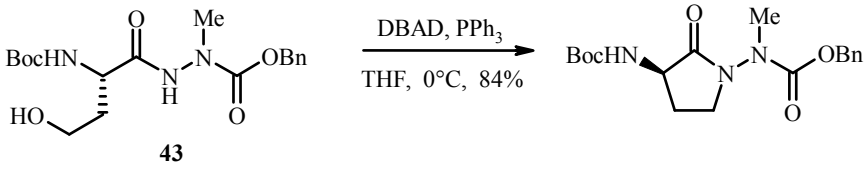


The bicyclic compounds **40** containing a γ-lactam fragment were obtained from the anilides of N-protected (2*S*,4*R*)-3-hydroxyproline **41** [44]. Cyclization did not occur if the benzylamide (**41,** R^1 = Bn, R^2 = 4-$O_2NC_6H_4CH_2$) was used instead of the anilides, and the monocyclic derivative, formed as a result of S_N2 substitution with the participation of the anion of diethyl hydrazinedicarboxylate, was isolated.



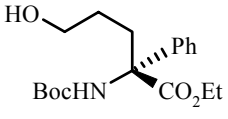
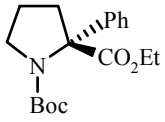
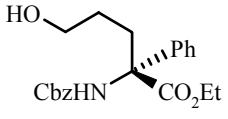
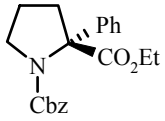
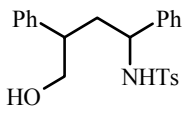
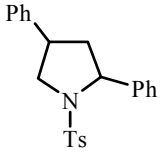
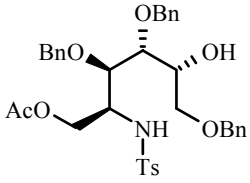
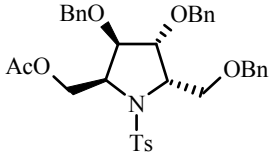
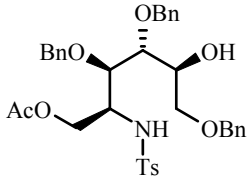
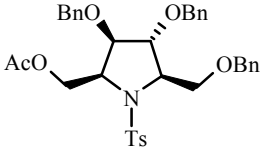
a R^1 = 4-$O_2NC_6H_4$; **b** R^1 = 2-$O_2NC_6H_4$; **c** R^1 = 2-(CH_2=$CHCH_2OOC$)C_6H_4;
d R^1 = 3-(CH_2=$CHCH_2OOC$)C_6H_4; **e** R^1 = Ph; **a**–**d** R^2 = CH_2CH=CH_2; **e** R^2 = 4-$O_2NC_6H_4CH_2$

The cyclization of the hydrazide **43** takes place readily with the formation of a five-membered ring [39].

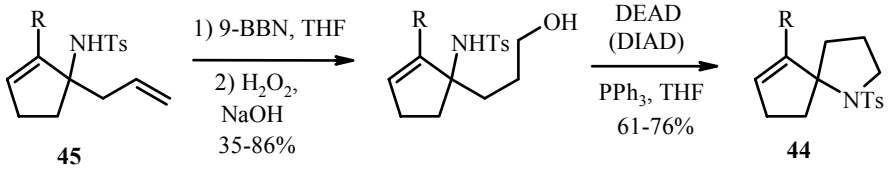


A series of methods has been described for the production of pyrrolidines, involving the cyclization of alcohols containing a sulfonylamide or carbamate group and using the classical DEAD–PPh_3 oxidation-reduction system [45-47]. The results of these investigations are summarized in Table 5. Whereas heating to 60°C is required for the cyclization of alcohols containing a carbamate group (Table 5, Nos. 1, 2), the sulfonamides are converted into the cyclization products with high yields even at 0°C (Table 5, Nos. 3-5).

TABLE 5. The Production of Pyrrolidines by Cyclization of Amino Alcohols Containing an Activating Group at the Nitrogen Atom

No.	Alcohol	Pyrrolidine	Yield, %	Ref.
1			55	[45]
2			63	[45]
3			91	[46]
4			88	[47]
5			70	[47]

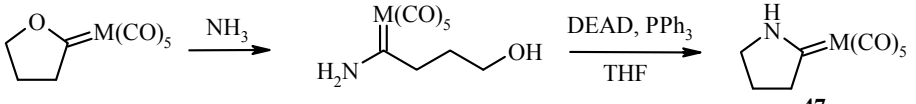
A series of spirocyclic compounds **44** was obtained from allylsulfonamides **45** as a result of hydroboronation followed by cyclization under Mitsunobu conditions [48].



45 **44**

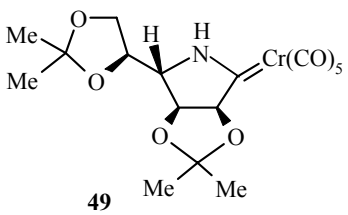
R = *n*-Bu, Me_3SiCH_2, Ph, *s*-Bu

9-BBN = 9-borabicyclo[3.3.1]nonane



46 **48** **47**

M = Cr, 65%; M = W, 88%



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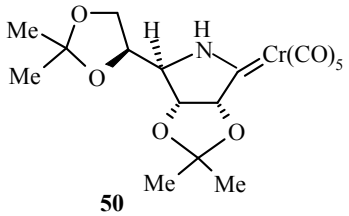
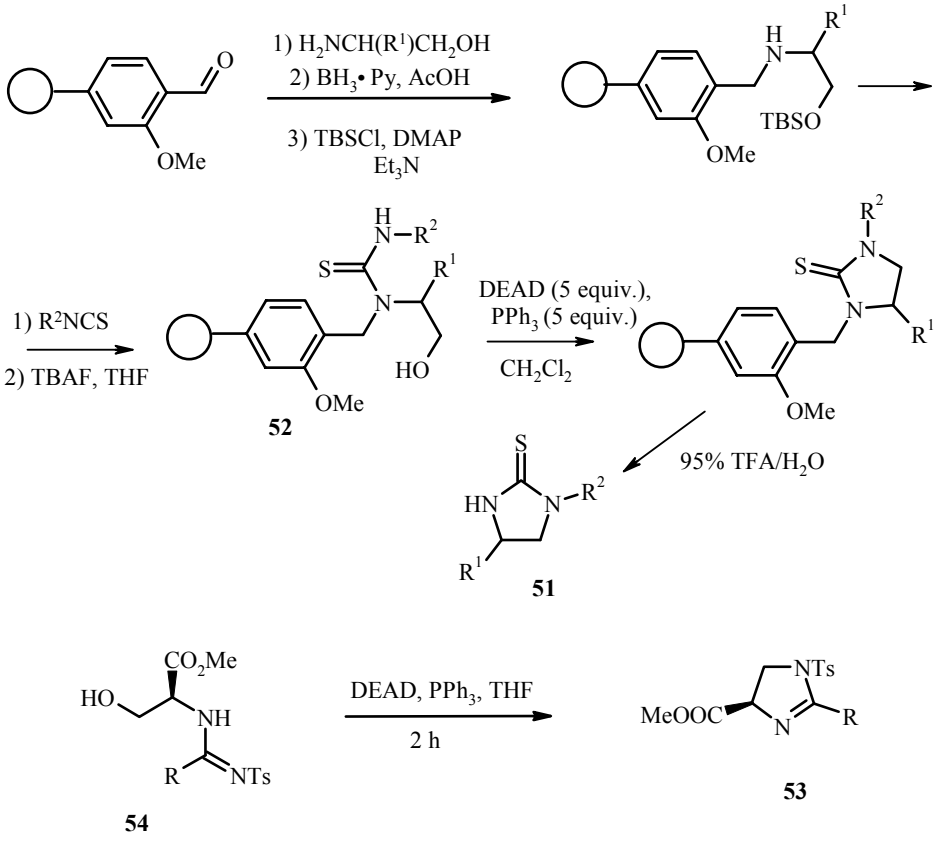


50

The transformation of oxacyclopentylidene complexes of chromium and tungsten **46** into the corresponding azacyclopentylidene analogs **47** with prior aminolysis, accompanied by ring opening and subsequent closure of a new pyrrolidine ring, was reported [49]. The cyclization of aminocarbene complexes **48** was conducted in the presence of PPh_3 and DEAD, and the azacyclopentylidene complexes were isolated with good yields. This approach was used in the synthesis of the iminofuranosylidene complexes **49** and **50** [50].

A solid-phase method was proposed for the synthesis of 2-imidazolidinethiones **51** by the cyclization of N-(2-hydroxyethyl)thioureas **52** attached to a polymer support under Mitsunobu reaction conditions (Table 6) [51].



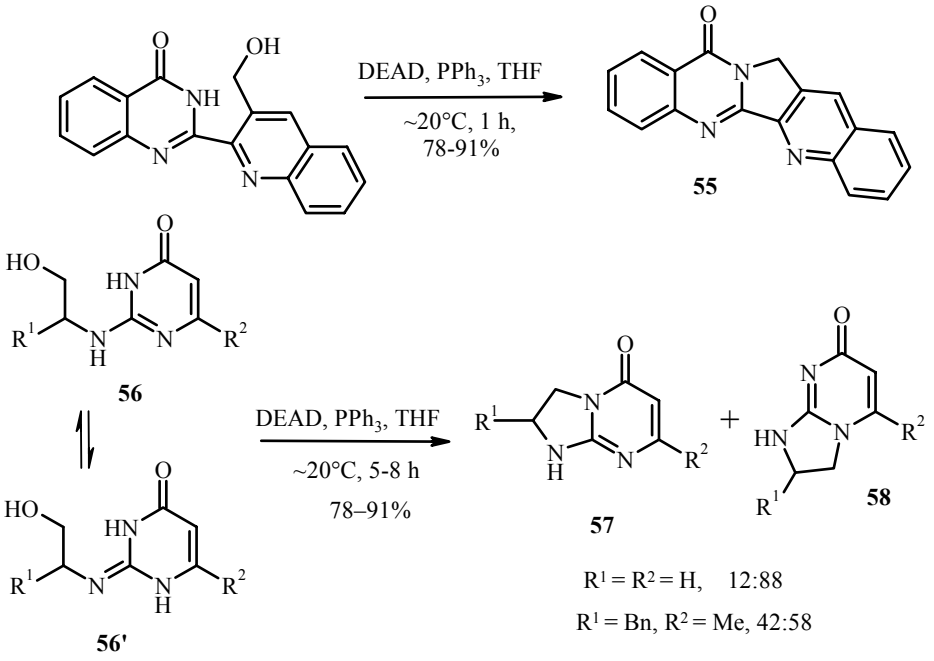
R = cyclopentyl, 45%; R = Pr, 39%; R = Bn, 32%; R = H, 0%

TABLE 6. The Solid-Phase Synthesis of 2-Imidazolidinethiones

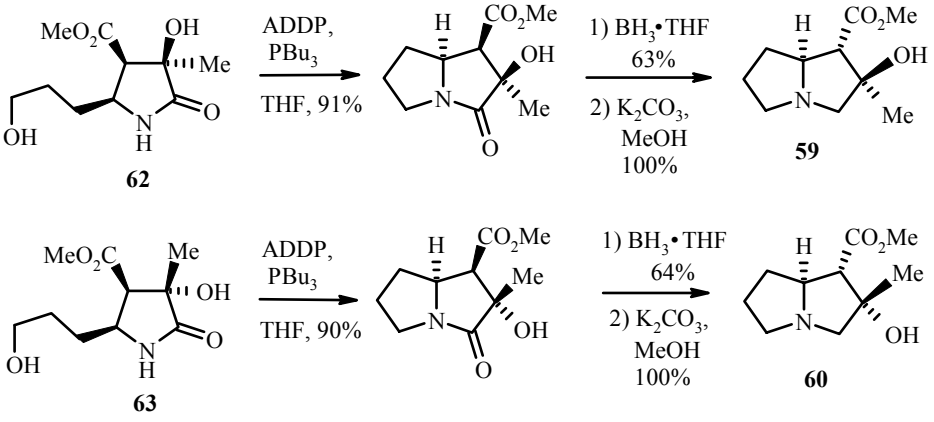
No.	R^1	R^2	Total yield **51**,%	Purity, %
1	H	*i*-Pr	45	72
2	H	Ph	52	74
3	H	4-MeC_6H_4	61	81
4	H	4-$O_2NC_6H_4$	50	99
5	H	4-ClC_6H_4	66	82
6	H	3-$CF_3C_6H_4$	40	90
7	H	4-NCC_6H_4	59	94
8	H	2-Cl-4-$O_2NC_6H_3$	71	93
9	H	2-MeO-4-$O_2NC_6H_3$	75	95
10	Me	4-$O_2NC_6H_4$	54	96
11	(*S*)-*i*-Pr	4-$O_2NC_6H_4$	63	92

A series of derivatives of 4,5-dihydroimidazole-4-carboxylic acid **53** was obtained as a result of intramolecular cyclization of the amidines **54** [52]. It is interesting to note that it was not possible to isolate a cyclization product when formamidine (**54,** R = H) was used.

The Mitsunobu reaction was used to design condensed heterocyclic systems containing an annulated five-membered fragment [53-55]. In the synthesis of imidazo[1,2-*a*]pyrimidinones [53] and the alkaloid luotonine A **55** [54], which has cytotoxic activity, intramolecular alkylation of the pyrimidinones fragment was realized in the presence of DEAD and PPh_3. The formation of two regioisomers **57** and **58** was observed during the cyclization of the pyrimidinones **56**, and the product from alkylation at the N-1 atom predominated.

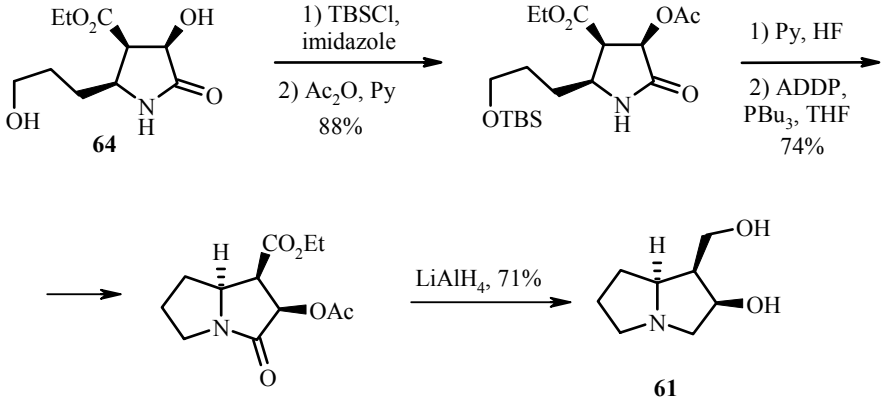


A method was proposed for the synthesis of the pyrrolizidine alkaloids isotussilagine **59**, tussilagine **60**, and (-)-petasinecine **61** with an intramolecular Mitsunobu reaction as key stage [55].

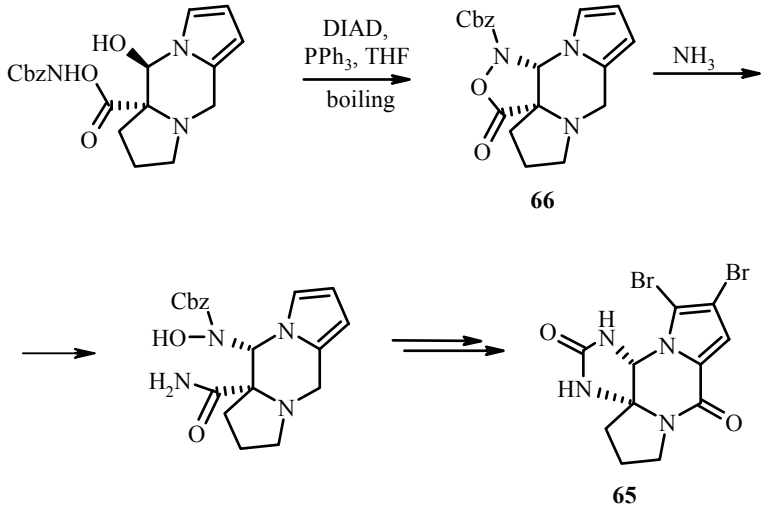


The cyclization of the pyrrolidine derivatives **62** and **63** in the presence of ADDP and PBu_3, reduction of the amide group to amine, and isomerization of the chiral center of the ester fragment led to the formation of the required tussilagine and isotussilagine. It was not possible to obtain (-)-petasinecine **61** in the same way

from the pyrrolidine **64** since the 3-hydroxy group is eliminated under the conditions of the Mitsunobu reaction. The preliminary introduction of a protecting group at the hydroxyl at position 3 of the pyrrolidine **64** secures the successful production of compound **61**.



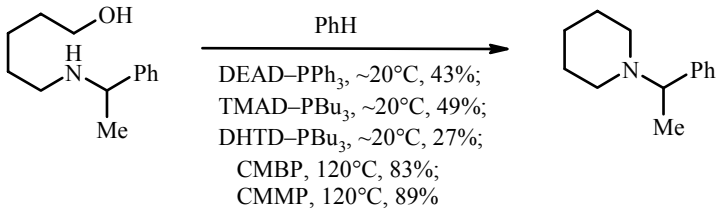
In the synthesis of (+)-dibromophakellstatin **65** [56], which has antitumor activity, the Mitsunobu reaction was used for the formation of the isoxazolone fragment of the tetracyclic compound **66**, which was then subjected to aminolysis. Thus, the use of the Mitsunobu reaction made it possible to create the aminal fragment at position 6 of the phakellstatin heterocyclic system **65**.



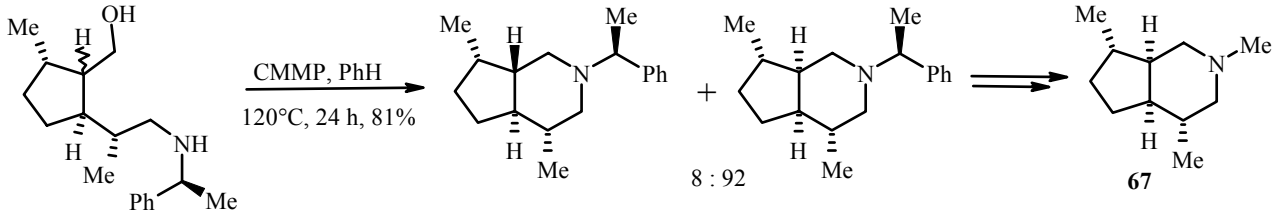
2.4. The Production of Six-Membered Rings

In the last ten years a series of papers have been devoted to the production of nitrogen-containing heterocycles with one and several nitrogen atoms under Mitsunobu reaction conditions [57-70]. Activated and nonactivated amino alcohols, amido alcohols, hydroxamates, and hydrazino alcohols were used for the construction of the heterocyclic system. The effectiveness of the various oxidation–reduction systems used for the Mitsunobu reaction was studied for the example of the cyclizations of a series of amino alcohols [21]. Thus, closure of the piperidine ring occurred with various dehydrating agents, but the highest yield was obtained during cyclization with the use of CMMP.

Thus, the unusual monoterpene alkaloid (+)-α-skytanthine **67** was synthesized with the use of CMMP [21].

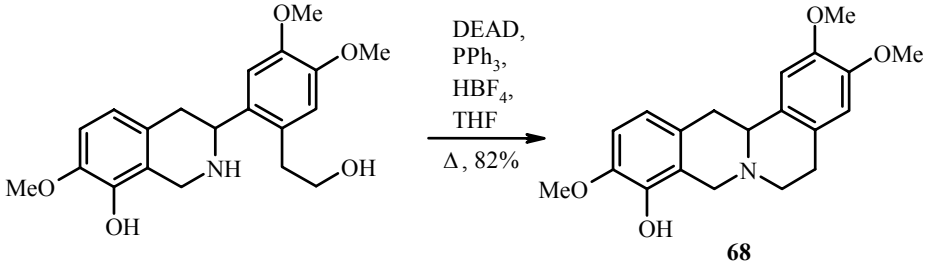


The yield in the cyclization of the amino alcohol under Mitsunobu reaction conditions with the classical oxidation–reduction system DEAD–PPh_3 can be increased with the addition of 1 equiv. of HBF_4 [57]. This method was used in the synthesis of the tetrahydroprotoberberine alkaloid (±)-schefferine **68**.



The acid secures protonation of the anion of diethyl hydrazinedicarboxylate, which makes it possible to avoid its participation in the formation of a side product of type **7**.

It was possible to increase the yield of the Mitsunobu reaction with the aniline **69** [58] in the synthesis of the precursor **70** of the fluoroquinolone antibiotic levofloxacin by adding anhydrous zinc chloride to the reaction mixture.



In the absence of zinc chloride the amount of the cyclic compound **70** in the reaction mixture did not exceed 18%, and the main reaction product was the hydrazine derivative **72**. With the addition of 4 equiv. of $ZnCl_2$ it was possible to obtain the oxazine **70** with a yield of 76%. If the amount of $ZnCl_2$ is reduced the yield of compound **70** is reduced, and the chlorine derivative **71** becomes the main product (Table 7).

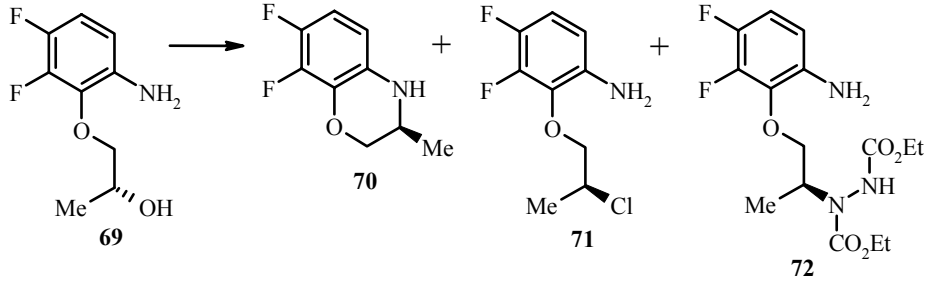


TABLE 7. The Cyclization of the Aniline **69** in the Presence of PPh_3, DEAD, and $ZnCl_2$

Equivalents			Conditions	Ratio, %		
PPh_3	DEAD	$ZnCl_2$		**70**	**71**	**72**
3	3	0	PhH, boiling, 1 h	—	—	Main
3	3	0	MeCN, boiling, 1 h	18	—	82
3	3	0.2	MeCN, boiling, 1 h	12	38	50
3	3	1	MeCN, boiling, 1 h	11	89	—
3	3	1.5	MeCN, boiling, 1 h	21	79	—
3	3	3	MeCN, boiling, 1 h	78	22	—
3	3	4	MeCN, boiling, 1 h	94 (76*)	6	—

* The yield of the isolated compound.

TABLE 8. The Production of Piperidine Derivatives under Mitsunobu Reaction Conditions

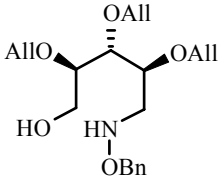
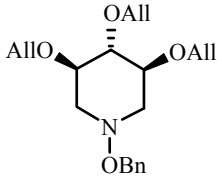
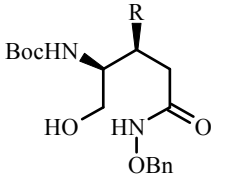
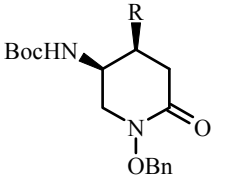
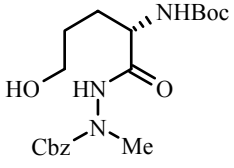
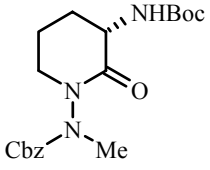
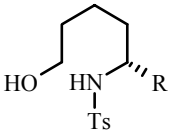
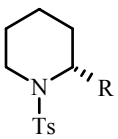
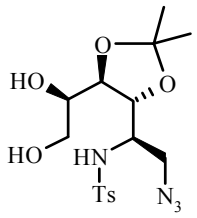
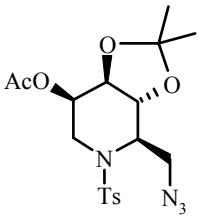
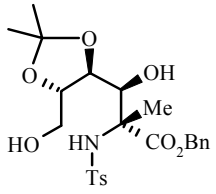
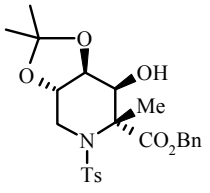
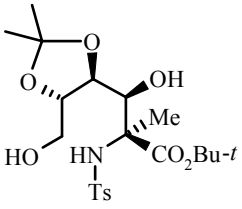
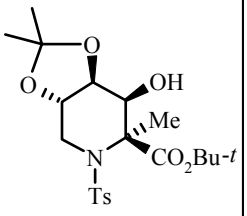
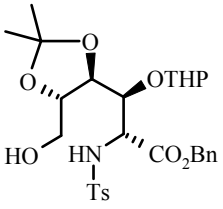
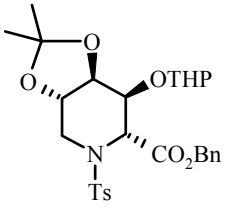
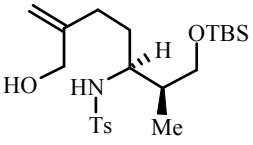
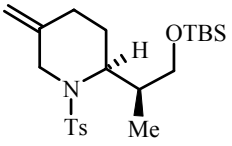
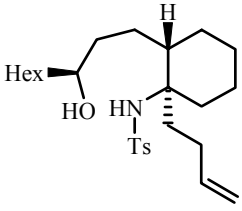
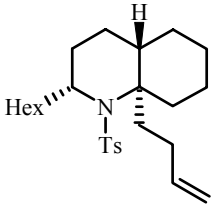
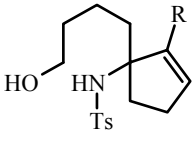
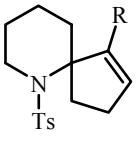
No.	Acyclic precursor	Piperidine derivative	Con-ditions	Yield, %	Ref.
1	2	3	4	5	6
1	 All = allyl		DEAD, PPh_3, THF, ~20°C	75	[63]
2	 R = OH, N(Bn)COPh	 R = OH, N(Bn)COPh	DEAD, PPh_3, THF, ~20°C	68-82	[59]
3			DBAD, PPh_3, THF, 0°C	82	[39]
4	 R = *i*-Pr, *s*-Bu, *i*-Bu, CH_2CH_2OTBS	 R = *i*-Pr, *s*-Bu, *i*-Bu, CH_2CH_2OTBS	DIAD, PPh3, THF, 0-20°C	80-96	[30]

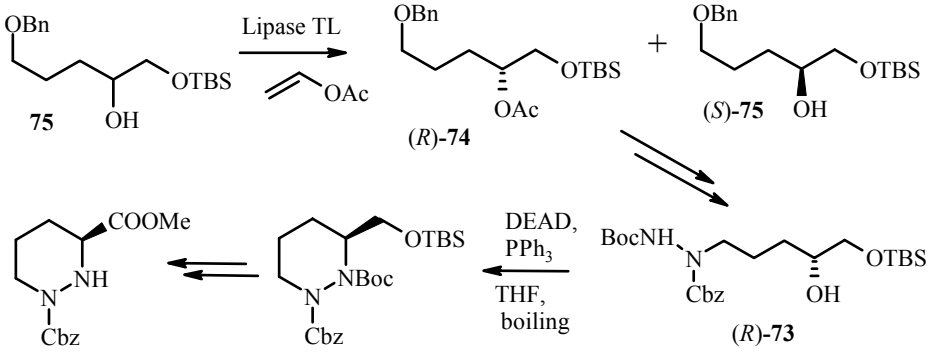
TABLE 8. (continued)

1	2	3	4	5	6
5			DEAD, PPh_3, THF, ~20°C	45*	[60]
6			DEAD, PPh_3, THF, ~20°C	92	[61]
7			DEAD, PPh_3, THF, ~20°C	75	[61]
8			DEAD, PPh_3, THF, ~20 °C	92	[61]
9			ADDP, PBu_3, PhH, ~20°C	87	[28]
10			DEAD, PPh_3, THF, ~20°C	78	[62]
11	 R= Bu, Me_3SiCH_2, Ph	 R= Bu, Me_3SiCH_2, Ph	DEAD (DIAD), PPh_3, THF ~20°C	76-87	[48]

* The overall yield of the two stages – the Mitsunobu reaction and the subsequent acylation – is shown.

Cyclizations of hydroxamates, hydrazides, and sulfonamides containing a hydroxy group at a suitable position under Mitsunobu reaction conditions have been widely used in the synthesis of piperidine alkaloids and their analogs (Table 8) [30, 39, 48, 59-62]. An intramolecular Mitsunobu reaction leading to the formation of a piperidine ring with the participation of an alkoxyamino group is also known (Table 8, No. 1) [63].

A method was proposed for the production of both enantiomers of the Cbz derivative of methyl hexahydropyridazine-3-carboxylate, requiring cyclization of the hydrazine alcohol derivative **73** under Mitsunobu reactionconditions [64]. The starting compound for the production of the hydrazine alcohol derivative (*R*)-**73** was the optically active acetate (*R*)-**74**, which was synthesized by kinetic resolution of the alcohol **75** with lipase TL. The (*R*)-isomer of hexahydropyridazine-3-carboxylic acid was obtained similarly after preliminary acetylation of the alcohol (*S*)-**75**.



An effective method, similar to that used for the production of the β- and γ-lactams [33, 42], was proposed for the synthesis of N-arylpiperazinones (Table 9) [65].

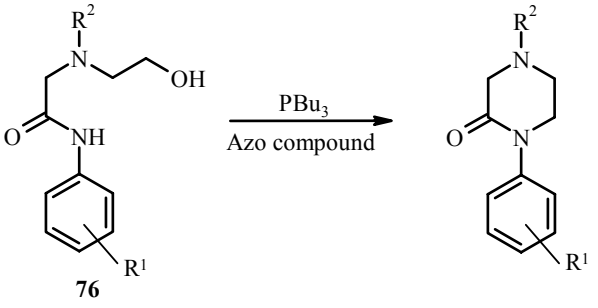


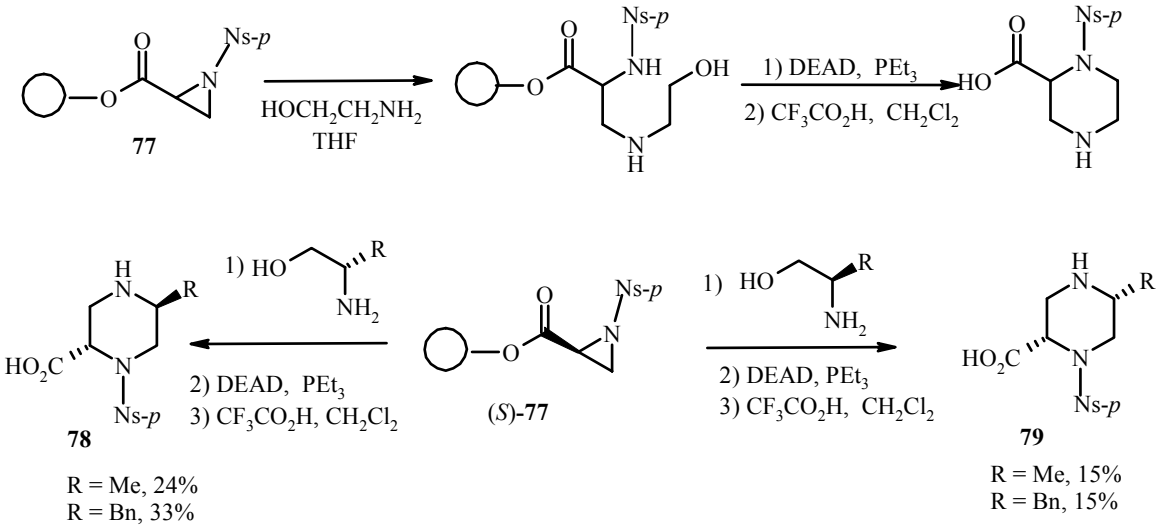
TABLE 9. The Synthesis of N-Arylpiperazinones under the Conditions of the Mitsunobu Reaction

No.	R^1	R^2	Azo compound	Yield, %
1	4-Cl	H	DBAD	72
2	3-Cl	H	DBAD	87
3	2-Cl	H	DIAD	83
4	3-OCF_3	H	DBAD	76
5	H	H	ADDP	83
6	H	Me	ADDP	89
7	3-OMe	H	ADDP	84
8	3-Br	H	DBAD	88
9	4-OMe	H	ADDP	82
10	3-Cl, 4-Me	H	DBAD	74
11	3-NO_2	H	DBAD	81

Despite the presence of an unprocted amino group in the structure of the precursors of the N-aryl-piperazinones (the amido alcohols **76**) the formation of the corresponding aziridines was not observed. The cyclization was conducted in ethyl acetate, and the obtained N-arylpiperazinones were isolated in the form of the hydrochlorides.

The intramolecular Mitsunobu reaction with the participation of nosylamide groups (*o*-Ns, *o*-nitrophenylsulfonyl, and *p*-Ns, *p*-nitrophenylsulfonyl) was used in the synthesis of piperazines and also for the creation of a piperazine fragment in polycyclic molecules [66-70]. It is worth noting that the use of nosylamides having high NH acidity as substrates in the Mitsunobu reaction is particularly effective [71] and moreover the removal of *o*- and *p*-nitrophenylsulfonyl groups is substantially easier [71] than the removal of other frequently employed sulfonyl groups.

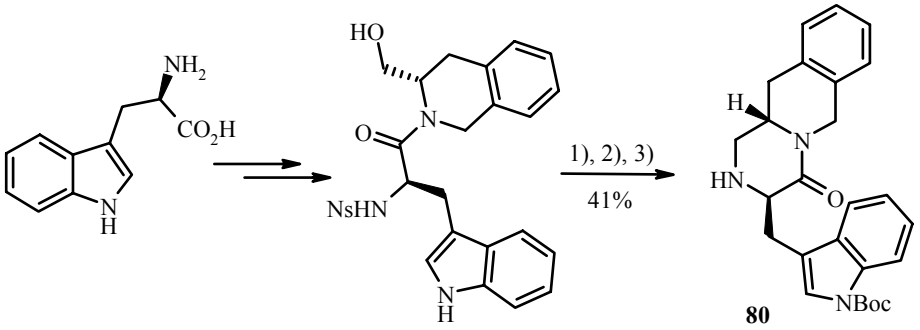
Thus, a solid-phase method was proposed for the production of piperazines, involving the reaction of N-*p*-nosylaziridine-2-carboxylic acid (**77**) attached to a support with amino alcohols and subsequent cyclization of the obtained nosylamide derivatives under Mitsunobu reaction conditions [66]. In this case the optimum combination of reagents for the cyclization was the DEAD–PEt_3 system; the use of other oxidation–reduction systems (ADDP–PMe_3, ADDP–PEt_3, DEAD–PPh_3) led to smaller yields of the cyclization products.



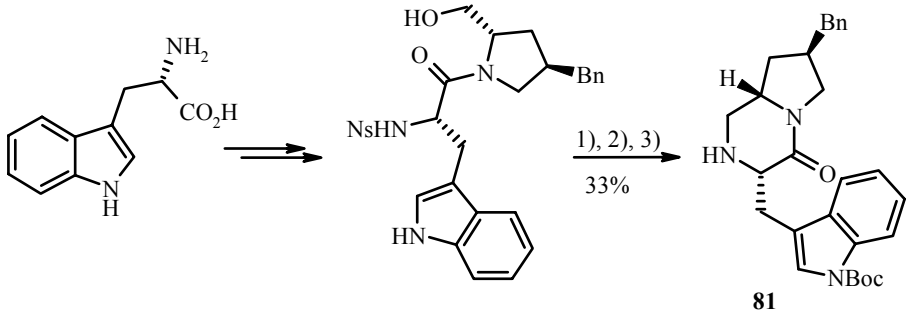
A series of other enantiomerically pure derivatives of piperazine-2-carboxylic acid was obtained by this method, starting from optically active N-nosylaziridine-2-carboxylic acid ((*S*)-**77**). It is interesting to note that piperazines with the (*S*,*S*)-configuration **78** are formed more readily than piperazines with the (*S*,*R*)-configuration **79**, which can be explained by the unfavorable axial position of the substituent R in the transition state, leading to the formation of the (*S*,*R*)-isomers [66].

Derivatives of piperazine **80** and **81** were obtained from D- and L-tryptophan [67]. The piperazine ring was formed as a result of an intramolecular Mitsunobu reaction with nosylamide.

A solid-phase method for the synthesis of a library of hexahydropyrazinoindole derivatives **82** was described. The key stage of the process requires cyclization of the nosylamides **83**, attached to Wang resin, with the DEAD–PPh_3 system [68]. The racemic indoline derivative was used to produce the nosylamide **83**, and the hexahydropyrazinoindoles **82** obtained by this method were mixtures of diastereomers, which were not separated.

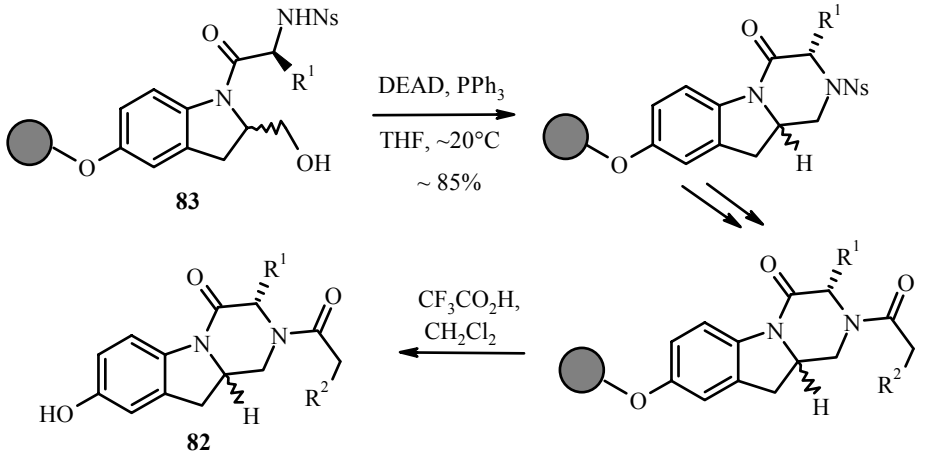


80



81

1) DIAD, PPh_3, THF; 2) Boc_2O, DMAP, MeCN; 3) PhSH, DBU, DMF



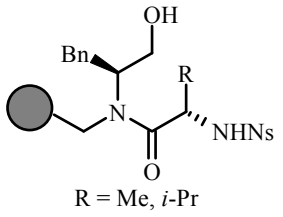
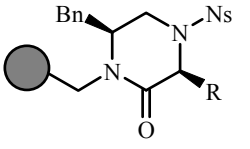
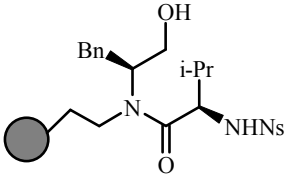
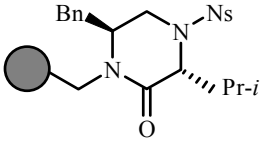
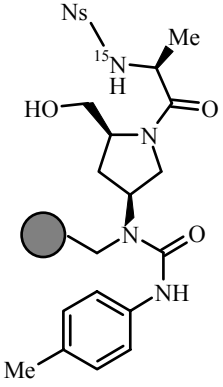
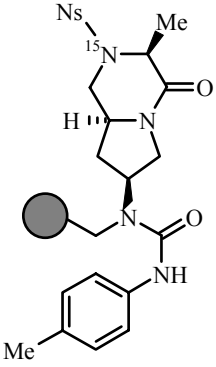
83 **82**

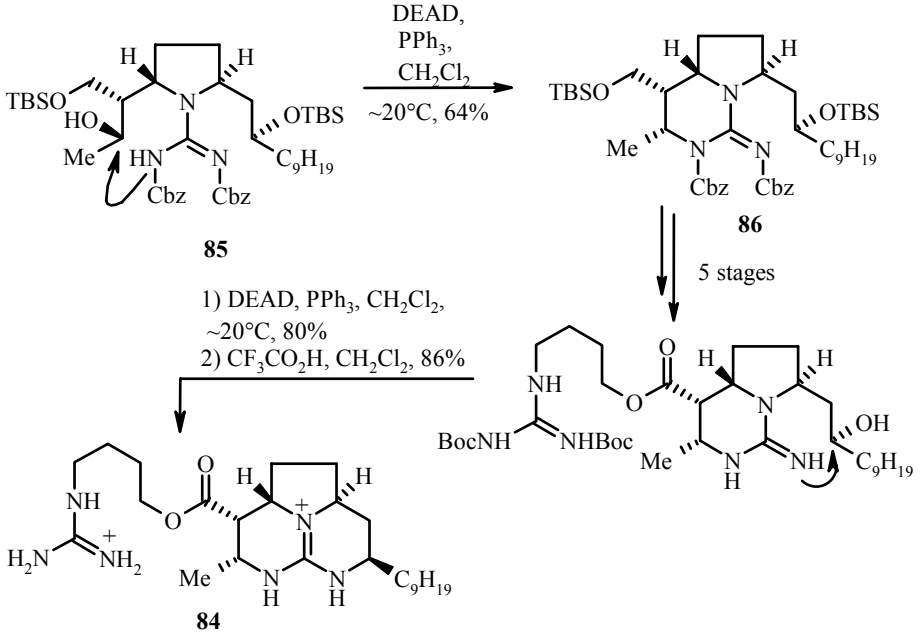
R^1= Me, Bn, *i*-Pr, *i*-Bu; R^2= 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$

Other examples of cyclizations of nosylamides attached to supports, leading to the formation of a piperazine ring, are summarized in Table 10.

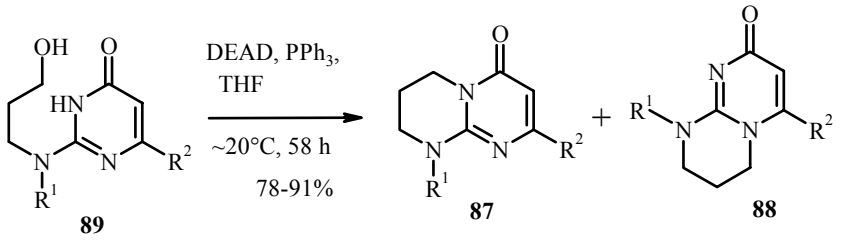
Cyclization under the conditions of the Mitsunobu reaction was used in the two key stages of the total synthesis of the new polycyclic guanidine alkaloid batzelladine D **84** [72]. Initially the guanidine **85** is transformed stereoselectively into the bicyclic guanidine **86** during reaction with the DEAD–PPh_3 system. The use of the same reagents at the final stage leads to the stereocontrolled formation of the tricyclic guanidine, and to complete the synthesis of batzelladine D it only remains to remove the butoxycarbonyl protecting groups.

TABLE 10. The Production of Piperazine Derivatives by Cyclization of Nosylamides Attached to a Support

No.	Acyclic precursor	Piperazine derivative	Conditions	Ref.
1	 R = Me, *i*-Pr	 R = Me, *i*-Pr	4 equiv. DEAD, 4 equiv. PPh_3, MeCN/DMF	[69]
2			4 equiv. DEAD, 4 equiv. PPh_3, MeCN/DMF	[69]
3			Betaine **8**, 5% DMF/CH_2Cl_2	[70]

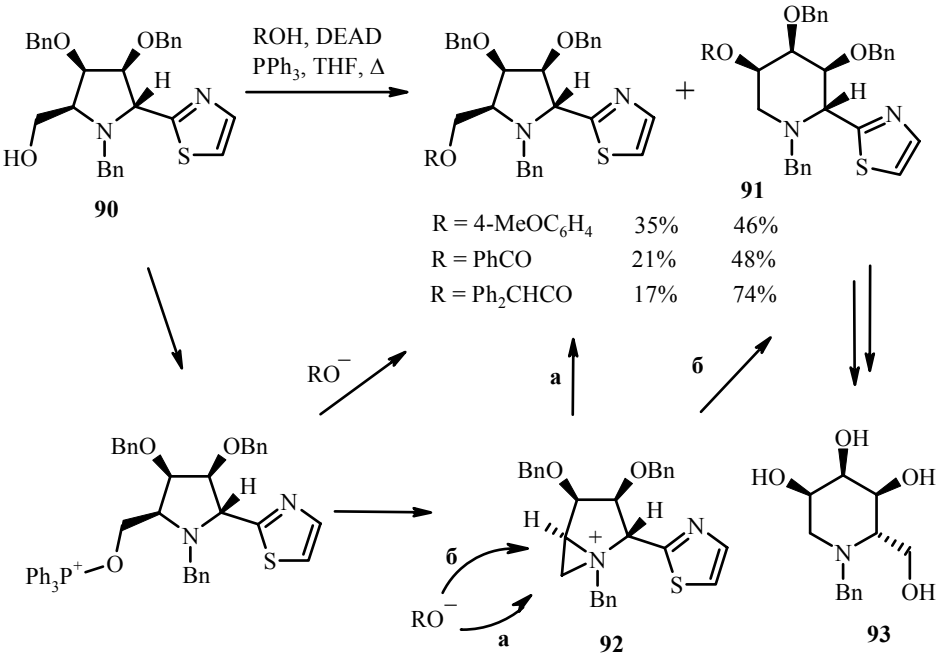


The isomeric pyrimido[1,2-*a*]pyrimidinones **87** and **88** were obtained as a result of intramolecular cyclization of the pyrimidinones **89** [53].



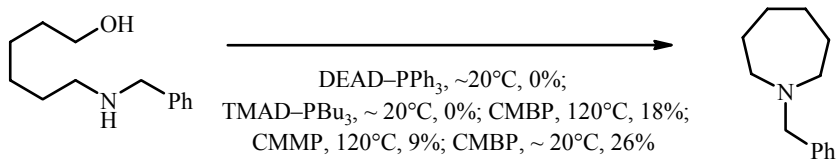
The reason for the formation of the two regioisomers is connected with the tautomerism of the guanidine fragment. (A similar pattern is observed during the formation of imidazo[1,2-*a*]pyrimidinones **57** and **58**, section 2.3.). Such tautomerism is impossible when R^1 = Me, and one regioisomer is formed.

In the reaction of the pyrrolidine **90** with phenol or a carboxylic acid under Mitsunobu reaction conditions (DEAD–PPh_3) the piperidine derivative **91** is formed as the main product with a yield of 46-74% [73]. The ring enlargement is clearly due to anchimeric assistance from the tertiary amino group, i.e., the process takes place through the intermediate formation of the aziridinium intermediate **92**. The highest yield of compound **91** was obtained with diphenylacetic acid, and the obtained piperidine derivative was used in the synthesis of 1-deoxy-L-allonojirimycin **93**.

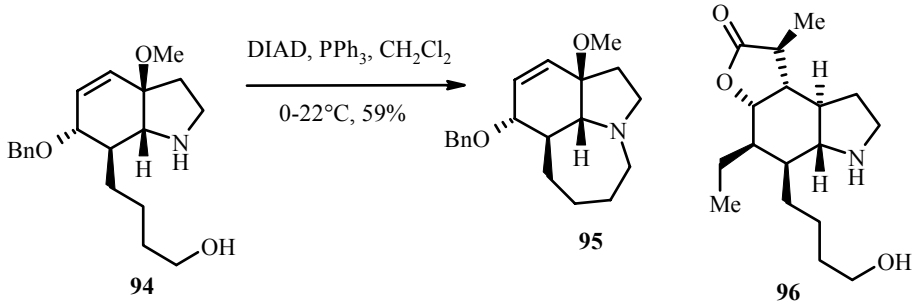


2.5. The Formation of Seven-Membered Rings

Study of the possibility of obtaining 1-benzylazepane under Mitsunobu reaction conditions by the cyclization of the corresponding amino alcohol showed that it was not possible to obtain high yields even with such effective reagents as CMMP and CMBP [21].



At the same time during the synthesis of *Stemona* alkaloids [74] cyclization of the amino alcohol **94** led to the formation of the decahydroazepinoindole system **95**. The success of the cyclization in this case is probably due to the favourable stereochemical factors in the substrate **94**. It was not possible to obtain the corresponding azepinoindole from the amino alcohol **96** with *trans* coupling of the five- and six-membered rings.



A series of papers has been devoted to the synthesis of 1,4-diazepine derivatives [75-77] under Mitsunobu reaction conditions. The possibility of producing 3,6-disubstituted 1,4-diazepane-2,5-diones by the cyclization of hydroxamates was studied for the case of compound **97** using various oxidation–reduction systems under various conditions (Table 11) [75].

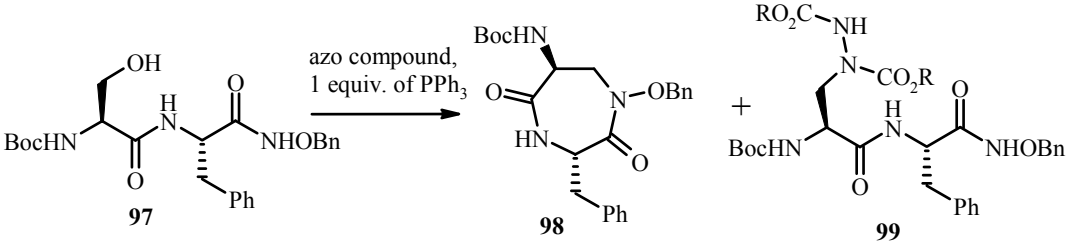
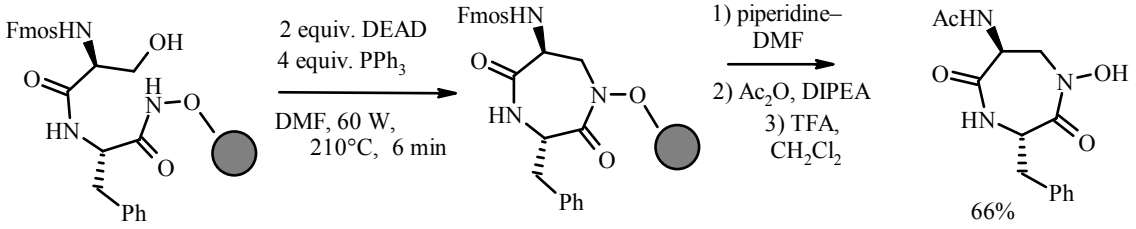


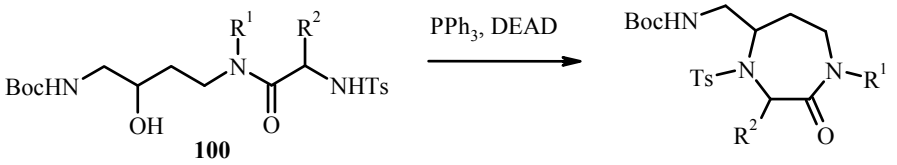
TABLE 11. The Synthesis of 1,4-Diazepane-2,5-diones **98** and **99** under Mitsunobu Reaction Conditions

No.	Azo compound (equiv.)	Conditions	Yield, %	
			98	**99**
1	DEAD (1)	THF, ~ 20°C, 12 h	31	40
2	DIAD (1)	THF, ~ 20°C, 12 h	46	36
3	DBAD (1)	THF, ~ 20°C, 12 h	42	26
4	DBAD (3)	THF, ~ 20°C, 12 h	47	28
5	DIAD (1)	PhMe, boiling, 12 h	63	26
6	DIAD (1)	DMF, ~ 20 °C, 12 h	46	22
7	DIAD (1)	DMF, MW 100 W, 210°C, 10 min	75	4

The best results were obtained with microwave exposure. This method of cyclization was also used in a solid-phase version of the synthesis.



In order to seek new peptidomimetics perhydro-1,4-diazepin-2-ones were prepared [76, 77], and the synthesis scheme presupposes cyclization of the tosylamides **100** under Mitsunobu reaction conditions (Table 12).



In addition, in this method of synthesis the tosyl activating group can be successfully replaced by a [(trimethylsilyl)ethyl]sulfonyl group (SES) [77]. The advantage of this group is the fact that it can be removed under very mild conditions by treatment with tetrabutylammonium fluoride.

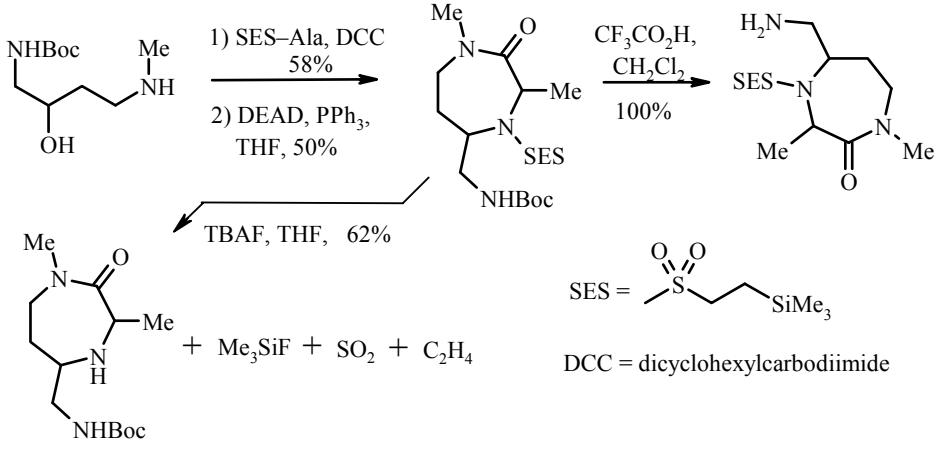
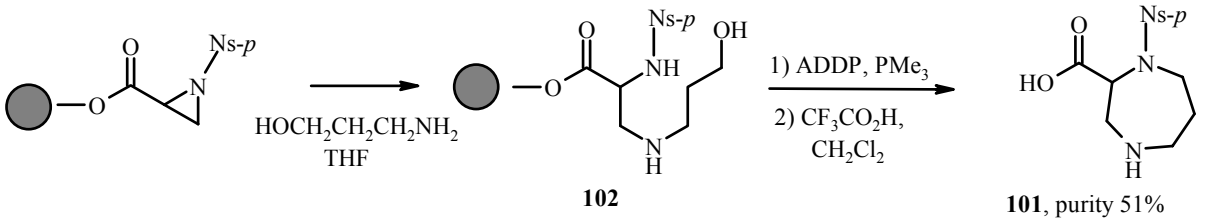


TABLE 12. The Synthesis of 1,4-Perhydro-1,4-diazepin-2-ones by the Mitsunobu Method

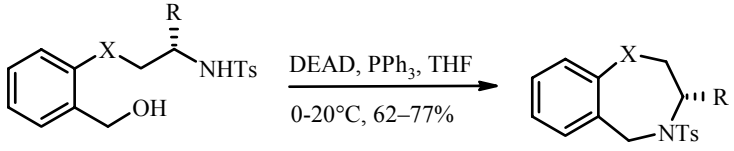
No.	R^1	R^2	Yield, %
1	Bn	Me	88
2	H	Me	0
3	Me	Me	86
4	Me	CH_2OBn	72
5	Me	CH_2CO_2Bn	65
6	Me	CH_2CHMe_2	36
7	Me	H	97
8	Me	Bn	70

The 1,4-diazepane-2-carboxylic acid derivative **101** was obtained in a solid-phase version of the cyclization of *p*-nosylamide **102** attached to a polymer support [66].



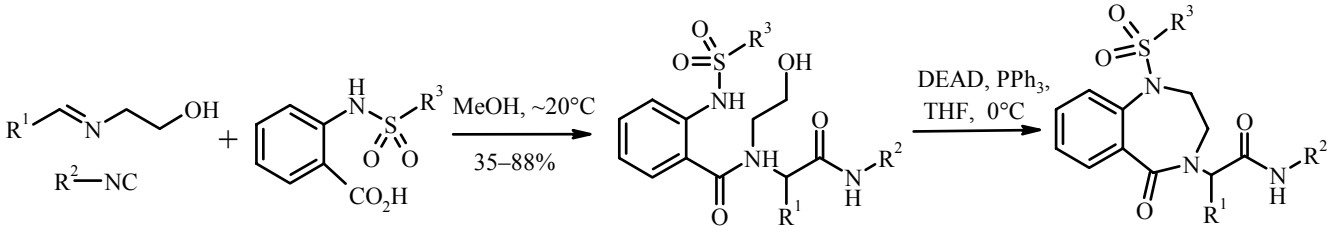
102 **101**, purity 51%

An intramolecular Mitsunobu reaction involving the tosylamino group was used in the synthesis of 2,3,4,5-tetrahydrobenzo[*e*]-1,4-diazepines and 2,3,4,5-tetrahydrobenzo[*f*]-1,4-thiazepines [79].



R = Bn, 4-PhCH$_2$OC$_6$H$_4$; X = NTs, S

A synthesis scheme involving a combination of the Ugi reaction with subsequent intramolecular Mitsunobu reaction with the participation of the sulfonyl groups was proposed for the production of derivatives of 2,3,4,5-tetrahydrobenzo[*e*]-1,4-diazepine **103** (Table 13) [80].



104 **103**

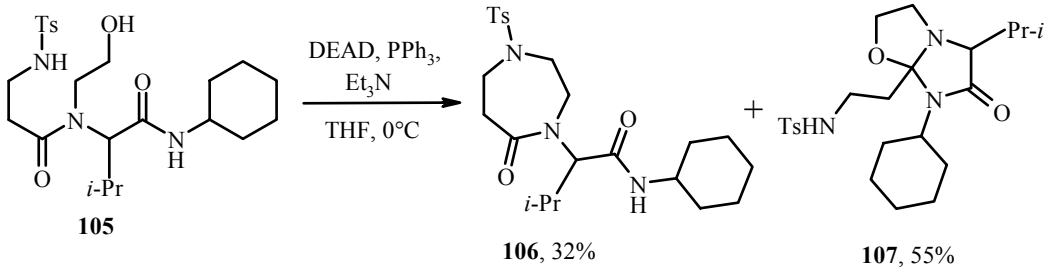
TABLE 13. Cyclization of the Products **104** of the Ugi Reaction under Mitsunobu Reaction Conditions

No*	R^1	R^2	R^3	Yield, %
1	*i*-Bu	*c*-Hex	4-MeC$_6$H$_4$	51
2*[2]	3-BrC$_6$H$_4$	Bu	4-MeC$_6$H$_4$	70
3	*c*-Hex	Bn	4-MeC$_6$H$_4$	85
4	*c*-Hex	1,1,3,3-Tetramethylbutyl	4-MeC$_6$H$_4$	82
5	3-BrC$_6$H$_4$	Bn	Me	98
6	*i*-Pr	*c*-Hex	Me	95
7	Ph	Bu	Me	91
8	2-Furyl	*c*-Hex	Me	92
9	*i*-Pr	2-(TBS-oxymethyl)phenyl	4-MeC$_6$H$_4$	91
10	*c*-Hex	CH$_2$CO$_2$*t*-Bu	Me	93

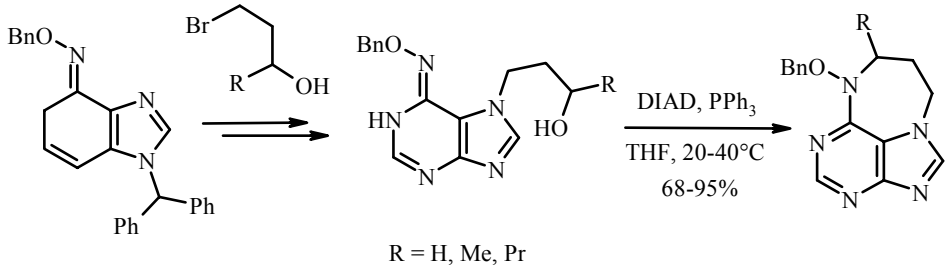
* The reaction was carried out in the presence of Et_3N (Nos. 1, 2, 4, and 5).
*[2] DBAD was used instead of DEAD.

The cyclization of the sulfonylamides **104** gives good and high yields, and the choice of azodicarboxylic ester (DEAD or DBAD) was based on considerations of the ease of chromatographic separation of the reaction product from the respective hydrazine dicarboxylic ester. As shown by the authors' investigations, the presence of triethylamine in the reaction mixture does not have a significant effect on the course of the reaction, and cyclization also takes place effectively in the absence of triethylamine.

It was also shown [80] that the cyclization of the sulfonylamide **105** under analogous conditions takes place in a more complicated manner. The diazepanone **106** is formed with a yield of only 32%, while the main product is the bicyclic compound **107** in the form of a mixture of diastereomers in a ratio of 15:1.

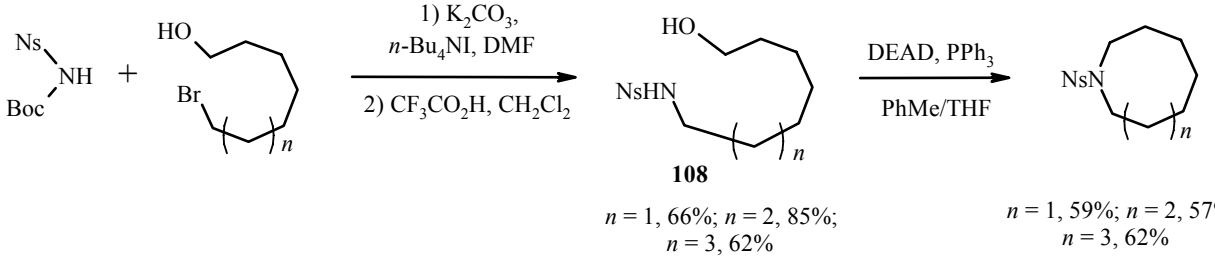


The synthesis of tetrahydrodiazepinopurines, which are analogs of the marine alkaloids asmarines and have antitumor activity, was reported [18]. Closure of the diazepine ring was achieved under Mitsunobu reaction conditions.

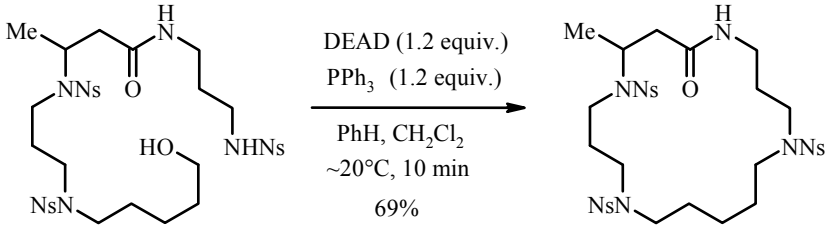


2.6. Production of Medium and Macro Rings

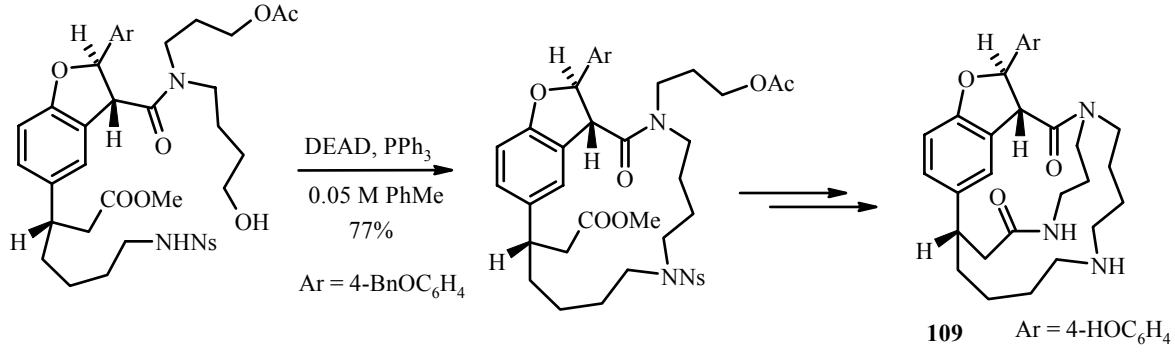
The strategy involving the cyclization of amino alcohols containing an *o*-nitrophenylsulfonyl (nosyl) group as protecting and activating group at the nitrogen atom under Mitsunobu reaction conditions proved extremely effective in the synthesis of rings of medium size and macrocycles [71, 82-87]. The unfavorable entropy factor does not have a significant effect in this case. Thus, eight-, nine- and ten-membered rings were obtained with good yields by cyclization of the alcohols **108** [82, 83].



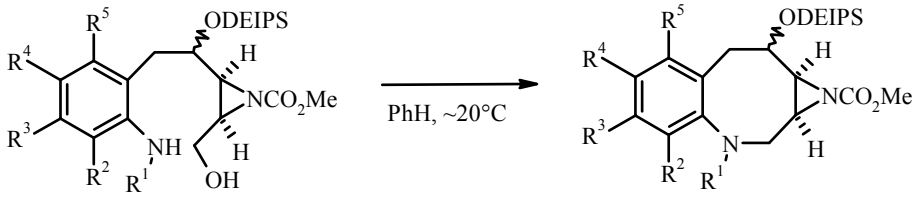
The wide distribution of macrocyclic polyamides in nature prompted the authors to extend the strategy they had developed to the production of rings of larger size [82, 84].



Macrocyclization with the participation of the nosylamide group was used in the total synthesis of the spermine alkaloid (-)-ephedradine **109** [85].



Cyclization under Mitsunobu reaction conditions with both nosyl and carbamate activating groups was used in the production of synthetic precursors for the antitumor product FR900482, containing an eight-membered ring [86, 87] (Table 14).



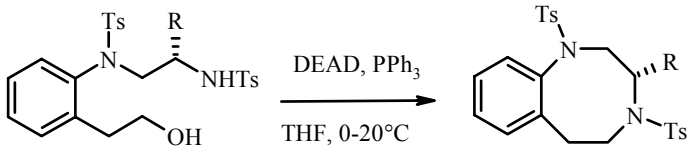
DEIPS = diethylisopropylsilyl

TABLE 14. Production of Benzazocines under Mitsunobu Reaction Conditions

No.	R^1*	R^2	R^3	R^4	R^5	Reagents	Yield, %
1	Ns	H	MeO_2C	H	$MeOCH_2O$	DEAD, PPh_3	95
2	Nvoc	H	MeO_2C	H	$MeOCH_2O$	DEAD, PPh_3	83
3	Alloc	H	MeO_2C	H	$MeOCH_2O$	TMAD, PBu_3	82
4	Ns	MeO	Me	MeO	MeO	DEAD, PPh_3	70
5	Alloc	MeO	Me	MeO	MeO	TMAD, PBu_3	83

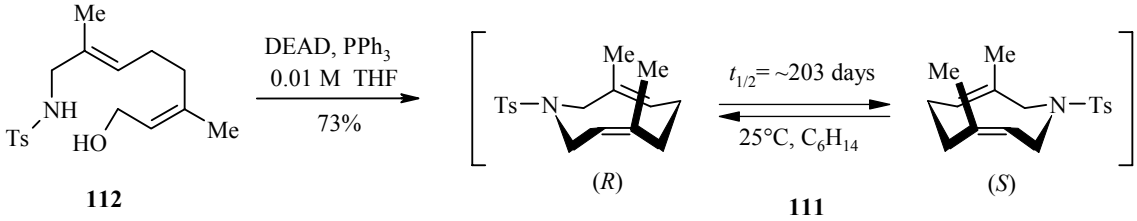
* Nvoc = 4,5-dimethoxy-2-nitrobenzyloxycarbonyl; Alloc = allyloxycarbonyl.

The intramolecular Mitsunobu reaction with the participation of a toslyamide group was used in the synthesis of 1,2,3,4,5,6-hexahydrobenzo[*e*]-1,4-diazocines **110** [79].



110
R = Bn, 86%
R = 4-$PhCH_2OC_6H_4$, 77%

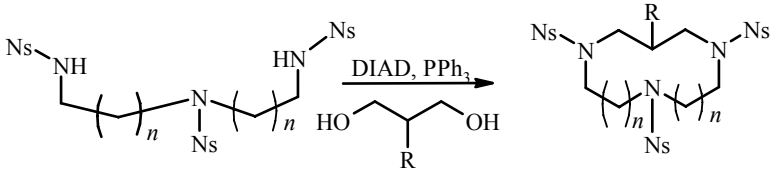
The nine-membered cyclic tosylamide **111**, which has planar chirality, was obtained from the corresponding alcohol **112** under conditions of high dilution, and the fraction of dimeric reaction products was not greater than 1% [88].



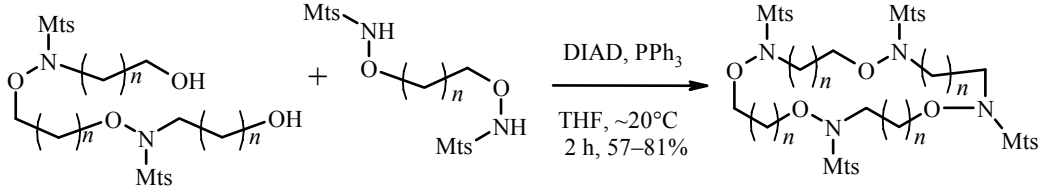
112 **111**

It is interesting to note that the enantiomers of **111**, separated by chromatography using a chiral stationary phase, are stable in the solid state and racemize extremely slowly in solution; the optical activity decreases by 50% in ~203 days.

The reaction of diols and di(sulfonylamides) under Mitsunobu reaction conditions was used for the production of ten-membered and larger rings [89, 90].

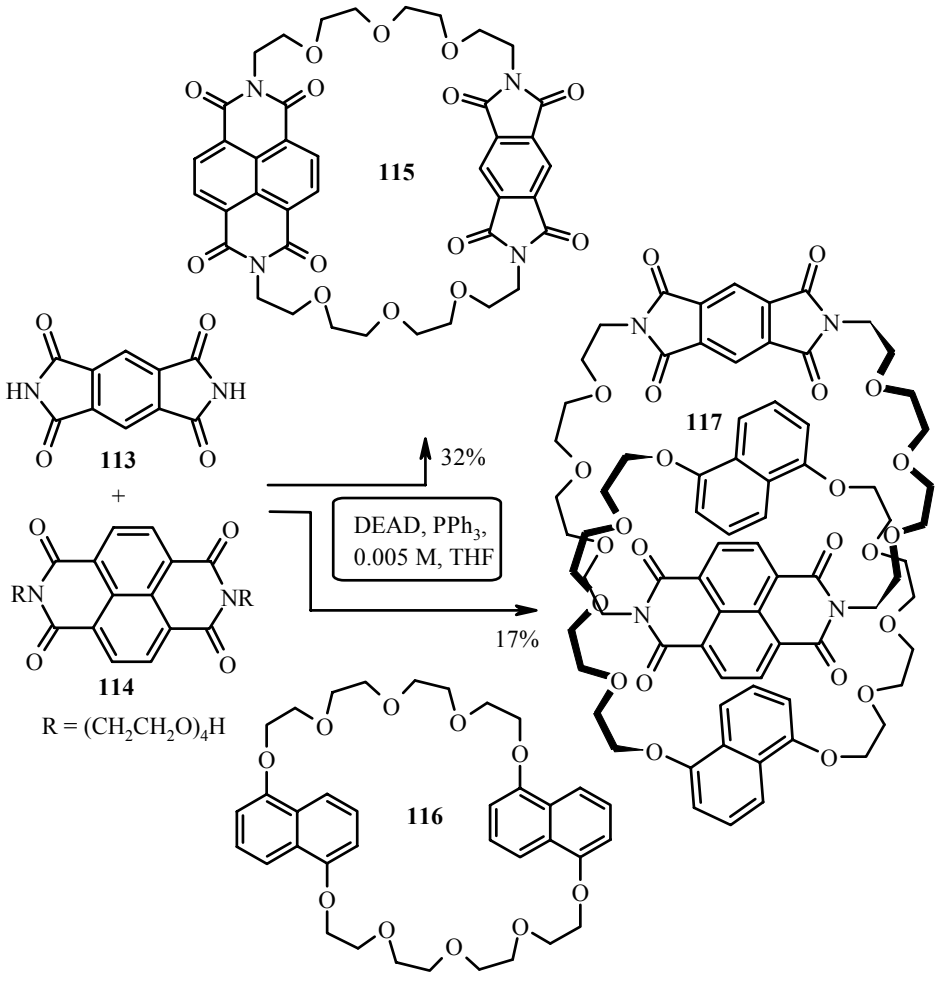


R = H, *n* = 1, 53%; R = CH_2OTr, *n* = 1, 78%; R=CH_2OTr, *n* = 2, 72%



n = 1, 2, Mts = 2,4,6-$Me_3C_6H_2SO_2$

A method was proposed for the creation of macrocycles and catenanes [91, 92], involving the alkylation of diimides by diols under Mitsunobu reaction conditions at the macrocyclization stage.



Thus, the reaction of the diimide **113** and the diol **114** under conditions of high dilution leads to the production of the macrocycle **115**. When the reaction was carried out under similar conditions with the addition of the crown ether **116** the catenane **117** was obtained with a 17% yield.

Thus, the data presented in this review demonstrate the extensive synthetic possibilities presented by the Mitsunobu reaction in the design of nitrogen-containing heterocyclic systems.

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