Application of the Mitsunobu Reaction in the Field of Alkaloids

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During the past two decades, the Mitsunobu reaction has emerged as a widely used methodology [1-4] in preparative organic chemistry. In the Mitsunobu reaction an alcohol is reacted with an HX acidic reagent in the presence of dialkyl azodicarboxylates and triaryl or trialkylphosphines. The outcome of the process is alkylation of the conjugated base (X) of the acidic reactant by the alcohol, and the by-products are the dialkyl hydrazinedicarboxylates and the corresponding tertiary phosphine oxides:

$$ROH + HX + R'_3P + R''O_2C\text{-}N{=}N\text{-}CO_2R'' \rightarrow RX + R'_3P{=}O + R''O_2C\text{-}NH\text{-}NH\text{-}CO_2R''$$

The mechanism of the reaction was studied by several groups [5-17], and it was established that the key-intermediate is an alkoxyphosphonium salt, whose existence was unequivocally proved by nmr and EI-ms measurements. Discussion of the mechanism of the Mitsunobu reaction is not the topic of this review paper, but emphasis on mechanistic considerations will be made in certain specific instances.

Although the Mitsunobu methodology has been extensively employed in preparative organic chemistry for solution of synthetic problems most particularly in the field of steroids, carbohydrates and nucleosides, relatively fewer data are reported [1-4] on the application of this procedure to alkaloidal compounds. The present review is aimed at a discussion of the results already collected with this reaction in the alkaloid field.

1. Formation of Carbon-Oxygen Bonds.

1.1. Synthesis of Ester Derivatives.

One of the most frequent goals of the application of the Mitsunobu reaction is the epimerization of optically active esters of secondary alcohols, and most of the published papers reported and discussed such types of transformations. In these procedures the optically active alcohol is reacted with a carboxylic acid (formic acid, acetic acid, monochloroacetic acid, benzoic acid and *p*-nitrobenzoic acid) under Mitsunobu conditions. In most cases the acid strength is not a determinant factor in the reaction, but for sterically hindered alcohols application of a strong acid (with low pK_a value) is recommended.

Numerous examples have been reported for such types of transformations in the field of alkaloidal compounds, as well. In certain cases a total synthetic approach calls for the development of chiral centers with the appropriate configuration, such as in the total synthesis of (±)-dumetorine, when the configurational inversion was achieved with benzoic acid preceding ring-closure to the required lactone [18] (Figure 1).

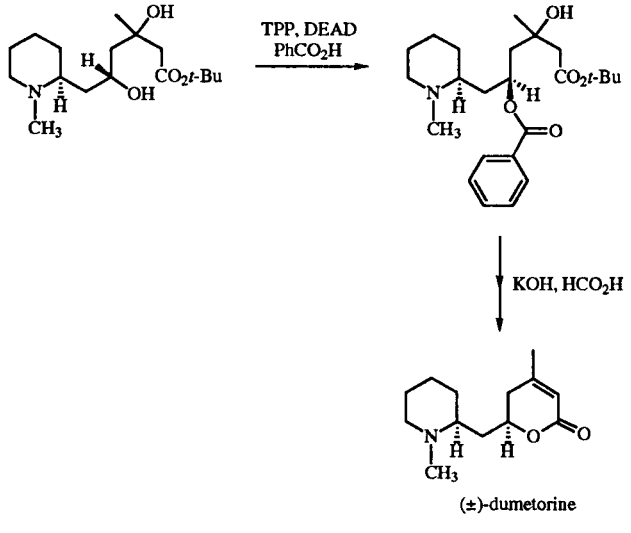


Figure 1.

A similar problem emerged during the synthesis of (±)-decaline, as well, when development of the macrocyclic lactone ring could not be directly achieved with the Mitsunobu reaction. Therefore, first the inversion of the configuration of the carbinol-carbon atom of the intermediate was accomplished by Kametani *et al.* [19, 20] (Figure 2).

The same Japanese group has elaborated the synthesis of another phenylquinolizidine alkaloids, as well. The production of (±)-lasubine II also required inversion of the configuration of the alcoholic hydroxyl function, and

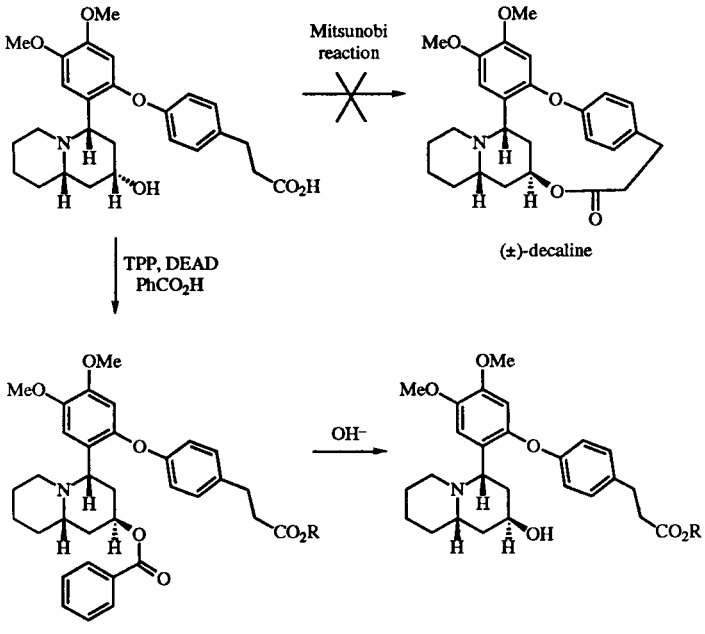


Figure 2.

thus after hydrolysis of the resulting benzoic ester and removal of the benzyl protecting group, methylation of the free phenolic hydroxyl function gave (±)-lasubine II [21] (Figure 3).

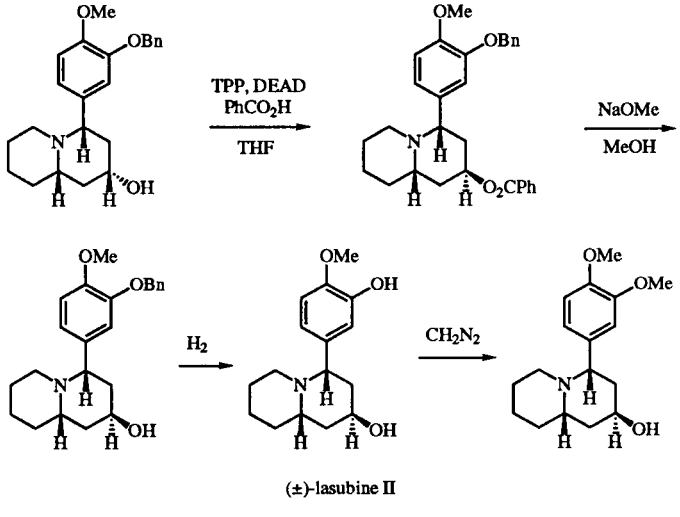


Figure 3.

In an other synthesis of this latter alkaloid, epimerization of the secondary hydroxyl group was achieved, again with benzoic acid [22], as shown in Figure 4.

Additional representatives of this group of alkaloids were also obtained with the aid of related methodology. As an example, (±)-abresoline was synthesized by using aryl-substituted (*E*)-cinnamic acid as the acidic reagent [21] (Figure 5).

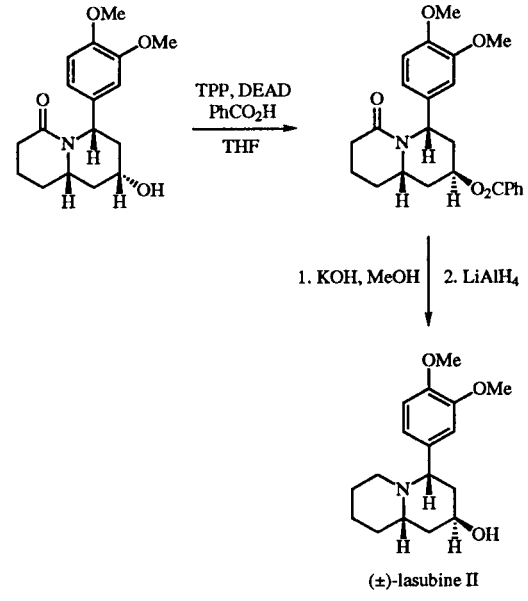


Figure 4.

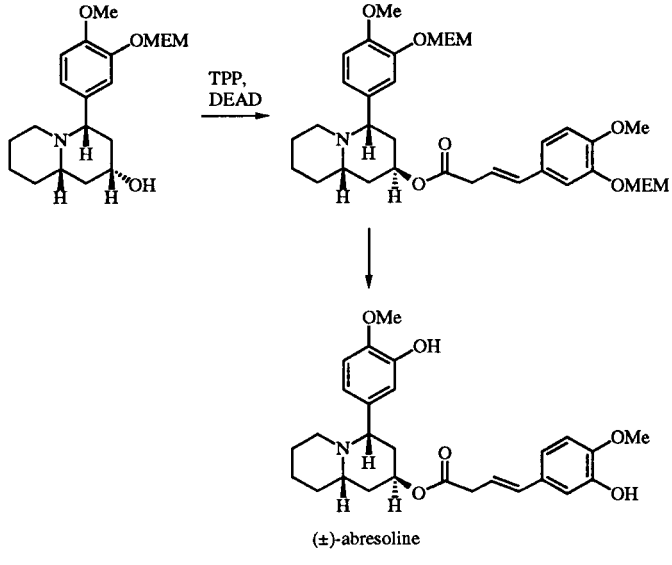


Figure 5.

In the final step of the total synthesis of (±)-elsewine inversion of the configuration of the alcoholic hydroxyl group was executed with formic acid, followed by hydrolysis of the resulting ester with sodium hydroxide [23] (Figure 6).

An essentially similar methodology was employed for the synthesis of (±)-magellanine [24] (Figure 7).

For the epimerization of the allylic alcohol intermediate of the synthesis of (+)-1-deoxylycorine [25] benzoic acid was found to provide higher yield than acetic acid (Figure 8).

A total synthesis of (+)-sesbanine also necessitated epimerization of the alcoholic hydroxyl group, and this

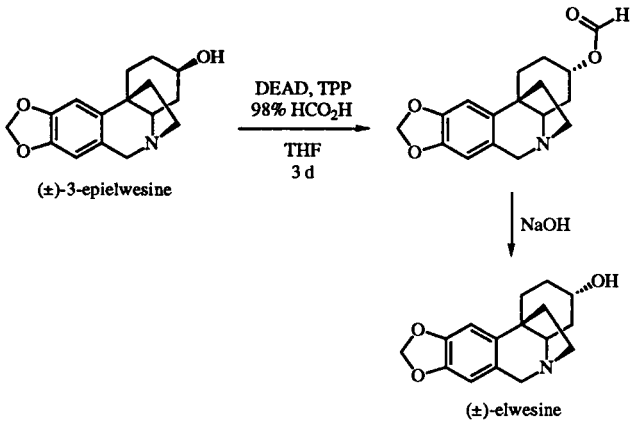


Figure 6.

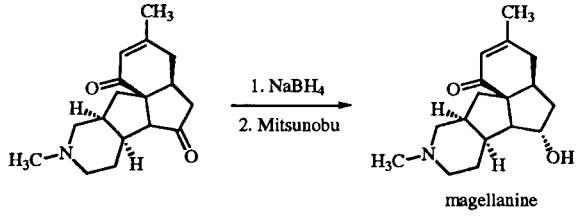


Figure 7.

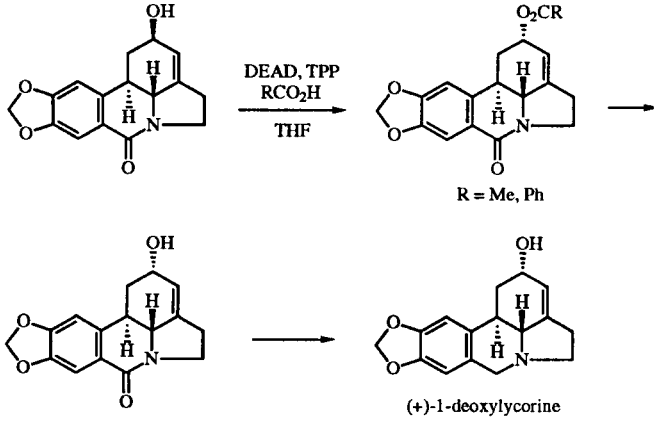


Figure 8.

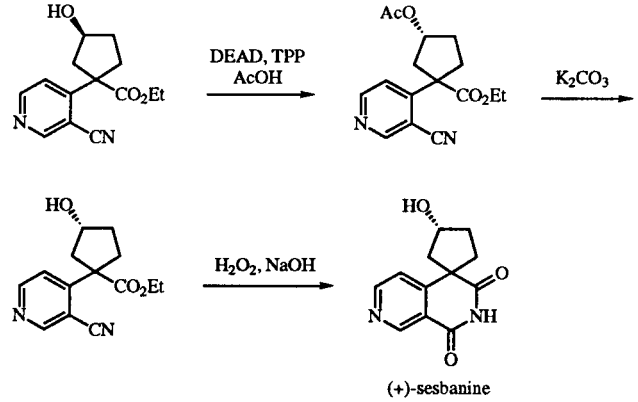


Figure 9.

was accomplished by using acetic acid as the acidic reagent [26] (Figure 9).

For a related configurational inversion, benzoic acid was employed by Takahata *et al.* for the production of 1-hydroxyindolizidine alkaloids [27] (Figure 10).

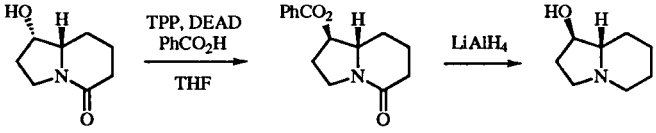


Figure 10.

French chemists used the Mitsunobu reaction (TPP, DEAD, $PhCO_2H$) for the establishment of the relative configuration of a stereoisomer, isolated as a minor component of echitamidine [28] (Figure 11).

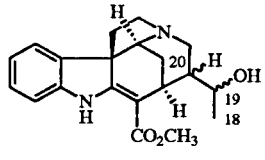


Figure 11.

The conversion of ajmalicine to 19-epiajmalicine was also carried out by the Mitsunobu epimerization [29] (Figure 12). Following ring cleavage of ajmalicine, inversion of the configuration at C-19 was carried out *via* the formate ester and subsequent hydrolysis and ring-closure.

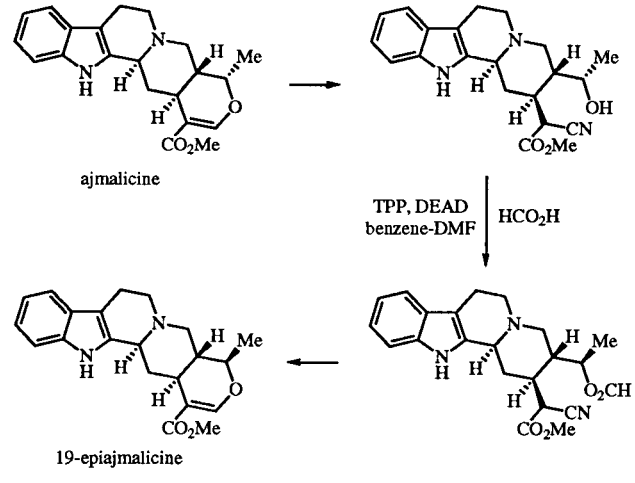


Figure 12.

Acetic acid was employed as the acidic reagent in the total syntheses of castanospermine and 1-*O*-acetylcastanospermine for changing configuration at C-3 [30,31]. Cleavage of the ester group in these case was performed with lithium aluminium hydride (Figure 13).

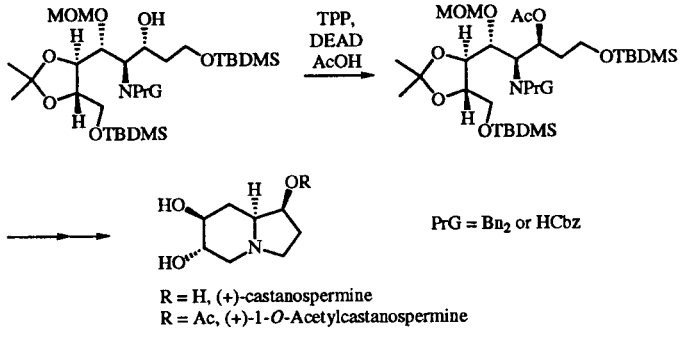


Figure 13.

Gössinger has elaborated two independent routes for the total synthesis of the alkaloid (±)-porantherilidine. In the first procedure, Mitsunobu epimerization was performed in the last step to obtain the target compound. The second method was based on the production of a common intermediate suitable for producing (±)-porantheridine, (±)-porantherilidine, as well as the C-6 epimer of the latter compound [32,33] (Figure 14).

Epimerization of the 6α-hydroxyl group of various codeine and morphine derivatives was also carried out by

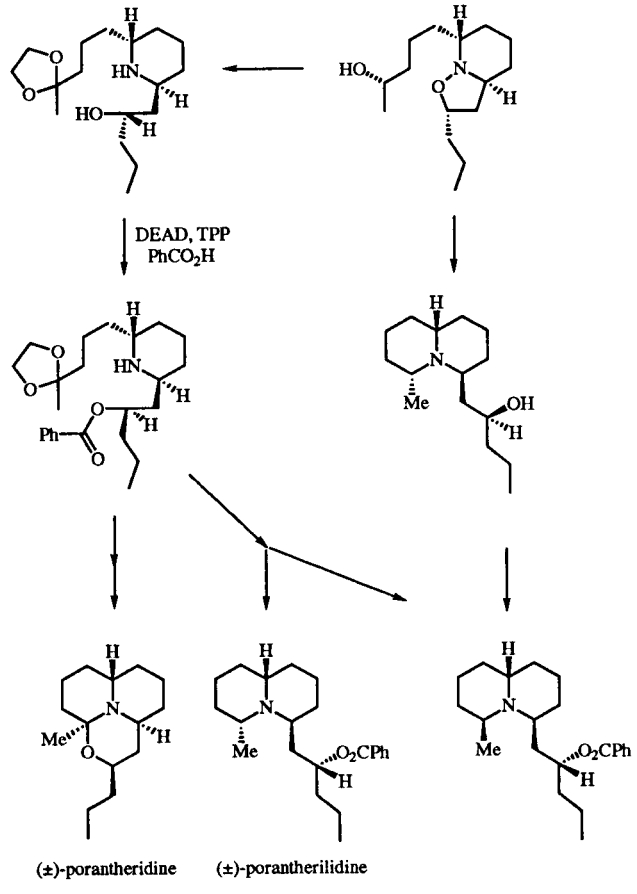


Figure 14.

means of the Mitsunobu reaction. In the case of the allylic alcohols containing a $\Delta^{7,8}$ double bond, benzoic acid was used [34,35] as the acidic reagent, whereas epimerization of the dihydro analogues with saturated ring-C, was executed with *p*-nitrobenzoic acid [36]. Then the target alkaloids carrying a 6β-hydroxyl substituent were prepared by hydrolysis of the ester function (Figure 15).

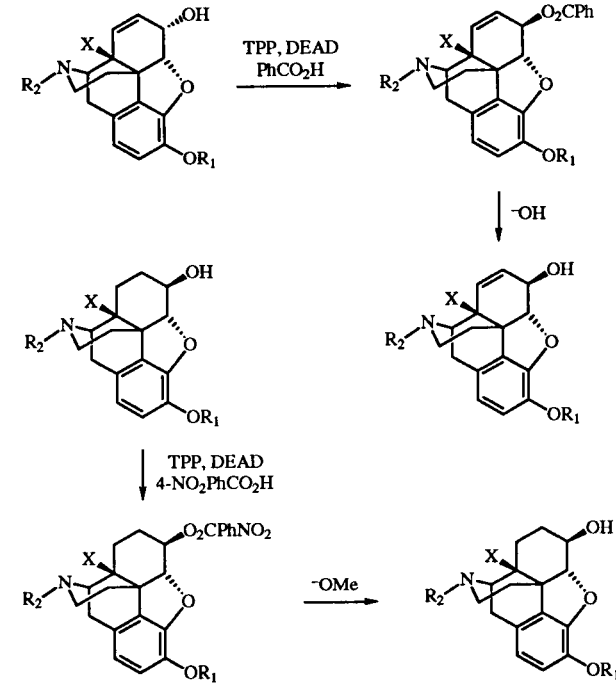


Figure 15.

For pharmacological investigations the nicotinic acid esters were also prepared by using nicotinic acid as the acidic reactant [37] (Figure 16).

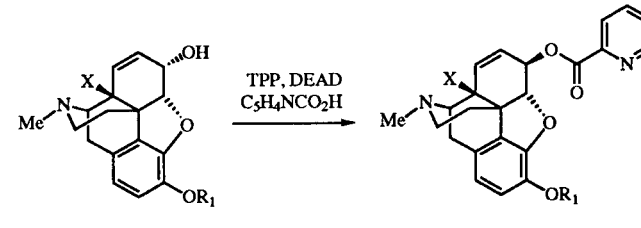


Figure 16.

An analogous epimerization can also be accomplished with the morphine alkaloids carrying a halogen substituent at position C-14. Thus, 14-bromo- and 14-chlorocodeine can be isomerized both with *p*-nitrobenzoic acid and monochloroacetic acid, but cleavage of the ester functions could only be realized with the 14-chloro derivatives [38]. Under the applied reaction conditions allylic migration of the C-14 bromo atom resulted in 7β-bromoisoneopine, as shown in Figure 17.

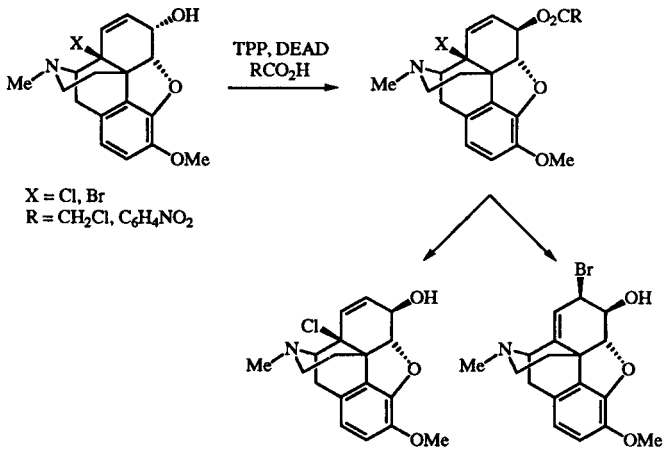


Figure 17.

1.2. Preparation of Lactones.

The Mitsunobu reaction has been successfully employed in the alkaloid field for the preparation of macrocyclic lactones. This methodology allowed the transformation of *cis*-rhoeadane into the *trans*-compound by the reaction of the *cis*-hydroxycarboxylic acid, obtained by ring-opening of the starting lactone, with diethyl azodicarboxylate in the presence of triphenylphosphine [39] (Figure 18).

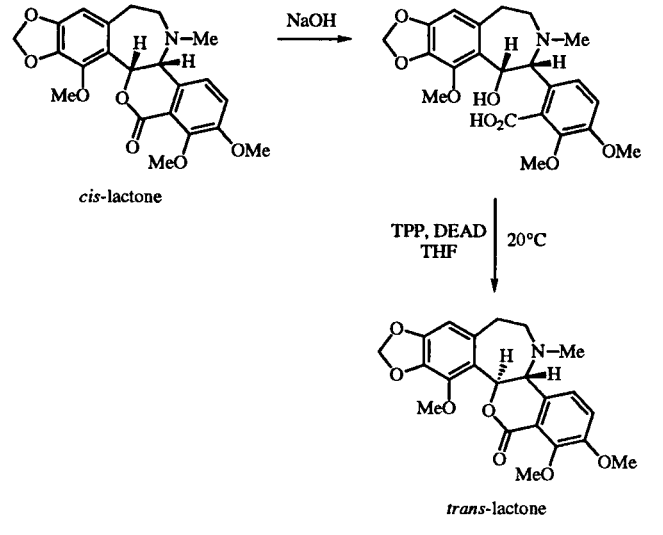


Figure 18.

1.3. Synthesis of Alkyl Phenyl Ethers.

The Mitsunobu procedure was found suitable for the preparation of alkyl phenyl ethers in the total syntheses of various types of alkaloid compounds. An interesting example for such a methodology is the preparation of noracronycine, where a tertiary alcohol is used for the transformation [40] (Figure 19). An analogous methodology has also been used for obtaining numerous 2,2-disubstituted chromene derivatives.

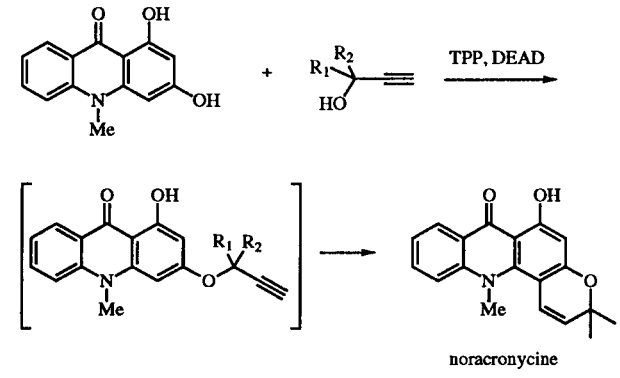


Figure 19.

In the total synthesis of (-)-nummuraline F (Figure 20) the key step was the reaction of an appropriately substituted pyrrolidinol with *p*-cyanophenol under Mitsunobu conditions. Then the target alkaloid was obtained in a multi-step sequence of transformations [41].

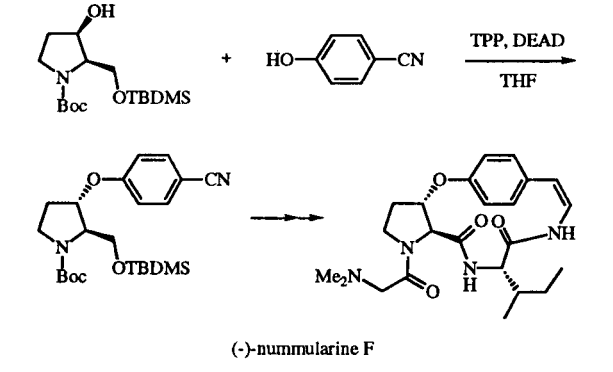


Figure 20.

To construct the molecule of dihydroisocodeine by total synthesis, Parker and Fokas treated a cyclohexendiol derivative with an appropriately substituted phenol in the presence

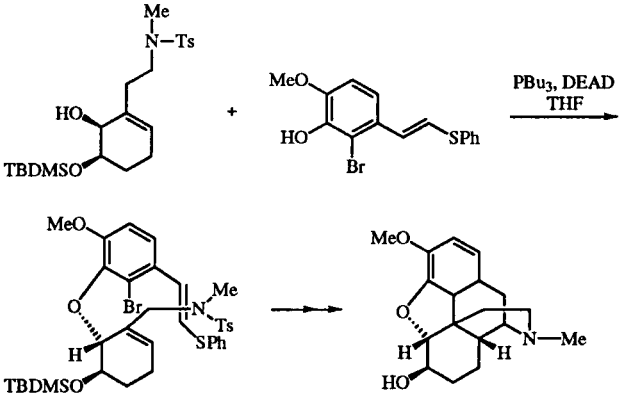
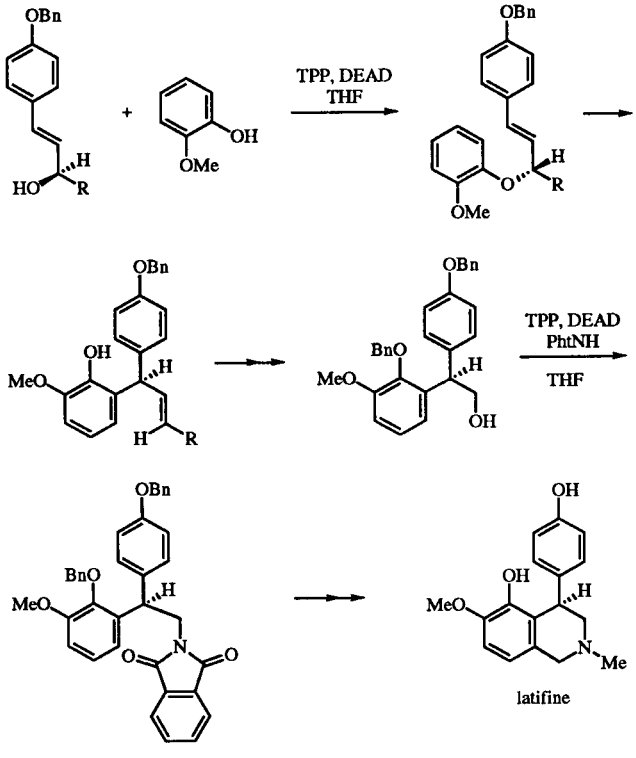


Figure 21.



R = CH_2OBn or H

Figure 22.

of tributylphosphine and diethyl azodicarboxylate [42] (Figure 21). In the following steps, the resulting aryl alkyl ether was submitted to radical cyclization and removal of the protecting groups furnished dihydroisocodeine.

Preparation of a key-intermediate of the synthesis of (+)-latifine and its racemic analogue was based on the reaction of 4-benzyloxycinnamoyl alcohol with guaiacol in the presence of DEAD and TPP, followed by Claisen rearrangement of the resulting allyl ether [43] (Figure 22). The following steps, to lead to the target alkaloids, involved a second Mitsunobu reaction with phthalimide (TPP, DEAD in THF).

In a synthesis of the fragment of sarain A, a marine alkaloid, the free primary alcoholic hydroxyl group of the starting unsaturated diol protected in form of the *p*-methoxyphenyl ether with the aid of the Mitsuno reaction [44] (Figure 23). After removal of the acetal protecting group upon oxidation with silver oxide, the primary amino group was introduced into the key-intermediate, again, under Mitsunobu conditions, to be discussed in detail in Section 2.3.

2. Formation of Carbon-nitrogen Bonds.

The formation of carbon-nitrogen bonds can be accomplished by various routes with the aid of the Mitsunobu reaction. In the field of alkaloids, construction of a C-N bonding is generally required for the introduction of a nitrogen-containing substituent, or for the development of a *N*-heterocyclic ring.

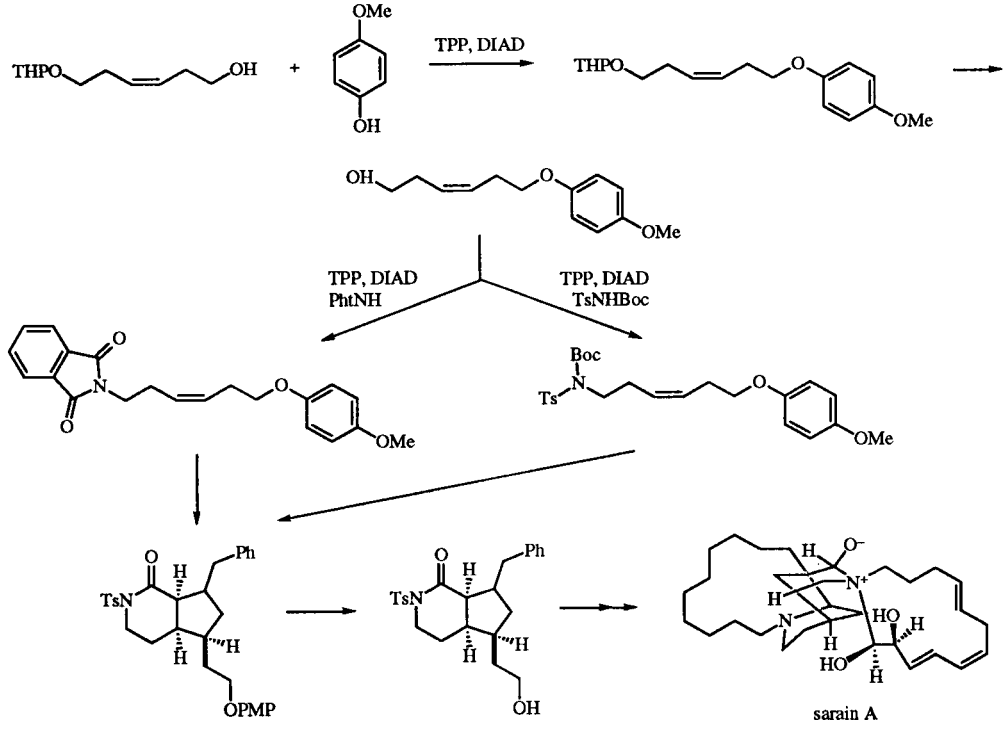


Figure 23.

2.1. Synthesis of Alkyl Azides.

For the preparation of alkyl azides according to the Mitsunobu technology several methods have been reported which employ, as the azide-source, hydrazoic acid, diphenylphosphoryl azide (DPPA) or the zinc azide-pyridine complex.

The reaction of quinine or cinchonine with hydrazoic acid led to the 9-azido-9-deoxy derivatives, which were readily reduced to the corresponding primary amines [45] (Figure 24), to be utilized in enantioselective syntheses.

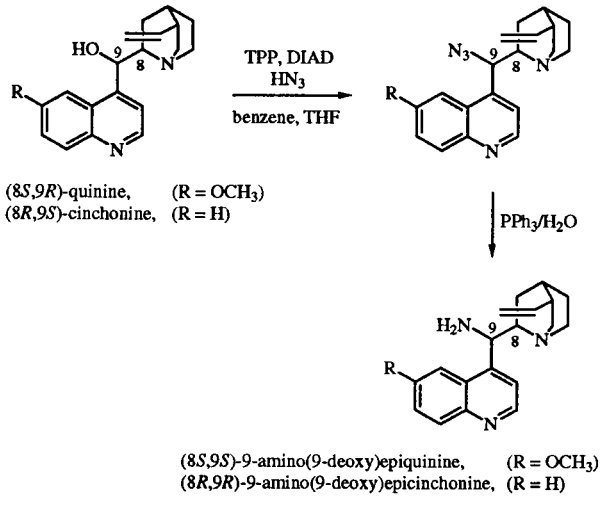


Figure 24.

The OH → N_3 displacement in the synthesis of (-)-colchicine (Figure 25) was executed with the zinc azide-pyridine complex to furnish, after reduction of the azido function and acetylation of the resulting amine, the target alkaloid [46].

Introduction and transformation of an azido function often serves for the development of the nitrogen-containing ring-system of alkaloid compounds. Thus, in a most recently reported synthesis of (+)-lycorine and (+)-1-deoxylycorine (Figure 26), the required alkyl azide was obtained under Mitsunobu conditions by applying DPPA [25]. Following iodolactonization, the imine was prepared by the reduction of the azidoketone with triphenylphosphine, and it was then converted to the target alkaloid in a few known steps.

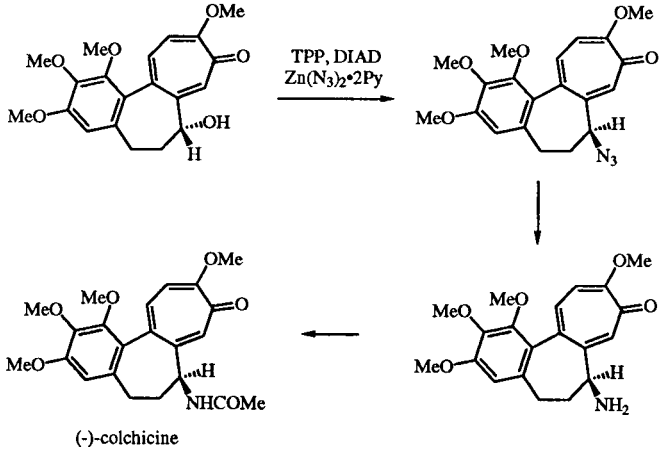


Figure 25.

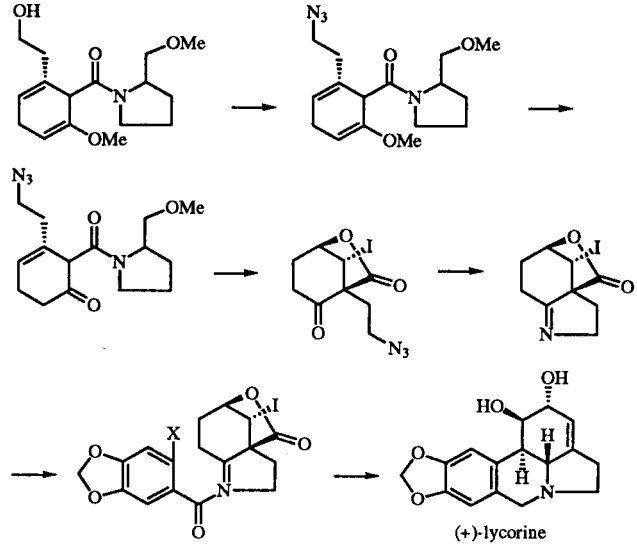


Figure 26.

The lactam ring of the alkaloid isonitramine was developed (Figure 27) by introduction of the azido function, again with DPPA, the thioacetal protecting group was hydrolyzed, and after reduction of the azide lactam-ring closure led to the target compound [47] (Figure 27).

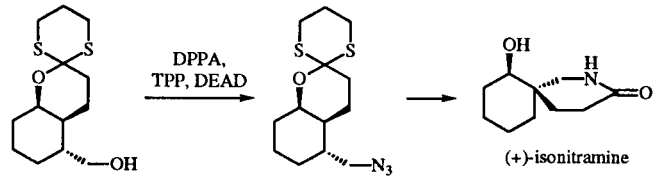


Figure 27.

The azidoketone intermediate of the total synthesis of sparteine was prepared with the aid of the zinc azide-pyridine complex [48] (Figure 28), and then intramolecular Schmidt reaction served for the development of the norbornane skeleton.

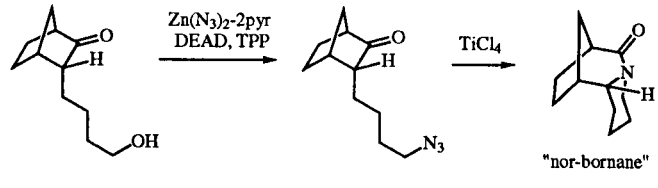


Figure 28.

Pearson and his co-workers also employed the Mitsunobu reaction for the OH → N_3 substitution in the total synthetic approaches to indolizidine alkaloids. The azido function of the obtained compounds could be further transformed in various ways. As an example, from *N*-benzylglutamic acid the azido aldehyde shown on Figure 29 was prepared [49], which was converted - *via* a cyclopropylimine derivative - to (-)-8a-epidesacetoxyslaframine.

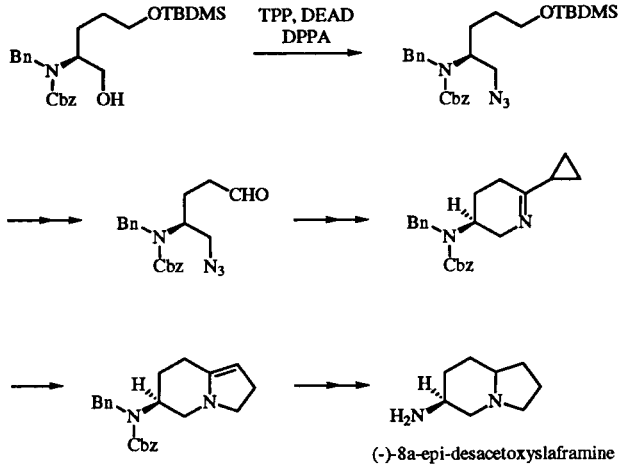


Figure 29.

In a synthesis of (-)-swainsonine (Figure 30) the starting ω-chloroalkenol was reacted with diphenylphosphoryl azide under Mitsunobu conditons [50]. 1,3-Dipolar cycloaddition of the resulting azide led to key-intermediate of the procedure, which was converted into (-)-swaisonine *via* an enamine.

The Pearson group has also reported the synthesis of another indolizidine alkaloids. Thus, the aldehyde shown in

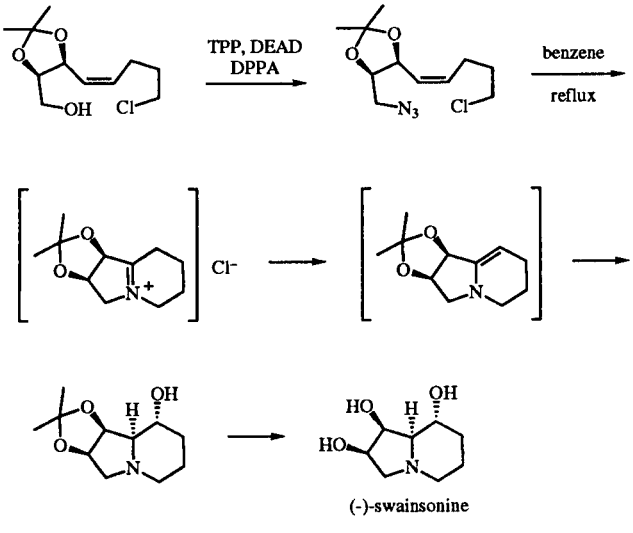


Figure 30.

Figure 31 was converted, with Wittig reaction, into the corresponding olefine. Epoxidation with 3-chloroperoxybenzoic acid gave a separable mixture of two diastereomeric epoxides, which were converted into (-)-slaframine and (-)-1,8a-diepislaframine [51,52]. The same strategy has been employed for obtaining additional related alkaloids [53,54].

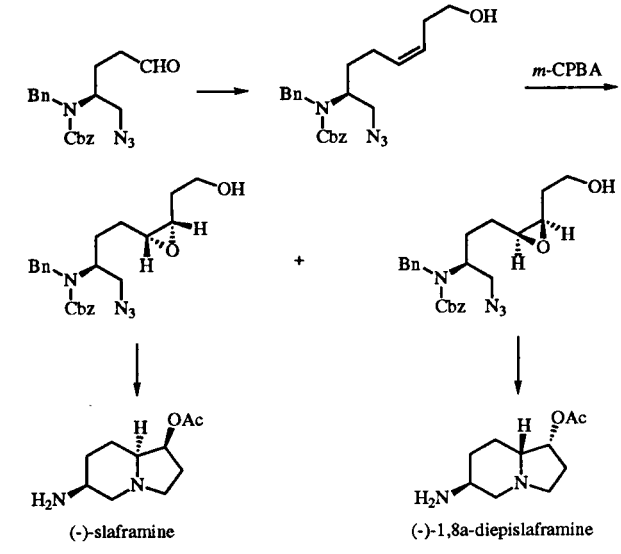


Figure 31.

In the synthesis of (±)-crinane the nitrogen function was introduced, again, with diphenylphosphoryl azide (Figure 32), followed by cycloaddition of the azidoolefine to obtain the required ring-system [55].

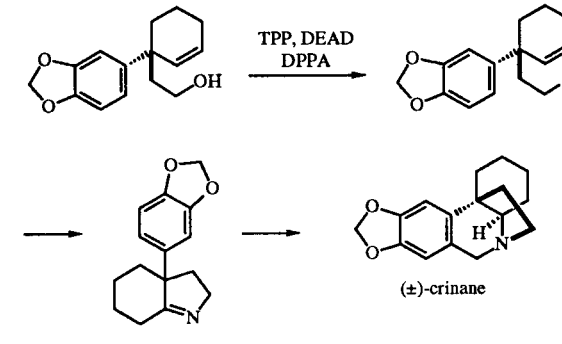


Figure 32.

Rao *et al.* used a similar methodology (Figure 33) for the synthesis of 1,2,3,4-tetrahydroisoquinoline derivatives *via* azido derivatives [56].

In the field of morphine alkaloids, the reaction of 14-chloro(bromo)codeine with DPPA led to the corresponding 6β-azido derivatives, as shown in Figure 34 [57].

2.2. Preparation of *N*-Alkylimide Derivatives.

Cyclic imides are quite suitable acidic reagents in the Mitsunobu reaction. The most frequently employed imine

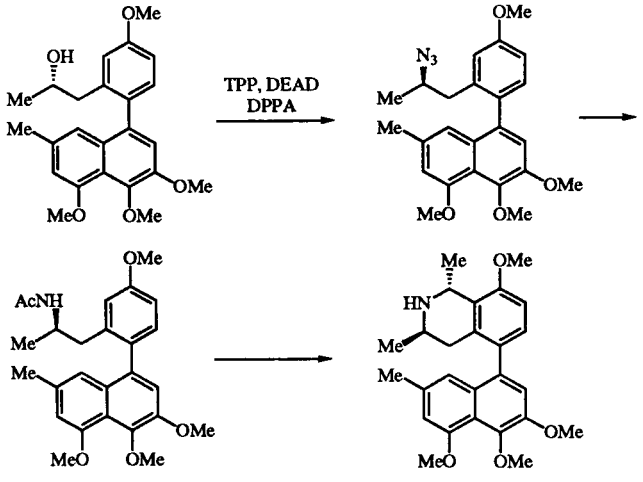


Figure 33.

Figure 34.

for these purposes is phthalimide, and by cleavage of the resulting *N*-alkylphthalimides primary amino compounds are prepared. This methodology has been successfully used for the synthesis of various alkaloids (see Figures 22, 23 and 48) [43,44,58,59].

A synthesis of (±)-lasubine I [an isomer of (±)-lasubine II, shown on Figures 3 and 4] was elaborated starting from veratraldehyde, which was reacted with glutarimide (Figure 35) to furnish an *N*-alkyl derivative [60]. Then, selective reduction of the imide, followed by cyclization with formic acid furnished a formate ester, which was

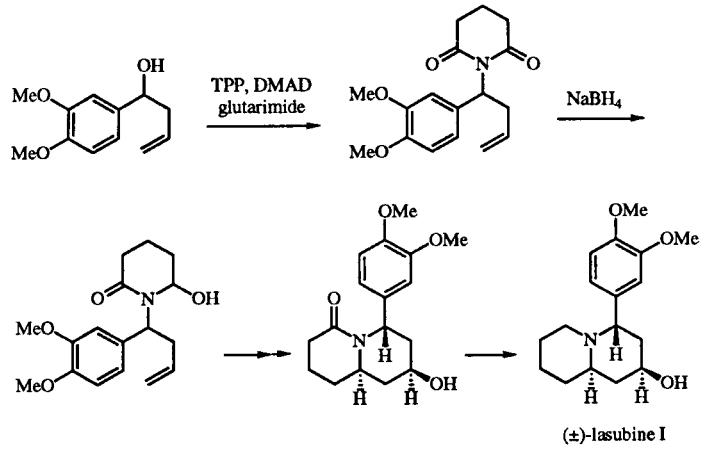


Figure 35.

hydrolyzed and the lactam reduced to allow the preparation of the target alkaloid. By using succinimide and an essentially similar methodology, elaeokaninine B was synthesized [61] (Figure 36).

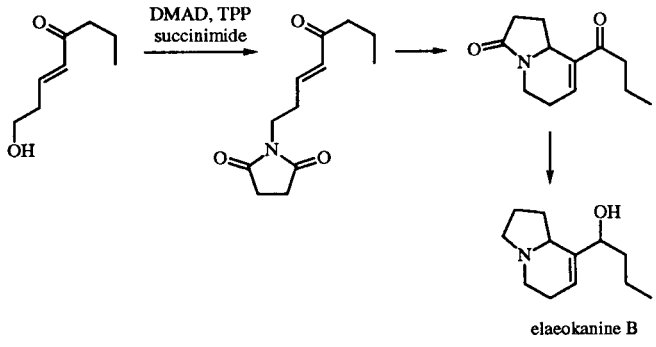


Figure 36.

Speckamp *et al.* developed the aspidospermane skeleton by *N*-alkylation of an imide under Mitsunobu conditions and subsequent cyclization of the resulting *N*-acyliminium salt [62] (Figure 37).

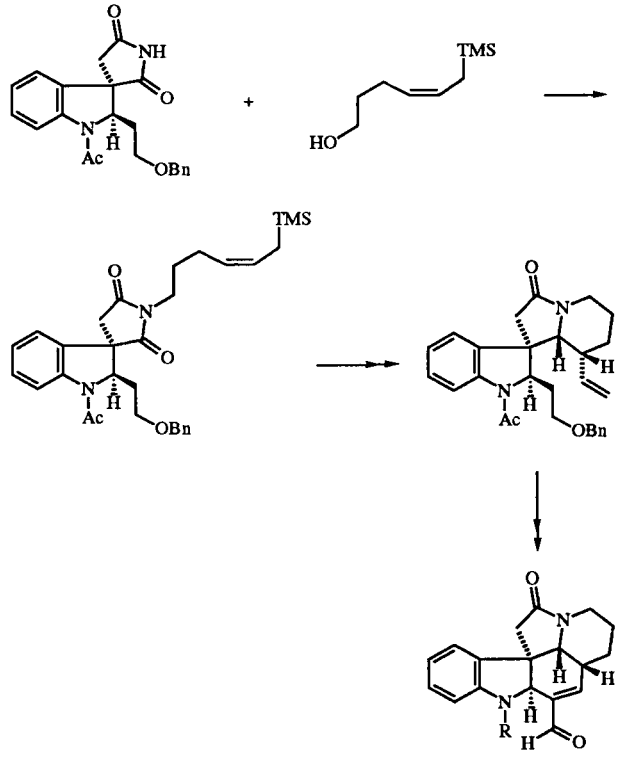


Figure 37.

In an other synthesis of swainsonine, D-tartaric acid was converted into a suitable succinimide derivative (Figure 38), whose *N*-alkylation with an acetylene-alcohol and subsequent radical cyclization gave the optically active compound, (-)-swainsonine [63].

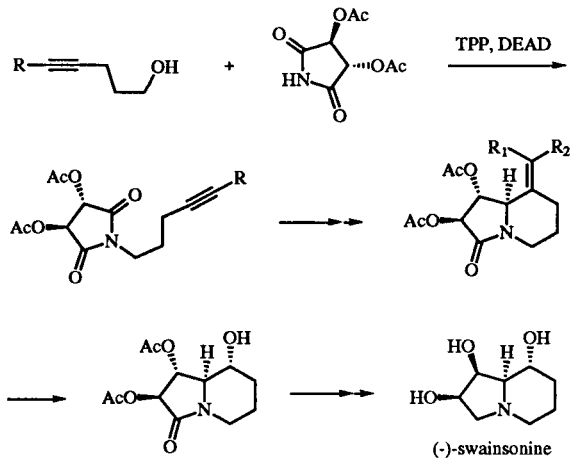


Figure 38.

By investigating the applicability of the Mitsunobu reaction, Makleit and his associates have synthesized numerous morphinane derivatives containing a primary amino function at the 6β-position [36,64,65]. The appropriately substituted codeine and morphine derivatives were reacted with phthalimide (Figure 39), and cleavage of the produced *N*-alkylphthalimides with hydrazine hydrate furnished the expected alkaloid compounds. It is to be noted that this is the only known procedure till now for the synthesis of $\Delta^{7,8}$-6β-amino derivatives.

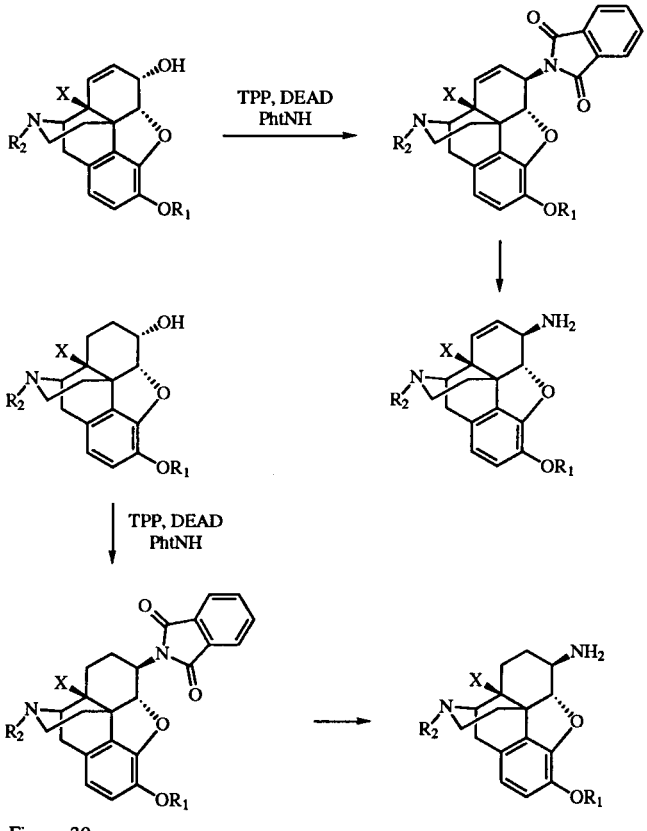


Figure 39.

Investigation of the related reactions of codeine derivatives carrying a halogeno substituent at position C-14, it was found that from 14-chlorocodeine the expected 6β-phthalimido derivative produced as a by-product, but the reaction of the 14-bromo analogue did not give the phthalimido derivative at all [57]. These findings are in good agreement with literature reports describing that the reactions carried out with phthalimide are much more influenced by steric factors than those performed with carboxylic acids. The major products from both 14-halogenocodeines were the corresponding 6,8-diene and the 6,14-dihalogeno compound. It is well demonstrated that with diethyl azodicarboxylate *N*-alkyl-*N,N'*-dicarboethoxyhydrazines are formed when the Mitsunobu reaction-mixture does not contain an acidic reagent, or the acidic component is a very weak acid, or if the attack of the nucleophile is sterically hindered.

It is presumed that the primary product of the above reactions with 14-halogenocodeines is the corresponding hydrazine derivative (Figure 40), from which the diene is produced by 1,4-elimination, and formation of the dihalogeno compound is the result of a Mitsunobu reaction with the hydrogen halide *in situ* developed in the reaction *(vide infra).*

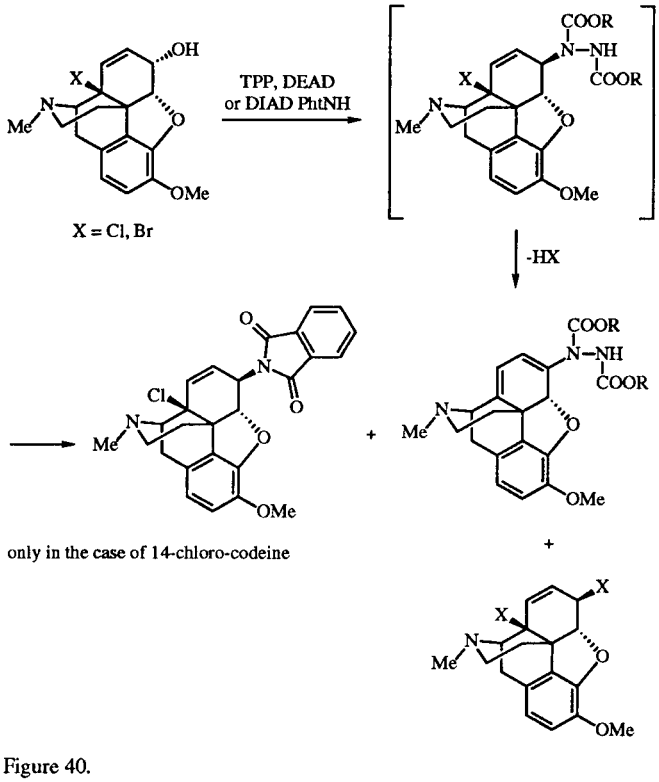


Figure 40.

2.3. Alkylation of Sulfonamides.

There are several examples in the literature when suitably substituted sulfonamides are used as the acidic components

of the Mitsunobu reaction for the development of *N*-containing heterocycles during the total syntheses of alkaloid compounds.

As shown on Figure 23, the primary amino fuction of sarain A was introduced with such a methodology [44]. For the development of the skeleton of cularin, the *N*-tosyl derivative of aminoacetaldehyde dimethylacetal was used as the acidic component [66] (Figure 41), and this reagent or the corresponding trifluoromethanesulfonic amide served in the Mitsunobu reaction to provide a dihydroisoquinoline-type compound [67] (Figure 42).

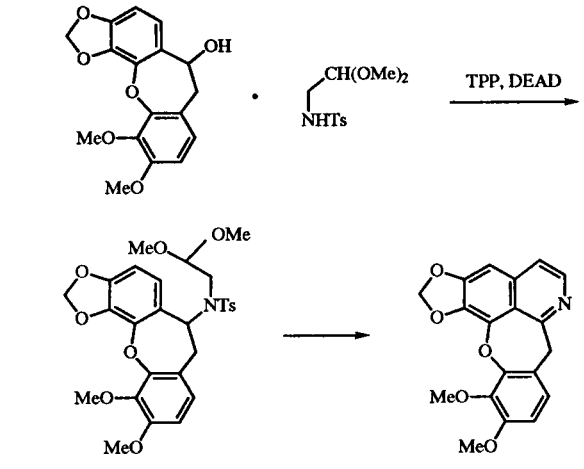


Figure 41.

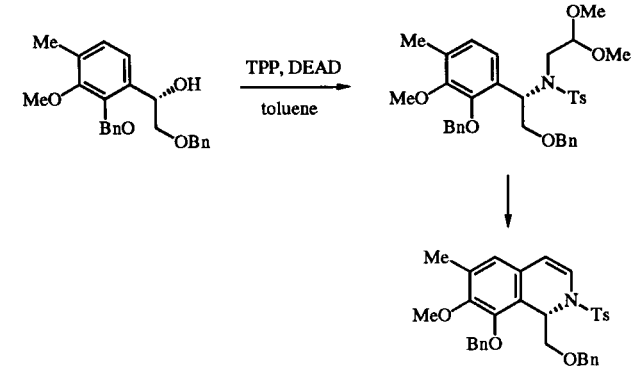


Figure 42.

When synthesizing lisergic acid, Ralbovsky *et al.* [68] performed ring closure of the *N*-tosyl derivative, shown on Figure 43, to obtain a tetracyclic compound.

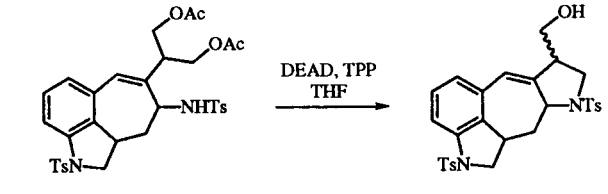


Figure 43.

An interesting example for such types of reactions is the synthesis of epibatidine, where ring closure was accomplished by intramolecular nucleophilic substitution [69] (Figure 44).

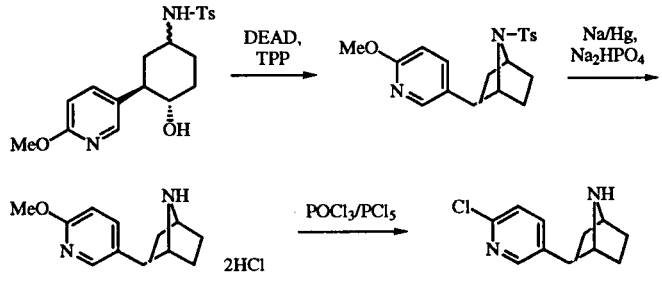


Figure 44.

Murphy and coworkers treated an appropriately substituted cyclohexenol with 2-nitrobenzenesulfonamide under Mitsunobu conditions [70,71]. Then, intramolecular cyclization of the diazoniumsalt of the resulting sulfonamide (Figure 45) furnished a tetracyclic structure, which is a structural element of the molecules of aspidospermidine and strychnine.

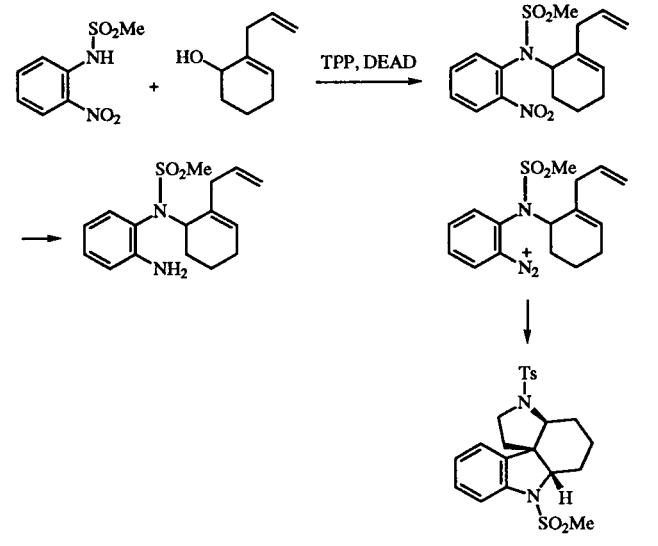


Figure 45.

The acidic reagent in the total synthesis of fragment of manzamine A (Figure 46) is, again, a sulfonamide suitable for the development of the tetracyclic system [72,73]. It is important to note that in this case the reaction proceeded with retention, which can be explained by the neighbouring group participation of the amide function (see Section 3).

2.4. Cyclization of Aminoalcohols.

In the chemistry of alkaloids, cyclization of aminoalcohols is an often used, important procedure. It is to be

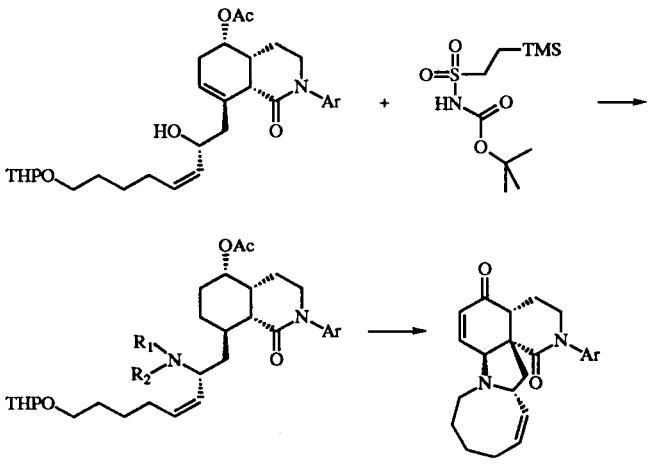


Figure 46.

noted that with this methodology certain azasugar derivatives have also become available [74].

The tricyclic hydroindole skeleton of the Stemona alkaloids was constructed with the aid of the Mitsunobu technology [75], as shown on Figure 47. The reaction proceeds with allylic migration and leads to the required tricyclic compound. However, if the olefinic bond of the side chain of the starting material has been saturated before a related transformation, the Mitsunobu reaction results in a product with a seven-membered ring-system (Figure 47).

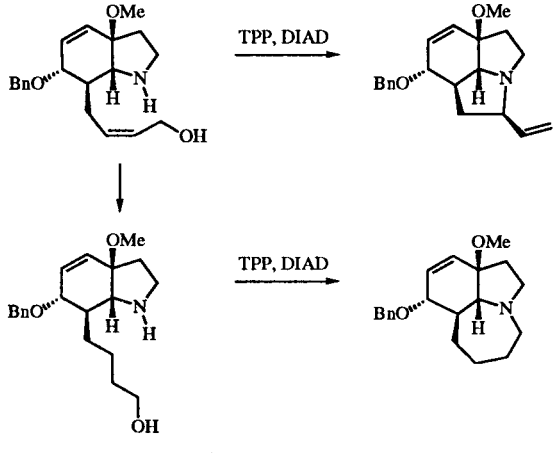


Figure 47.

For the synthesis of the unnatural enantiomer of castanospermine (Figure 48) Mulzer *et al.* applied phthalimide as the acidic component for constructing the required protected primary amine with the Mitsunobu reaction [59]. Removal of the phthalimido function resulted in the closure of the pyrrolidine ring, and in a later step of the reaction sequence cyclization of the intermediary aminoalcohol was also executed by means of the Mitsunobu technology (Figure 48). At the same time, attempted cyclization of an appropriate aminoalcohol in order to synthesize the alkaloid oncinotine was unsuccessful [76].

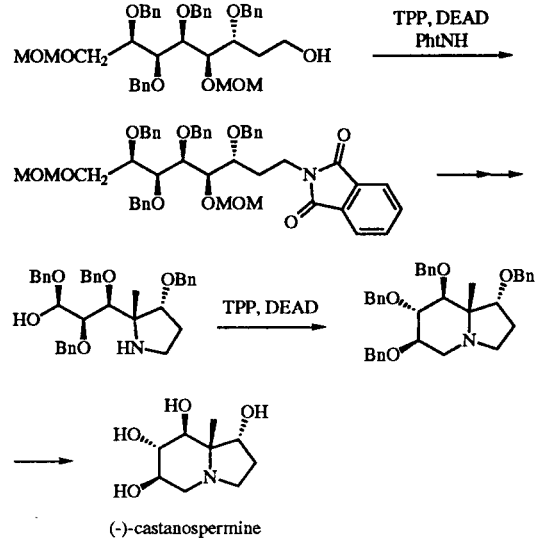


Figure 48.

Tsunoda *et al.* introduced a new reagent, cyanomethylene trimethylphosphorane (CMMP) which was applied for the cyclization of aminoalcohols *e. g.* in the synthesis of (+)-α-skytanthine, and certain structurally related alkaloids [77] (Figure 49).

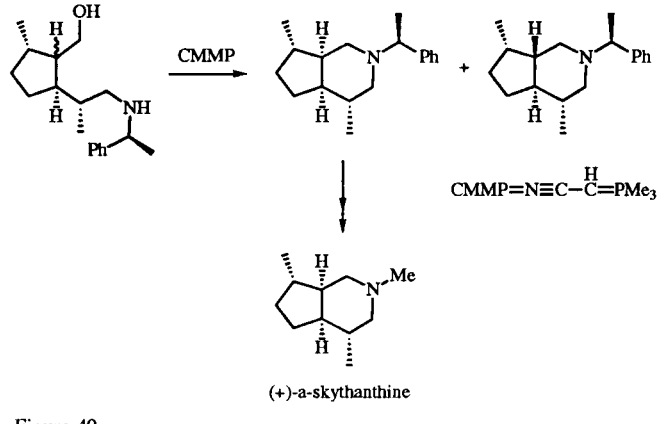


Figure 49.

2.5. *N*-Alkylation of *N*-containing Heterocycles.

For the synthesis of (±)-camptothecin Comins *et al.* synthesized the 2-pyridone derivative shown on Figure 50 [78]. By applying 2-hydroxymethyl-3-bromoquinoline as the alcoholic component, Mitsunobu reaction (DEAD, TPP in THF) resulted in the corresponding *N*-alkylated derivative, which was then converted into the target alkaloid, (±)-camptothecin. When the optically active form of the 2-pyridone was employed for the transformation, the natural (*S*)-camptothecin was obtained [79].

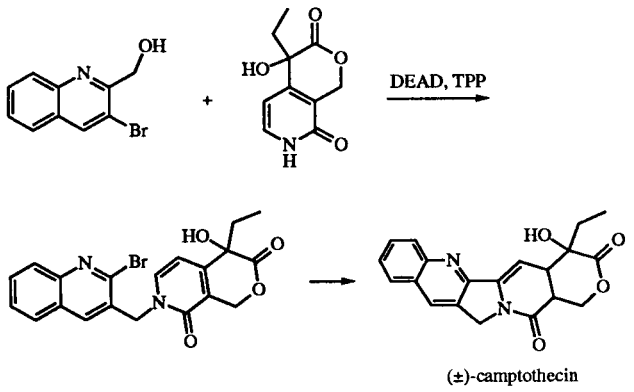


Figure 50.

When studying the *N*-alkylation of theophylline under Mitsunobu conditions [80], it was found that of the employed alcohols, the two substituted butynol gave the corresponding 9-substituted product, whereas with butenol rearranged compounds were isolated (Figure 51).

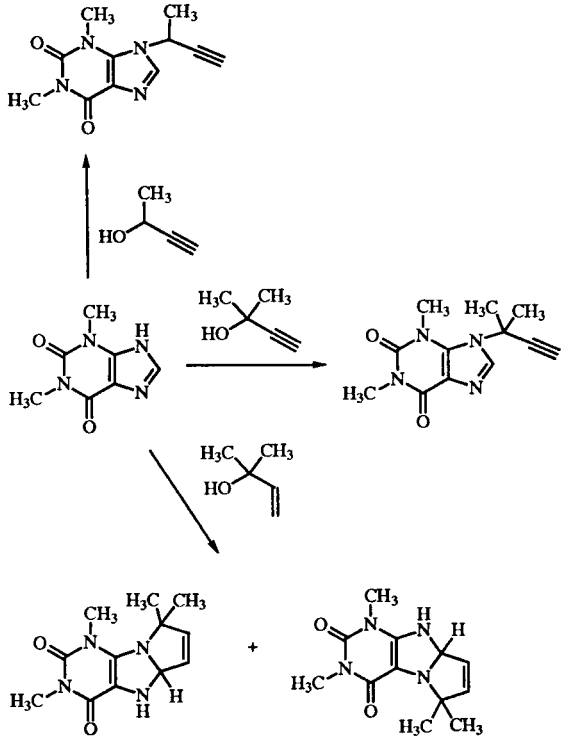


Figure 51.

3. Neighbouring Group Participations.

In this Section examples are given to illustrate the influence of the chemical environment inside the molecule on the outcome of the Mitsunobu reaction.

A key-step in a total synthesis of eudistomin was the conversion of a hydroxyl group into a primary amino function [81]. However, treatment of the starting material with phthalimide did not give the expected product, but instead, a compound formed by ring-contraction was obtained, as shown on Figure 52. The mechanism of this transformation was explained by the intramolecular nucleophilic substitution of the sulfur atom at the intermediary alkoxyphosphorane to result in a thiirane, which was then converted into the final product. An essentially similar result was obtained with the zinc azide-pyridine complex, but in this case the product with the desired seven-membered ring was also produced in a low a yield (5-12%).

However, this latter substance is not a "normal" Mitsunobu product, it is rather formed by the opening of the thiirane ring, as proved by the fact that introduction of the azido group carried out by retention of the configuration.

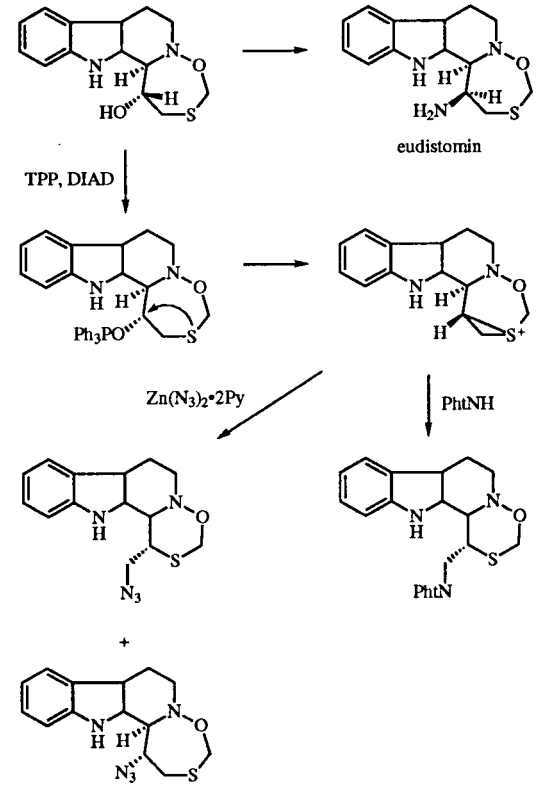


Figure 52.

Upon examination of the reactions of ephedrine and ψ-ephedrine Poelert *et al.* [82] observed a similar neighbouring group participation. It is known that in the case of *N*-benzoyl-ψ-ephedrine with *threo*-configuration an N→O acyl migration is readily carried out and proceeds with the retention of the configuration to give *O*-benzoyl-ψ-ephedrine. In the case of the *erythro* compound, this reaction is much slower to result in the same product with the inversion of the configuration. Therefore, investigation of the ψ-ephedrine → ephedrine conversion under Mitsunobu conditions (Figure 53) appeared to be rather interesting and challenging.

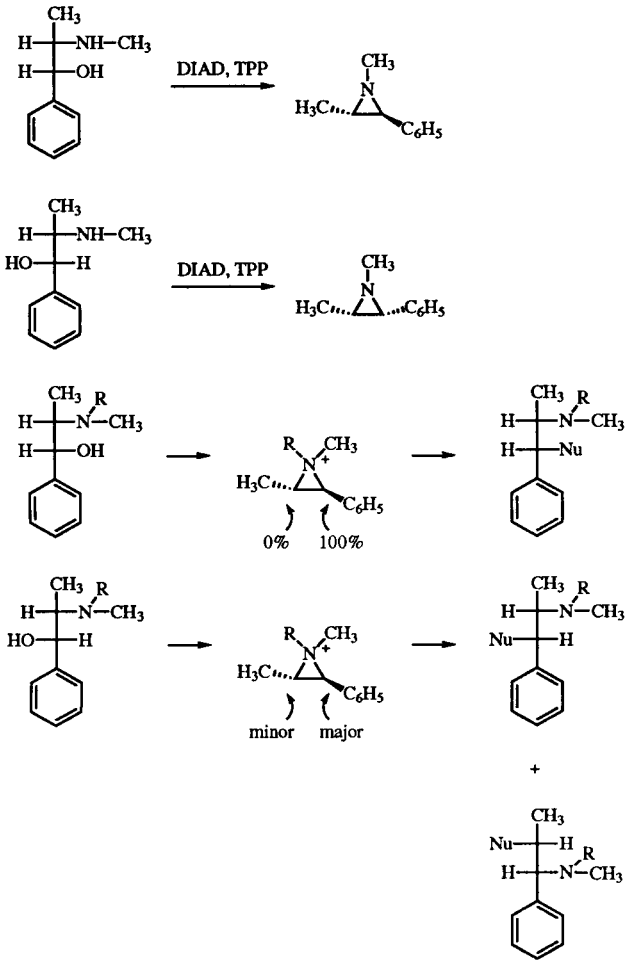


Figure 53.

When either of the two compounds were treated with diisopropyl azodicarboxylate and triphenylphosphine in the absence of an acidic component the aziridines, shown on Figure 53, were produced by an internal nucleophilic attack of the nitrogen atom at the alkoxyphosphorane formed in the Mitsunobu process. It was supposed that by enhancing the bulkiness of the *N*-substituent, formation of the aziridines could be inhibited. When *N*-methyl or *N*-benzylephedrine was reacted with either of *p*-nitrobenzoic acid or phthalimide the product was developed with the retention of the configuration. The results with ψ-ephedrine (of *threo* configuration) were essentially similar, with the difference that the reaction did not proceed with a complete regioselectivity, and thus furnished two products. The fact that these transformations proceeded with retention of the configuration, the existence of an intermediary aziridinium salt was supposed to be most likely - although no such a substance could be isolated from the reaction mixtures.

As an *N*-alkyl substitution did not decrease the nucleophilicity of the nitrogen atom sufficiently, the derivatives carrying Boc and Cbz substituents at the nitrogen atom were prepared (Figure 54). The Mitsunobu reaction of the protected ephedrine led to the cleavage of the protecting groups and gave ephedrine and benzyl *p*-nitrobenzoate. However, the analogous transformation of the ψ-ephedrine derivative proceeded with inversion of the configuration to yield the expected product: the *p*-nitrobenzoic ester of ephedrine. Most interestingly, in this latter case no cleavage of the *N*-protecting group was observed, and ephedrine was obtained upon hydrolysis of the ester function.

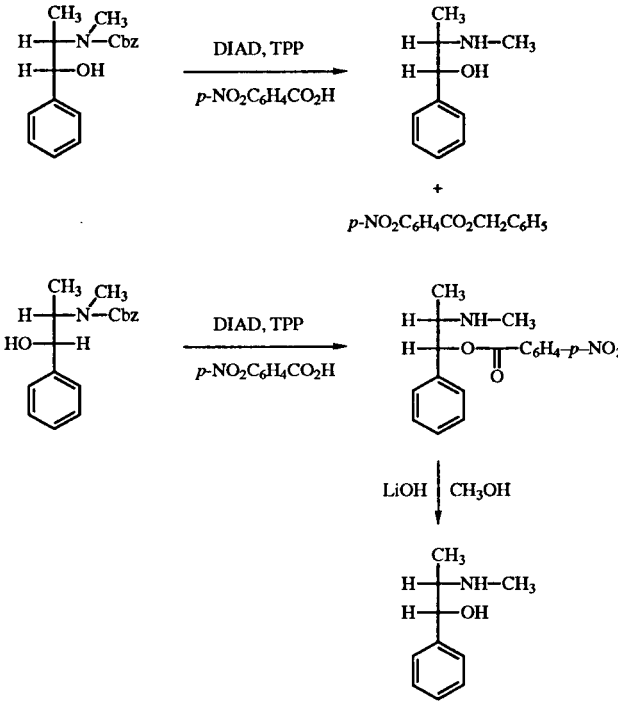


Figure 54.

4. Formation of Carbon-sulfur Bonds.

Data in the literature show that the Mitsunobu reaction is a widely applied procedure for constructing C-S bonds. The acidic reactants in these reactions are usually thioacetic acid and heterocycles containing an SH-functionality. In the field of alkaloids, and most particularly for morphine alkaloids Kanematsu and coworkers employed thioacetic acid to produce the corresponding 6β-thioacetates, from which the 6β-thiols were obtained. In the case of morphine, carrying a free phenolic hydroxyl function, acetylation of this group also occurred [83].

The Mitsunobu reaction of dihydromorphine under analogous conditions led to 3-*O*-acetyldihydromorphine, as the major product, and only 7% of the desired 6β-thioacetate could be isolated (Figure 55). From

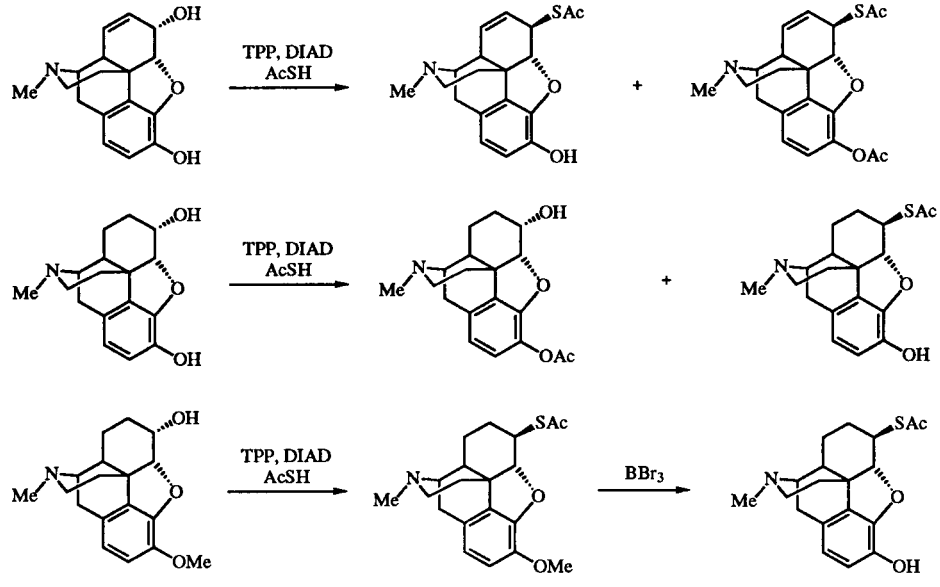


Figure 55.

dihydrocodeine the expected 6β-thioester could be synthesized with a quantitative yield, and subsequent *O*-demethylation with boron tribromide led to the target dihydromorphine analogue.

Based on an essentially similar procedure, numerous 6β-thioacetyl derivatives, including the *N*-cyclopropylmethyl analogue, have been prepared for pharmacological investigations, and the structures of these new compounds were elucidated by means of ^{1}H nmr and X-ray measurements [84]. It is interesting to note that the Kanematsu group obtained 7% of the respective 6α-thioacetate from 14-hydroxydihydroisocodeine by treatment with thioacetic acid under Mitsunobu conditions. In a recent paper the Japanese chemists have reported [85] the preparation of the desired thioacetate from 10-oxo-*N*-demethyl-*N*-cyclopropylmethyldihydromorphine, as well (Figure 56).

5. Synthesis of Halogenated Derivatives.

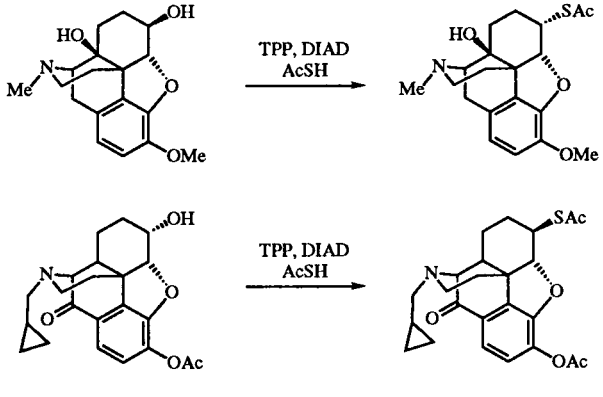


Figure 56.

By investigating the reaction of 14-halogenocodeine derivatives with phthalimide, the formation of the dihalogeno analogues was explained by the Mitsunobu reaction of the *in situ* produced hydrogen halide. To prove this assumption, the Mitsunobu reaction of the hydrochloride and hydrobromide salts of various codeine and morphine derivatives with diethyl azodicarboxylate and triphenylphosphine was studied. It has been found that under these conditions the products were the 6β-substituted halogeno derivatives, and by this procedure 6β-bromo-6-deoxycodeine and 6β-bromo-6-deoxymorphine, assumed earlier only as intermediates, could be isolated [86]. The 14-hydroxy analogues of these compounds were also synthesized, and it is to be emphasized that this is the hitherto only procedure for the synthesis of the $\Delta^{7,8}$-6β-bromo derivatives of the morphine alkaloids (Figure 57).

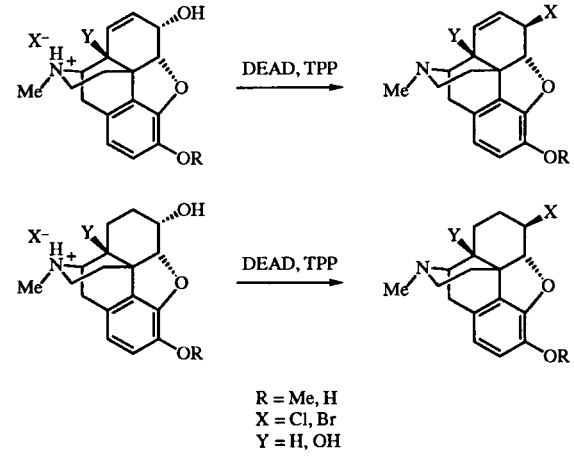


Figure 57.

Abbreviations

TPP	triphenylphosphine
DMAD	dimethyl azodicarboxylate
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
Me	methyl
Ph	phenyl
Bu	*n*-butyl
t-Bu	*t*-butyl
Bn	benzyl
Ac	acetyl
MOM	methoxymethyl
MEM	β-methoxyethoxymethyl
Cbz	benzyloxycarbonyl
Boc	*t*-butoxycarbonyl
PMP	*p*-methoxyphenyl
TMS	trimethylsilyl
TBDMS	*t*-butyldimethylsilyl
DPPA	diphenylphosphoryl azide
Ts	*p*-toluenesulfonyl
m-CPBA	3-chloroperoxybenzoic acid
PhtNH	phthalimide
THP	tetrahydropyranyl
THF	tetrahydrofuran
DMF	*N,N*-dimethylformamide

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