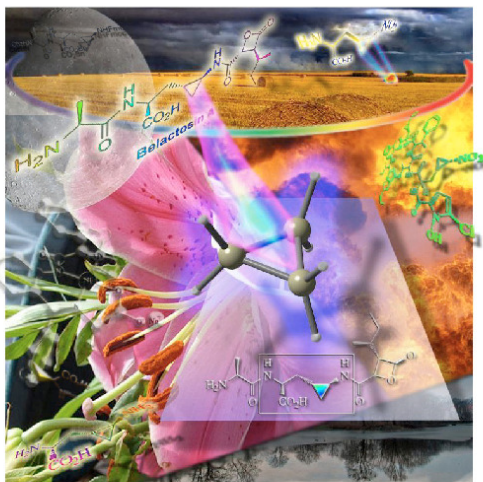Oleg Larinov (Autor)
Novel Synthese of Biologically Active Compounds Containing Cyclopropane Moieties

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Containing Cyclopropane Moieties

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A. Introduction and Background

1. General Considerations

Organic chemistry provides molecular structures of nearly infinite complexity and diversity. A subtle structural change almost inevitably brings about tremendous and often hardly predictable changes in physical, chemical, and biological properties of the chemical compound. Thus, the arsenal of the organic chemist should comprise methods, which allow to build molecules with desired structures in a concise and economical manner. Although the state-of-the-art of organic methodology has achieved a high degree of sophistication, it often lacks simple and direct protocols, especially if it comes to the synthesis of molecules comprising several densely clustered nontrivial structural elements.

The "case in point" is, for example, to prepare cyclopropanes with *given* configurations of chiral centers in the cycle, attached to further chiral moieties and/or (hetero)aromatic rings with *defined* substitution patterns. Since nature makes use of such molecules, not only does their target-oriented synthesis provide a ready access to these valuable compounds, but also helps to evaluate the known synthetic methodology, and sheds light onto new methodological challenges.
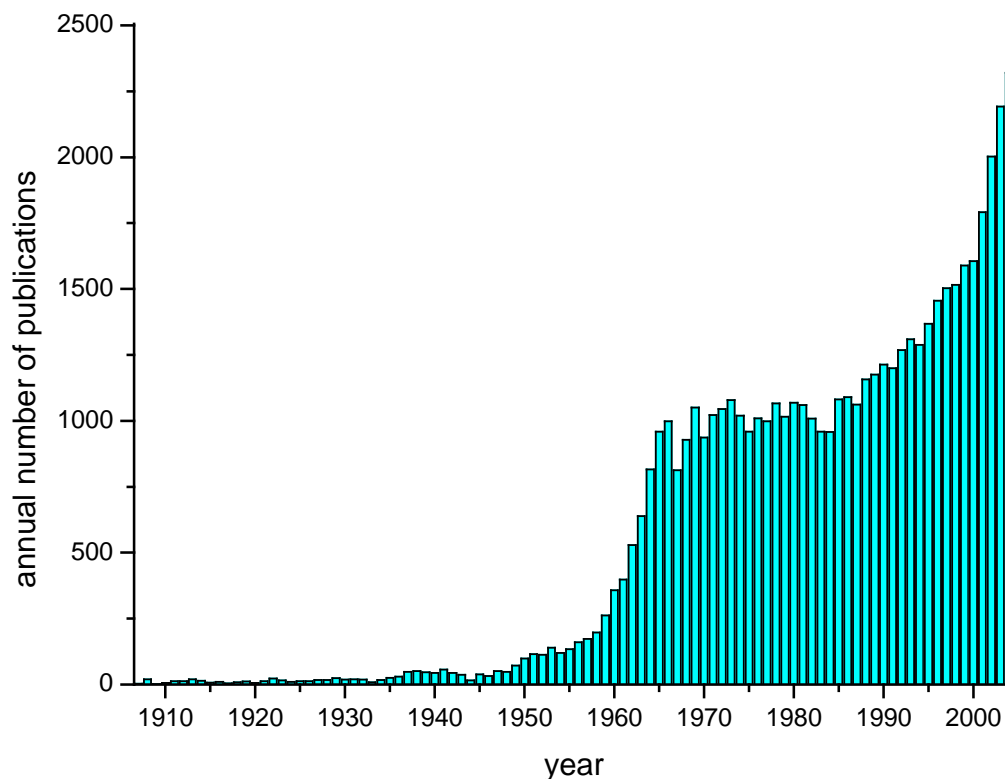
Graph 1. Annual numbers of publications, relevant to the chemistry of cyclopropanes
(SciFinder).

Regarding these trends in the chemistry of cyclopropanes (Graph 1), one may notice
the spectacular splash of interest in these compounds in the 1960s. Since then the
discipline was developing with a stable rate of approximately 1000 publications
annually, until it has seen the second impressive upsurge in the last two decades,
mainly owing to the increasing awareness for the biological and medicinal relevance of
cyclopropane-containing compounds.

Among such substances, hormaomycin (**1**) and belactosin A (**2**) appear to be
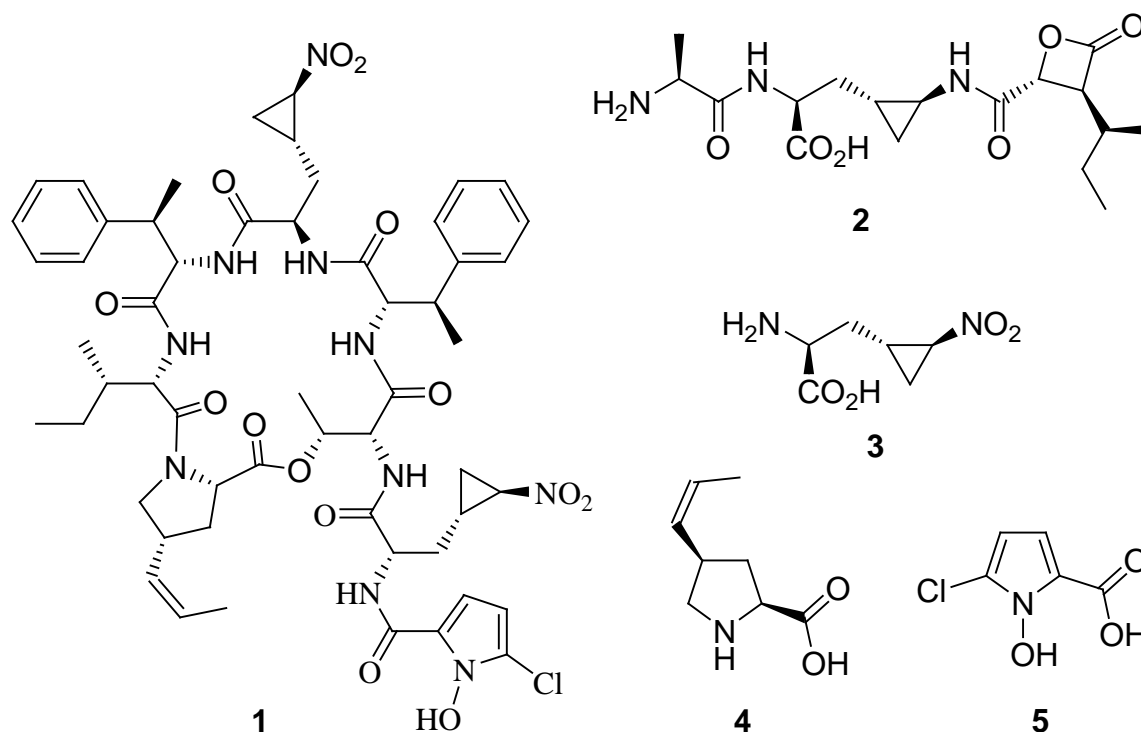remarkably representative examples (Figure 1).

Figure 1. Hormaomycin (**1**), Belactosin A (**2**), and the new amino acid 3-(*trans*-2-nitrocyclopropyl)alanine (**3**).

2. Hormaomycin

Hormaomycin (**1**) was isolated from *Streptomyces griseoflavus*, strain W-384, during the screening of intermolecular signal substances by ZÄNER et al. in 1989.[1,2] It was the first substance with a peptide structure, which induced the production of antibiotics and aerial mycelium formation not only in this strain itself but also in other Streptomyces species, *e.g.* hydroxystreptomycin in *S. flaveolus*, streptolin in *S. fridae*, tirandamycin in *S. griseoflavus*, strain 1306, and bafilomycin in *S. griseus*.[3] A significant increase in the production of antibiotics was observed already at 0.05 µg/L concentration of hormaomycin. This substance also showed strong antibiotic activity against coryneform bacteria (MIC = 0.0005 µg/mL for *Arthrobacter oxydans*).[4] The structural diversity implemented in this molecule is unusual even for this flexible class of compounds, and

the structure elucidation required notable synthetic and analytical efforts, mainly from the groups of DE MEIJERE and ZEECK, which have spanned over a period of more than a decade. Thus, it contains two diastereomers of the structurally unique 3-(*trans*-2-nitrocyclopropyl)alanine [(N*c*P)Ala] (**3**), the unusual amino acid 4-(*Z*)-propenylproline (**4**), and the seemingly trivial, but understudied and only laboriously accessible 5-chloro-1-hydroxy-1*H*-pyrrole-2-carboxylic acid (**5**).

3. 3-(*trans*-2-Nitrocyclopropyl)alanine

It has been established that (2*S*,1'*R*,2'*R*)-**3** acquires the exocyclic position in **1**, while (2*R*,1'*R*,2'*R*)-**3** is incorporated in the hexapeptolide ring constituent of the pentapeptidic ring.[5]
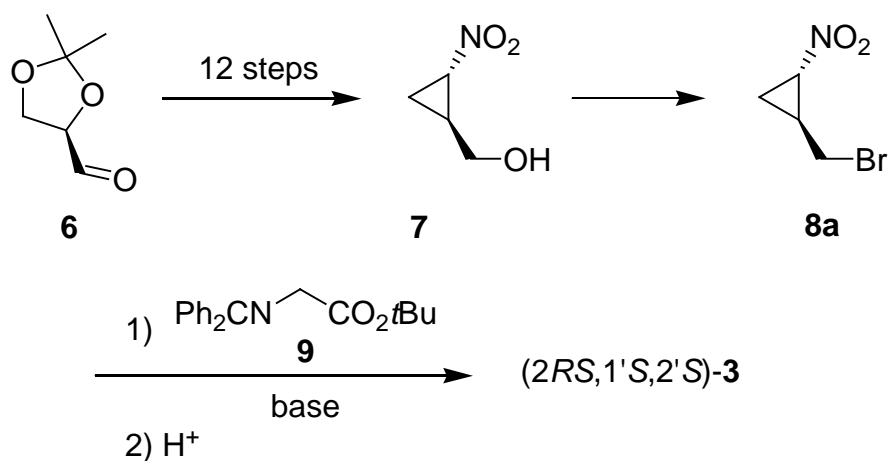

Scheme 1. First synthesis of 3-(*trans*-2-nitrocyclopropyl)alanine (**3**).[6]

The first syntheses of the racemate, as well as certain diastereomeric mixtures[6] of 3-(*trans*-2-nitrocyclopropyl)alanine [(N*c*P)Ala] (**3**), described by ZINDEL and DE MEIJERE, relied on a multistep transformation of the protected glycerin aldehyde **6** to enantiomerically enriched (*trans*-2-nitrocyclopropyl)methanol (**7**), which, after

conversion into the corresponding bromide **8a**, was reacted with O'DONNELL glycine equivalent **9**, in the presence of a base to give, after deprotection, the desired amino acid **3** (Scheme 1).

Whereas the last steps of the synthetic scheme comprise the highly productive and general amino acid synthesis based on an electrophilic alkylation of a glycine equivalent, which was employed in all further syntheses of **3**, the preparation of the alkylating agent **8a** was too lengthy, and suffered from low yields. Thus, in a second generation approach to the amino acid **3**, the more reactive alkylating agent (*trans*-2-nitrocyclopropyl)methyl iodide (**8b**) was employed, and a novel synthetic route to its precursor **7** was developed.[7]
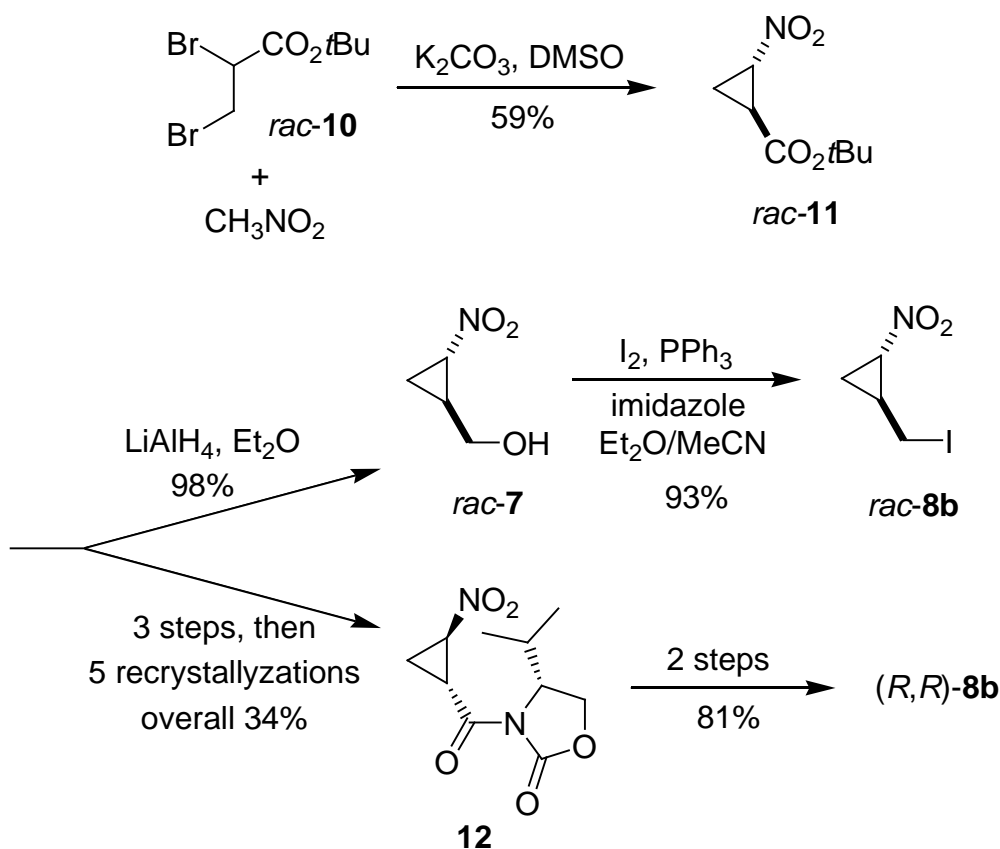
Scheme 2. Synthesis of racemic and enantiomerically enriched iodide **8b**.[8]

The racemic iodide **8b** was prepared in three simple steps, starting from *tert*-butyl 2,3-dibromopropionate (**10**). To begin with, the known synthesis of *tert*-butyl *trans*-2-nitrocyclopropanecarboxylate (**11**)[6] was significantly improved (Scheme 2). By adding the dibromoester **10** to a mixture of nitromethane and potassium carbonate in dimethyl sulfoxide (DMSO), the yield of **11** increased from 31 to 59%.

Reduction of the ester **11** with lithium aluminum hydride afforded the racemic alcohol **7** in 98% yield. This was converted into the iodide *rac*-**8b** in 93% yield by treatment with iodine, imidazole and triphenylphosphine.[8] A synthesis of enantiomerically enriched iodide **8b** was elaborated by KOZHUSHKOV, BRANDL, and DE MEIJERE.[7] The optical resolution of *trans*-2-nitrocyclopropanecarboxylic acid by crystallization of the corresponding acyl 4-isopropyl-1,3-oxazolidin-2-ones **12** allowed to prepare the target alcohol only in 5 steps, in contrast to the initial tedious twelve-step route starting from expensive enantiomerically pure protected glycerin aldehyde.

The thus obtained enantiomerically enriched iodide **8b** was employed in the asymmetric alkylation of SCHÖLLKOPF's chiral glycine equivalent (LOSCHA, DE MEIJERE) to give (2*S*,1′*R*,2′*R*)-3-(2-nitrocyclopropyl)alanine (**3**), albeit only 50 mg of this amino acid was prepared,[9] reflecting certain shortcomings of this synthesis, *e.g.* the inevitable necessity of employing two different and expensive chiral reagents. As the total synthesis of hormaomycin was envisaged, multigram quantities of different diastereomers of **3** were required. This made the development of a new and efficient synthesis of all four diastereomers of **3** indispensable for any further progress towards the chemistry of hormaomycin at the outset of this doctoral study. This part of work is discussed in the first Chapter of the main part of this dissertation.

4. Pyrrole Syntheses

After the complete elucidation of the hormaomycin configuration, and the execution of its first total synthesis by ZLATOPOLSKY and DE MEIJERE in 2003,[10] new challenges have become evident. Thus, since the mode of action and the structure-activity

relationship of hormaomycin have to a larger extent remained understudied, a major effort has been applied to the synthesis of further analogs of hormaomycin. One of the possible residues to modify may be the *N*-hydroxypyrrolecarboxylic acid component **5**. Difficulties encountered in its synthesis[10] may prompt to turn attention to different substitution patterns at the nitrogen atom. Hence, a general and efficient synthesis of substituted pyrroles (*e.g.* substituted pyrrole-2-carboxylic acids) could help clarification of the role of the pyrrolic component in **1**. On the other hand, development of new and productive synthesis of oligosubstituted pyrroles could have a considerable impact on pyrrole chemistry in general, owing to the pivotal role of pyrroles among five-membered heterocycles, and to the vast number of natural products,[11] potent pharmaceuticals,[12] molecular sensors and devices.[13] which contain pyrrole subunits.
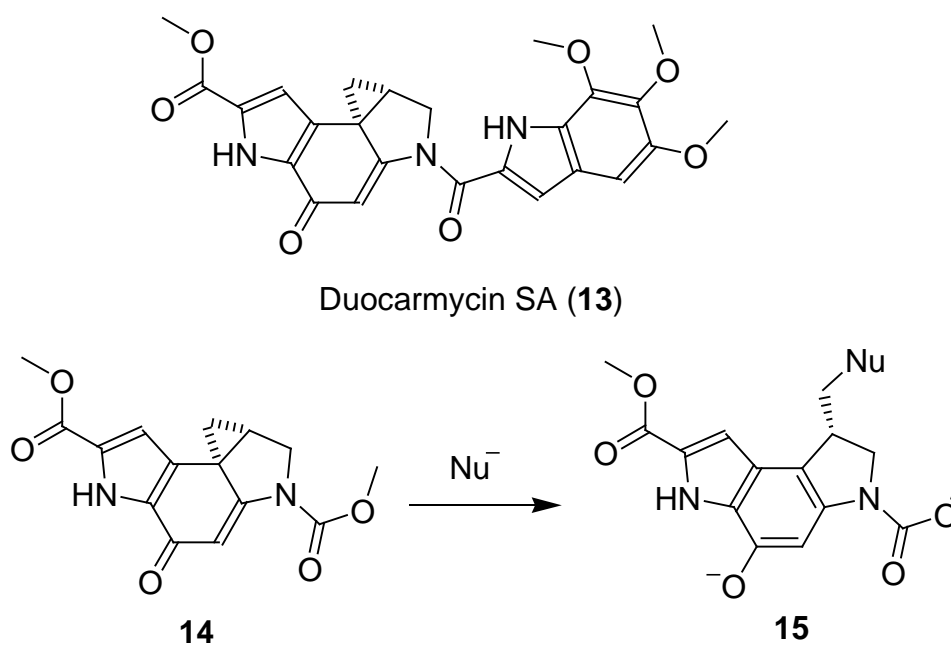
Duocarmycin SA (**13**)

Scheme 3. Duocarmycin SA (**13**) and its mode of action.

Noteworthy, that an interplay of adjacent cyclopropyl and pyrrole moieties is often crucial for the observed high biological activity, as in the case of the potent antitumor agent Duocarmycin SA (**13**), effecting selective DNA alkylation (Scheme 3).[14] Whereas the pyrrole units provide a sequence-specific DNA intercalation, the

electrophilic cyclopropane ring irreversibly binds to nucleophilic functionalities. These appear to be the nucleotide bases, as the intercalation gives rise to an exceptional proximity to the DNA strand. The cyclopropane ring opening is facilitated by the ring strain and subsequent aromatization of the cyclohexadiene ring system. The replication damage as a consequence of the DNA alkylation by Duocarmycin SA leads to the cell death or cell differentiation.

$$X = O, NR, CR_2$$
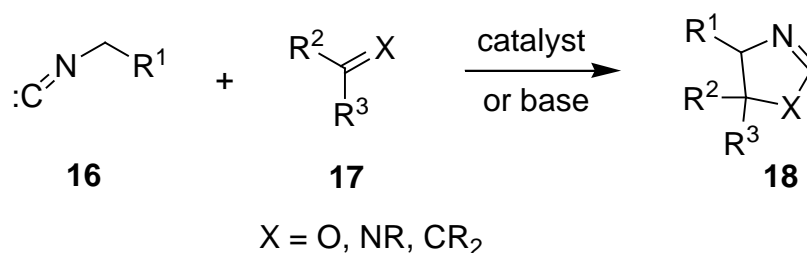
Scheme 4. Additions of isocyanides across double bonds.

Additions of isocyanides across double bonds were first described by SCHÖLLKOPF,[[15]] and since then have proven to be an efficient entry into a number of five-membered heterocycles (Scheme 4).[16]. The reaction proceeds both in the presence of stoichiometric amounts of a sufficiently strong base, and under transition metal catalysis. Silver(I), gold(I), and copper(I), as well as zinc(II), and palladium(II) salts have been employed as catalysts.

An asymmetric variant of this formal cycloaddition with gold(I) / chiral ferrocenyldiphosphine catalytic pair was described by ITO, SAWAMURA and HAYASHI,[17] and high levels of diastereo- and enantioselectivity were achieved (Scheme 5), providing an efficient access to enantiomerically pure α-amino-β-hydroxy acids.
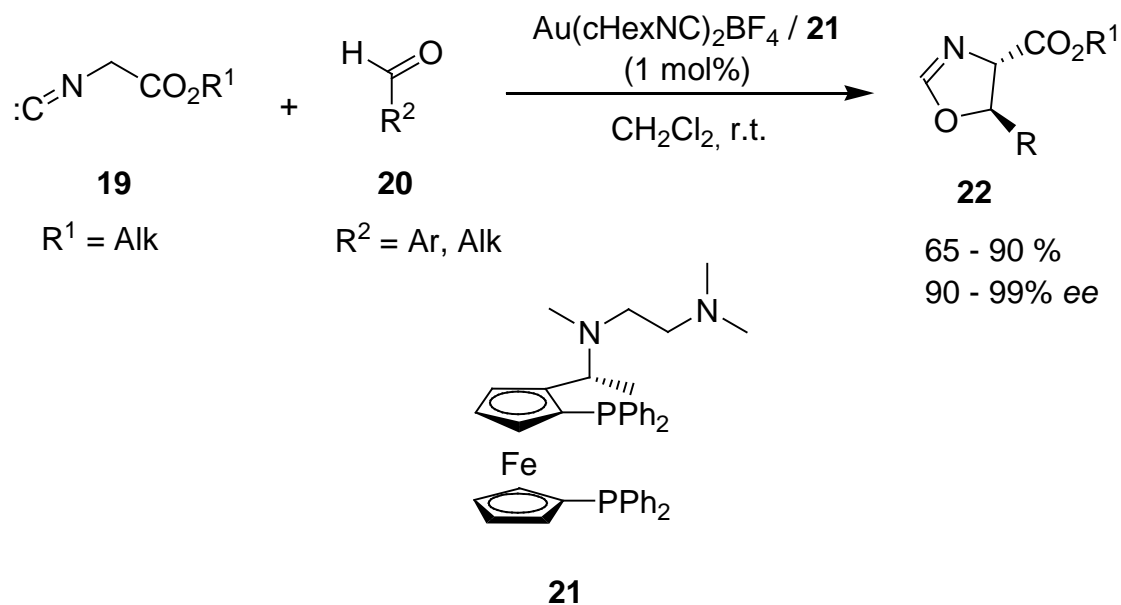
Scheme 5. Highly enantioselective cycloaddition of substituted methyl isocyanides to aldehydes, according to ITO, SAWAMURA and HAYASHI.[17]

If the formed pyrrolidine contains an appropriate leaving group, it can be transformed into the corresponding pyrrole (Scheme 5). The leaving group can be embedded into the isocyanide moiety (the VAN LEUSEN pyrrole synthesis with p-tolenesulfinate as a leaving group), or arise from the α,β-unsaturated component (the BARTON-ZARD pyrrole synthesis).[18]

In the first case p-toluenesulfonylmethyl isocyanide (TosMIC) (**22**) adds to electron-deficient alkenes giving rise to pyrrolines, which in the second step undergo elimination of p-toluenesulfinic acid to give the corresponding pyrroles. That is, the p-toluenesulfonyl group has to be inevitably lost during the reaction. Thus, all the previously described syntheses of pyrroles from isocyanides are *indirect*, with alkenes as starting materials and an inevitably formed by-product.